

**1. A genetic rat model of depression, Flinders sensitive line, has a lower density of 5-HT1A receptors, but a higher density of 5-HT1B receptors, compared to control rats**

By Nishi, Kyoko; Kanemaru, Kazuya; Diksic, Mirko

From *Neurochemistry International* (2009), 54(5-6), 299-307. Language: English, Database: CAPLUS,

DOI:10.1016/j.neuint.2008.12.011

Deficiencies in brain serotonergic neurotransmission, which is in part assocd. with the alteration of brain serotonin (5-HT) receptors, have been proposed as part of a neurochem. imbalance in affective disorders, including depression. The drugs used for the treatment of these disorders generally act through and/or on the serotonergic system. Different animal models of depression have provided researchers with tools to obtain a better understanding of drug actions and possibilities to obtain insight into the neurochem. bases of these disorders. The measurements of the 5-HT1A and 5-HT1B receptor densities in a rat model of depression, Flinders sensitive line (FSL) rats, and comparisons with Sprague-Dawley (SPD) and Flinders resistant line (FRL) rats, are reported here. The receptor sites were quantified by autoradiog. in more than 25 distinct brain regions known to have relatively large densities of resp. sites. Some brain regions (e.g., dental gyrus, septal nucleus) were divided into several parts, according to previously known subdivisions, because of a substantial heterogeneity of these receptors. The densities in the FSL rats ("depressed" rats) were compared statistically to those in the SPD rats. In addn., comparisons were made to the densities in the FRL rats (rats not showing depressive symptoms). Comparisons were performed with the SPD and FRL rats because both of these strains have been used as control animals in studies of FSL rats. The results show that the densities of 5-HT1A receptors are not significantly different between the FSL and SPD rats, but they are significantly different from the FRL rats. 5-HT1A receptor d. is significantly higher in the FRL rats than the SPD rats. The 5-HT1B receptors were significantly greater in the FSL rats than in either the SPD or FRL rats. In addn., the FRL rats have 5-HT1B receptor densities significantly lower in many brain regions than the SPD rats. The data presented here, in addn. to previously reported differences in regional synthesis between these strains and the effect of acute citalopram on synthesis, suggest that SPD rats are likely a more appropriate control than FRL rats, when studies of FSL rats are performed with drugs acting directly or indirectly on, or through, the brain serotonergic system. However, comparisons, particularly of neurochem. and/or biol. parameters in FRL rats, may reveal new insight into the alterations of 5-HT neurotransmission in this animal model of depression and possibly human depression, as well as the elevation of symptoms with treatments. The data also suggest that there could be a different fraction of 5-HT1A receptors in high and low affinity states in these strains, as well as the possibility of different intracellular signaling.

**~12 Citings**

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**2. Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study**

By Reimold, M.; Batra, A.; Knobel, A.; Smolka, M. N.; Zimmer, A.; Mann, K.; Solbach, C.; Reischl, G.; Schwaerzler, F.; Gruender, G.; et al

From *Molecular Psychiatry* (2008), 13(6), 606-613. Language: English, Database: CAPLUS,

DOI:10.1038/sj.mp.4002149

Serotonergic dysfunction may contribute to neg. mood states in affective disorders. Some in vivo imaging studies showed reduced availability of serotonin transporters (5-HTT) in the brainstem and thalamus of patients with major depression. We tested the hypothesis that 5-HTT availability is reduced in unmedicated unipolar patients with major depression compared to healthy control subjects matched for gender, age, genotype and smoking status. Availability of 5-HTT was measured in vivo with positron emission tomog. and [11C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) in the midbrain, thalamus and amygdala. DASB binding was correlated with the severity of depression (Beck's Depression Inventory), anxiety (Spielberger's State-Trait Anxiety Inventory) and personality traits (Temperament and Character Inventory). Patients with major depression displayed reduced 5-HTT availability in the thalamus ( $P=0.005$ ). In patients, low serotonin transporter availability correlated with high anxiety (thalamus:  $r=-0.78$ ,  $P=0.004$ ; midbrain:  $r=-0.78$ ,  $P=0.004$ ; amygdala:  $r=-0.80$ ,  $P=0.003$ ). Correlations with severity of depression were weaker and did not survive correction for multiple testing. These results support the hypothesis that central serotonergic dysfunction is assocd. with neg. mood states in affective disorders. In the thalamus, a low serotonin reuptake capacity may interfere with thalamic control of cortical excitability and contribute to anxiety rather than depression per se in major depression. *Mol. Psychiatry* (2008) 13, 606-613; doi:10.1038/sj.mp.4002149; published online 12 Feb. 2008.

**~8 Citings**

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**3. Serotonin Receptors**

By Nichols, David E.; Nichols, Charles D.

From *Chemical Reviews* (Washington, DC, United States) (2008), 108(5), 1614-1641. Language: English, Database: CAPLUS, DOI:10.1021/cr078224o

A review on phylogeny, structural features, oligomerization, classification and functions of serotonin receptors.

## ~79 Citings

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### **4. Chronic buspirone treatment normalizes open field behavior in olfactory bulbectomized rats: Assessment with a quantitative autoradiographic evaluation of the 5-HT<sub>1A</sub> binding sites**

By Sato, Hiroki; Skelin, Ivan; Debonnel, Guy; Diksic, Mirko  
From Brain Research Bulletin (2008), 75(5), 545-555. Language: English, Database: CAPLUS,  
DOI:10.1016/j.brainresbull.2007.09.005

The olfactory bulbectomized (OBX) rat model of depression has been widely used in studies on the behavioral and neurochem. aspects of human depression. The objective of the present investigation was to assess open field (OF) activity and the brain regional 5-HT<sub>1A</sub> receptor densities of the sham operated (SHX) and OBX rats treated with saline (SHX-SAL, OBX-SAL), and either 10 mg/(kg day) (SHX-B10, OBX-B10) or 20 mg/(kg day) (SHX-B20, OBX-B20) of buspirone for 14 days, delivered by a s.c. osmotic minipump. Adult Sprague-Dawley rats were used for this expt. The surgery was performed on the first day of the expt. and the rats were randomly assigned to either the SHX or OBX groups. The results of the OF tests were organized in eight groups. Following 14 days of treatment and the final OF tests, the rats were sacrificed and the brains were used for 5-HT<sub>1A</sub> receptor autoradiog. using [<sup>3</sup>H]8-OH-DPAT. The data showed that the OF activities, 14 days following surgery, in the OBX rats were significantly elevated when compared to the SHX rats. In the OBX rats, only the 14-day treatment with 20 mg/(kg day) of buspirone normalized the elevated OF activity, the same dose shown previously to be needed for the normalization of the regional 5-HT synthesis. A significant redn. in the no. of 5-HT<sub>1A</sub> receptor sites was found in most brain regions in the OBX rats when compared to the SHX rats. Data also show that the regional d. of the 5-HT<sub>1A</sub> receptors in OBX-SAL treated rats is lower than that of the SHX-SAL rats. The 14-day treatment with either 10 or 20 mg/(kg day) of buspirone reduced the 5-HT<sub>1A</sub> receptors in most brain regions of the SHX rats, without an obvious dose-dependent effect of the buspirone. The comparison between the OBX-B20 and control (SHX-B20) rats suggests that the buspirone treatment resulted in a regional balance in the 5-HT<sub>1A</sub> sites. A dose dependent redn. in the d. of 5-HT<sub>1A</sub> sites was obsd. in the sham rats, but the buspirone treatment had very little effect on the d. of the 5-HT<sub>1A</sub> receptors in the OBX rats. From these observations, we conclude that the antidepressant effects of buspirone in the OBX rat model of depression are likely mediated through the fine tuning of the regional imbalance of 5-HT<sub>1A</sub> receptors with even increases of about 20% in some limbic regions. The data suggest that the neurochem. effects of antidepressants should be studied in animal models of depression rather than in normal rats.

## ~17 Citings

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### **5. The vanadium (IV) compound rescues septo-hippocampal cholinergic neurons from neurodegeneration in olfactory bulbectomized mice**

By Han, F.; Shioda, N.; Moriguchi, S.; Qin, Z.-H.; Fukunaga, K.  
From Neuroscience (San Diego, CA, United States) (2008), 151(3), 671-679. Language: English, Database: CAPLUS,  
DOI:10.1016/j.neuroscience.2007.11.011

The bilateral olfactory bulbectomy (OBX) mouse exhibits neurodegeneration of cholinergic neurons in the medial septum with concomitant cognitive deficits. Consistent with our previous observations, choline acetyltransferase (ChAT) protein levels in the medial septum decreased by 43.5% 2 wk after OBX without changes in glutamic acid decarboxylase-65 (GAD65) levels. Interestingly, levels of the vesicular acetylcholine transporter (VACHT), which is localized at cholinergic neuron terminals, decreased both in hippocampal CA1 and CA3 regions following OBX. Confocal microscopy showed that VACHT expression was more severely reduced in CA3 14 days after OBX compared with CA1. Intriguingly, chronic treatment with a vanadium (IV) compd., VO(OPT) [bis(1-N-oxide-pyridine-2-thiolato)oxovanadium(IV)] (0.5-1 mg as vanadium (V)/kg/day, i.p.), significantly rescued cholinergic neurons in the medial septum in a dose-dependent manner. VO(OPT) treatment also prevented decreased VACHT immunoreactivity both in CA1 and CA3 regions in the hippocampus. Consistent with these findings, an impaired hippocampal long-term potentiation (LTP) and memory deficits seen in OBX mice were significantly prevented by VO(OPT) treatment. Taken together, OBX induces neurodegeneration of septo-hippocampal cholinergic neurons and impairment of memory-related behaviors. The neuroprotective effect of VO(OPT) could lead to novel therapeutic strategies to ameliorate cognitive deficits assocd. with cholinergic neuron degeneration in Alzheimer's disease and other neurodegenerative disorders.

## ~11 Citings

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## 6. Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis

By Sakai, Y.; Dobson, C.; Diksic, M.; Aube, M.; Hamel, E.  
From *Neurology* (2008), 70(6), 431-439. Language: English, Database: CAPLUS,  
DOI:10.1212/01.wnl.0000299095.65331.6f

Altered serotonin (5-HT) neurotransmission has been implicated in the pathophysiol. of migraine headache. To test this hypothesis in migraine patients in vivo using PET and  $\alpha$ -[11C]methyl-L-tryptophan as a surrogate marker of brain 5-HT synthetic rate during different phases of their migraine attack and after acute antimigraine therapy with sumatriptan, and to compare them with normal controls. Six patients were scanned 1) within 6 h after the onset of a spontaneous migraine attack, 2) 2 h after s.c. sumatriptan, and 3) interictally when migraine free for at least 3 days. Head pain was rated before each scan, and before and every 15 min after sumatriptan. Brain 5-HT synthesis was highest during attacks, lowest after sumatriptan, and intermediate when patients were migraine free. All states were statistically different from the others in virtually all brain regions examd. 5-HT synthetic rates in patients during migraine attacks did not differ from those of age- and sex-matched controls, whereas they were significantly lower after sumatriptan in a majority of regions. Interictally, global brain 5-HT synthetic rate was slightly, albeit not significantly, lower (-14%) in migraine patients than in controls, with specific cortical areas exhibiting proportionally more severe redns. (-28% to 31%). These findings point to a low cortical serotonergic tone in migraine patients interictally. Further, they demonstrate widespread increases in brain serotonin (5-HT) synthetic rate in migraine patients during attacks, and that triptans exert a neg. feedback regulation of brain 5-HT synthesis concurrently with modulation of pain pathways.

### ~12 Citings

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## 7. Theory of active antidepressants: A nonsynaptic approach to the treatment of depression

By Kiss, Janos P.  
From *Neurochemistry International* (2008), 52(1-2), 34-39. Language: English, Database: CAPLUS,  
DOI:10.1016/j.neuint.2007.04.006

A review. Although depression is one of the major neuropsychiatric disorders, the success rate of medication for any drug is about 60%, which means that approx. 40% of the patients does not respond to the initial treatment. The major aim of this review is to provide a possible explanation for the relative inefficacy of currently used antidepressants and to propose a novel mechanism of action, which might improve the success rate of clin. treatment. According to the monoamine theory the most important neurochem. process in depression is the impairment of monoaminergic neurotransmission and the concomitant decrease of extracellular concn. of noradrenaline and/or serotonin. Since the vast majority of monoaminergic varicosities makes no synaptic contact but is able to release transmitters directly into the extrasynaptic space, the monoaminergic neurotransmission is predominantly nonsynaptic in nature. Depression can be regarded, therefore, as a disease, which is developed (at least in part) on the basis of the impairment of nonsynaptic interactions and the effective treatment has to improve this non-conventional communication in the nervous system. The currently used antidepressants (reuptake inhibitors, neg. feedback inhibitors, monoamine oxidase inhibitors) can increase the monoamine levels in the extracellular space only if the monoaminergic cells are elec. active and without an action potential-induced vesicular exocytosis these compds. are ineffective. It is proposed that a selective and moderate induction of the carrier-mediated release of NA and 5-HT might be a better therapeutic approach to the treatment of depression, since this new class of antidepressants, the so-called active antidepressants' have a mechanism of action, which is independent from the elec. activity of monoaminergic cells, therefore the extrasynaptic concn. of monoamines and thereby the nonsynaptic communication can be enhanced more efficiently.

### ~21 Citings

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## 8. The promiscuity of the dopamine transporter: Implications for the kinetic analysis of [3H]serotonin uptake in rat hippocampal and striatal synaptosomes

By Norrholm, Seth D.; Horton, David B.; Dwoskin, Linda P.  
From *Neuropharmacology* (2007), 53(8), 982-989. Language: English, Database: CAPLUS,  
DOI:10.1016/j.neuropharm.2007.10.001

Evidence indicates that monoaminergic neurotransmitter transporters are promiscuous, transporting substrates other than their cognate neurotransmitters. For example, serotonin is transported by the dopamine transporter (DAT) under conditions in which serotonin transporter (SERT) activity is eliminated (e.g., pharmacol. inhibition). We performed a kinetic anal. of [3H]serotonin uptake in rat striatal synaptosomes (expressing DAT and SERT) and hippocampal synaptosomes (expressing SERT, but not DAT). Nonspecific [3H]serotonin uptake was defined as the amt. of uptake remaining in the presence of fluoxetine (10  $\mu$ M) or paroxetine (0.05  $\mu$ M). In hippocampal synaptosomes,  $K_m$  and  $V_{max}$  values for [3H]serotonin uptake did not differ whether fluoxetine or paroxetine was used to define nonspecific uptake. However, in striatal synaptosomes, both  $K_m$  and  $V_{max}$  values for [3H]serotonin uptake were greater when fluoxetine, rather than paroxetine, was used to define nonspecific uptake. These data suggest that, at the concns. employed, fluoxetine inhibits serotonin uptake at both DAT and SERT, whereas paroxetine only inhibits serotonin uptake at SERT. Thus, when DAT is inhibited by GBR 12909, kinetic parameters for serotonin uptake via SERT in striatum are not different from those obtained in hippocampus. These findings have important implications regarding the anal. of monoaminergic reuptake in brain regions exhibiting heterogeneous transporter expression.

## ~5 Citings

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### 9. Elevated Serotonin Transporter Binding in Major Depressive Disorder Assessed Using Positron Emission Tomography and [11C]DASB; Comparison with Bipolar Disorder

By Cannon, Dara M.; Ichise, Masanori; Rollis, Denise; Klaver, Jacqueline M.; Gandhi, Shilpa K.; Charney, Dennis S.; Manji, Husseini K.; Drevets, Wayne C.  
From Biological Psychiatry (2007), 62(8), 870-877. Language: English, Database: CAPLUS,  
DOI:10.1016/j.biopsych.2007.03.016

Background: Altered serotonergic function is thought to play a role in the pathophysiol. of major depressive episodes based upon evidence from neuroimaging, pharmacol., postmortem and genetic studies. It remains unclear, however, whether depressed samples that differ with respect to having shown a unipolar vs. a bipolar illness course also would show distinct patterns of abnormalities within the serotonergic system. The current study compared serotonin transporter (5-HTT) binding between unipolar-depressives (MDD), bipolar-depressives (BD) and healthy-controls (HC) to assess whether the abnormalities in 5-HTT binding recently found in depressed subjects with BD extend to depressed subjects with MDD. Methods: The 5-HTT binding-potential (BP) measured using positron emission tomog. (PET) and [11C]DASB was compared between unmedicated, depressed subjects with MDD (n = 18) or BD (n = 18) and HC (n = 34). Results: Relative to the healthy group both MDD and BD groups showed significantly increased 5-HTT BP in the thalamus (24%, 14%, resp.), insula (15%) and striatum (12%). The unipolar-depressives had elevated 5-HTT BP relative to both BD and HC groups in the vicinity of the periaqueductal gray (PAG, 20%, 22%, resp.). The bipolar-depressives had reduced 5-HTT BP relative to both HC and MDD groups in the vicinity of the pontine raphe nuclei. Depression-severity correlated neg. with 5-HTT BP in the thalamus in MDD-subjects. Conclusions: The depressed phases of MDD and BD both were assocd. with elevated 5-HTT binding in the insula, thalamus and striatum, but showed distinct abnormalities in the brainstem. The latter findings conceivably could underlie differences in the patterns of illness symptoms and pharmacol. sensitivity obsd. between MDD and BD.

## ~25 Citings

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### 10. Effect of chronic administration of duloxetine on serotonin and norepinephrine transporter binding sites in rat brain

By Gould, Georgianna G.; Javors, Martin A.; Frazer, Alan  
From Biological Psychiatry (2007), 61(2), 210-215. Language: English, Database: CAPLUS,  
DOI:10.1016/j.biopsych.2006.02.029

Chronic treatment of rats with certain selective serotonin or norepinephrine reuptake inhibitors produces significant decreases, resp., in serotonin and norepinephrine transporter binding sites in brain. Duloxetine may be a dual serotonin/norepinephrine reuptake inhibitor, as it is only a slightly more potent inhibitor of serotonin than norepinephrine uptake in vitro. Consequently, we hypothesized that chronic duloxetine treatment, at doses producing serum levels within its therapeutic range, would affect both monoamine transporters dose-dependently, with a higher dose causing greater redns. of binding sites for both transporters. Rats were treated with either 4 or 8 mg/kg/d of duloxetine, paroxetine, desipramine, or vehicle via s.c. osmotic minipumps for 21 days. Binding sites for serotonin and norepinephrine transporters were measured in amygdala and hippocampus using quant. autoradiog. Both doses of duloxetine and paroxetine produced equiv. and significant decreases in [3H] cyanoimipramine binding to serotonin transporters, but only desipramine treatment significantly reduced [3H] nisoxetine binding to norepinephrine transporters. At doses producing rat serum concns. in the range achieved in patients at recommended daily doses of the drug, duloxetine behaves in vivo more as a selective serotonin reuptake inhibitor than a dual reuptake inhibitor in its capacity to selectively reduce serotonin transporter d.

## ~3 Citings

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**11. Chronic buspirone treatment normalizes regional serotonin synthesis in the olfactory bulbectomized rat brain: an autoradiographic study**

By Watanabe, Arata; Hasegawa, Shu; Nishi, Kyoko; Nguyen, Khanh Q.; Diksic, Mirko  
From Brain Research Bulletin (2006), 69(2), 101-108. Language: English, Database: CAPLUS,  
DOI:10.1016/j.brainresbull.2005.11.008

The effects of chronic buspirone treatments, administered by minipump at doses of 10 and 20 mg/(kg day) for 14 days, on brain 5-HT synthesis in olfactory bulbectomized (OBX) rats were evaluated. The  $\alpha$ -[14C]methyl-L-tryptophan autoradiog. method was used. We compared the synthesis in the buspirone treated OBX rats (administered either 10 mg/(kg day) (OBX-10) or 20 mg/(kg day) (OBX-20)) to that of the saline treated OBX rats (OBX-SAL), and the sham operated rats (SHX) treated with saline. In addn., OBX-10 rats were compared to SHX rats treated with 10 mg/(kg day) (SHX-10) of buspirone. All treatments were carried out for 14 days. Adult Sprague-Dawley rats were used. Two weeks following the OBX or SHX procedures, the rats were assigned to the OBX-10, OBX-20, OBX-SAL, SHX-10, or SHX-SAL groups, resp. The 5-HT synthesis rates R (pmol/(g/min)) were calcd. from the trapping const. of  $\alpha$ -[14C]MTrp ( $K^*$ ; ml/(g min)) and the plasma concn. of the plasma non-protein-bound tryptophan (Cp; pmol/mL) using the lumped const. (LC) measured previously in the rat brain. There was no significant difference in the plasma free or total tryptophan among these groups. The overall synthesis in the OBX-10 group was not statistically different from the OBX-SAL group, but it was different from the OBX-20 and SHX-SAL groups. The OBX-20 rats had an overall significant redn. in 5-HT synthesis, when compared to the OBX-SAL group, but did not differ from the SHX-SAL group, which did not differ from the SHX-10 group. These results suggest that 10 mg/(kg day) of buspirone for 14 days in the OBX rats did not produce a significant alteration in 5-HT synthesis, but 20 mg/(kg day) for 14 days resulted in an overall significant redn. in brain 5-HT synthesis. The latter treatment brought the synthesis to the level found in the sham operated rats, i.e., a normal level. These results suggest that normalization (redn. to the level found in the SHX-SAL rats) of 5-HT synthesis in the OBX requires a greater dose of buspirone (20 mg/(kg day)) than that needed to produce a desensitization of the 5-HT<sub>1A</sub> receptors in the sham operated rats (10 mg/(kg day)). This probably indicates that 5-HT<sub>1A</sub> receptors have different functionality in the OBX rats than that found in the intact or sham operated rats. Furthermore, our results support the hypothesis that 5-HT<sub>1A</sub> receptors mediate the antidepressant-like effect of 5-HT<sub>1A</sub> agonists, as the chronic 5-HT<sub>1A</sub> agonist treatment in the depression model known to be sensitive to antidepressants resulted in the normalization of 5-HT synthesis.

## ~16 Citings

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**12. Chronic administration of citalopram in olfactory bulbectomy rats restores brain 5-HT synthesis rates: an autoradiographic study**

By Hasegawa, Shu; Watanabe, Arata; Nguyen, Khanh Q.; Debonnel, Guy; Diksic, Mirko  
From Psychopharmacology (Berlin, Germany) (2005), 179(4), 781-790. Language: English, Database: CAPLUS,  
DOI:10.1007/s00213-004-2122-1

The olfactory bulbectomized (OBX) rat model is widely accepted as an animal model of depression with a proposed serotonergic imbalance in the brain. To study the effects of chronic administration of citalopram on serotonin (5-HT) synthesis rates. Serotonin synthesis was evaluated using the  $\alpha$ -[14C]methyl-L-tryptophan ( $\alpha$ -MTrp) autoradiog. method in OBX rats. Citalopram was administered continuously (10 mg kg<sup>-1</sup> day<sup>-1</sup>) for 14 days using a s.c. osmotic minipump. The OBX rats treated with citalopram (OBX-CTP) have the same 5-HT synthesis rates as the sham-operated rats treated with citalopram (Sham-CTP). The OBX-CTP rats, relative to the OBX rats treated with saline (OBX-SAL), showed a redn. in the majority of the terminal brain structures, suggesting a normalization of 5-HT synthesis in the OBX-CTP rats following treatment. The OBX-SAL rats have significantly greater synthesis than the Sham-SAL rats in a majority of the terminal structures, but lower rates in the dorsal raphe. A few structures in the OBX-CTP group have lower synthesis than in the Sham-SAL group (e.g., dorsal raphe, hippocampus, amygdala). The data suggest that receptors in some brain areas are likely still responsive to the elevated levels of the extracellular 5-HT produced by citalopram. There is no significant global or individual structure difference in the synthesis between the Sham-CTP and OBX-CTP groups. The similarity in the synthesis between the OBX-CTP, Sham-CTP and Sham-SAL groups is likely a result of changes in the sensitivity of the receptors through which 5-HT synthesis is controlled. Because of some of the differences in the synthesis between the Sham-CTP and Sham-SAL groups, the data suggest that receptors throughout the brain are not fully desensitized.

## ~23 Citings

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### 13. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes

By Meyer, Jeffrey H.; Houle, Sylvain; Sagrati, Sandra; Carella, Anna; Hussey, Doug F.; Ginovart, Nathalie; Goulding, Verdell; Kennedy, James; Wilson, Alan A.

From Archives of General Psychiatry (2004), 61(12), 1271-1279. Language: English, Database: CAPLUS, DOI:10.1001/archpsyc.61.12.1271

Background: Although brain serotonin transporter (5-HTT) d. has been investigated in subjects with a history of major depressive episodes (MDE), there has never been an investigation of brain 5-HTT during a current MDE. Brain 5-HTT binding potential (BP) may have an important role during MDE due to major depressive disorder, because the 5-HTT regulates extracellular 5-HT. The BP is an index of receptor d. Carbon 11-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) positron emission tomog. (PET) is the first brain imaging technique that can measure the 5-HTT BP in cortical and subcortical brain regions in vivo. The purposes of this study were to investigate 5-HTT BP during MDE and to det. the relationship between 5-HTT BP and negativistic dysfunctional attitudes during MDE. Dysfunctional attitudes are neg. biased assumptions and beliefs regarding oneself, the world, and the future. Our recent publication of increased serotonin2 BP in MDE with severely negativistic dysfunctional attitudes suggests that this subgroup of MDE subjects has very low levels of extracellular serotonin. Methods: Regional 5-HTT BP was measured in 20 nonsmoking medication-free ( $\geq 3$  mo) depressed subjects and 20 age-matched nonsmoking, medication-free, healthy subjects using [11C]DASB PET. Dysfunctional attitudes were measured using the Dysfunctional Attitudes Scale. Results: No difference in regional 5-HTT BP was found between MDE and healthy subjects; however, the subgroup of MDE subjects with highly negativistic dysfunctional attitudes had significantly higher 5-HTT BP compared with healthy subjects in brain regions mainly sampling serotonergic nerve terminals (prefrontal cortex, anterior cingulate, thalamus, bilateral caudate, and bilateral putamen; av., 21% greater;  $F_{1,26}$ , 5.6-12.2 [P values, .03-.002]). In the MDE subjects, increased 5-HTT BP was strongly assocd. with more negativistic dysfunctional attitudes in brain regions primarily sampling serotonergic nerve terminals (prefrontal cortex, anterior cingulate, thalamus, caudate, and putamen;  $r=0.64-0.74$  [P values, .003 to  $<.001$ ]). Conclusions: Serotonin transporters play an important role during depression. The magnitude of regional 5-HTT BP can provide a vulnerability to low levels of extracellular serotonin and symptoms of extremely negativistic dysfunctional attitudes.

~65 Citings

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### 14. Serotonin1B receptors: from protein to physiological function and behavior

By Sari, Youssef

From Neuroscience and Biobehavioral Reviews (2004), 28(6), 565-582. Language: English, Database: CAPLUS, DOI:10.1016/j.neubiorev.2004.08.008

A review. The serotonin (5-HT)1B receptor is expressed in the central nervous system (CNS) of rodents and its homologous 5-HT1D $\beta$  receptor is expressed in human. These receptors are distributed in both serotonergic and non-serotonergic neurons, where they act as auto- or heteroreceptors, resp. Studies from ours and other labs. have shown that 5-HT1B receptors are densely expressed in the ventral pallidum, globus pallidus, substantia nigra and dorsal subiculum and moderately expressed in the cerebral cortex, the mol. layer of the hippocampus, the entopeduncular nucleus, the superficial gray layer of the superior colliculus, the caudate putamen and the deep nuclei of the cerebellum. At the ultrastructural level, 5-HT1B receptors were found distributed in axons and axon terminals and these receptors are located on the plasma membrane of unmyelinated axon terminals and in the cytoplasm close to the plasmalemma. The terminal localization of the 5-HT1B receptors in CNS suggests that there is a signal responsible for the protein transport toward the nerve terminals. Studies from ours and other groups using lesion, radioligand binding sites, viral transfection and anterograde methods have shown that 5-HT1B receptors are located at the nerve terminals of different pathways. The 5-HT1B receptors act as terminal receptors and are involved in regulation of the release of various neurotransmitters, including 5-HT itself. The regulation of gamma-aminobutyric acid release by 5-HT1B receptors has been found in projections: from caudate putamen to the globus pallidus or substantia nigra, from nucleus accumbens to the ventral tegmentum area, and from Purkinje neurons to the deep nuclei of the cerebellum. The control of glutamate release by 5-HT1B receptors has been found in projections from hippocampus to the dorsal subiculum and of N-acetyl-aspartyl-glutamate release from retinal ganglion cells to the superficial gray layer of the superior colliculus. The control of 5-HT release by 5-HT1B receptors was shown in projections arising from the raphe nuclei to fore- and midbrain regions. Multiple evidences suggest that 5-HT1B receptors are implicated in several physiol. functions, behavior and psychiatric diseases including migraine, locomotor activity, drug abuse reinforcement, aggressive behavior, depression and anxiety states.

~92 Citings

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### 15. 5-HT1B receptor mRNA levels in dorsal raphe nucleus: inverse association with anxiety behavior in the elevated plus maze

By Kaiyala, Karl J.; Vincow, Evelyn S.; Sexton, Timothy J.; Neumaier, John F.

From Pharmacology, Biochemistry and Behavior (2003), 75(4), 769-776. Language: English, Database: CAPLUS, DOI:10.1016/S0091-3057(03)00152-7

Serotonergic neurons in the dorsal raphe nucleus, the major source of forebrain serotonin projections, synthesize a terminal autoreceptor that inhibits serotonin release, the 5-HT<sub>1B</sub> autoreceptor. Overexpression of this autoreceptor is hypothesized to contribute to anxiety. Antidepressants decrease (while learned helplessness increases) 5-HT<sub>1B</sub> mRNA in dorsal raphe neurons, and viral-mediated overexpression of 5-HT<sub>1B</sub> here increases anxiety behavior after stress. However, 5-HT<sub>1B</sub> mRNA levels in dorsal raphe are substantially elevated in unstressed rats in two models of stress resistance. Thus, the role of dorsal raphe 5-HT<sub>1B</sub> autoreceptors in anxiety is complex. Therefore, we tested whether different stressors differentially affect dorsal raphe 5-HT<sub>1B</sub> mRNA [via in situ hybridization histochem.] and anxiety behavior (using the elevated plus maze). Rats were assigned to a stressor (either forced swim, water restraint, dry restraint, or elec. tail shock) or a control condition, then were tested and sacrificed 24 h later. Overall, controls exhibited less anxiety than stressed rats as indicated by a higher ratio of open arm to total arm entries (OTR). The stressors did not differentially affect the OTR, nor did any alter dorsal raphe 5-HT<sub>1B</sub> mRNA levels. There was, however, a significant pos. correlation between the OTR and 5-HT<sub>1B</sub> mRNA intensity in controls ( $r=.64$ ), but not in stressed rats ( $r=.16$ ), providing further evidence that elevated dorsal raphe 5-HT<sub>1B</sub> levels are assocd. with reduced anxiety in animals that have not been exposed to stress.

### ~10 Citings

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### 16. Regional brain serotonin synthesis is increased in the olfactory bulbectomy rat model of depression: An autoradiographic study

By Watanabe, Arata; Tohyama, Yoshihiro; Nguyen, Khanh Q.; Hasegawa, Shu; Debonnel, Guy; Diksic, Mirko

From Journal of Neurochemistry (2003), 85(2), 469-475. Language: English, Database: CAPLUS, DOI:10.1046/j.1471-4159.2003.01702.x

Serotonin synthesis rates were evaluated using  $\alpha$ -[<sup>14</sup>C]methyl-L-tryptophan ( $\alpha$ -MTrp) autoradiog. methods in olfactory bulbectomized (OBX) rats. They were significantly ( $p < 0.05$ ) increased in the frontal (50%) and parietal (40%) cortices, superior olive (over 30%), and the substantia nigra (30%) in the OBX rats as compared to the sham operated animals. There were also increases in 5-hydroxytryptamine (5-HT) synthesis in some limbic areas: the cingulate (32%), the medial forebrain bundle (58%), the hippocampus (13-25%) and the thalamus (22-40%). The largest increase in 5-HT synthesis after OBX was obsd. in the sensory-motor cortex (67%). 5-HT synthesis rates were significantly decreased in the dorsal and medial raphe nuclei, but there was no significant change the ventral tegmental area and the locus coeruleus following OBX. These results indicate that olfactory bulbectomy causes an imbalance in 5-HT synthesis in some projection areas by disproportionally increasing 5-HT synthesis rates in specific brain regions and making more 5-HT available for neurotransmission. This imbalance in 5-HT synthesis and the subsequent elevation of tissue 5-HT may be responsible for the creation of non-physiol. circuitry which may, in part, be reflected in the symptoms resembling human depression.

### ~33 Citings

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### 17. Overexpression of 5-HT<sub>1B</sub> receptor in dorsal raphe nucleus using herpes simplex virus gene transfer increases anxiety behavior after inescapable stress

By Clark, Michael S.; Sexton, Timothy J.; McClain, Molly; Root, Daniel; Kohen, Ruth; Neumaier, John F.

From Journal of Neuroscience (2002), 22(11), 4550-4562. Language: English, Database: CAPLUS

5-HT<sub>1B</sub> autoreceptors have been implicated in animal models of stress and are regulated selectively by serotonin-selective reuptake inhibitors such as fluoxetine. These terminal autoreceptors regulate serotonin release from dorsal raphe nucleus (DRN) projections throughout rat forebrain. However, it has not been previously possible to manipulate 5-HT<sub>1B</sub> autoreceptor activity selectively without also changing 5-HT<sub>1B</sub> activity in other neurons mediating different behavioral responses. Therefore, the authors have developed a viral-mediated gene transfer strategy to express hemagglutinin-tagged 5-HT<sub>1B</sub> and manipulate these autoreceptors in DRN. Green fluorescent protein (GFP) was coexpressed from a sep. transcriptional unit on the same amplicon to assist in monitoring infection and expression. The authors confirmed the expression and biol. activity of both transgenic proteins in vitro. When injected directly into DRN using stereotaxic procedure, HA-5-HT<sub>1B</sub> receptors were expressed in serotonergic neurons and translocated to the forebrain. The effect of DRN expression of HA-5-HT<sub>1B</sub> on stress-induced behaviors was compared with control rats that received GFP-only amplicons. There was no change in immobility in the forced swim test. However, HA-5-HT<sub>1B</sub> expression significantly reduced entrances into the central region of an open-field arena after water-restraint stress without altering overall locomotor activity, but not in the absence of stress exposure. HA-5-HT<sub>1B</sub> expression also reduced entries into the open arms of the elevated plus maze after water restraint. Because these tests are sensitive to increase in anxiety-like behavior, the authors' results suggest that overactivity of 5-HT<sub>1B</sub> autoreceptors in DRN neurons may be an important mediator of pathol. responses to stressful events.

## ~56 Citings

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## 18. Neurobiology of depression

By Nestler, Eric J.; Barrot, Michel; DiLeone, Ralph J.; Eisch, Amelia J.; Gold, Stephen J.; Monteggia, Lisa M.  
From *Neuron* (2002), 34(1), 13-25. Language: English, Database: CAPLUS, DOI:10.1016/S0896-6273(02)00653-0

A review. Current treatments for depression are inadequate for many individuals, and progress in understanding the neurobiol. of depression is slow. Several promising hypotheses of depression and antidepressant action have been formulated recently. These hypotheses are based largely on dysregulation of the hypothalamic-pituitary-adrenal axis and hippocampus and implicate corticotropin-releasing factor, glucocorticoids, brain-derived neurotrophic factor, and CREB. Recent work has looked beyond hippocampus to other brain areas that are also likely involved. For example, nucleus accumbens, amygdala, and certain hypothalamic nuclei are crit. in regulating motivation, eating, sleeping, energy level, circadian rhythm, and responses to rewarding and aversive stimuli, which are all abnormal in depressed patients. A neurobiol. understanding of depression also requires identification of the genes that make individuals vulnerable or resistant to the syndrome. These advances will fundamentally improve the treatment and prevention of depression.

## ~726 Citings

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## 19. Equilibrium modeling of 5-HT<sub>2a</sub> receptors with [18F]deuteroaltanserin and PET: feasibility of a constant infusion paradigm

By van Dyck, C. H.; Soares, J. C.; Tan, P.-Z.; Staley, J. K.; Baldwin, R. M.; Amici, L. A.; Fu, X.; Garg, P. K.; Seibyl, J. P.; Charney, D. S.; et al  
From *Nuclear Medicine and Biology* (2000), 27(8), 715-722. Language: English, Database: CAPLUS, DOI:10.1016/S0969-8051(00)00160-8

[18F]Altanserin has emerged as a promising positron emission tomog. (PET) ligand for serotonin-2A (5-HT<sub>2A</sub>) receptors. The deuterium substitution of both of the 2'-hydrogens of altanserin ([18F]deuteroaltanserin) yields a metabolically more stable radiotracer with higher ratios of parent tracer to radiometabolites and increased specific brain uptake than [18F]altanserin. The slower metab. of the deuterated analog might preclude the possibility of achieving stable plasma and brain activities with a bolus plus const. infusion within a reasonable time frame for an 18F-labeled tracer (T<sub>1/2</sub> 110 min). Thus, the purpose of this study was to test the feasibility in human subjects of a const. infusion paradigm for equil. modeling of [18F]deuteroaltanserin with PET. Seven healthy male subjects were injected with [18F]deuteroaltanserin as a bolus plus const. infusion lasting 10 h postinjection. PET acquisitions and venous blood sampling were performed throughout the infusion period. Linear regression anal. revealed that time-activity curves for both specific brain uptake and plasma [18F]deuteroaltanserin concn. stabilized after about 5 h. This permitted equil. modeling and estn. of V<sub>3</sub> (ratio of specific uptake to total plasma parent concn.) and the binding potential V<sub>3</sub> (ratio of specific uptake to free plasma parent concn.). Cortical/cerebellar ratios were increased by 26% relative to those we previously obsd. with [18F]altanserin using similar methodol. in a somewhat older subject sample. These results demonstrate feasibility of equil. imaging with [18F]deuteroaltanserin and suggest that it may be superior to [18F]altanserin as a PET radioligand.

## ~7 Citings

**20. Effects of chronic antidepressant treatments on serotonin transporter function, density, and mRNA level**

By Benmansour, Saloua; Cecchi, Marco; Morilak, David A.; Gerhardt, Greg A.; Javors, Martin A.; Gould, Georgianna G.; Frazer, Alan

From Journal of Neuroscience (1999), 19(23), 10494-10501. Language: English, Database: CAPLUS

To investigate functional changes in the brain serotonin transporter (SERT) after chronic antidepressant treatment, several techniques were used to assess SERT activity, d., or its mRNA content. Rats were treated by osmotic minipump for 21 d with the selective serotonin reuptake inhibitors (SSRIs) paroxetine or sertraline, the selective norepinephrine reuptake inhibitor desipramine (DMI), or the monoamine oxidase inhibitor phenelzine. High-speed in vivo electrochem. recordings were used to assess the ability of the SSRI fluvoxamine to modulate the clearance of locally applied serotonin in the CA3 region of hippocampus in drug- or vehicle-treated rats. Fluvoxamine decreased the clearance of serotonin in rats treated with vehicle, DMI, or phenelzine but had no effect on the clearance of serotonin in SSRI-treated rats. SERT d. in the CA3 region of the hippocampus of the same rats, assessed by quant. autoradiog. with tritiated cyanoimipramine ([<sup>3</sup>H]CN-IMI), was decreased by 80-90% in SSRI-treated rats but not in those treated with phenelzine or DMI. The serotonin content of the hippocampus was unaffected by paroxetine or sertraline treatment, ruling out neurotoxicity as a possible explanation for the SSRI-induced decrease in SERT binding and alteration in 5-HT clearance. Levels of mRNA for the SERT in the raphe nucleus were also unaltered by chronic paroxetine treatment. Based on these results, it appears that the SERT is downregulated by chronic administration of SSRIs but not other types of antidepressants; furthermore, the downregulation is not caused by decreases in SERT gene expression.

**~141 Citings****21. Activation and desensitization by cyclic antidepressant drugs of  $\alpha$ 2-autoreceptors,  $\alpha$ 2-heteroreceptors and 5-HT1A-autoreceptors regulating monoamine synthesis in the rat brain in vivo**

By Esteban, Susana; Llado, Jeronia; Sastre-Coll, Antoni; Garcia-Sevilla, Jesus A.

From Naunyn-Schmiedeberg's Archives of Pharmacology (1999), 360(2), 135-143. Language: English, Database: CAPLUS, DOI:10.1007/s002109900045

The effects of antidepressant drugs on the synthesis of noradrenaline and serotonin (5-HT) were assessed using the accumulation of 3,4-dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) after decarboxylase inhibition as a measure of the rate of tyrosine and tryptophan hydroxylation in the rat brain in vivo. Three inhibitory synthesis-modulating receptors were investigated simultaneously: the  $\alpha$ 2C-autoreceptor modulating dopa/noradrenaline synthesis, and the  $\alpha$ 2A-heteroreceptor and 5-HT1A-autoreceptor modulating 5-HTP/5-HT synthesis. Acute treatment (2 h, i.p.) with desipramine (1-10 mg/kg), protriptyline (0.3-10 mg/kg) and nisoxetine (3-10 mg/kg), selective NA reuptake blockers, dose-dependently decreased dopa synthesis in cortex (15%-40%) and hippocampus (20%-53%). Fluoxetine (1-10 mg/kg) and zimelidine (1-10 mg/kg), selective 5-HT reuptake blockers, did not alter dopa synthesis. Fluoxetine and zimelidine dose-dependently decreased 5-HTP synthesis in cortex (14%-43%) and hippocampus (27%-54%). Desipramine and protriptyline did not alter 5-HTP synthesis in cortex but in hippocampus it was decreased (36%). Repeated desipramine (10 mg/kg for 1-21 days) or fluoxetine (3 mg/kg for 3-21 days) treatment resulted in a time-dependent loss in their ability to decrease dopa or 5-HTP synthesis. Desipramine (1-21 days) did not alter 5-HTP synthesis in cortex, but in hippocampus it was decreased (21%-37%, days 1-14) followed by recovery to control values (day 21). Fluoxetine (3-21 days) did not alter brain dopa synthesis. To further assess the desensitization of  $\alpha$ 2C-autoreceptors,  $\alpha$ 2A-heteroreceptors and 5-HT1A autoreceptors regulating the synthesis of dopa/NA or 5-HTP/5-HT after chronic desipramine and fluoxetine, the effects of clonidine (agonist at  $\alpha$ 2-auto/heteroreceptors) and 8-OH-DPAT (agonist at 5-HT1A-autoreceptors) were tested. In saline-treated rats, clonidine (1 mg/kg, 1 h) decreased dopa and 5-HTP synthesis in cortex (58% and 54%) and hippocampus (54% and 42%). In desipramine-treated rats (10 mg/kg, 21 days), but not in fluoxetine-treated ones (3 mg/kg, 14 days), the effect of clonidine was attenuated in cortex (12% and 18%) and only for dopa synthesis in hippocampus (31%). In saline-treated rats, 8-OH-DPAT (1 mg/kg, 1 h) decreased 5-HTP synthesis in cortex (63%) and hippocampus (75%). In fluoxetine-treated rats, but not in desipramine-treated ones, this inhibitory effect was markedly attenuated in cortex (26%) and hippocampus (9%). These findings indicate that acute treatment with cyclic antidepressant drugs results in activation of inhibitory  $\alpha$ 2C-autoreceptors,  $\alpha$ 2A-heteroreceptors and/or 5-HT1A-autoreceptors regulating the synthesis of dopa/NA and/or 5-HTP/5-HT in brain, whereas chronic treatment with these drugs is followed by desensitization of these presynaptic receptors.

**~44 Citings**

## 22. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: A positron emission tomography study with fluorine-18-labeled setoperone

By Yatham, Lakshmi N.; Liddle, Peter F.; Dennie, Joelle; Shiah, I-Shin; Adam, Michael J.; Lane, Carol J.; Lam, Raymond W.; Ruth, Thomas J.

From Archives of General Psychiatry (1999), 56(8), 705-711. Language: English, Database: CAPLUS, DOI:10.1001/archpsyc.56.8.705

Background: The neuroreceptor changes involved in therapeutic efficacy of various antidepressants remain unclear. Preclin. studies have shown that long-term administration of various antidepressants causes downregulation of brain serotonin 2 (5-HT<sub>2</sub>) receptors in rodents, but it is unknown if similar changes occur following antidepressant treatment in depressed patients. Our purpose, therefore, was to assess the effects of treatment with desipramine hydrochloride on brain 5-HT<sub>2</sub> receptors in depressed patients using positron emission tomog. (PET) and fluorine-18 (18F)-labeled setoperone. Methods: Eleven patients who met DSM-IV criteria for major depression as detd. by a structured clin. interview for DSM-III-R diagnosis and suitable for treatment with desipramine were recruited. Ten patients underwent a PET scan before and another after 3 to 4 wk of treatment with desipramine. Results: Eight of the 10 patients responded to desipramine treatment as indicated by more than 50% decrease in Hamilton Depression Rating Scale scores. Depressed patients showed a significant decrease in 5-HT<sub>2</sub> receptor binding as measured by setoperone binding in frontal, temporal, parietal, and occipital cortical regions following desipramine treatment. The decrease in 5-HT<sub>2</sub> receptor binding was obsd. bilaterally and was particularly prominent in frontal cortex. Conclusions: Depressed patients showed a significant redn. in available 5-HT<sub>2</sub> receptors in the brain following desipramine treatment, but it is unknown if this change in 5-HT<sub>2</sub> receptors is due to clin. improvement or an effect of desipramine that is unrelated to clin. status.

~73 Citings

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## 23. The effects of single dose nefazodone and paroxetine upon 5-HT<sub>2A</sub> binding potential in humans using [18F]-setoperone PET

By Meyer, J. H.; Cho, R.; Kennedy, S.; Kapur, S.

From Psychopharmacology (Berlin) (1999), 144(3), 279-281. Language: English, Database: CAPLUS, DOI:10.1007/s002130051004

Alterations in 5-HT<sub>2A</sub> receptor binding are implicated in suicidality and depression. 5-HT<sub>2A</sub> receptors may also be involved in the therapeutic effects of antidepressants. The purpose of this study was to assess the effect of paroxetine and nefazodone on 5-HT<sub>2A</sub> receptors after a single dose. Seven subjects received a single dose of nefazodone 200 mg and five subjects received a single dose of paroxetine 20 mg. Before and after the dose, 5-HT<sub>2A</sub> binding potentials (B<sub>max</sub>/K<sub>d</sub>) were detd. in each subject using [18F]-setoperone PET. Nefazodone induced a significant change in 5-HT<sub>2A</sub> binding potential ( $-39 \pm 17\%$ ,  $P = 0.003$ ) while paroxetine showed no significant alteration of 5-HT<sub>2A</sub> binding potential ( $+3 \pm 13\%$ ,  $P = 0.73$ ). The change in 5-HT<sub>2A</sub> binding potential seen with nefazodone represents blockade of 5-HT<sub>2A</sub> receptors by the drug. We do not find evidence for acute down-regulation of 5-HT<sub>2A</sub> receptors with paroxetine within 9 h.

~26 Citings

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## 24. Serotonergic hyperinnervation of the frontal cortex in an animal model of depression, the bulbectomized rat

By Zhou, Dan; Grecksch, Gisela; Becker, Axel; Frank, Christian; Pilz, Jurgen; Huether, Gerald

From Journal of Neuroscience Research (1998), 54(1), 109-116. Language: English, Database: CAPLUS, DOI:10.1002/(SICI)1097-4547(19981001)54:1<109::AID-JNR11>3.0.CO;2-2

We studied the influence of olfactory bulbectomy in rats on three different parameters of serotonin (5-HT) presynapses, 5-HT transporter d., tryptophan hydroxylase apoenzyme concn., and the levels of 5-HT and 5-HIAA in various brain regions. Compared with sham-operated controls, the B<sub>max</sub> values of [3H]paroxetine binding, the apoenzyme concn. of tryptophan hydroxylase and the level of 5-HIAA, and, therefore, the 5-HIAA/5-HT ratio were significantly and selectively increased in the frontal cortex of bulbectomized rats, measured 12 wk after surgery. The most likely explanation of the concomitant increase in levels of all three markers of 5-HT presynapses in the frontal cortex is an increased d. of 5-HT innervation in this remote projection field of the raphe nuclei. It is suggested that the bulbectomy-assocd. axotomy of 5-HT fibers projecting to the bulb stimulates collateral sprouting and synaptogenesis, esp. in the frontal cortex. The resulting 5-HT hyperinnervation must be expected to alter global neuronal activity in this region and to impair the balance of information flow between this and other brain regions, resulting in a multitude of secondary behavioral and neurochem. changes. The frontocortical abnormalities obsd. by brain imaging studies in the brains of depressed patients may also be explained by a selective 5-HT hyperinnervation of this brain region.

## ~33 Citings

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## 25. Influence of olfactory bulbectomy and subsequent imipramine treatment on 5-hydroxytryptaminergic presynapses in the rat frontal cortex: behavioral correlates

By Grecksch, Gisela; Zhou, Dan; Franke, Christian; Schroder, Ulrike; Sabel, Bernhard; Becker, Axel; Huether, Gerald  
From British Journal of Pharmacology (1997), 122(8), 1725-1731. Language: English, Database: CAPLUS,  
DOI:10.1038/sj.bjp.0701530

Alterations of 5-hydroxytryptaminergic mechanisms are thought to play a special role in the pathogenesis of depression, and antidepressant treatments are assumed to restore these changes. One of the most reliable models of depression, the olfactory-bulbectomized rat, was used to study the long-term consequences of this manipulation and of subchronic imipramine treatment on 2 parameters of 5-hydroxytryptaminergic presynapses: 5-hydroxytryptamine (5-HT) transporter d. and tryptophan hydroxylase apoenzyme concn., in the frontal cortex, as well as on active avoidance learning several weeks after bulbectomy. The Bmax value of [3H]paroxetine binding and the concn. of the 5-HT-synthesizing enzyme were both elevated in the frontal cortex of bulbectomized rats compared to sham-operated controls. Imipramine treatment, either by daily injections or by s.c. implantation of slow-release imipramine-contg. polymers, reduced the elevated tryptophan hydroxylase apoenzyme levels in the frontal cortex of bulbectomized, but not of sham-operated, control rats and restored the deficient learning performance of bulbectomized rats. Both effects were more pronounced after continuous drug administration by imipramine-releasing polymers than after daily i.p. injections. These findings indicate that bulbectomy leads to a compensatory 5-hydroxytryptaminergic hyperinnervation of the frontal cortex. Chronic antidepressant treatment seems to attenuate the increased output of the 5-hydroxytryptaminergic projections in the frontal cortex through the destabilization of the rate-limiting enzyme of 5-HT synthesis of the 5-hydroxytryptaminergic nerve endings in this brain region.

## ~39 Citings

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## 26. The olfactory bulbectomized rat as a model of depression: an update

By Kelly, J. P.; Wrynn, A. S.; Leonard, B. E.  
From Pharmacology & Therapeutics (1997), 74(3), 299-316. Language: English, Database: CAPLUS,  
DOI:10.1016/S0163-7258(97)00004-1

A review, with 161 refs. The olfactory bulbectomized (OB) rat has been proposed as an animal model of depression. The following behavioral changes have been obsd. following bilateral olfactory bulbectomy: hyperactivity in an enclosed arena, such as the open-field; enhanced nocturnal hyperactivity in a 24-h home cage activity monitor; deficits in memory, as shown by passive avoidance behavior and in the Morris maze and the 8-arm radial maze; increased open arm entries in the elevated plus-maze; and changes in food motivated and conditioned taste aversion behavior. Alterations in the noradrenergic, serotonergic, cholinergic,  $\gamma$ -aminobutyric acid (GABA)ergic and glutamatergic neurotransmitter systems are also assocd. with olfactory bulbectomy. The variety of immune changes following olfactory bulbectomy includes reduced neutrophil phagocytosis, lymphocyte mitogenesis, lymphocyte no. and neg. acute phase proteins, increased leukocyte adhesiveness/aggregation, monocyte phagocytosis, neutrophil no. and pos. acute phase proteins. An enhanced nocturnal secretion of corticosterone is obsd. in OB rats, which is normally suppressed by dexamethasone. The most commonly employed behavioral indicator of antidepressant activity is attenuation of the OB-related hyperactivity in the open-field. However, many of the other behavioral, neurotransmitter and immune changes have been shown to be attenuated by chronic (but not acute) antidepressant treatment. Tricyclic antidepressants (amitriptyline, desipramine), atypical agents (mianserin), selective serotonin reuptake inhibitors (paroxetine, sertraline, fluvoxamine), reversible inhibitors of monoamine oxidase A (moclobemide), as well as putative antidepressants such as 5-hydroxytryptamine<sub>1A</sub> agonists (zalospirone, ipsapirone), noncompetitive N-methyl-D-aspartate antagonists (MK-801) and triazolobenzodiazepines (alprazolam, adinazolam), have demonstrated antidepressant-like activity in this model. As many of the changes exhibited by the OB rat are qual. similar to those obsd. in depressed patients, it may be concluded that the OB rat is a model of depression and not just a means whereby putative antidepressants may be tested.

## ~228 Citings

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## 27. Effects of chronic treatment with fluoxetine and citalopram on 5-HT uptake, 5-HT<sub>1B</sub> autoreceptors, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in rats

By Gobbi, Marco; Crespi, Daniela; Foddi, Maria Cristina; Fracasso, Claudia; Mancini, Laura; Parotti, Luca; Mennini, Tiziana

From Naunyn-Schmiedeberg's Archives of Pharmacology (1997), 356(1), 22-28. Language: English, Database: CAPLUS, DOI:10.1007/PL00005024

The effect in rats of chronic treatment with two specific 5-HT reuptake inhibitors (SSRI) with antidepressant properties, citalopram (10 mg/kg, i.p. twice a day for 14 days, one day washout) and fluoxetine (15 mg/kg, p.o. twice a day for 21 days, 7 days washout), was evaluated on some mechanisms involved in central 5-HT neurotransmission. No adaptive modifications of brain 5-HT uptake (sites) were found by measuring functional [ $^3\text{H}$ ]5-HT uptake and [ $^3\text{H}$ ] citalopram binding in cortical and hippocampal synaptosomes, and by [ $^3\text{H}$ ]citalopram binding autoradiog. in the raphe nuclei (5-HT cell bodies) and the ventral tegmental area (5-HT axonal pathway). Chronic treatments had no effect on presynaptic 5-HT $_{1B}$  autoreceptors, functionally evaluated by measuring 5-HT $_{1B}$ -mediated inhibition of depolarization-induced [ $^3\text{H}$ ]5-HT release from cortical and hippocampal synaptosomes. Chronic citalopram or fluoxetine did not significantly affect the binding of [ $^3\text{H}$ ]BRL-43694 to 5-HT $_3$  receptors in the rat brain cortex. Citalopram had no effect on [ $^{125}\text{I}$ ]SB-207710 binding to 5-HT $_4$  receptors, measured by autoradiog. in the substantia nigra. Neg. results, such as those reported in the present study, could be due to a no. of variables including the animal species, the treatment schedule or the brain areas considered, thus explaining the differences from some previous reports of significant effects of SSRI. However, the authors neg. data are in agreement with many other published studies, suggesting that adaptive modifications of brain 5-HT transporters, terminal 5-HT $_{1B}$  receptors, 5-HT $_3$  and 5-HT $_4$  receptors may not be a general effect induced by all SSRI.

#### ~45 Citings

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#### **28. Chronic fluoxetine reduces serotonin transporter mRNA and 5-HT $_{1B}$ mRNA in a sequential manner in the rat dorsal raphe nucleus**

By Neumaier, John F.; Root, Daniel C.; Hamblin, Mark W.

From Neuropsychopharmacology (1996), 15(5), 515-522. Language: English, Database: CAPLUS, DOI:10.1016/S0893-133X(96)00095-4

In major depression in humans and in animal models of depression, there is a defect in serotonergic neurotransmission that can be relieved by chronic antidepressant treatment. One possibility is that this pathol. state is caused by excessive presynaptic autoreceptor activity in serotonergic neurons, and that antidepressants down-regulate the no. of these inhibitory receptors, allowing more normal serotonin release to occur. To evaluate this hypothesis, we measured the effects of the antidepressant fluoxetine on neuronal levels of 5-HT $_{1B}$  receptor mRNA, the putative serotonin terminal autoreceptor in rat brain, and on serotonin transporter mRNA, the direct site of fluoxetine binding. Fluoxetine reduced serotonin transporter mRNA briefly, but this was not sustained after 21 days of treatment. However, fluoxetine reduced dorsal raphe 5-HT $_{1B}$  mRNA levels in a time-dependent and washout-reversible manner. This redn. in 5-HT $_{1B}$  mRNA was specific to dorsal raphe nucleus and was not found in several postsynaptic (nonserotonergic) regions. These results suggest that chronic fluoxetine may increase serotonin release from axonal terminals by down-regulating the mRNA coding for presynaptic 5-HT $_{1B}$  autoreceptors while causing only transient effects on serotonin transporter mRNA.

#### ~71 Citings

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#### **29. Interleukin-2-induced changes in behavioral, neurotransmitter, and immunological parameters in the olfactory bulbectomized rat**

By Song, Cai; Leonard, Brian E.

From NeuroImmunoModulation (1996), 2(5), 263-273. Language: English, Database: CAPLUS, DOI:10.1159/000097205

The macrophage theory of depression proposes that abnormal secretions of the macrophage cytokines, an increase in interleukin (IL) 1, and a decrease of IL-2 may cause depression. The olfactory bulbectomized (OB) rat has been developed as an animal model of depression. In the present study, the effects of intracerebroventricular administration of IL-2 (10 U) for 7 days on behavior, neurotransmitter concns., corticosterone levels, and some immune functions were investigated. In the novel environment of the 'open-field' app., the OB rat showed increases in ambulation, rearing, grooming, and defecation scores as compared with sham-operated animals. Following IL-2 administration, grooming and defecation were significantly attenuated, while the ambulation and rearing scores were unaffected. In the elevated plus-maze, the increase in the time spent on the open arms of the maze by the OB animal was normalized by IL-2 administration. In the brain of untreated OB rats, the concns. of noradrenaline were reduced; IL-2 treatment significantly increased the concns. of noradrenaline and serotonin. After administration of IL-2 for 7 days, the impairments in the immune functions were also largely reversed in OB rats. Thus IL-2 significantly normalized the hyperactivity of mononuclear cells, the suppression of lymphocyte proliferation, and the redn. in the monocyte percentage in the white blood cell count in the OB rat. The concns. of corticosterone in the serum of the OB rat were significantly reduced, but returned to control values following IL-2 treatment. The results suggest that IL-2 may have modulatory functions on behavioral, neurochem., hormonal, and immunol. aspects of the OB rat model of depression.

#### ~29 Citings

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### **30. Downregulation of muscarinic- and 5-HT1B-mediated modulation of [3H]acetylcholine release in hippocampal slices of rats with fimbria-fornix lesions and intrahippocampal grafts of septal origin**

By Cassel, J.-C.; Jeltsch, H.; Neufang, B.; Lauth, D.; Szabo, B.; Jackisch, R.

From Brain Research (1995), 704(2), 153-66. Language: English, Database: CAPLUS, DOI:10.1016/0006-8993(95)01092-0

Adult Long-Evans female rats sustained electrolytic fimbria-fornix lesions and, two weeks later, received intrahippocampal suspension grafts of fetal septal tissue. Sham-operated and lesion-only rats served as controls. Between 6.5 and 8 mo after grafting, both the [3H]choline accumulation and the elec. evoked [3H]acetylcholine ([3H]ACh) release were assessed in hippocampal slices. The release of [3H]ACh was measured in presence of atropine (muscarinic antagonist, 1  $\mu$ M), physostigmine (acetylcholinesterase inhibitor, 0.1  $\mu$ M), oxotremorine (muscarinic agonist, 0.01  $\mu$ M-10  $\mu$ M), mecamylamine (nicotinic antagonist, 10  $\mu$ M), methiothepin (mixed 5-HT1/5-HT2 antagonist, 10  $\mu$ M), 8-OH-DPAT (5-HT1A agonist, 1  $\mu$ M), 2-methyl-serotonin (5-HT3 agonist, 1  $\mu$ M) and CP 93129 (5-HT1B agonist, 0.1  $\mu$ M-100  $\mu$ M), or without any drug application as a control. In lesion-only rats, the specific accumulation of [3H]choline was reduced to 46% of normal and the release of [3H]ACh to 32% (nCt) and 43% (% of tissue tritium content). In the grafted rats, these parameters were significantly increased to 63%, 98% and 116% of control, resp. Physostigmine reduced the evoked [3H]ACh release and was significantly more effective in grafted (-70%) than in sham-operated (-56%) or lesion-only (-54%) rats. When physostigmine was superfused throughout, mecamylamine had no effect. Conversely, atropine induced a significant increase of [3H]ACh release in all groups, but this increase was significantly larger in sham-operated rats (+209%) than in the other groups (lesioned: +80%; grafted: +117%). Oxotremorine dose-dependently decreased the [3H]ACh release, but in lesion-only rats, this effect was significantly lower than in sham-operated rats. Whatever group was considered, 8-OH-DPAT, methiothepin and 2-methyl-serotonin failed to induce any significant effect on [3H]ACh release. In contrast, CP 93129 dose-dependently decreased [3H]ACh release. This effect was significantly weaker in grafted rats than in the rats of the two other groups. Our data confirm that cholinergic terminals in the intact hippocampus possess inhibitory muscarinic autoreceptors and serotonin heteroreceptors of the 5-HT1B subtype. They also show that both types of receptors are still operative in the cholinergic terminals which survived the lesions and in the grafted cholinergic neurons. However, the muscarinic receptors in both lesioned and grafted rats, as well as the 5-HT1B receptors in grafted rats show a sensitivity which seems to be downregulated in comparison to that found in sham-operated rats. In the grafted rats, both types of downregulations might contribute to (or reflect) an increased cholinergic function that results from a redn. of the inhibitory tonus which ACh and serotonin exert at the level of the cholinergic terminal.

#### ~48 Citings

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### **31. The effect of paroxetine on 5-HT efflux in the rat dorsal raphe nucleus is potentiated by both 5-HT1A and 5-HT1B/D receptor antagonists**

By Davidson, Colin; Stamford, Jonathan A.

From Neuroscience Letters (1995), 188(1), 41-4. Language: English, Database: CAPLUS, DOI:10.1016/0304-3940(95)11390-I

Serotonin (5-HT) efflux in slices of rat dorsal raphe nucleus (DRN) was evoked by pseudo one pulse elec. stimulation (20 pulses at 100 Hz, 190 ms train duration) and measured, along with 5-HT uptake, by fast cyclic voltammetry (FCV). The selective serotonin re-uptake inhibitor (SSRI) paroxetine ( $10^{-7}$  M) increased 5-HT efflux to  $147 \pm 6\%$  of pre-drug values at max. (mean  $\pm$  SEM,  $n = 5$ ) and the half-life of uptake to  $443 \pm 38\%$ . The non-selective 5-HT<sub>1</sub> antagonist methiothepin ( $2 \times 10^{-7}$  M) increased 5-HT efflux to  $147 \pm 9\%$  at max. but had no effect on uptake half-life. In contrast, (+)-WAY 100135 ( $10^{-6}$  M) and GR 127935 ( $5 \times 10^{-8}$  M), selective antagonists at 5-HT<sub>1A</sub> and 5-HT<sub>1B/D</sub> receptors, resp., affected neither 5-HT efflux nor uptake. When given in combination with paroxetine, the antagonists significantly increased the effect of paroxetine on efflux: methiothepin to  $228 \pm 24\%$  ( $P < 0.001$ ), (+)-WAY 100135 to  $212 \pm 31\%$  ( $P < 0.05$ ) and GR 127935 to  $203 \pm 23\%$  ( $P < 0.01$ ). These data suggest that, under these exptl. conditions, DRN 5-HT autoreceptors are tonically activated in the presence of the uptake blocker and that the antagonists act by blocking this counteracting auto-inhibitory tone. The data also strongly indicate that 5-HT efflux in the rat DRN is under the control not only of 5-HT<sub>1A</sub> but also of 5-HT<sub>1B/D</sub> receptors.

#### ~46 Citings

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### 32. Autoradiographic distribution of cholinergic muscarinic receptors and serotonin<sub>2</sub> receptors in olfactory bulbectomized (OB) rats after chronic treatment with mianserin and desipramine

By Earley, B.; Glennon, M.; Lally, M.; Leonard, B. E.; Junien, J-L.

From Human Psychopharmacology (1994), 9(6), 397-407, 2 plates. Language: English, Database: CAPLUS, DOI:10.1002/hup.470090603

Bilateral removal of the olfactory bulbs in rats produces a behavioral abnormality that is defined by hyperactivity in the open-field test. This abnormality may be related to depression since these behavioral effects can be attenuated by antidepressant drugs. Moreover, changes in the cholinergic and serotonergic system may be involved in the pathogenesis of depression. Thus, muscarinic cholinergic and serotonin<sub>2</sub> receptors were measured by quant. autoradiog. after the bilateral removal of the olfactory bulbs from the rat. In OB rats, muscarinic receptor d. was decreased in several brain regions including the amygdaloid cortex, the basal ganglia, hippocampus, hypothalamus, cortex and olfactory regions. Serotonin<sub>2</sub> receptors were increased in all cortical regions, in the hippocampus and the thalamus. When OB rats were treated chronically for 35 days with mianserin (5 mg/kg i.p.) or desipramine (7.5 mg/kg i.p.) the behavioral hyperactivity was reversed and muscarinic receptor d. was increased in the hippocampus and cortical regions while serotonin<sub>2</sub> receptors were normalized. The results are consistent with a cholinergic and serotonin involvement in depressive illness and suggest that the cholinergic and serotonergic modulatory properties of antidepressant drugs may contribute to their therapeutic effectiveness.

#### ~28 Citings

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### 33. Enhanced aggressive behavior in mice lacking 5-HT<sub>1B</sub> receptor

By Saudou, Frederic; Amara, Djamel Ait; Dierich, Andree; LeMeur, Marianne; Ramboz, Sylvie; Segu, Louis; Buhot, Marie-Christine; Hen, Rene

From Science (Washington, DC, United States) (1994), 265(5180), 1875-8. Language: English, Database: CAPLUS, DOI:10.1126/science.8091214

The neuromodulator serotonin (5-hydroxytryptamine, 5-HT) has been assocd. with mood disorders such as depression, anxiety, and impulsive violence. To define the contribution of 5-HT receptor subtypes to behavior, mutant mice lacking the 5-HT<sub>1B</sub> receptor were generated by homologous recombination. These mice did not exhibit any obvious developmental or behavioral defects. However, the hyperlocomotor effect of the 5-HT<sub>1A/1B</sub> agonist RU24969 was absent in mutant mice, indicating that this effect is mediated by 5-HT<sub>1B</sub> receptors. Moreover, when confronted with an intruder, mutant mice attacked the intruder faster and more intensely than did wild-type mice, suggesting the participation of 5-HT<sub>1B</sub> receptors in aggressive behavior.

#### ~374 Citings

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### 34. Antidepressant-like behavioral effects of serotonin receptor agonists

By Lucki, Irwin; Singh, Ashish; Kreiss, Deborah S.

From Neuroscience & Biobehavioral Reviews (1994), 18(1), 85-95. Language: English, Database: CAPLUS, DOI:10.1016/0149-7634(94)90039-6

A review with 63 refs. The clin. discoveries that drugs that stimulate 5-HT neurotransmission, either by inhibiting 5-HT uptake or by stimulating postsynaptic receptors directly, have antidepressant properties has stimulated interest in defining the role of the 5-HT receptor system in the clin. effects of antidepressant drugs. Two approaches are reviewed in this paper that address the neurochem. mediation of the therapeutic effects of antidepressant drugs from the standpoint of animal behavior. The first approach utilizes a behavioral response in rats, the forced swimming test, that correlates well with predicting antidepressant drugs in humans. Studies are reviewed that examd. serotonergic compds. in the forced swimming test, from the standpoint of identifying better serotonergic mechanisms involved in the antidepressant response. Both 5-HT uptake inhibitors and 5-HT<sub>1A</sub> receptor agonists produce effects in the forced swimming test that are similar to those of other classes of antidepressant drugs. In contrast, agonists at other 5-HT receptors or 5-HT receptor antagonists do not produce antidepressant-like behavioral effects. Evidence for an important role of 5-HT<sub>1A</sub> receptors in the antidepressant response is supported by findings that antagonists of 5-HT<sub>1A</sub> receptors prevent the ability of 5-HT<sub>1A</sub> receptor agonists to reduce immobility in the forced swimming test. The results of studies interfering with 5-HT neurotransmission, either by inhibition of 5-HT synthesis or by the destruction of 5-HT neurons, favor the idea that the effects of 5-HT<sub>1A</sub> receptor agonists are produced by the stimulation of postsynaptic 5-HT<sub>1A</sub> receptors. The second approach for studying the behavioral effects of antidepressant drugs employs drug discrimination studies, conducted using a discriminated taste aversion procedure, to provide a method for studying the discriminative stimulus effects of the antidepressant 5-HT uptake inhibitor sertraline. Rats were trained to discriminate the effects of sertraline (10 mg/kg) from saline. Other 5-HT uptake inhibitors, such as fluoxetine, fluvoxamine and paroxetine, substituted for the sertraline stimulus. High doses of norepinephrine uptake inhibitors, such as desipramine or maprotiline, were required to produce similar effects. These two behavioral approaches promise to be useful for defining the important pharmacol. effects assocd. with the behavioral effects of antidepressant drugs.

~88 Citings

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### 35. Central pre- and postsynaptic 5-HT<sub>1A</sub> receptors in rats treated chronically with a novel antidepressant, cericlamine

By Jolas, T.; Haj-Dahmane, S.; Kidd, E. J.; Langlois, X.; Lanfumey, L.; Fattaccini, C. M.; Vantalon, V.; Laporte, A. M.; Adrien, J.; et al.

From Journal of Pharmacology and Experimental Therapeutics (1994), 268(3), 1432-43. Language: English, Database: CAPLUS

Biochem. and electrophysiol. approaches were used to assess the possible changes in 5-hydroxytryptamine (serotonin) 5-HT<sub>1A</sub> receptors in the rat brain after a long-term treatment with cericlamine [2-(3,4-dichlorobenzyl)-2-dimethylamino-1-propanol], a novel serotonin reuptake inhibitor with antidepressant properties. Possible changes in other serotonin receptor binding sites (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> and 5-HT<sub>3</sub>) were also investigated after this treatment. Cericlamine was injected for 2 wk at a dose (16 mg/kg i.p., twice daily) that ensured complete prevention of 4-methyl- $\alpha$ -ethyl-meta-tyramine-induced depletion of brain serotonin. In vitro binding and quant. autoradiog. studies showed that neither 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> nor 5-HT<sub>3</sub> receptor binding sites in various brain areas were affected by the 14-day treatment with cericlamine. Although forskolin-stimulated adenylate cyclase activity was significantly increased in hippocampal homogenates from cericlamine-treated rats, the redn. in this enzymic activity due to 5-HT<sub>1A</sub> receptor stimulation by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) was unchanged in these animals as compared with controls. In contrast, in vitro and in vivo electrophysiol. recordings of serotonergic neurons in the dorsal raphe nucleus revealed a clearcut functional desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors. Thus the potency of 8-OH-DPAT and ipsapirone to depress the firing rate of these neurons in brain stem slices was significantly reduced after the 2-wk treatment with cericlamine. In vivo, the potency of an injection of cericlamine to inhibit the discharge of serotonergic neurons was also markedly less in rats that had been pretreated for 2 wk with this drug as compared with controls. However, the inhibitory effects of systemically injected 8-OH-DPAT and ipsapirone on the elec. activity of serotonergic neurons were as pronounced in cericlamine-treated rats as in controls. In addn., the redn. in serotonin synthesis due to an acute treatment with 8-OH-DPAT (0.1 or 0.3 mg/kg s.c.) was not significantly different in both groups of rats. These data support the idea that postsynaptic (in the hippocampus) and somatodendritic (in the dorsal raphe nucleus) 5-HT<sub>1A</sub> receptors are differently regulated in the rat brain, because only the latter receptors desensitized after a long-term blockade of serotonin reuptake by cericlamine. They also suggest that the inhibitory influence of systemically administered direct 5-HT<sub>1A</sub> agonists such as 8-OH-DPAT and ipsapirone on the elec. and metabolic activity of serotonergic neurons does not result solely from the stimulation of somatodendritic 5-HT<sub>1A</sub> autoreceptors.

~61 Citings

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### 36. Excitation of noradrenergic cell firing by 5-hydroxytryptamine<sub>1A</sub> agonists correlates with dopamine antagonist properties

By Piercey, M. F.; Smith, M. W.; Lum-Ragan, J. T.

From Journal of Pharmacology and Experimental Therapeutics (1994), 268(3), 1297-303. Language: English, Database: CAPLUS

The 5-HT<sub>1A</sub> receptor agonists buspirone, 8-hydroxy-N,N-dipropyl-2-aminotetralin, gepirone and ipsapirone were evaluated for their receptor binding profiles and their effects on firing rates of 5-HT, dopamine (DA) and noradrenaline (NA) neurons in the dorsal raphe, substantia nigra pars compacta and the locus ceruleus, resp. All agents bound to 5-HT<sub>1A</sub> receptors with high affinities. All agents also bound to dopamine D<sub>2</sub> receptors but, with the exception of buspirone, affinities were usually much lower than for 5-HT<sub>1A</sub> receptors. All agents depressed 5-HT neurons, with 8-hydroxy-N,N-dipropyl-2-aminotetralin having a potency about 8 - 12 times those for the other three. All agents also antagonized the inhibition of DA neurons by amphetamine, an index of DA antagonist properties. Buspirone reversed amphetamine's effects with doses similar to those for depressing 5-HT neurons, but the remaining three required much higher doses to affect DA neuron function. All four 5-HT<sub>1A</sub> agonists excited NA neurons. In each case, doses required for excitation of NA cells were similar to those reversing amphetamine's effects on DA cells, but not to those for depressing 5-HT cells. Haloperidol also stimulated NA cells. It is concluded that excitation of NA neurons by 5-HT<sub>1A</sub> agonists may be due to interactions with dopaminergic, rather than serotonergic, receptors.

### ~37 Citings

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### 37. Long-lasting enhancement of NMDA receptor-mediated synaptic transmission by metabotropic glutamate receptor activation

By O'Connor, John J.; Rowan, Michael J.; Anwyl, Roger

From Nature (London, United Kingdom) (1994), 367(6463), 557-9. Language: English, Database: CAPLUS, DOI:10.1038/367557a0

Synaptic transmission mediated by the N-methyl-D-aspartate (NMDA) glutamate receptor plays a key role in a range of plastic processes in the nervous system. These include long-term potentiation of synaptic transmission mediated by the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor, neuronal development, excitotoxicity and certain learning tasks. Recently, long-term potentiation of NMDA receptor-mediated synaptic transmission was found to occur following high-frequency (tetanic) stimulation via an unknown mechanism. The authors show here that activation of metabotropic glutamate (mGlu) receptors by neurally released transmitter underlies this type of long-term potentiation. The whole-cell patch-clamp technique in the 'thick' slice of the rat dentate gyrus was used to measure NMDA receptor-mediated excitatory postsynaptic currents. The authors have found that mGlu receptor activation by a selective agonist produced a long-lasting enhancement which was mutually exclusive with long-term potentiation of these NMDA currents. Moreover, both forms of potentiation were greatly reduced by the mGlu receptor antagonists 1-2-amino-3-phosphonopropionate and (R,S)- $\alpha$ -methyl-4-carboxyphenylglycine.

### ~82 Citings

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### 38. Chronic fluoxetine treatment up-regulates 5-HT uptake sites and 5-HT<sub>2</sub> receptors in rat brain: An autoradiographic study

By Hrdina, Pavel D.; Vu, Thu B.

From Synapse (New York, NY, United States) (1993), 14(4), 324-31. Language: English, Database: CAPLUS, DOI:10.1002/syn.890140410

This study was undertaken to investigate the effect of chronic treatment with fluoxetine, a selective serotonin uptake inhibitor used widely in the treatment of depression, on the distribution and d. of 5-HT uptake sites, 5-HT<sub>2</sub> receptors, and vesicular amine uptake sites in rat brain. Fluoxetine (10 mg/kg i.p.) was administered daily for 21 days. The d. of 5-HT uptake sites labeled by [<sup>3</sup>H]paroxetine, 5-HT<sub>2</sub> receptors labeled by [<sup>3</sup>H]ketanserin in presence of tetrabenazine, and vesicular amine uptake sites labeled by [<sup>3</sup>H]ketanserin in the presence of mianserin were measured by quant. autoradiog. in 22 areas of rat brain, using coronal tissue sections. Chronic administration of fluoxetine produced significant increases in the d. of 5-HT uptake sites in layers of frontoparietal cortex (by 32-43%), of striate cortex (by 55%), in CA1 field of hippocampus (by 111%) and in superior colliculus (by 20%). Fluoxetine treatment also resulted in up-regulation of 5-HT<sub>2</sub> receptors in layers of frontoparietal cortex (31-38%) and in CA2-3 fields of hippocampus (by 39%). The d. of tetrabenazine-sensitive vesicular amine uptake sites in the caudate-putamen was also significantly increased (by 66%). The obsd. alterations in 5-HT uptake site and 5-HT<sub>2</sub> receptor densities are likely a part of adaptive neuronal changes that occur after chronic administration of fluoxetine and may be related to the antidepressant effect of the drug.

### ~80 Citings

**39. From synapse to vesicle: the reuptake and storage of biogenic amine neurotransmitters**

By Rudnick, Gary; Clark, Janet

From *Biochimica et Biophysica Acta, Bioenergetics* (1993), 1144(3), 249-63. Language: English, Database: CAPLUS, DOI:10.1016/0005-2728(93)90109-S

A review, with 144 refs., on the reuptake and storage of biogenic amine neurotransmitters, including neurotransmitter transporters and their ionic requirements, stoichiometry, and mechanism as well as the identification and characterization of Na<sup>+</sup>-dependent biogenic amine transporter cDNA, how Na<sup>+</sup>-dependent biogenic amine transport is regulated, how storage vesicles transport amines, and cloning of the amine transporter cDNA.

~241 Citings

**40. Partial agonists, full agonists, antagonists: dilemmas of definition**

By Hoyer, Daniel; Boddeke, Hendrikus W. G. M.

From *Trends in Pharmacological Sciences* (1993), 14(7), 270-5. Language: English, Database: CAPLUS, DOI:10.1016/0165-6147(93)90129-8

A review with 48 refs. The absence of selective antagonists makes receptor characterization difficult, and largely dependent on the use of agonists. However, there has been considerable debate as to whether certain drugs acting at G protein-coupled receptors are better described as agonists, partial agonists or antagonists. Indeed many agonists tend to display differences in intrinsic activity, depending on the prep. used to study receptor pharmacol. It has been argued that variations in intrinsic activity of drugs, may be a reflection of receptor subtypes rather than varying degrees of receptor-effector coupling. However, it has often been overlooked that classical receptor theory predicts that a drug acting at a given receptor type can display a range of intrinsic activities depending on the extent of receptor reserve. Furthermore, because any receptor can couple to different effector systems, different degrees of intrinsic activity may be obsd. for a given drug. The authors review recent data which provide explanations for why drugs display such variations in intrinsic activity.

~140 Citings

**41. Differential properties of pre- and postsynaptic 5-hydroxytryptamine<sub>1A</sub> receptors in the dorsal raphe and hippocampus: II. Effect of pertussis and cholera toxins**

By Blier, Pierre; Lista, Alvaro; De Montigny, Claude

From *Journal of Pharmacology and Experimental Therapeutics* (1993), 265(1), 16-23. Language: English, Database: CAPLUS

The injection of 1 µg of pertussis toxin, which inactivates Gi/o proteins, in the rat dorsal raphe nearly abolished the responsiveness of serotonin (5-HT) neurons to microiontophoretic applications of 5-HT and selective 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) without altering their responsiveness to γ-aminobutyric acid (GABA). In contrast, the injection of 1 µg of cholera toxin, which causes an activation of G<sub>s</sub> proteins, did not alter the responsiveness of 5-HT neurons to 5-HT, 8-OH-DPAT or GABA. Such in situ injection of either toxin in the dorsal hippocampus decreased by about 90% the responsiveness of CA3 pyramidal neurons to microiontophoretic applications onto their cell body of 5-HT and 8-OH-DPAT, but not of GABA. The effectiveness of the stimulation of the ascending 5-HT pathway in suppressing the firing activity of the same neurons, which results from the release of 5-HT at the level of their dendritic tree, was also markedly decreased in the cholera toxin-treated rats, but intriguingly not in the pertussis toxin-treated rats. These results indicate that, on 5-HT neurons, the somatodendritic 5-HT<sub>1A</sub> autoreceptor is coupled to Gi/o, but insensitive to the persistent activation of G<sub>s</sub> proteins. In the CA3 region of the hippocampus, there would be two subsets of postsynaptic 5-HT<sub>1A</sub> receptors on the pyramidal neurons: those apposed to 5-HT terminals on their dendritic tree (denoted intrasynaptic) and those located on their cell body (denoted extrasynaptic). The former are cholera toxin sensitive, whereas the latter are sensitive to both pertussis and cholera toxins.

~52 Citings

**42. Olfactory bulbectomy as a model for agitated hyposerotonergic depression**

By Lumia, Augustus R.; Teicher, Martin H.; Salchli, Frederic; Ayers, Elise; Possidente, Bernard  
From Brain Research (1992), 587(2), 181-5. Language: English, Database: CAPLUS, DOI:10.1016/0006-8993(92)90995-L

Ablation of olfactory bulbs in rats reduced male sexual behavior, and altered the distribution of wheel-running activity between the light and dark phases of a 12:12 LD photoperiod. These effects were partially reversed by the tricyclic antidepressant amitriptyline. Olfactory bulbectomy also altered serotonin metab. (5-HIAA/5-HT ratio) in the frontal cortex, nucleus accumbens, hippocampus, and corpus striatum. Thus, olfactory bulbectomy in rodents can serve as a model of agitated hyposerotonergic depression.

~84 Citings

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**43. Actions and some interactions of 5-HT<sub>1A</sub> ligands in the elevated X-maze and effects of dorsal raphe lesions**

By Critchley, M. A. E.; Njung'e, K.; Handley, Sheila L.  
From Psychopharmacology (Berlin, Germany) (1992), 106(4), 484-90. Language: English, Database: CAPLUS, DOI:10.1007/BF02244819

Effects of 5 HT<sub>1A</sub> agonists and partial agonists on open/total arm entry ratio (OTR) were examd. in the elevated X-maze anxiety model. 8-OH-DPAT (0.05-0.2 mg/kg), RU 24969 (0.5-2.0 mg/kg) and BAY R 1521 (0.1-1.2 mg/kg) produced dose-dependent redns. in OTR, signifying anxiogenic effects. Buspirone reduced OTR only at doses (0.25-5.0 mg/kg) decreasing total entries; gepirone (0.1-5.0 mg/kg) was inactive. Ipsapirone (0.25-5.0 mg/kg) increased OTR and at 1.0 mg/kg antagonized the anxiogenic action of 8-OH-DPAT, RU 24969, and BAY R 1531. Gepirone (2.5 mg/kg) failed to antagonize 8-OH-DPAT, but the dose was limited by its effect on total entries. The anxiogenic effect of a low dose of 8-OH-DPAT was also prevented by p-chlorophenylamine (p-CPA) pretreatment and reversed to anxiolytic by 5,7-dihydroxytryptamine lesions of dorsal raphe, which spared the median raphe. These lesions also abolished the anxiolytic effect of ipsapirone without affecting the anxiogenic response to yohimbine. This study provides preliminary evidence that 8-OH-DPAT may be capable of acting as an agonist and ipsapirone as an antagonist at a presynaptic site related to dorsal raphe which is sep. from the site of action of yohimbine. 5-HT<sub>1A</sub> agonists and partial agonists may have multiple sites and/or mechanisms of action in the elevated X-maze.

~22 Citings

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**44. Serotonin uptake and serotonin uptake inhibition**

By Fuller, Ray W.; Wong, David T.  
From Annals of the New York Academy of Sciences (1990), 600(Neuropharmacol. Serotonin), 68-80. Language: English, Database: CAPLUS, DOI:10.1111/j.1749-6632.1990.tb16873.x

A review and discussion, with 87 refs., of brain neuron serotonin uptake and inhibition of uptake which discusses chem. classes of serotonin uptake inhibitors, selectivity of serotonin uptake inhibitors in vitro and in vivo, demonstration of serotonin uptake inhibition in vivo, uptake inhibitors as radiolabels for serotonin uptake carriers, evidence for increased serotonin in the synaptic cleft after serotonin uptake inhibition, pharmacol. effects of serotonin uptake inhibitors in animals, and therapeutic effects of serotonin uptake inhibitors.

~59 Citings

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**45. Chronic treatment with clozapine or haloperidol differentially regulates dopamine and serotonin receptors in rat brain**

By O'Dell, Steven J.; La Hoste, Gerald J.; Widmark, Clifford B.; Shapiro, Raymond M.; Potkin, Steven G.; Marshall, John F.  
From Synapse (New York, NY, United States) (1990), 6(2), 146-53. Language: English, Database: CAPLUS, DOI:10.1002/syn.890060205

Long-term administration of the atypical neuroleptic clozapine (CLZ) poses a much lower risk of extrapyramidal side effects (EPS) than does the use of typical neuroleptics such as haloperidol (HAL). To investigate the neural mechanisms of the differing CNS activities of these two drugs, the authors used quant. autoradiog. to measure changes in dopamine and serotonin receptors in rats after injection with CLZ or HAL for 21 days at clin. relevant dose ratios. Levels of D1, D2, and 5-HT2 receptors were detd. in frontal cortex, caudate-putamen, and nucleus accumbens. Rats that received CL chronically showed CNS receptor changes markedly different from those in chronic HAL-treated animals. Whereas rats treated chronically with HAL showed enhanced striatal D2 binding (av. increase of 42%), those treated with CLZ did not. In contrast, chronic CLZ, but not chronic HAL, induced enhanced striatal D1 binding (av. increase of 43%). Finally, CLZ treatment decreased 5-HT2 receptor binding by an av. of 37%, while HAL had no significant effect. The effects of chronic HAL or CLZ treatment on receptors were similar in all forebrain areas examd. However, since D1 and 5-HT2 receptors are more abundant than D2 sites in limbic and neocortical areas, the preferential modulation of D1 and 5-HT2 receptors by CL suggests a greater impact of this atypical neuroleptic on activity of the limbic system than that achieved by the typical neuroleptic, HAL. These findings suggest that the clin. profile of atypical neuroleptics such as CLZ may be attributed to their effects on a receptor profile differing in pharmacol. characteristics and anatomical distribution from that affected by typical neuroleptics.

#### ~47 Citings

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#### 46. The effects of 5-HT1B characterizing agents in the mouse elevated plus-maze

By Benjamin, Daniel; Lal, Harbans; Meyerson, Laurence R.  
From Life Sciences (1990), 47(3), 195-203. Language: English, Database: CAPLUS, DOI:10.1016/0024-3205(90)90320-Q

The effects of drugs that act preferentially at 5-HT1B receptors were evaluated on the mouse behavior elicited in the elevated plus-maze, an animal model of anxiety. Variations in the light intensity affected the plus-maze behavior. Lower light intensity increased the entries to and time spent in the open arm in a manner similar to that seen with stress-attenuating circumstances. Opposite effects were obsd. in a high light intensity, similar to the effects seen under elevated stress conditions. Chlordiazepoxide produced increased entries and time spent in the open arm, whereas pentylenetetrazole (PTZ) produced opposite effects. The preferential 5-HT1B agents TFMPP and m-chlorophenylpiperazine (mCPP) exhibited a profile similar to PTZ. The effects of TFMPP in the plus-maze were reversed by chlordiazepoxide, but not by the benzodiazepine receptor antagonist flumazenil, which suggests that this effect was not directly mediated by benzodiazepine receptors. The decreased entries and time spent in the open arm of the maze following TFMPP or mCPP administration was possibly mediated by an antagonistic action at 5-HT1B receptors, since this effect was reversed by the selective 5-HT1B agonist CGS 12066B. The present study further demonstrates the utility of mouse behavior in the elevated plus-maze as a model for identifying anxiomodulatory substances.

#### ~39 Citings

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#### 47. Effects of psychotropic drugs on the behavior and neurochemistry of olfactory bulbectomized rats

By Van Riezen, H.; Leonard, B. E.  
From Pharmacology & Therapeutics (1990), 47(1), 21-34. Language: English, Database: CAPLUS, DOI:10.1016/0163-7258(90)90043-2

A review with 108 refs. Since its first characterization as a model for the detection of antidepressant drugs, a large body of data now supports the view that olfactory bulbectomy produces changes in animal behavior that are reversed by chronic treatment with antidepressants. The behavioral deficits seen in olfactory bulbectomized rats (such as irritability, deficits in acquisition of avoidance and of appetitive motivated conditioning and hyperactivity in a new environment) are probably the results of a reduced ability to adapt to environmental changes. These behavioral changes, their biochem. consequences and the effects of treatments with psychotropic drugs are reviewed. These studies suggest that the olfactory bulbectomized rat is a model of depression useful to detect antidepressant drugs.

#### ~80 Citings

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#### 48. Animal models of depression: an overview

By Willner, Paul

From Pharmacology & Therapeutics (1990), 45(3), 425-55. Language: English, Database: CAPLUS, DOI:10.1016/0163-7258(90)90076-E

A review with 301 refs. with emphasis on the evaluation of the validity of animal model simulations of depression. The neurochem. basis of depression and the responses to antidepressants are also discussed.

**~157 Citings**

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**49. Changes in [3H]-imipramine binding sites in relation to muricide following olfactory bulbectomy and the effect of nomifensine in brain of rats**

By Al-Khatib, I. M. H.; Fujiwara, M.; Kataoka, Y.; Ueki, S.

From Archives Internationales de Pharmacodynamie et de Therapie (1988), 296, 282-92. Language: English, Database: CAPLUS

The effects of olfactory bulbectomy (OB) and nomifensine (NOM) on the binding of [3H]-imipramine (3H-IMP) in brain of rat were investigated. Seventy-five percent of OB rats exhibited muricidal behavior. Acute NOM suppressed muricidal behavior in 55% and chronic NOM suppressed it in 60-80% of OB rats. In killer rats, OB increased Bmax of high-affinity (HA) and low-affinity sites (LA) in cortex (Cx) and both Bmax and KDof HA in amygdala (AMG). In rats with muricidal behavior suppressed by acute NOM 10 mg·kg<sup>-1</sup> i.p., Bmax and KDof HA in Cx and of both HA and LA in AMG were reduced. Injection of NOM for 10 days produced further redn. of Bmax, esp. of HA binding in Cx. Neither OB nor NOM exerted any significant effect on binding consts. in caudate-putamen and hypothalamus. The possible relation between the changes of 3H-IMP binding, exhibition of muricide by OB rats and the antimuricidal activity of NOM are discussed.

**~2 Citings**

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**50. The chronic effects of desipramine and sertraline on platelet and synaptosomal 5-HT uptake in olfactory bulbectomized rats**

By Butler, Jackie; Tannian, Miriam; Leonard, Brian E.

From Progress in Neuro-Psychopharmacology & Biological Psychiatry (1988), 12(5), 585-94. Language: English, Database: CAPLUS, DOI:10.1016/0278-5846(88)90004-8

Depressed patients show a characteristic decrease in the rate of uptake of 5-HT (serotonin) into their platelets, which is normalized only by clin. effective antidepressant treatment. A decrease in platelet 5-HT uptake rates was found in the olfactory bulbectomized (OB) rat model of depression, that returned to normal following 3 wk of treatment with desipramine or sertraline. Synaptosomal 5-HT uptake appears to consist of a low-affinity, high-capacity component and a high-affinity, low-capacity component, both of which are increased in the OB rat, compared to its sham-operated control, and normalized by chronic antidepressant treatment. The low-affinity uptake of serotonin is not inhibited by in vitro incubation with sertraline, suggesting that the low-affinity system may be assocd. with a nonspecific uptake of 5-HT into noradrenergic or dopaminergic nerve endings.

**~12 Citings**

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**51. Selective agonists and antagonists for 5-hydroxytryptamine receptor subtypes, and interactions with yohimbine and FG 7142 using the elevated plus-maze test in the rat**

By Pellow, Sharon; Johnston, Amanda L.; File, Sandra E.

From Journal of Pharmacy and Pharmacology (1987), 39(11), 917-28. Language: English, Database: CAPLUS, DOI:10.1111/j.2042-7158.1987.tb03129.x

The effects of some 5-HT receptor ligands were investigated on measures of anxiety in an elevated plus-maze test in the rat. Quipazine, a nonspecific 5-HT agonist, and ritanserin, a 5-HT<sub>2</sub> receptor antagonist, displayed anxiogenic profiles by reducing both of the measures of anxiety used in this test. Two 5-HT<sub>1A</sub> receptor ligands, buspirone and ipsapirone and the 5-HT<sub>1</sub> agonist, RU 24969 reduced only the percentage of time spent on the open arms. (-)-Propranolol, a 5-HT<sub>1</sub> receptor antagonist, reduced only the percentage of entries made onto the open arms. Metergoline, a nonspecific 5-HT antagonist, displayed anxiolytic effects in this test by increasing both measures of anxiety. The 5-HT<sub>1A</sub> receptor agonist, 8-OH-DPAT had no effect on either of the measures of anxiety. The results from the nonspecific ligands (quipazine and metergoline) are consistent with the theory that a redn. in 5-HT function reduces anxiety. However, in spite of their more selective effects on 5-HT receptors the results in this test from the more specific ligands are not consistent with a strong involvement of any single receptor subtype. The interaction studies with yohimbine and FG 7142 ( $\beta$ -carboline-3-carboxylate methylamide) provided no clear evidence for a major role of 5-HT pathways in the mediation of their anxiogenic effects.

### ~32 Citings

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## 52. Serotonin receptors in the human brain. IV. Autoradiographic mapping of serotonin-2 receptors

By Pazos, A.; Probst, A.; Palacios, J. M.  
From Neuroscience (Oxford, United Kingdom) (1987), 21(1), 123-39. Language: English, Database: CAPLUS,  
DOI:10.1016/0306-4522(87)90327-7

The anatomical distribution of serotonin-2 receptors (S<sub>2</sub>R) in the human brain was studied by light microscopic autoradiog., with [<sup>3</sup>H]ketanserin as a ligand. The S<sub>2</sub>R densities were quantified by microdensitometry with the aid of a computer-assisted image-anal. system. A heterogeneous distribution of S<sub>2</sub>R densities was found in the human brain. Very high concns. were localized over several cortical areas, whereas only low to very low densities of S<sub>2</sub>R were found in areas such as the thalamus, brain stem, cerebellum, and spinal cord. A very high level of nonspecific binding, which was not displaceable by any S<sub>2</sub> compd., was found in some areas of the human brain, including the caudatus and putamen nuclei, the substantia nigra and the raphe nuclei. The distribution of S<sub>2</sub>R receptors in the human brain is discussed with respect to the distribution of serotonergic innervation, the central effects which have been proposed to be S<sub>2</sub>R-mediated, and the neuropathol. characteristics of diseases where a modification in the no. of S<sub>2</sub>R receptors has been reported.

### ~135 Citings

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## 53. Antidepressant-like action of 5-HT<sub>1A</sub> agonists and conventional antidepressants in an animal model of depression

By Kennett, G. A.; Dourish, C. T.; Curzon, G.  
From European Journal of Pharmacology (1987), 134(3), 265-74. Language: English, Database: CAPLUS,  
DOI:10.1016/0014-2999(87)90357-8

Previous results have suggested that behavioral adaptation to restraint might be promoted by postrestraint stimulation of 5-HT<sub>1A</sub> receptors. Therefore, rats were restrained for 2 h and injected with vehicle or 60-1000  $\mu$ g/kg of the 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(di-n-propylamino)tetrilin (8-OH-DPAT) [78950-78-4] s.c. Vehicle treated restrained rats showed reduced locomotor activity and increased defecation in an open-field test the day after the end of restraint. A single injection of 250 or 1000  $\mu$ g/kg 8-OH-DPAT attenuated these effects. The above locomotor deficits were also attenuated by chronic pretreatment with the antidepressants desipramine [50-47-5] and sertraline [79617-96-2] but not by a single treatment with desipramine or the benzodiazepine anxiolytic drugs chlordiazepoxide [58-25-3] and diazepam [439-14-5]; none of these treatments unambiguously reversed stress-induced increases in defecation. Evidence suggests that the above action of 8-OH-DPAT is mediated by 5-HT<sub>1A</sub> receptors since it was antagonized by the 5-HT<sub>1A</sub> antagonist spiperone but not by the 5-HT<sub>2</sub> antagonist ketanserin and was not mimicked by the 5-HT<sub>1B</sub> agonist RU 24969. However, the 5-HT<sub>1A</sub> agonists buspirone [36505-84-7] and TVXQ 7821 (ipsapirone) [92589-98-5] and the nonspecific 5-HT agonist quipazine [4774-24-7] all possess similar properties to 8-OH-DPAT in this test. The results suggest that 5-HT<sub>1A</sub> agonists may have rapid antidepressant properties.

### ~42 Citings

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## 54. Characterization of the 5-hydroxytryptamine 1A receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes

By De Vivo, Michael; Maayani, Saul

From Journal of Pharmacology and Experimental Therapeutics (1986), 238(1), 248-53. Language: English, Database: CAPLUS

The inhibition of forskolin-stimulated adenylate cyclase [9012-42-4] activity by 5-HT [50-67-9] receptor agonists, as measured in guinea pig and rat hippocampal membranes, was consistent with the inhibition being mediated by a single, homogeneous population of receptors. In guinea pig hippocampal membranes, 8-hydroxy-2-(di-n-propylamino)tetralin [78950-78-4], d-lysergic acid diethylamide [50-37-3], 5-HT, and buspirone [36505-84-7] were potent in inhibiting forskolin-stimulated adenylate cyclase activity, with EC<sub>50</sub> values of 18, 24, 53, and 146 nM, resp. Spiperone and methiothepin were potent competitive antagonists at this receptor, whereas a high-affinity 5-HT<sub>2</sub> receptor ligand and a high-affinity peripheral neuronal (M) receptor ligand were not. In rat hippocampal membranes, 8-hydroxy-2-(di-n-propylamino)tetralin, d-lysergic acid diethylamide, 5-HT, and buspirone were potent agonists and exhibited the same rank order of potency as in guinea pig hippocampal membranes. The maximal percentage of inhibition by buspirone was less than that of inhibition by 5-HT in rat membranes, suggesting that it is a partial agonist at this receptor, with an intrinsic activity relative to 5-HT of 0.5. The concn.-response data show that the inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes is mediated by a receptor with the characteristics of the 5-HT<sub>1A</sub> binding site. The inhibition of adenylate cyclase activity may be a functional correlate of this binding site. This response is suitable for measuring activities and affinities of drugs acting at 5-HT<sub>1A</sub> receptors.

#### ~107 Citings

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#### 55. 1-(2-Pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat

By Caccia, Silvio; Conti, Ivana; Vigano, Gianluigi; Garattini, Silvio

From Pharmacology (1986), 33(1), 46-51. Language: English, Database: CAPLUS, DOI:10.1159/000138199

Buspirone (BP)(I) [36505-84-7] a newly developed antianxiety agent, forms 1-(2-pyrimidinyl)-piperazine (PmP)(II) [20980-22-7] during its biotransformation in rats and man. After oral administration of pharmacol. EDs of BP-HCl to rats (1 and 10 mg/kg), the metabolite appears in significant amts. in body fluids and tissues; it is highly concd. in the central nervous system, the brain-to-plasma concn. ratios being approx. 5 at the time of the max. concns. (C<sub>max</sub>). In humans given the anxiolytic dose (20 mg) of BP, the metabolite reaches higher plasma C<sub>max</sub> values than its parent drug. Its plasma elimination t<sub>1/2</sub> is more than double that for BP. These results, together with the fact that PmP is biochem. and pharmacol. active, suggest that the metabolite may contribute significantly to the central effects of the parent drug.

#### ~30 Citings

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#### 56. Effects of antidepressant drugs on the behavior of olfactory bulbectomized and sham-operated rats

By Jesberger, James A.; Richardson, J. Steven

From Behavioral Neuroscience (1986), 100(2), 256-74. Language: English, Database: CAPLUS, DOI:10.1037/0735-7044.100.2.256

Removal of the main olfactory bulbs in rats alters neuronal function in brain resulting in maladaptive behavioral patterns and elevated plasma 11-hydroxycorticosterone that are suggestive of the symptom profile of patients with unipolar depression. Chronic antidepressant treatment [amitriptyline [50-48-6] (10 mg/kg), mianserin [24219-97-4] (10 mg/kg), tranylcypromine [155-09-9] (10 mg/kg), and iprindole [5560-72-5] (25 mg/kg) all i.p. for 28 days] resulted in the reversal of the olfactory bulb lesion deficits. The beneficial effects of chronic antidepressant administration were still present 5 days after the last dose of the drugs, suggesting that the endocrine and behavioral improvements are due to some physiol. change produced by chronic exposure to antidepressant drugs. A brief review of the parallels between patients with primary depression and rats with olfactory bulb lesions with respect to pathophysiol. and therapy is presented.

#### ~25 Citings

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#### 57. Characterization of [<sup>3</sup>H]paroxetine binding to rat cortical membranes

By Habert, Estelle; Graham, David; Tahraoui, Lila; Claustre, Yves; Langer, Salomon Z.

From European Journal of Pharmacology (1985), 118(1-2), 107-14. Language: English, Database: CAPLUS, DOI:10.1016/0014-2999(85)90668-5

Paroxetine [61869-08-7] is a selective and potent inhibitor of 5-hydroxytryptamine [50-67-9] uptake into serotonergic neurons. The specific binding of [3H]paroxetine to rat cortical membranes at 22° was examd. The results indicate the presence of a single saturable high affinity binding component for [3H]paroxetine. Scatchard anal. revealed a K<sub>d</sub> (dissocn. const.) of 0.15 nM, and a B<sub>max</sub> (binding const.) of 549 fmol/mg protein. The kinetically derived K<sub>d</sub> was 0.034 nM. [3H]Paroxetine binding was inhibited selectively by 5-HT uptake blockers, and a good correlation was demonstrated between the potency of various drugs to inhibit [3H]paroxetine binding and [3H]5-hydroxytryptamine uptake. Serotonergic nerve terminal lesion induced by the neurotoxin 5,7-dihydroxytryptamine resulted in a 94% decrease in endogenous 5-hydroxytryptamine levels with a concomitant 90% redn. in [3H]paroxetine binding when compared to sham controls. These results indicate that the binding site labeled by [3H]paroxetine is assocd. with the neuronal 5-hydroxytryptamine transporter complex.

#### ~62 Citings

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### 58. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors

By Pazos, A.; Palacios, J. M.

From Brain Research (1985), 346(2), 205-30. Language: English, Database: CAPLUS, DOI:10.1016/0006-8993(85)90856-X

The distribution of serotonin-1 (5-HT<sub>1</sub>) receptors in the rat brain was studied by light microscopic quant. autoradiog. Receptors were labeled with tritiated 5-HT [50-67-9], 8-hydroxy-2[N-dipropylamino]tetralin (8-OH-DPAT) [78950-78-4], LSD [50-37-3], and mesulergine [64795-35-3], and the densities quantified by microdensitometry with the aid of a computer-assisted image-anal. system. Competition expts. for [3H]5-HT binding by several serotonin-1 agonists led to the identification of brain areas enriched in each of the 3 subtypes of 5-HT<sub>1</sub> recognition sites already described (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>). The existence of these selective areas allowed a detailed pharmacol. characterization of these sites to be made in a more precise manner than has been attained in membrane-binding studies. Whereas [3H]5-HT labeled with nanomolar affinity all the 5-HT<sub>1</sub> subtypes, the other 3H-labeled ligands labeled selectively 5-HT<sub>1A</sub> (8-OH-[3H]DPAT), 5-HT<sub>1C</sub> ([3H]mesulergine) and both of them ([3H]LSD). Very high concns. of 5-HT<sub>1</sub> receptors were localized in the choroid plexus, lateroseptal nucleus, globus pallidus and ventral pallidum, dentate gyrus, dorsal subiculum, olivary pretectal nucleus, substantia nigra, reticular and external layer of the entorhinal cortex. The different fields of the hippocampus (CA1CA4), some nuclei of the amygdaloid complex, the hypothalamic nuclei, and the dorsal raphe, among others, also presented high concns. of sites. Areas contg. intermediate densities of 5-HT<sub>1</sub> receptors included the claustrum, olfactory tubercle, accumbens, central grey, and lateral cerebellar nucleus. The nucleus caudate-putamen and the cortex, at the different levels studied, presented receptor densities ranging from intermediate to low. Finally, in other brain areas, pons, medulla, spinal cord, only ow or very low concns. of 5-HT<sub>1</sub> receptors were found. From the areas strongly enriched in 5-HT<sub>1</sub> sites, dentate gyrus and septal nucleus contained 5-HT<sub>1A</sub> sites, whereas globus pallidus, dorsal subiculum, substantia nigra, and olivary pretectal nucleus were enriched in 5-HT<sub>1B</sub>. The sites in the choroid plexus, which presented the highest d. of receptors in the rat brain, were of the 5-HT<sub>1C</sub> subtype. The distribution of 5-HT<sub>1</sub> receptors is discussed in correlation with the distribution of serotonergic neurons and fibers, the related anatomical pathways, and the effects which appear to be mediated by these sites.

#### ~438 Citings

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### 59. Olfactory projection systems, drugs and behavior: a review

By Cairncross, K. D.; Cox, B.; Forster, C.; Wren, A. F.

From Psychoneuroendocrinology (1979), 4(3), 253-72. Language: English, Database: CAPLUS, DOI:10.1016/0306-4530(79)90009-X

A review with 60 refs. on the bulbectomized rat as a model of psychiatric disorders and its usefulness in differentiating between different classes of psychotropic drugs. The model appears to be particularly valuable for screening of antidepressants.

#### ~38 Citings

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### 60. Biochemical correlates in mouse-killing behavior of the rat: prolonged isolation and brain cholinergic function

By Yoshimura, Hiroyuki; Ueki, Showa

From Pharmacology, Biochemistry and Behavior (1977), 6(2), 193-6. Language: English, Database: CAPLUS, DOI:10.1016/0091-3057(77)90073-9

After 30 days of isolation, 45% of the rats exhibited mouse-killing behavior. The killing response was suppressed by atropine (5 mg/kg and 8 mg/kg, i.p.) and scopolamine (8 mg/kg, i.p.), whereas methylatropine was ineffective. Acetylcholine (ACh) content and acetylcholinesterase (AChE) activity were measured in 5 discrete areas of rat brain. As compared with aggregated rats only the killer rats exhibited higher ACh levels in the diencephalon. The activity of AChE in all brain areas was unchanged by isolation; no difference was found between the killer and nonkiller rats. These results suggest that central cholinergic mechanisms participate in the mediation of mouse-killing behavior in the rat.

#### ~4 Citings

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#### **61. Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study**

By Reimold M; Batra A; Knobel A; Smolka M N; Zimmer A; Mann K; Solbach C; Reischl G; Schwarzler F; Grunder G; et al

From Molecular psychiatry (2008), 13(6), 606-13, 557, English, Database: MEDLINE

Serotonergic dysfunction may contribute to negative mood states in affective disorders. Some in vivo imaging studies showed reduced availability of serotonin transporters (5-HTT) in the brainstem and thalamus of patients with major depression. We tested the hypothesis that 5-HTT availability is reduced in unmedicated unipolar patients with major depression compared to healthy control subjects matched for gender, age, genotype and smoking status. Availability of 5-HTT was measured in vivo with positron emission tomography and [(11)C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) in the midbrain, thalamus and amygdala. DASB binding was correlated with the severity of depression (Beck's Depression Inventory), anxiety (Spielberger's State-Trait Anxiety Inventory) and personality traits (Temperament and Character Inventory). Patients with major depression displayed reduced 5-HTT availability in the thalamus ( $P=0.005$ ). In patients, low serotonin transporter availability correlated with high anxiety (thalamus:  $r=-0.78$ ,  $P=0.004$ ; midbrain:  $r=-0.78$ ,  $P=0.004$ ; amygdala:  $r=-0.80$ ,  $P=0.003$ ). Correlations with severity of depression were weaker and did not survive correction for multiple testing. These results support the hypothesis that central serotonergic dysfunction is associated with negative mood states in affective disorders. In the thalamus, a low serotonin reuptake capacity may interfere with thalamic control of cortical excitability and contribute to anxiety rather than depression per se in major depression.

#### ~3 Citings

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#### **62. Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis**

By Sakai Y; Dobson C; Diksic M; Aube M; Hamel E

From Neurology (2008), 70(6), 431-9, English, Database: MEDLINE

**BACKGROUND:** Altered serotonin (5-HT) neurotransmission has been implicated in the pathophysiology of migraine headache. **OBJECTIVES:** To test this hypothesis in migraine patients in vivo using PET and alpha-[(11)C]methyl-L-tryptophan as a surrogate marker of brain 5-HT synthetic rate during different phases of their migraine attack and after acute antimigraine therapy with sumatriptan, and to compare them with normal controls. **METHODS:** Six patients were scanned 1) within 6 hours after the onset of a spontaneous migraine attack, 2) 2 hours after subcutaneous sumatriptan, and 3) interictally when migraine free for at least 3 days. Head pain was rated before each scan, and before and every 15 minutes after sumatriptan. **RESULTS:** Brain 5-HT synthesis was highest during attacks, lowest after sumatriptan, and intermediate when patients were migraine free. All states were statistically different from the others in virtually all brain regions examined. 5-HT synthetic rates in patients during migraine attacks did not differ from those of age- and sex-matched controls, whereas they were significantly lower after sumatriptan in a majority of regions. Interictally, global brain 5-HT synthetic rate was slightly, albeit not significantly, lower (-14%) in migraine patients than in controls, with specific cortical areas exhibiting proportionally more severe reductions (-28% to 31%). **CONCLUSIONS:** These findings point to a low cortical serotonergic tone in migraine patients interictally. Further, they demonstrate widespread increases in brain serotonin (5-HT) synthetic rate in migraine patients during attacks, and that triptans exert a negative feedback regulation of brain 5-HT synthesis concurrently with modulation of pain pathways.

#### ~1 Citing

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**63. The vanadium (IV) compound rescues septo-hippocampal cholinergic neurons from neurodegeneration in olfactory bulbectomized mice**

By Han F; Shioda N; Moriguchi S; Qin Z-H; Fukunaga K

From Neuroscience (2008), 151(3), 671-9, English, Database: MEDLINE

The bilateral olfactory bulbectomy (OBX) mouse exhibits neurodegeneration of cholinergic neurons in the medial septum with concomitant cognitive deficits. Consistent with our previous observations, choline acetyltransferase (ChAT) protein levels in the medial septum decreased by 43.5% 2 weeks after OBX without changes in glutamic acid decarboxylase-65 (GAD65) levels. Interestingly, levels of the vesicular acetylcholine transporter (VACHT), which is localized at cholinergic neuron terminals, decreased both in hippocampal CA1 and CA3 regions following OBX. Confocal microscopy showed that VACHT expression was more severely reduced in CA3 14 days after OBX compared with CA1. Intriguingly, chronic treatment with a vanadium (IV) compound, VO(OPT) [bis(1-N-oxide-pyridine-2-thiolato)oxovanadium(IV)] (0.5-1 mg as vanadium (V)/kg/day, i.p.), significantly rescued cholinergic neurons in the medial septum in a dose-dependent manner. VO(OPT) treatment also prevented decreased VACHT immunoreactivity both in CA1 and CA3 regions in the hippocampus. Consistent with these findings, an impaired hippocampal long-term potentiation (LTP) and memory deficits seen in OBX mice were significantly prevented by VO(OPT) treatment. Taken together, OBX induces neurodegeneration of septo-hippocampal cholinergic neurons and impairment of memory-related behaviors. The neuroprotective effect of VO(OPT) could lead to novel therapeutic strategies to ameliorate cognitive deficits associated with cholinergic neuron degeneration in Alzheimer's disease and other neurodegenerative disorders.

**~1 Citing**

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**64. The validity of animal models of predisposition to depression**

By Willner P; Mitchell P J

From Behavioural pharmacology (2002), 13(3), 169-88, English, Database: MEDLINE

Some animal models of depression, including the majority of the more recently introduced models, are better characterized as models of predisposition to depression. In the first part of this paper, we show that the basis for such a model could be either a procedure that increases the ease with which an analogue of major depression may be evoked, or a presentation analogous to dysthymia (chronic mild depression). We then consider how the concepts of predictive, face, and construct validity apply to such models. Next, we review the validity of the available models of predisposition to depression, which derive from genetics, genomics, developmental manipulations, and brain lesioning. Finally, we compare the performance of the different models, using a novel scoring system that formalizes the evaluation of animal models against each of the three sets of validation criteria.

**~10 Citings**

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**65. Equilibrium modeling of 5-HT(2A) receptors with [18F]deuteroaltanserin and PET: feasibility of a constant infusion paradigm**

By van Dyck C H; Soares J C; Tan P Z; Staley J K; Baldwin R M; Amici L A; Fu X; Garg P K; Seibyl J P; Charney D S; et al

From Nuclear medicine and biology (2000), 27(8), 715-22, English, Database: MEDLINE

[(18)F]Altanserin has emerged as a promising positron emission tomography (PET) ligand for serotonin-2A (5-HT(2A)) receptors. The deuterium substitution of both of the 2'-hydrogens of altanserin ([18F]deuteroaltanserin) yields a metabolically more stable radiotracer with higher ratios of parent tracer to radiometabolites and increased specific brain uptake than [(18)F]altanserin. The slower metabolism of the deuterated analog might preclude the possibility of achieving stable plasma and brain activities with a bolus plus constant infusion within a reasonable time frame for an (18)F-labeled tracer ( $T_{1/2}$  110 min). Thus, the purpose of this study was to test the feasibility in human subjects of a constant infusion paradigm for equilibrium modeling of [(18)F]deuteroaltanserin with PET. Seven healthy male subjects were injected with [(18)F]deuteroaltanserin as a bolus plus constant infusion lasting 10 h postinjection. PET acquisitions and venous blood sampling were performed throughout the infusion period. Linear regression analysis revealed that time-activity curves for both specific brain uptake and plasma [(18)F]deuteroaltanserin concentration stabilized after about 5 h. This permitted equilibrium modeling and estimation of  $V'_{(3)}$  (ratio of specific uptake to total plasma parent concentration) and the binding potential  $V_{(3)}$  (ratio of specific uptake to free plasma parent concentration). Cortical/cerebellar ratios were increased by 26% relative to those we previously observed with [(18)F]altanserin using similar methodology in a somewhat older subject sample. These results demonstrate feasibility of equilibrium imaging with [(18)F]deuteroaltanserin and suggest that it may be superior to [(18)F]altanserin as a PET radioligand.

## ~1 Citing

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### 66. The effect of paroxetine on 5-HT(2A) receptors in depression: an [(18)F]setoperone PET imaging study

By Meyer J H; Kapur S; Eisfeld B; Brown G M; Houle S; DaSilva J; Wilson A A; Rafi-Tari S; Mayberg H S; Kennedy S H

From The American journal of psychiatry (2001), 158(1), 78-85, English, Database: MEDLINE

**OBJECTIVE:** In the cortex of animals, serotonin (5-HT) levels increase after several weeks of treatment with selective serotonin reuptake inhibitors (SSRIs). Studies using an intrasubject design to examine the effects of SSRI treatment on 5-HT(2A) receptors in the cortex of drug-free depressed patients are needed. In theory, agonist stimulation of 5-HT(2A) receptors could be relevant to SSRI treatment by promoting neuronal growth and survival as well as direct elevation of mood. The objective of this study was to evaluate the effect of 6 weeks of paroxetine treatment on 5-HT(2A) receptors in depressed patients. **METHOD:** After a medication-free period of at least 3 months, 19 depressed patients were treated for 6 weeks with paroxetine, 20 mg/day. The authors used [(18)F]setoperone and positron emission tomography to assess 5-HT(2A) receptor binding potential in the patients before and after treatment and in 19 age-matched healthy subjects. **RESULTS:** 5-HT(2A) binding potential declined with age in all cortical regions in the depressed and healthy subjects. There was a significant interaction between age and treatment effect on 5-HT(2A) binding potential in all cortical regions. Subjects aged 20 to 30 years had a 10% decrease in 5-HT(2A) binding potential after treatment, whereas subjects aged 30 to 40 had no change. No regional differences in 5-HT(2A) binding potential between depressed and healthy subjects were found. **CONCLUSIONS:** 5-HT(2A) receptors down-regulate in young depressed subjects after treatment with paroxetine, but this down-regulation attenuates with age. This suggests that over 6 weeks paroxetine treatment increases 5-HT agonism on 5-HT(2A) receptors in the cortex of young patients with depression.

## ~9 Citings

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### 67. PET imaging of serotonin type 2A receptors in late-life neuropsychiatric disorders

By Meltzer C C; Price J C; Mathis C A; Greer P J; Cantwell M N; Houck P R; Mulsant B H; Ben-Eliezer D; Lopresti B; DeKosky S T; et al

From The American journal of psychiatry (1999), 156(12), 1871-8, English, Database: MEDLINE

**OBJECTIVE:** To determine whether there are abnormalities in the in vivo status of the serotonin type 2A (5-HT<sub>2A</sub>) receptor in late-life depression and Alzheimer's disease, the authors used positron emission tomography (PET) to assess patients with these two conditions and healthy subjects. **METHOD:** PET was performed by using [18F]altanserin to evaluate 5-HT<sub>2A</sub> receptor binding in 11 elderly patients with depression (four men, seven women; mean age = 65.0 years, SD = 5.5); nine Alzheimer's disease patients, including three with concurrent depression (two men, seven women; mean age = 69.7 years, SD = 5.0); and 10 age-matched healthy subjects (four men, six women; mean age = 69.8 years, SD = 5.0). Partial-volume correction of regional specific binding estimates was performed by using a method based on magnetic resonance imaging. **RESULTS:** No significant abnormalities in [18F]altanserin binding (binding potential) were observed in the patients with late-life depression, and no effect of depression on binding potential was present within the Alzheimer's disease group. However, the patients with Alzheimer's disease had significantly lower binding than the normal subjects in several brain regions, including the anterior cingulate, prefrontal cortex, and sensorimotor cortex. **CONCLUSIONS:** These results suggest that the 5-HT<sub>2A</sub> receptor is differentially affected in late-life depression and Alzheimer's disease, a finding that has implications for the etiological basis of mood and cognitive features of neuropsychiatric disorders of late life.

## ~4 Citings

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### 68. Effects of chronic antidepressant treatments on serotonin transporter function, density, and mRNA level

By Benmansour S; Cecchi M; Morilak D A; Gerhardt G A; Javors M A; Gould G G; Frazer A

From The Journal of neuroscience : the official journal of the Society for Neuroscience (1999), 19(23), 10494-501, English, Database: MEDLINE

To investigate functional changes in the brain serotonin transporter (SERT) after chronic antidepressant treatment, several techniques were used to assess SERT activity, density, or its mRNA content. Rats were treated by osmotic minipump for 21 d with the selective serotonin reuptake inhibitors (SSRIs) paroxetine or sertraline, the selective norepinephrine reuptake inhibitor desipramine (DMI), or the monoamine oxidase inhibitor phenelzine. High-speed in vivo electrochemical recordings were used to assess the ability of the SSRI fluvoxamine to modulate the clearance of locally applied serotonin in the CA3 region of hippocampus in drug- or vehicle-treated rats. Fluvoxamine decreased the clearance of serotonin in rats treated with vehicle, DMI, or phenelzine but had no effect on the clearance of serotonin in SSRI-treated rats. SERT density in the CA3 region of the hippocampus of the same rats, assessed by quantitative autoradiography with tritiated cyanoimipramine ([<sup>3</sup>H]CN-IMI), was decreased by 80-90% in SSRI-treated rats but not in those treated with phenelzine or DMI. The serotonin content of the hippocampus was unaffected by paroxetine or sertraline treatment, ruling out neurotoxicity as a possible explanation for the SSRI-induced decrease in SERT binding and alteration in 5-HT clearance. Levels of mRNA for the SERT in the raphe nucleus were also unaltered by chronic paroxetine treatment. Based on these results, it appears that the SERT is downregulated by chronic administration of SSRIs but not other types of antidepressants; furthermore, the downregulation is not caused by decreases in SERT gene expression.

#### ~18 Citings

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### 69. Activation and desensitization by cyclic antidepressant drugs of alpha2-autoreceptors, alpha2-heteroreceptors and 5-HT1A-autoreceptors regulating monamine synthesis in the rat brain in vivo

By Esteban S; Llado J; Sastre-Coll A; Garcia-Sevilla J A

From Naunyn-Schmiedeberg's archives of pharmacology (1999), 360(2), 135-43, English, Database: MEDLINE

The effects of antidepressant drugs on the synthesis of noradrenaline and serotonin (5-HT) were assessed using the accumulation of 3,4-dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) after decarboxylase inhibition as a measure of the rate of tyrosine and tryptophan hydroxylation in the rat brain in vivo. Three inhibitory synthesis-modulating receptors were investigated simultaneously: the alpha2C-autoreceptor modulating dopa/noradrenaline synthesis, and the alpha2A-heteroreceptor and 5-HT1A-autoreceptor modulating 5-HTP/5-HT synthesis. Acute treatment (2 h, i.p.) with desipramine (1-10 mg/kg), protriptyline (0.3-10 mg/kg) and nisoxetine (3-10 mg/kg), selective NA reuptake blockers, dose-dependently decreased dopa synthesis in cortex (15%-40%) and hippocampus (20%-53%). Fluoxetine (1-10 mg/kg) and zimelidine (1-10 mg/kg), selective 5-HT reuptake blockers, did not alter dopa synthesis. Fluoxetine and zimelidine dose-dependently decreased 5-HTP synthesis in cortex (14%-43%) and hippocampus (27%-54%). Desipramine and protriptyline did not alter 5-HTP synthesis in cortex but in hippocampus it was decreased (36%). Repeated desipramine (10 mg/kg for 1-21 days) or fluoxetine (3 mg/kg for 3-21 days) treatment resulted in a time-dependent loss in their ability to decrease dopa or 5-HTP synthesis. Desipramine (1-21 days) did not alter 5-HTP synthesis in cortex, but in hippocampus it was decreased (21%-37%, days 1-14) followed by recovery to control values (day 21). Fluoxetine (3-21 days) did not alter brain dopa synthesis. To further assess the desensitization of alpha2C-autoreceptors, alpha2A-heteroreceptors and 5-HT1A autoreceptors regulating the synthesis of dopa/NA or 5-HTP/5-HT after chronic desipramine and fluoxetine, the effects of clonidine (agonist at alpha2-auto/heteroreceptors) and 8-OH-DPAT (agonist at 5-HT1A-autoreceptors) were tested. In saline-treated rats, clonidine (1 mg/kg, 1 h) decreased dopa and 5-HTP synthesis in cortex (58% and 54%) and hippocampus (54% and 42%). In desipramine-treated rats (10 mg/kg, 21 days), but not in fluoxetine-treated ones (3 mg/kg, 14 days), the effect of clonidine was attenuated in cortex (12% and 18%) and only for dopa synthesis in hippocampus (31%). In saline-treated rats, 8-OH-DPAT (1 mg/kg, 1 h) decreased 5-HTP synthesis in cortex (63%) and hippocampus (75%). In fluoxetine-treated rats, but not in desipramine-treated ones, this inhibitory effect was markedly attenuated in cortex (26%) and hippocampus (9%). These findings indicate that acute treatment with cyclic antidepressant drugs results in activation of inhibitory alpha2C-autoreceptors, alpha2A-heteroreceptors and/or 5-HT1A-autoreceptors regulating the synthesis of dopa/NA and/or 5-HTP/5-HT in brain, whereas chronic treatment with these drugs is followed by desensitization of these presynaptic receptors.

#### ~4 Citings

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### 70. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone

By Yatham L N; Liddle P F; Dennie J; Shiah I S; Adam M J; Lane C J; Lam R W; Ruth T J

From Archives of general psychiatry (1999), 56(8), 705-11, English, Database: MEDLINE

**BACKGROUND:** The neuroreceptor changes involved in therapeutic efficacy of various antidepressants remain unclear. Preclinical studies have shown that long-term administration of various antidepressants causes down-regulation of brain serotonin 2 (5-HT<sub>2</sub>) receptors in rodents, but it is unknown if similar changes occur following antidepressant treatment in depressed patients. Our purpose, therefore, was to assess the effects of treatment with desipramine hydrochloride on brain 5-HT<sub>2</sub> receptors in depressed patients using positron emission tomography (PET) and fluorine-18 (18F)-labeled setoperone. **METHODS:** Eleven patients who met DSM-IV criteria for major depression as determined by a structured clinical interview for DSM-III-R diagnosis and suitable for treatment with desipramine were recruited. Ten patients underwent a PET scan before and another after 3 to 4 weeks of treatment with desipramine. **RESULTS:** Eight of the 10 patients responded to desipramine treatment as indicated by more than 50% decrease in Hamilton Depression Rating Scale scores. Depressed patients showed a significant decrease in 5-HT<sub>2</sub> receptor binding as measured by setoperone binding in frontal, temporal, parietal, and occipital cortical regions following desipramine treatment. The decrease in 5-HT<sub>2</sub> receptor binding was observed bilaterally and was particularly prominent in frontal cortex. **CONCLUSIONS:** Depressed patients showed a significant reduction in available 5-HT<sub>2</sub> receptors in the brain following desipramine treatment, but it is unknown if this change in 5-HT<sub>2</sub> receptors is due to clinical improvement or an effect of desipramine that is unrelated to clinical status.

## ~11 Citings

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### **71. The effects of single dose nefazodone and paroxetine upon 5-HT<sub>2A</sub> binding potential in humans using [18F]-setoperone PET**

By Meyer J H; Cho R; Kennedy S; Kapur S  
From Psychopharmacology (1999), 144(3), 279-81, English, Database: MEDLINE

**RATIONALE:** Alterations in 5-HT<sub>2A</sub> receptor binding are implicated in suicidality and depression. 5-HT<sub>2A</sub> receptors may also be involved in the therapeutic effects of antidepressants. **OBJECTIVES:** The purpose of this study was to assess the effect of paroxetine and nefazodone on 5-HT<sub>2A</sub> receptors after a single dose. **METHODS:** Seven subjects received a single dose of nefazodone 200 mg and five subjects received a single dose of paroxetine 20 mg. Before and after the dose, 5-HT<sub>2A</sub> binding potentials (B<sub>max</sub>/K<sub>d</sub>) were determined in each subject using [18F]-setoperone PET. **RESULTS:** Nefazodone induced a significant change in 5-HT<sub>2A</sub> binding potential (-39±17%, P = 0.003) while paroxetine showed no significant alteration of 5-HT<sub>2A</sub> binding potential (+3±13%, P = 0.73). **CONCLUSIONS:** The change in 5-HT<sub>2A</sub> binding potential seen with nefazodone represents blockade of 5-HT<sub>2A</sub> receptors by the drug. We do not find evidence for acute downregulation of 5-HT<sub>2A</sub> receptors with paroxetine within 9 h.

## ~2 Citings

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### **72. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders**

By Blier P; de Montigny C  
From Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology (1999), 21(2 Suppl), 91S-98S, English, Database: MEDLINE

The therapeutic effectiveness of antidepressant drugs in major depression was discovered by pure serendipity. It took over 20 years before the neurobiological modifications that could mediate the antidepressive response were put into evidence. Indeed, whereas the immediate biochemical effects of these drugs had been well documented, their antidepressant action generally does not become apparent before 2 to 3 weeks of treatment. The different classes of antidepressant treatments were subsequently shown to enhance serotonin neurotransmission albeit via different pre- and postsynaptic mechanisms. Clinical trials based on this hypothesis led to the development of treatment strategies producing greater efficacy and more rapid onset of antidepressant action; that, is lithium addition and pindolol combination, respectively. It is expected that the better understanding recently obtained of the mechanism of action of certain antidepressant drugs in obsessive-compulsive and panic disorders will also lead to more effective treatment strategies for those disorders.

## ~11 Citings

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### **73. Serotonergic hyperinnervation of the frontal cortex in an animal model of depression, the bulbectomized rat**

By Zhou D; Grecksch G; Becker A; Frank C; Pilz J; Huether G  
From Journal of neuroscience research (1998), 54(1), 109-16, English, Database: MEDLINE

We studied the influence of olfactory bulbectomy in rats on three different parameters of serotonin (5-HT) presynapses, 5-HT transporter density, tryptophan hydroxylase apoenzyme concentration, and the levels of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) in various brain regions. Compared with sham-operated controls, the Bmax values of [3H]paroxetine binding, the apoenzyme concentration of tryptophan hydroxylase and the level of 5-HIAA, and, therefore, the 5-HIAA/5-HT ratio were significantly and selectively increased in the frontal cortex of bulbectomized rats, measured 12 weeks after surgery. The most likely explanation of the concomitant increase in levels of all three markers of 5-HT presynapses in the frontal cortex is an increased density of 5-HT innervation in this remote projection field of the raphe nuclei. It is suggested that the bulbectomy-associated axotomy of 5-HT fibers projecting to the bulb stimulates collateral sprouting and synaptogenesis, especially in the frontal cortex. The resulting 5-HT hyperinnervation must be expected to alter global neuronal activity in this region and to impair the balance of information flow between this and other brain regions, resulting in a multitude of secondary behavioral and neurochemical changes. The frontocortical abnormalities observed by brain imaging studies in the brains of depressed patients may also be explained by a selective 5-HT hyperinnervation of this brain region.

### ~3 Citings

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#### 74. Serotonin 5-HT<sub>2</sub> receptor imaging in major depression: focal changes in orbito-insular cortex

By Biver F; Wikler D; Lotstra F; Damhaut P; Goldman S; Mendlewicz J

From The British journal of psychiatry : the journal of mental science (1997), 171:444-8, English, Database: MEDLINE

**BACKGROUND:** Serotonin receptors may play an important role in the pathophysiology of affective disorders. We studied type-2 serotonin (5-HT<sub>2</sub>) receptors in the brain of patients with major depression. **METHOD:** Using positron emission tomography (PET) and the selective radioligand [18F]altanserin, we investigated 5-HT<sub>2</sub> receptor distribution in eight drug-free unipolar depressed patients and 22 healthy subjects. Data were analysed using Statistical Parametric Mapping 95. **RESULTS:** In depressed patients, [18F]altanserin uptake was significantly reduced in a region of the right hemisphere including the posterolateral orbitofrontal cortex and the anterior insular cortex. A trend to similar changes was found in the left hemisphere. No correlation was found between the uptake and the Hamilton rating scale score. **CONCLUSIONS:** Pathophysiology of depression may involve changes in 5-HT<sub>2</sub> receptor in brain regions selectively implicated in mood regulation.

### ~4 Citings

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#### 75. Influence of olfactory bulbectomy and subsequent imipramine treatment on 5-hydroxytryptaminergic presynapses in the rat frontal cortex: behavioural correlates

By Grecksch G; Zhou D; Franke C; Schroder U; Sabel B; Becker A; Huether G

From British journal of pharmacology (1997), 122(8), 1725-31, English, Database: MEDLINE

1. Alterations of 5-hydroxytryptaminergic mechanisms are thought to play a special role in the pathogenesis of depression and antidepressant treatments are assumed to restore these changes. 2. We have used one of the most reliable models of depression, the olfactory bulbectomized rat to study the long term consequences of this manipulation and of subchronic imipramine treatment on two parameters of 5-hydroxytryptaminergic presynapses, 5-hydroxytryptamine (5-HT) transporter density and tryptophan hydroxylase apoenzyme concentration, in the frontal cortex as well as on active avoidance learning several weeks after bulbectomy. 3. The Bmax value of [3H]-paroxetine binding and the concentration of the 5-HT synthesizing enzyme were both significantly elevated in the frontal cortex of bulbectomized rats compared to sham-operated controls. 4. Imipramine treatment, either by daily injections or by subcutaneous implantation of slow release imipramine-containing polymers reduced the elevated tryptophan hydroxylase apoenzyme levels in the frontal cortex of bulbectomized, but not of sham-operated control rats and restored the deficient learning performance of bulbectomized rats. 5. Both effects were more pronounced after continuous drug administration by imipramine-releasing polymers compared to daily i.p. injections. 6. These findings indicate that bulbectomy leads to a compensatory 5-hydroxytryptaminergic hyperinnervation of the frontal cortex. Chronic antidepressant treatment seems to attenuate the increased output of the 5-hydroxytryptaminergic projections in the frontal cortex through the destabilization of the rate limiting enzyme of 5-HT synthesis of the 5-hydroxytryptaminergic nerve endings in this brain region.

### ~1 Citing

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#### 76. The olfactory bulbectomized rat as a model of depression: an update

By Kelly J P; Wrynn A S; Leonard B E

From Pharmacology & therapeutics (1997), 74(3), 299-316, English, Database: MEDLINE

The olfactory bulbectomized (OB) rat has been proposed as an animal model of depression. The following behavioural changes have been observed following bilateral olfactory bulbectomy: hyperactivity in an enclosed arena, such as the open-field; enhanced nocturnal hyperactivity in a 24-hr home cage activity monitor; deficits in memory, as shown by passive avoidance behaviour and in the Morris maze and the 8-arm radial maze; increased open arm entries in the elevated plus-maze; and changes in food motivated and conditioned taste aversion behaviour. Alterations in the noradrenergic, serotonergic, cholinergic, gamma-aminobutyric acid (GABA)ergic and glutamatergic neurotransmitter systems are also associated with olfactory bulbectomy. The variety of immune changes following olfactory bulbectomy includes reduced neutrophil phagocytosis, lymphocyte mitogenesis, lymphocyte number and negative acute phase proteins, increased leucocyte adhesiveness/aggregation, monocyte phagocytosis, neutrophil number and positive acute phase proteins. An enhanced nocturnal secretion of corticosterone is observed in OB rats, which is normally suppressed by dexamethasone. The most commonly employed behavioural indicator of antidepressant activity is attenuation of the OB-related hyperactivity in the open-field. However, many of the other behavioural, neurotransmitter and immune changes have been shown to be attenuated by chronic (but not acute) antidepressant treatment. Tricyclic antidepressants (amitriptyline, desipramine), atypical agents (mianserin), selective serotonin reuptake inhibitors (paroxetine, sertraline, fluvoxamine), reversible inhibitors of monoamine oxidase A (moclobemide), as well as putative antidepressants such as 5-hydroxytryptamine<sub>1A</sub> agonists (zalospirone, ipsapirone), noncompetitive N-methyl-D-aspartate antagonists (MK-801) and triazolobenzodiazepines (alprazolam, adinazolam), have demonstrated antidepressant-like activity in this model. As many of the changes exhibited by the OB rat are qualitatively similar to those observed in depressed patients, it may be concluded that the OB rat is a model of depression and not just a means whereby putative antidepressants may be tested.

#### ~16 Citings

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### 77. The functional neuroanatomy of mood disorders

By Soares J C; Mann J J

From Journal of psychiatric research (1997), 31(4), 393-432, English, Database: MEDLINE

Mood disorders may be associated with global and regional changes in cerebral blood flow and metabolism. The accumulated functional neuroimaging findings in mood disorders were reviewed in order to examine a proposed neuroanatomic model of pathophysiology. Global cerebral blood flow and glucose metabolism appear normal, but may be decreased in late-life depression. Regional cerebral blood flow and glucose metabolism deficits are present, and may be indicators of brain regions participating in neuroanatomic circuits involved in mood disorders. Decreased pre-frontal cortex blood flow and metabolism in depressed unipolar and bipolar patients are the most consistently replicated findings, and correlate with severity of illness. Basal ganglia abnormalities have been found in depressed unipolar and bipolar patients, involving decreased blood flow and metabolism. Temporal lobe abnormalities are present in bipolar disorder patients, and perhaps unipolar depression. There is conflicting evidence of abnormalities in other limbic regions. Cognitive impairment may correlate with decreased metabolism in frontal and cerebellar areas. The relationship between functional neuroimaging findings and clinical course, and therefore state and trait characteristics, has not been systematically investigated. Antidepressant medications, but not ECT, seem to reverse some of the identified functional brain changes in the depressed state. The structural, neurotransmitter and neuropathological correlates of these functional abnormalities are yet to be determined. Functional abnormalities in frontal, subcortical and limbic structures appear to be part of the pathophysiology of mood disorders.

#### ~19 Citings

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### 78. Effects of chronic treatment with fluoxetine and citalopram on 5-HT uptake, 5-HT<sub>1B</sub> autoreceptors, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in rats

By Gobbi M; Crespi D; Foddi M C; Fracasso C; Mancini L; Parotti L; Mennini T

From Naunyn-Schmiedeberg's archives of pharmacology (1997), 356(1), 22-8, English, Database: MEDLINE

The effect in rats of chronic treatment with two specific 5-HT reuptake inhibitors (SSRI) with antidepressant properties, citalopram (10 mg/kg, i.p. twice a day for 14 days, one day washout) and fluoxetine (15 mg/kg, p.o. twice a day for 21 days, 7 days washout), was evaluated on some mechanisms involved in central 5-HT neurotransmission. No adaptive modifications of brain 5-HT uptake (sites) were found by measuring functional [3H]5-HT uptake and [3H]citalopram binding in cortical and hippocampal synaptosomes, and by [3H]citalopram binding autoradiography in the raphe nuclei (5-HT cell bodies) and the ventral tegmental area (5-HT axonal pathway). Chronic treatments had no effect on presynaptic 5-HT<sub>1B</sub> autoreceptors, functionally evaluated by measuring 5-HT<sub>1B</sub>-mediated inhibition of depolarization-induced [3H]5-HT release from cortical and hippocampal synaptosomes. Chronic citalopram or fluoxetine did not significantly affect the binding of [3H]BRL-43694 to 5-HT<sub>3</sub> receptors in the rat brain cortex. Citalopram had no effect on [125I]SB-207710 binding to 5-HT<sub>4</sub> receptors, measured by autoradiography in the substantia nigra. Negative results, such as those reported in the present study, could be due to a number of variables including the animal species, the treatment schedule or the brain areas considered, thus explaining the differences from some previous reports of significant effects of SSRI. However, our negative data are in agreement with many other published studies, suggesting that adaptive modifications of brain 5-HT transporters, terminal 5-HT<sub>1B</sub> receptors, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors may not be a general effect induced by all SSRI.

## ~1 Citing

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### **79. Chronic fluoxetine reduces serotonin transporter mRNA and 5-HT<sub>1B</sub> mRNA in a sequential manner in the rat dorsal raphe nucleus**

By Neumaier J F; Root D C; Hamblin M W

From Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology (1996), 15(5), 515-22, English, Database: MEDLINE

In major depression in humans and in animal models of depression, there is a defect in serotonergic neurotransmission that can be relieved by chronic antidepressant treatment. One possibility is that this pathologic state is caused by excessive presynaptic autoreceptor activity in serotonergic neurons, and that antidepressants down-regulate the number of these inhibitory receptors, allowing more normal serotonin release to occur. To evaluate this hypothesis, we measured the effects of the antidepressant fluoxetine on neuronal levels of 5-HT<sub>1B</sub> receptor mRNA, the putative serotonin terminal autoreceptor in rat brain, and on serotonin transporter mRNA, the direct site of fluoxetine binding. Fluoxetine reduced serotonin transporter mRNA briefly, but this was not sustained after 21 days of treatment. However, fluoxetine reduced dorsal raphe 5-HT<sub>1B</sub> mRNA levels in a time-dependent and washout-reversible manner. This reduction in 5-HT<sub>1B</sub> mRNA was specific to dorsal raphe nucleus and was not found in several postsynaptic (nonserotonergic) regions. These results suggest that chronic fluoxetine may increase serotonin release from axonal terminals by down-regulating the messenger RNA coding for presynaptic 5-HT<sub>1B</sub> autoreceptors while causing only transient effects on serotonin transporter mRNA.

## ~6 Citings

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### **80. Downregulation of muscarinic- and 5-HT<sub>1B</sub>-mediated modulation of [3H]acetylcholine release in hippocampal slices of rats with fimbria-fornix lesions and intrahippocampal grafts of septal origin**

By Cassel J C; Jeltsch H; Neufang B; Lauth D; Szabo B; Jackisch R

From Brain research (1995), 704(2), 153-66, English, Database: MEDLINE

Adult Long-Evans female rats sustained electrolytic fimbria-fornix lesions and, two weeks later, received intrahippocampal suspension grafts of fetal septal tissue. Sham-operated and lesion-only rats served as controls. Between 6.5 and 8 months after grafting, both the [3H]choline accumulation and the electrically evoked [3H]acetylcholine ([3H]ACh) release were assessed in hippocampal slices. The release of [3H]ACh was measured in presence of atropine (muscarinic antagonist, 1 microM), physostigmine (acetylcholinesterase inhibitor, 0.1 microM), oxotremorine (muscarinic agonist, 0.01 microM-10 microM), mecamylamine (nicotinic antagonist, 10 microM), methiothepin (mixed 5-HT1/5-HT2 antagonist, 10 microM), 8-OH-DPAT (5-HT1A agonist, 1 microM), 2-methyl-serotonin (5-HT3 agonist, 1 microM) and CP 93129 (5-HT1B agonist, 0.1 microM-100 microM), or without any drug application as a control. In lesion-only rats, the specific accumulation of [3H]choline was reduced to 46% of normal and the release of [3H]ACh to 32% (nCi) and 43% (% of tissue tritium content). In the grafted rats, these parameters were significantly increased to 63%, 98% and 116% of control, respectively. Physostigmine reduced the evoked [3H]ACh release and was significantly more effective in grafted (-70%) than in sham-operated (-56%) or lesion-only (-54%) rats. When physostigmine was superfused throughout, mecamylamine had no effect. Conversely, atropine induced a significant increase of [3H]ACh release in all groups, but this increase was significantly larger in sham-operated rats (+209%) than in the other groups (lesioned: +80%; grafted: +117%). Oxotremorine dose-dependently decreased the [3H]ACh release, but in lesion-only rats, this effect was significantly lower than in sham-operated rats. Whatever group was considered, 8-OH-DPAT, methiothepin and 2-methyl-serotonin failed to induce any significant effect on [3H]ACh release. In contrast, CP 93129 dose-dependently decreased [3H]ACh release. This effect was significantly weaker in grafted rats than in the rats of the two other groups. Our data confirm that cholinergic terminals in the intact hippocampus possess inhibitory muscarinic autoreceptors and serotonin heteroreceptors of the 5-HT1B subtype. They also show that both types of receptors are still operative in the cholinergic terminals which survived the lesions and in the grafted cholinergic neurons. However, the muscarinic receptors in both lesioned and grafted rats, as well as the 5-HT1B receptors in grafted rats show a sensitivity which seems to be downregulated in comparison to that found in sham-operated rats. In the grafted rats, both types of downregulations might contribute to (or reflect) an increased cholinergic function that results from a reduction of the inhibitory tonus which ACh and serotonin exert at the level of the cholinergic terminal.

### ~3 Citings

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#### **81. Interleukin-2-induced changes in behavioural, neurotransmitter, and immunological parameters in the olfactory bulbectomized rat**

By Song C; Leonard B E

From Neuroimmunomodulation (1995), 2(5), 263-73, English, Database: MEDLINE

The macrophage theory of depression proposes that abnormal secretions of the macrophage cytokines, an increase in interleukin (IL) 1, and a decrease in IL-2 may cause depression. The olfactory bulbectomized (OB) rat has been developed as an animal model of depression. In the present study, the effects of intracerebroventricular administration of IL-2 (10 U) for 7 days on behaviour, neurotransmitter concentrations, corticosterone levels, and some immune functions were investigated. In the novel environment of the 'open-field' apparatus, the OB rat showed increases in ambulation, rearing, grooming, and defaecation scores as compared with sham-operated animals. Following IL-2 administration, grooming and defaecation were significantly attenuated, while the ambulation and rearing scores were unaffected. In the elevated plus-maze, the increase in the time spent on the open arms of the maze by the OB animal was normalized by IL-2 administration. In the brain of untreated OB rats, the concentrations of noradrenaline were reduced; IL-2 treatment significantly increased the concentrations of noradrenaline and serotonin. After administration of IL-2 for 7 days, the impairments in the immune functions were also largely reversed in OB rats. Thus IL-2 significantly normalized the hyperactivity of mononuclear cells, the suppression of lymphocyte proliferation, and the reduction in the monocyte percentage in the white blood cell count in the OB rat. The concentrations of corticosterone in the serum of the OB rat were significantly reduced, but returned to control values following IL-2 treatment. The results suggest that IL-2 may have modulatory functions on behavioural, neurochemical, hormonal, and immunological aspects of the OB rat model of depression.

### ~0 Citings

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#### **82. The effect of paroxetine on 5-HT efflux in the rat dorsal raphe nucleus is potentiated by both 5-HT1A and 5-HT1B/D receptor antagonists**

By Davidson C; Stamford J A

From Neuroscience letters (1995), 188(1), 41-4, English, Database: MEDLINE

Serotonin (5-HT) efflux in slices of rat dorsal raphe nucleus (DRN) was evoked by pseudo one pulse electrical stimulation (20 pulses at 100 Hz, 190 ms train duration) and measured, along with 5-HT uptake, by fast cyclic voltammetry (FCV). The selective serotonin re-uptake inhibitor (SSRI) paroxetine (10(-7) M) increased 5-HT efflux to 147 +/- 6% of pre-drug values at maximum (mean +/- SEM, n = 5) and the half-life of uptake to 443 +/- 38%. The non-selective 5-HT1 antagonist methiothepin (2 x 10(-7) M) increased 5-HT efflux to 147 +/- 9% at maximum but had no effect on uptake half-life. In contrast, (+)-WAY 100135 (10(-6) M) and GR 127935 (5 x 10(-8) M), selective antagonists at 5-HT1A and 5-HT1B/D receptors, respectively, affected neither 5-HT efflux nor uptake. When given in combination with paroxetine, the antagonists significantly increased the effect of paroxetine on efflux: methiothepin to 228 +/- 24% (P < 0.001), (+)-WAY 100135 to 212 +/- 31% (P < 0.05) and GR 127935 to 203 +/- 23% (P < 0.01). These data suggest that, under these experimental conditions, DRN 5-HT autoreceptors are tonically activated in the presence of the uptake blocker and that the antagonists act by blocking this counteracting autoinhibitory tone. The data also strongly indicate that 5-HT efflux in the rat DRN is under the control not only of 5-HT1A but also of 5-HT1B/D receptors.

## ~1 Citing

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### 83. Enhanced aggressive behavior in mice lacking 5-HT1B receptor

By Saudou F; Amara D A; Dierich A; LeMeur M; Ramboz S; Segu L; Buhot M C; Hen R  
From Science (New York, N.Y.) (1994), 265(5180), 1875-8, English, Database: MEDLINE

The neuromodulator serotonin (5-hydroxytryptamine, 5-HT) has been associated with mood disorders such as depression, anxiety, and impulsive violence. To define the contribution of 5-HT receptor subtypes to behavior, mutant mice lacking the 5-HT1B receptor were generated by homologous recombination. These mice did not exhibit any obvious developmental or behavioral defects. However, the hyperlocomotor effect of the 5-HT1A/1B agonist RU24969 was absent in mutant mice, indicating that this effect is mediated by 5-HT1B receptors. Moreover, when confronted with an intruder, mutant mice attacked the intruder faster and more intensely than did wild-type mice, suggesting the participation of 5-HT1B receptors in aggressive behavior.

## ~31 Citings

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### 84. Antidepressant-like behavioral effects of serotonin receptor agonists

By Lucki I; Singh A; Kreiss D S  
From Neuroscience and biobehavioral reviews (1994), 18(1), 85-95, English, Database: MEDLINE

The clinical discoveries that drugs that stimulate 5-HT neurotransmission, either by inhibiting 5-HT uptake or by stimulating postsynaptic receptors directly, have antidepressant properties has stimulated interest in defining the role of the 5-HT receptor system in the clinical effects of antidepressant drugs. Two approaches are reviewed in this paper that address the neurochemical mediation of the therapeutic effects of antidepressant drugs from the standpoint of animal behavior. The first approach utilizes a behavioral response in rats, the forced swimming test, that correlates well with predicting antidepressant drugs in humans. Studies are reviewed that examined serotonergic compounds in the forced swimming test, from the standpoint of identifying better serotonergic mechanisms involved in the antidepressant response. Both 5-HT uptake inhibitors and 5-HT1A receptor agonists produce effects in the forced swimming test that are similar to those of other classes of antidepressant drugs. In contrast, agonists at other 5-HT receptors or 5-HT receptor antagonists do not produce antidepressant-like behavioral effects. Evidence for an important role of 5-HT1A receptors in the antidepressant response is supported by findings that antagonists of 5HT1A receptors prevent the ability of 5-HT1A receptor agonists to reduce immobility in the forced swimming test. The results of studies interfering with 5-HT neurotransmission, either by inhibition of 5-HT synthesis or by the destruction of 5-HT neurons, favor the idea that the effects of 5-HT1A receptor agonists are produced by the stimulation of postsynaptic 5-HT1A receptors. The second approach for studying the behavioral effects of antidepressant drugs employs drug discrimination studies, conducted using a discriminated taste aversion procedure, to provide a method for studying the discriminative stimulus effects of the antidepressant 5-HT uptake inhibitor sertraline. Rats were trained to discriminate the effects of sertraline (10 mg/kg) from saline. Other 5-HT uptake inhibitors, such as fluoxetine, fluvoxamine and paroxetine, substituted for the sertraline stimulus. High doses of norepinephrine uptake inhibitors, such as desipramine or maprotiline, were required to produce similar effects. These two behavioral approaches promise to be useful for defining the important pharmacological effects associated with the behavioral effects of antidepressant drugs.

## ~5 Citings

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**85. Central pre- and postsynaptic 5-HT1A receptors in rats treated chronically with a novel antidepressant, cericlamine**

By Jolas T; Haj-Dahmane S; Kidd E J; Langlois X; Lanfumey L; Fattaccini C M; Vantalon V; Laporte A M; Adrien J; Gozlan H; et al  
From The Journal of pharmacology and experimental therapeutics (1994), 268(3), 1432-43, English, Database: MEDLINE

Biochemical and electrophysiological approaches were used to assess the possible changes in 5-hydroxytryptamine (serotonin) 5-HT1A receptors in the rat brain after a long-term treatment with cericlamine [2-(3,4-dichlorobenzyl)-2-dimethylamino-1-propanol], a novel serotonin reuptake inhibitor with antidepressant properties. Possible changes in other serotonin receptor binding sites (5-HT2A, 5-HT2C and 5-HT3) were also investigated after this treatment. Cericlamine was injected for 2 weeks at a dose (16 mg/kg i.p., twice daily) that ensured complete prevention of 4-methyl-alpha-ethyl-meta-tyramine-induced depletion of brain serotonin. In vitro binding and quantitative autoradiographic studies showed that neither 5-HT1A, 5-HT2A, 5-HT2C nor 5-HT3 receptor binding sites in various brain areas were affected by the 14-day treatment with cericlamine. Although forskolin-stimulated adenylate cyclase activity was significantly increased in hippocampal homogenates from cericlamine-treated rats, the reduction in this enzymatic activity due to 5-HT1A receptor stimulation by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) was unchanged in these animals as compared with controls. In contrast, in vitro and in vivo electrophysiological recordings of serotonergic neurons in the dorsal raphe nucleus revealed a clearcut functional desensitization of somatodendritic 5-HT1A autoreceptors. Thus the potency of 8-OH-DPAT and ipsapirone to depress the firing rate of these neurons in brain stem slices was significantly reduced after the 2-week treatment with cericlamine. In vivo, the potency of an injection of cericlamine to inhibit the discharge of serotonergic neurons was also markedly less in rats that had been pretreated for 2 weeks with this drug as compared with controls. However, the inhibitory effects of systemically injected 8-OH-DPAT and ipsapirone on the electrical activity of serotonergic neurons were as pronounced in cericlamine-treated rats as in controls. In addition, the reduction in serotonin synthesis due to an acute treatment with 8-OH-DPAT (0.1 or 0.3 mg/kg s.c.) was not significantly different in both groups of rats. These data support the idea that postsynaptic (in the hippocampus) and somatodendritic (in the dorsal raphe nucleus) 5-HT1A receptors are differently regulated in the rat brain, because only the latter receptors desensitized after a long-term blockade of serotonin reuptake by cericlamine. They also suggest that the inhibitory influence of systemically administered direct 5-HT1A agonists such as 8-OH-DPAT and ipsapirone on the electrical and metabolic activity of serotonergic neurons does not result solely from the stimulation of somatodendritic 5-HT1A autoreceptors.

**~4 Citings**

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**86. Excitation of noradrenergic cell firing by 5-hydroxytryptamine1A agonists correlates with dopamine antagonist properties**

By Piercey M F; Smith M W; Lum-Ragan J T  
From The Journal of pharmacology and experimental therapeutics (1994), 268(3), 1297-303, English, Database: MEDLINE

The 5-HT1A receptor agonists buspirone, 8-hydroxy-N,N-dipropyl-2-aminotetralin, gepirone and ipsapirone were evaluated for their receptor binding profiles and their effects on firing rates of 5-HT, dopamine (DA) and noradrenaline (NA) neurons in the dorsal raphe, substantia nigra pars compacta and the locus ceruleus, respectively. All agents bound to 5-HT1A receptors with high affinities. All agents also bound to dopamine D2 receptors but, with the exception of buspirone, affinities were usually much lower than for 5-HT1A receptors. All agents depressed 5-HT neurons, with 8-hydroxy-N,N-dipropyl-2-aminotetralin having a potency about 8 to 12 times those for the other three. All agents also antagonized the inhibition of DA neurons by amphetamine, an index of DA antagonist properties. Buspirone reversed amphetamine's effects with doses similar to those for depressing 5-HT neurons, but the remaining three required much higher doses to affect DA neuron function. All four 5-HT1A agonists excited NA neurons. In each case, doses required for excitation of NA cells were similar to those reversing amphetamine's effects on DA cells, but not to those for depressing 5-HT cells. Haloperidol also stimulated NA cells. It is concluded that excitation of NA neurons by 5-HT1A agonists may be due to interactions with dopaminergic, rather than serotonergic, receptors.

**~1 Citing**

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**87. Long-lasting enhancement of NMDA receptor-mediated synaptic transmission by metabotropic glutamate receptor activation**

By O'Connor J J; Rowan M J; Anwyl R  
From Nature (1994), 367(6463), 557-9, English, Database: MEDLINE

Synaptic transmission mediated by the N-methyl-D-aspartate (NMDA) glutamate receptor plays a key role in a range of plastic processes in the nervous system. These include long-term potentiation of synaptic transmission mediated by the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor, neuronal development, excitotoxicity and certain learning tasks. Recently, long-term potentiation of NMDA receptor-mediated synaptic transmission was found to occur following high-frequency (tetanic) stimulation via an unknown mechanism. We show here that activation of metabotropic glutamate (mGlu) receptors by neurally released transmitter underlies this type of long-term potentiation. The whole-cell patch-clamp technique in the 'thick' slice of the rat dentate gyrus was used to measure NMDA receptor-mediated excitatory postsynaptic currents. We have found that mGlu receptor activation by a selective agonist produced a long-lasting enhancement which was mutually exclusive with long-term potentiation of these NMDA currents. Moreover, both forms of potentiation were greatly reduced by the mGlu receptor antagonists L-2-amino-3-phosphonopropionate and (R,S)-alpha-methyl-4-carboxyphenylglycine.

### ~13 Citings

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## 88. Chronic fluoxetine treatment upregulates 5-HT uptake sites and 5-HT<sub>2</sub> receptors in rat brain: an autoradiographic study

By Hrdina P D; Vu T B

From Synapse (New York, N.Y.) (1993), 14(4), 324-31, English, Database: MEDLINE

This study was undertaken to investigate the effect of chronic treatment with fluoxetine, a selective serotonin uptake inhibitor used widely in the treatment of depression, on the distribution and density of 5-HT uptake sites, 5-HT<sub>2</sub> receptors, and vesicular amine uptake sites in rat brain. Fluoxetine (10 mg/kg i.p.) was administered daily for 21 days. The density of 5-HT uptake sites labelled by [<sup>3</sup>H]paroxetine, 5-HT<sub>2</sub> receptors labelled by [<sup>3</sup>H]ketanserin in presence of tetrabenazine and vesicular amine uptake sites labelled by [<sup>3</sup>H]ketanserin in the presence of mianserin were measured by quantitative autoradiography in 22 areas of rat brain, using coronal tissue sections. Chronic administration of fluoxetine produced significant increases in the density of 5-HT uptake sites in layers of frontoparietal cortex (by 32-43%), of striate cortex (by 55%), in CA1 field of hippocampus (by 111%) and in superior colliculus (by 20%). Fluoxetine treatment also resulted in upregulation of 5-HT<sub>2</sub> receptors in layers of frontoparietal cortex (31-38%) and in CA2-3 fields of hippocampus (by 39%). The density of tetrabenazine-sensitive vesicular amine uptake sites in the caudate-putamen was also significantly increased (by 66%). The observed alterations in 5-HT uptake site and 5-HT<sub>2</sub> receptor densities are likely a part of adaptive neuronal changes that occur after chronic administration of fluoxetine and may be related to the antidepressant effect of the drug.

### ~10 Citings

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## 89. Partial agonists, full agonists, antagonists: dilemmas of definition

By Hoyer D; Boddeke H W

From Trends in pharmacological sciences (1993), 14(7), 270-5, English, Database: MEDLINE

The absence of selective antagonists makes receptor characterization difficult, and largely dependent on the use of agonists. However, there has been considerable debate as to whether certain drugs acting at G protein-coupled receptors are better described as agonists, partial agonists or antagonists. Indeed many agonists tend to display differences in intrinsic activity, depending on the preparation used to study receptor pharmacology. It has been argued that variations in intrinsic activity of drugs, may be a reflection of receptor subtypes rather than varying degrees of receptor-effector coupling. However, it has often been overlooked that classical receptor theory predicts that a drug acting at a given receptor type can display a range of intrinsic activities depending on the extent of receptor reserve. Furthermore, because any receptor can couple to different effector systems, different degrees of intrinsic activity may be observed for a given drug. Daniel Hoyer and Hendrikus Boddeke review recent data which provide explanations for why drugs display such variations in intrinsic activity.

### ~14 Citings

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## 90. From synapse to vesicle: the reuptake and storage of biogenic amine neurotransmitters

By Rudnick G; Clark J

From Biochimica et biophysica acta (1993), 1144(3), 249-63, English, Database: MEDLINE

Biogenic amine transport systems in the presynaptic plasma membrane and the synaptic vesicle provide a mechanism for rapidly terminating the action of released transmitters and for recycling neurotransmitters. Alterations in the activity of these transporters, either by endogenous regulatory mechanisms or by drugs, affect the regulation of synaptic transmitter levels. For drugs such as antidepressants and stimulants that interact with these transport systems, the therapeutic and behavioral consequences are profound. Now that the cDNAs encoding the transporters have been isolated, we can expect rapid progress in understanding how the individual proteins work at the molecular level to couple ion gradients to the reuptake and storage of biogenic amine neurotransmitters.

#### ~27 Citings

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### **91. Differential properties of pre- and postsynaptic 5-hydroxytryptamine<sub>1A</sub> receptors in the dorsal raphe and hippocampus: II. Effect of pertussis and cholera toxins**

By Blier P; Lista A; De Montigny C

From The Journal of pharmacology and experimental therapeutics (1993), 265(1), 16-23, English, Database: MEDLINE

The injection of 1 microgram of pertussis toxin, which inactivates Gi/o proteins, in the rat dorsal raphe nearly abolished the responsiveness of serotonin (5-HT) neurons to microiontophoretic applications of 5-HT and selective 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) without altering their responsiveness to gamma-aminobutyric acid (GABA). In contrast, the injection of 1 microgram of cholera toxin, which causes an activation of Gs proteins, did not alter the responsiveness of 5-HT neurons to 5-HT, 8-OH-DPAT or GABA. Such in situ injection of either toxin in the dorsal hippocampus decreased by about 90% the responsiveness of CA3 pyramidal neurons to microiontophoretic applications onto their cell body of 5-HT and 8-OH-DPAT, but not of GABA. The effectiveness of the stimulation of the ascending 5-HT pathway in suppressing the firing activity of the same neurons, which results from the release of 5-HT at the level of their dendritic tree, was also markedly decreased in the cholera toxin-treated rats, but intriguingly not in the pertussis toxin-treated rats. These results indicate that, on 5-HT neurons, the somato-dendritic 5-HT<sub>1A</sub> autoreceptor is coupled to Gi/o, but insensitive to the persistent activation of Gs proteins. In the CA3 region of the hippocampus, there would be two subsets of postsynaptic 5-HT<sub>1A</sub> receptors on the pyramidal neurons: those apposed to 5-HT terminals on their dendritic tree (denoted intrasynaptic) and those located on their cell body (denoted extrasynaptic). The former are cholera toxin sensitive, whereas the latter are sensitive to both pertussis and cholera toxins.

#### ~4 Citings

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### **92. Olfactory bulbectomy as a model for agitated hyposerotonergic depression**

By Lumia A R; Teicher M H; Salchli F; Ayers E; Possidente B

From Brain research (1992), 587(2), 181-5, English, Database: MEDLINE

Ablation of olfactory bulbs in rats reduced male sexual behavior, and altered the distribution of wheel-running activity between the light and dark phases of a 12:12 LD photoperiod. These effects were partially reversed by the tricyclic antidepressant amitriptyline. Olfactory bulbectomy also altered serotonin metabolism (5-HIAA/5-HT ratio) in the frontal cortex, nucleus accumbens, hippocampus and corpus striatum. These observations support the hypothesis that olfactory bulbectomy in rodents serves as a model of agitated hyposerotonergic depression.

#### ~4 Citings

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### **93. Actions and some interactions of 5-HT<sub>1A</sub> ligands in the elevated X-maze and effects of dorsal raphe lesions**

By Critchley M A; Njung'e K; Handley S L

From Psychopharmacology (1992), 106(4), 484-90, English, Database: MEDLINE

Effects of 5-HT<sub>1A</sub> agonists and partial agonists on open/total arm entry ratio (OTR) have been examined in the elevated X-maze anxiety model. 8-OH-DPAT (0.05-0.2 mg/kg), RU 24969 (0.5-2.0 mg/kg) and BAY R 1521 (0.1-1.2 mg/kg) produced dose-dependent reductions in OTR, signifying anxiogenic effects. Buspirone reduced OTR only at doses (0.25-5.0 mg/kg) decreasing total entries; gepirone (0.1-5.0 mg/kg) was inactive. Ipsapirone (0.25-5.0 mg/kg) increased OTR and at 1.0 mg/kg antagonised the anxiogenic action of 8-OH-DPAT, RU 24969 and BAY R 1531. Gepirone (2.5 mg/kg) failed to antagonise 8-OH-DPAT, but the dose was limited by its effect on total entries. The anxiogenic effect of a low dose of 8-OH-DPAT was also prevented by p-chlorophenylalanine (p-CPA) pretreatment and reversed to anxiolytic by 5,7-dihydroxytryptamine lesions of dorsal raphe, which spared median raphe. These lesions also abolished the anxiolytic effect of ipsapirone without affecting the anxiogenic response to yohimbine. This study provides preliminary evidence that 8-OH-DPAT may be capable of acting as an agonist and ipsapirone as an antagonist at a presynaptic site related to dorsal raphe which is separate from the site of action of yohimbine. 5-HT<sub>1A</sub> agonists and partial agonists may have multiple sites and/or mechanisms of action in the elevated X-maze.

#### ~0 Citings

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### 94. 5-Hydroxytryptamine and its role in migraine

By Lance J W

From European neurology (1991), 31(5), 279-81, English, Database: MEDLINE

Platelet 5-hydroxytryptamine (5-HT) is diminished during migraine headache and the injection of reserpine, which releases 5-HT from body stores, induces a typical headache in migrainous subjects. The intravenous injection of 5-HT relieves established migraine headache, but causes side-effects of nausea, faintness, paraesthesia and dyspnoea. The 5-HT<sub>1</sub>-like agonist sumatriptan exerts the beneficial effects of 5-HT with minimal side-effects. Receptors for 5-HT are present in cranial arteries and are also widely distributed in the central nervous system, where they play a role in the neural control of the cranial circulation and endogenous pain control system. The pathophysiology of migraine involves interaction between these central pathways and cranial blood vessels. It is probable that many prophylactic agents exert their action by central 5-HT<sub>2</sub> antagonism, whereas termination of an established attack of migraine depends upon constriction of cranial vessels mediated by 5-HT<sub>1</sub> receptors.

#### ~6 Citings

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### 95. Serotonin receptors and headache

By Raskin N H

From The New England journal of medicine (1991), 325(5), 353-4, English, Database: MEDLINE

#### ~2 Citings

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### 96. Serotonin uptake and serotonin uptake inhibition

By Fuller R W; Wong D T

From Annals of the New York Academy of Sciences (1990), 60068-78; discussion 79-80, English, Database: MEDLINE

Serotonin uptake carriers occur on serotonin neurons, on glial cells and on blood platelets. The uptake carrier on serotonin neurons inactivates serotonin that has been released into the synaptic cleft by transporting it back into the nerve terminal. The serotonin uptake carrier is the means by which blood platelets acquire serotonin, since they do not synthesize it. The function of the serotonin uptake carrier on glial cells is poorly understood. Selective inhibitors of serotonin uptake enhance neurotransmission via serotonergic neurons and have been useful pharmacologic tools for studying physiologic roles of serotonin neurons. Some serotonin uptake inhibitors are finding therapeutic uses in mental depression and other psychiatric disorders and in treating obesity and bulimia; other therapeutic applications continue to be evaluated.

#### ~4 Citings

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**97. Chronic treatment with clozapine or haloperidol differentially regulates dopamine and serotonin receptors in rat brain**

By O'Dell S J; La Hoste G J; Widmark C B; Shapiro R M; Potkin S G; Marshall J F  
From Synapse (New York, N.Y.) (1990), 6(2), 146-53, English, Database: MEDLINE

Long-term administration of the atypical neuroleptic clozapine (CLZ) poses a much lower risk of extrapyramidal side effects (EPS) than does the use of typical neuroleptics such as haloperidol (HAL). To investigate the neural mechanisms of the differing CNS activities of these two drugs, we used quantitative autoradiography to measure changes in dopamine and serotonin receptors in rats after injection with CLZ or HAL for 21 days at clinically relevant dose ratios. Levels of D1, D2, and 5-HT2 receptors were determined in frontal cortex, caudate-putamen, and nucleus accumbens. Rats that received CLZ chronically showed CNS receptor changes markedly different from those in chronic HAL-treated animals. Whereas rats treated chronically with HAL showed enhanced striatal D2 binding (average increase of 42%), those treated with CLZ did not. In contrast, chronic CLZ, but not chronic HAL, induced enhanced striatal D1 binding (average increase of 43%). Finally, CLZ treatment decreased 5-HT2 receptor binding by an average of 37%, while HAL had no significant effect. The effects of chronic HAL or CLZ treatment on receptors were similar in all forebrain areas examined. However, since D1 and 5-HT2 receptors are more abundant than D2 sites in limbic and neocortical areas, the preferential modulation of D1 and 5-HT2 receptors by CLZ suggests a greater impact of this atypical neuroleptic on activity of the limbic system than that achieved by the typical neuroleptic, HAL. These findings suggest that the clinical profile of atypical neuroleptics such as CLZ may be attributed to their effects on a receptor profile differing in pharmacological characteristics and anatomical distribution from that affected by typical neuroleptics.

**~3 Citings**

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**98. The effects of 5-HT1B characterizing agents in the mouse elevated plus-maze**

By Benjamin D; Lal H; Meyerson L R  
From Life sciences (1990), 47(3), 195-203, English, Database: MEDLINE

Although the serotonergic system has been implicated in the modulation of anxiety states, the specific receptor subtypes that mediate these states require clarification. The effects of drugs that act preferentially at 5-HT1B receptors were evaluated on the behavior elicited in the elevated plus-maze, an animal model of anxiety. Variations in the intensity of light affected mouse behavior in the plus-maze; lower light intensity increased the entries to and time spent on the open arm in a manner similar to that seen with stress-attenuating circumstances. Opposite effects were observed in high light-intensity, similar to effects seen under elevated stress conditions. Chlordiazepoxide produced increased entries and time spent on the open arm, whereas pentylentetrazol (PTZ) produced opposite effects. The preferential 5-HT1B agents TFMPP and mCPP exhibited a profile similar to PTZ. The effects of TFMPP in the plus-maze were reversed by chlordiazepoxide, but not by the benzodiazepine receptor antagonist flumazenil, which suggests that this effect is not directly mediated by benzodiazepine receptors. The decreased entries and time spent on the open arm of the maze following TFMPP or mCPP administration was possibly mediated by an antagonistic action at 5-HT1B receptors, since this effect was reversed by the selective 5-HT1B agonist CGS 12066B. The present study further demonstrates the utility of mouse behavior in the elevated plus-maze as a model for identifying anxiomodulatory substances.

**~0 Citings**

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**99. Differential effect of gepirone on presynaptic and postsynaptic serotonin receptors: single-cell recording studies**

By Blier P; de Montigny C  
From Journal of clinical psychopharmacology (1990), 10(3 Suppl), 13S-20S, English, Database: MEDLINE

The sustained administration of the serotonin (5-hydroxytryptamine<sub>1A</sub>, 5-HT<sub>1A</sub>) agonist gepirone (15 mg/kg/day subcutaneously) in the rat produced an initial decrease of the firing activity of dorsal raphe 5-HT neurons, which was followed by a progressive recovery to normal after 14 days of treatment. At this point, the somatodendritic 5-HT<sub>1A</sub> autoreceptor had desensitized, as indicated by the reduced effectiveness of intravenous lysergic acid diethylamide (LSD) and of microiontophoretic applications of 5-HT, LSD, 8-hydroxy-2-(N,N-propylamino) tetralin (8-OH-DPAT), and gepirone, but not of gamma-aminobutyric acid in depressing the firing activity of 5-HT neurons. In contrast, the responsiveness of postsynaptic dorsal hippocampus pyramidal neurons to 5-HT, 8-OH-DPAT, and gepirone was not altered by the 14-day gepirone treatment. In an attempt to unravel the differential effect of sustained gepirone administration on presynaptic and postsynaptic 5-HT<sub>1A</sub> receptors, the properties of gepirone at these two receptors were assessed. The concurrent microiontophoretic application of gepirone readily blocked the effect of 5-HT on dorsal hippocampus pyramidal neurons, but not on dorsal raphe 5-HT neurons, thus indicating that gepirone is a partial agonist at postsynaptic 5-HT<sub>1A</sub> receptors and a full agonist at somatodendritic 5-HT<sub>1A</sub> receptors. It is proposed that gepirone, being a partial agonist at postsynaptic 5-HT<sub>1A</sub> receptors, fails to desensitize them; whereas, because of its full agonistic activity at the somatodendritic 5-HT<sub>1A</sub> receptor, it desensitizes this autoreceptor with long-term administration. (ABSTRACT TRUNCATED AT 250 WORDS)

## ~1 Citings

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### 100. Effects of psychotropic drugs on the behavior and neurochemistry of olfactory bulbectomized rats

By van Riezen H; Leonard B E

From Pharmacology & therapeutics (1990), 47(1), 21-34, English, Database: MEDLINE

Since its first characterization as a model for the detection of antidepressant drugs (van Riezen et al., 1976) a large body of data now supports the view that olfactory bulbectomy produces changes in animal behavior that are reversed by chronic treatment with antidepressants. The behavioral deficits seen in olfactory bulbectomized rats (such as irritability, deficits in acquisition of avoidance and of appetitive motivated conditioning and hyperactivity in a new environment) are probably the results of a reduced ability to adapt to environmental changes. These behavioral changes, their biochemical consequences and the effects of treatments with psychotropic drugs are reviewed. These studies suggest that the olfactory bulbectomized rat is a model of depression useful to detect antidepressant drugs.

## ~5 Citings

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### 101. Animal models of depression: an overview

By Willner P

From Pharmacology & therapeutics (1990), 45(3), 425-55, English, Database: MEDLINE

## ~10 Citings

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### 102. Changes in [3H]-imipramine binding sites in relation to muricide following olfactory bulbectomy and the effect of nomifensine in brain of rats

By Al-Khatib I M; Fujiwara M; Kataoka Y; Ueki S

From Archives internationales de pharmacodynamie et de therapie (1988), 296282-92, English, Database: MEDLINE

The effects of olfactory bulbectomy (OB) and nomifensine (NOM) on the binding of [3H]-imipramine (3H-IMP) in brain of rat were investigated. Seventy-five per cent of OB rats exhibited muricide. Acute NOM suppressed muricide in 55% and chronic NOM suppressed it in 60-80% of OB rats. In killer rats, OB increased B<sub>max</sub> of high-affinity (HA) and low-affinity sites (LA) in cortex (Cx) and both B<sub>max</sub> and K<sub>D</sub> of HA in amygdala (AMG). In rats with muricide suppressed by acute NOM 10 mg.kg<sup>-1</sup> i.p., B<sub>max</sub> and K<sub>D</sub> of HA in Cx and of both HA and LA in AMG were reduced. Injection of NOM for 10 days produced further reduction of B<sub>max</sub>, especially of HA binding in Cx. Neither OB nor NOM exerted any significant effect on binding constants in caudate-putamen and hypothalamus. The possible relation between the changes of 3H-IMP binding, exhibition of muricide by OB rats and the antimuricidal activity of NOM are discussed.

## ~0 Citings

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**103. The chronic effects of desipramine and sertraline on platelet and synaptosomal 5HT uptake in olfactory bulbectomised rats**

By Butler J; Tannian M; Leonard B E

From Progress in neuro-psychopharmacology & biological psychiatry (1988), 12(5), 585-94, English, Database: MEDLINE

1. Depressed patients show a characteristic decrease in the rate of uptake of serotonin into their platelets, which is normalised only by clinically effective antidepressant treatment. 2. We also find a decrease in platelet 5HT uptake rates in the olfactory bulbectomised (OB) rat model of depression, which return to normal following three weeks of treatment with desipramine or sertraline. 3. Synaptosomal 5HT uptake appears to consist of a low affinity, high capacity component and a high affinity, low capacity component, both of which are increased in the OB rat, compared to its sham operated control, and normalised by chronic antidepressant treatment. 4. The low affinity uptake of serotonin is not inhibited by in vitro incubation with sertraline, which suggests that the low affinity system may be associated with a non-specific uptake of 5HT into noradrenergic or dopaminergic nerve endings.

~0 Citings

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**104. Brain output dysregulation induced by olfactory bulbectomy: an approximation in the rat of major depressive disorder in humans?**

By Jesberger J A; Richardson J S

From The International journal of neuroscience (1988), 38(3-4), 241-65, English, Database: MEDLINE

Mounting evidence indicates that the emotional, cognitive, neurovegetative and behavioral symptoms of patients with major depressive disorder are due to abnormal neurochemical substrates in the brain. Although the specific neurochemical abnormalities responsible have not been identified, the presenting symptoms of major depression are consistent with a disruption of normal neural communications between the limbic system and hypothalamus. Following removal of the olfactory bulbs, rats display a syndrome of behavioral deficits that also reflect a disruption of the limbic-hypothalamic axis. Moreover, the bulbectomy induced deficits are selectively reduced by the chronic administration of the same drugs that alleviate the symptoms of depression when given chronically to the patients. In addition to this pharmacological similarity, there are also numerous behavioral parallels between bulbectomized rats and major depression patients. The bulbectomized rat provides a good model in which to study antidepressant drugs and also may provide neurochemical and neuroanatomical data that are relevant to understanding the biological substrates of emotion and the causes of depression in humans.

~1 Citing

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**105. Selective agonists and antagonists for 5-hydroxytryptamine receptor subtypes, and interactions with yohimbine and FG 7142 using the elevated plus-maze test in the rat**

By Pellow S; Johnston A L; File S E

From The Journal of pharmacy and pharmacology (1987), 39(11), 917-28, English, Database: MEDLINE

The effects of some 5-HT receptor ligands were investigated on measures of anxiety in an elevated plus-maze test in the rat. Quipazine (2 and 4 mg kg<sup>-1</sup>), a non-specific 5-HT agonist and ritanserin (0.25-10 mg kg<sup>-1</sup>), a 5-HT<sub>2</sub> receptor antagonist displayed anxiogenic profiles by reducing both of the measures of anxiety used in this test. Two 5-HT<sub>1A</sub> receptor ligands, buspirone (4 and 8 mg kg<sup>-1</sup>) and ipsapirone (2.5-10 mg kg<sup>-1</sup>) and the 5-HT<sub>1</sub> agonist, RU 24969 (0.1875-1.5 mg kg<sup>-1</sup>) significantly reduced only the percentage of time spent on the open arms. (-)-Propranolol (5 and 10 mg kg<sup>-1</sup>), a 5-HT<sub>1</sub> receptor antagonist significantly reduced only the percentage of entries made onto the open arms. Metergoline (4 mg kg<sup>-1</sup>), a non-specific 5-HT antagonist displayed anxiolytic effects in this test by increasing both measures of anxiety. The 5-HT<sub>1A</sub> receptor agonist, 8-OH-DPAT (0.0625-0.25 mg kg<sup>-1</sup>) had no effect on either of the measures of anxiety. The results from the non-specific ligands (quipazine and metergoline) are consistent with the theory that a reduction in 5-HT function reduces anxiety. However, in spite of their more selective effects on 5-HT receptors the results in this test from the more specific ligands are not consistent with a strong involvement of any single receptor subtype. The interaction studies with yohimbine and FG 7142 (beta-carboline-3-carboxylate methylamide) provided no clear evidence for a major role of 5-HT pathways in the mediation of their anxiogenic effects.

~2 Citings

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**106. Serotonin receptors in the human brain--IV. Autoradiographic mapping of serotonin-2 receptors**

By Pazos A; Probst A; Palacios J M

From Neuroscience (1987), 21(1), 123-39, English, Database: MEDLINE

The anatomical distribution of serotonin-2 receptors in the human brain was studied by light microscopic autoradiography, using [3H]ketanserin as a ligand. The receptor densities were quantified by microdensitometry with the aid of a computer-assisted image-analysis system. A heterogeneous distribution of serotonin-2 receptor densities was found in the human brain. Very high concentrations were localized over layers III and V of several cortical areas, including the frontal, parietal, temporal and occipital lobes, the anterogenual cortex and the entorhinal area, as well as in the corpus mamillare of the hypothalamus. The claustrum, nucleus lateralis of the amygdala and some cortical layers also presented a high density of serotonin-2 receptors. Intermediate concentrations were found over the hippocampus, the caudatus, putamen and accumbens nuclei, and some nuclei of the amygdala, among other structures. Areas such as the thalamus, brain stem, cerebellum and spinal cord contained, in general, only low to very low densities of serotonin-2 receptors. A very high level of non-specific binding, which was not displaceable by any serotonin-2 compound, was found in some areas of the human brain, including the caudatus and putamen nuclei, the substantia nigra and the raphe nuclei. The distribution of serotonin-2 receptors in the human brain described herein is discussed in relation to the distribution of serotonergic innervation, the central effects which have been proposed to be serotonin-2-mediated, and the neuropathological characteristics of the diseases where a modification in the number of serotonin-2 receptors has been reported.

**~10 Citings**

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**107. Antidepressant-like action of 5-HT<sub>1A</sub> agonists and conventional antidepressants in an animal model of depression**

By Kennett G A; Dourish C T; Curzon G

From European journal of pharmacology (1987), 134(3), 265-74, English, Database: MEDLINE

Previous results have suggested that behavioural adaptation to restraint might be promoted by post-restraint stimulation of 5-HT<sub>1A</sub> receptors. Therefore, rats were restrained for 2 h and injected with vehicle or 60-1,000 micrograms/kg of the 5-HT<sub>1A</sub> agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) s.c. Vehicle-treated restrained rats showed reduced locomotor activity and increased defaecation in an open field test the day after the end of restraint. A single injection of 250 or 1,000 micrograms/kg 8-OH-DPAT attenuated these effects. The above locomotor deficits were also attenuated by chronic pretreatment with the antidepressants desipramine and sertraline but not by a single treatment with desipramine or the benzodiazepine anxiolytic drugs chlordiazepoxide and diazepam; none of these treatments unambiguously reversed stress-induced increases in defaecation. Evidence suggests that the above action of 8-OH-DPAT is mediated by 5-HT<sub>1A</sub> receptors since it was antagonised by the 5-HT<sub>1A</sub> antagonist spiperone but not by the 5-HT<sub>2</sub> antagonist ketanserin and was not mimicked by the 5-HT<sub>1B</sub> agonist RU 24969. However, the 5-HT<sub>1A</sub> agonists buspirone and TVXQ 7821 (ipsapirone) and the non-specific 5-HT agonist quipazine all possess similar properties to 8-OH-DPAT in this test. The results suggest that 5-HT<sub>1A</sub> agonists may have rapid antidepressant properties.

**~9 Citings**

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**108. 1-(2-Pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat**

By Caccia S; Conti I; Vigano G; Garattini S

From Pharmacology (1986), 33(1), 46-51, English, Database: MEDLINE

Buspirone (BP), a newly developed antianxiety agent, forms 1-(2-pyrimidinyl)-piperazine (PmP) during its biotransformation in rats and man. After oral administration of pharmacologically effective doses of BP-hydrochloride to rats (1 and 10 mg/kg), the metabolite appears in significant amounts in body fluids and tissues; it is highly concentrated in the central nervous system, the brain-to-plasma concentration ratios being approximately 5 at the time of the maximum concentrations (C<sub>max</sub>). In man given the anxiolytic dose (20 mg) of BP the metabolite reaches higher plasma C<sub>max</sub> values than its parent drug. Its plasma elimination t<sub>1/2</sub> is more than double that for BP. These results, together with the fact that PmP is biochemically and pharmacologically active, suggest that the metabolite may contribute significantly to the central effects of the parent drug.

**~6 Citings**

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**109. Open trial of buspirone in the treatment of major depressive disorder**

By Schweizer E E; Amsterdam J; Rickels K; Kaplan M; Droba M  
From Psychopharmacology bulletin (1986), 22(1), 183-5, English, Database: MEDLINE

~2 Citings

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**110. Characterization of the 5-hydroxytryptamine<sub>1A</sub> receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes**

By De Vivo M; Maayani S  
From The Journal of pharmacology and experimental therapeutics (1986), 238(1), 248-53, English, Database: MEDLINE

The inhibition of forskolin-stimulated adenylate cyclase activity by 5-hydroxytryptamine (5-HT) receptor agonists was measured in guinea pig and rat hippocampal membranes. The results were consistent with the inhibition being mediated by a single, homogeneous population of receptors. In guinea pig hippocampal membranes 8-hydroxy-2-(di-n-propylamino)tetralin, d-lysergic acid diethylamide, 5-HT and buspirone were potent in inhibiting forskolin-stimulated adenylate cyclase activity, with EC<sub>50</sub> values of 18, 24, 53 and 146 nM, respectively. Spiperone (K<sub>b</sub> = 26 nM) and methiothepin (K<sub>b</sub> = 13 nM) were potent competitive antagonists at this receptor whereas ketanserin, a high affinity 5-HT<sub>2</sub> receptor ligand, and ICS 205-930, a high affinity peripheral neuronal (M) receptor ligand, were not. In rat hippocampal membranes, 8-hydroxy-2-(di-n-propylamino)tetralin, d-lysergic acid diethylamide, 5-HT and buspirone were potent agonists and exhibited the same rank order of potency as in guinea pig hippocampal membranes. The maximal percentage of inhibition by buspirone was significantly less than the maximal percentage of inhibition by 5-HT in rat membranes, suggesting that it is a partial agonist at this receptor, with an intrinsic activity relative to 5-HT of 0.5. The concentration-response data show that the inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes is mediated by a receptor with the characteristics of the 5-HT<sub>1A</sub> binding site. We propose that the inhibition of adenylate cyclase activity is a functional correlate of this binding site. This response is suitable for measuring activities and affinities of drugs acting at 5-HT<sub>1A</sub> receptors.

~25 Citings

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**111. Effects of antidepressant drugs on the behavior of olfactory bulbectomized and sham-operated rats**

By Jesberger J A; Richardson J S  
From Behavioral neuroscience (1986), 100(2), 256-74, English, Database: MEDLINE

Removal of the main olfactory bulbs in rats has been shown to alter neuronal function in brain areas involved in emotional regulation and homeostasis. These neuronal alterations result in maladaptive behavioral patterns and elevated plasma corticosterone that are suggestive of the symptom profile of patients with primary unipolar depression. Moreover, the endocrine and behavioral deficits of bulbectomized rats are reversed by the chronic administration of drugs that reverse the symptoms of depression in people when given chronically. However, the therapeutic improvements seen in patients with depression are not directly due to molecules of the antidepressant drug but rather to some relatively long-lasting compensatory change induced in the neuronal substrate by the drug. The present research demonstrates that the reversal of the olfactory bulb lesion deficits following chronic antidepressant drug administration in rats is not due to molecules of the drug per se but rather to some drug-induced change in the neuronal substrate that continues for at least 5 days after the last dose of drug. These endocrine, behavioral, and pharmacological similarities suggest that the study of rats with olfactory bulb ablation may make significant contributions to the understanding of the neuroscience of primary unipolar depression in humans.

~1 Citing

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**112. Characterization of [<sup>3</sup>H]paroxetine binding to rat cortical membranes**

By Habert E; Graham D; Tahraoui L; Claustre Y; Langer S Z  
From European journal of pharmacology (1985), 118(1-2), 107-14, English, Database: MEDLINE

Paroxetine is a selective and potent inhibitor of 5-hydroxytryptamine uptake into serotonergic neurons. The specific binding of [3H]paroxetine to rat cortical membranes at 22 degrees C was examined in this study. Our results indicate the presence of a single saturable high affinity binding component for [3H]paroxetine. Scatchard analysis revealed a  $K_d$  of  $0.15 \pm 0.01$  nM, and a  $B_{max}$  of  $549 \pm 36$  fmol/mg protein. The kinetically derived dissociation constant was  $0.034 \pm 0.008$  nM. [3H]Paroxetine binding was inhibited selectively by 5-HT uptake blockers, and a good correlation was demonstrated between the potency of various drugs to inhibit [3H]paroxetine binding and [3H]5-hydroxytryptamine uptake. Also, lesions performed with the neurotoxin, 5,7-dihydroxytryptamine resulted in a 94% decrease in endogenous 5-hydroxytryptamine levels and concomitantly, a 90% reduction in [3H]paroxetine binding when compared to sham controls. These results indicate that the binding site labelled by [3H]paroxetine is associated with the neuronal 5-hydroxytryptamine transporter complex.

#### ~5 Citings

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### 113. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors

By Pazos A; Palacios J M

From Brain research (1985), 346(2), 205-30, English, Database: MEDLINE

The distribution of serotonin-1 (5-HT<sub>1</sub>) receptors in the rat brain was studied by light microscopic quantitative autoradiography. Receptors were labeled with [3H]serotonin (5-[3H]HT), 8-hydroxy-2-[N-dipropylamino-3H]tetralin (8-OH-[3H]DPAT), [3H]LSD and [3H]mesulergine, and the densities quantified by microdensitometry with the aid of a computer-assisted image-analysis system. Competition experiments for 5-[3H]HT binding by several serotonin-1 agonists led to the identification of brain areas enriched in each one of the three subtypes of 5-HT<sub>1</sub> recognition sites already described (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1C</sub>). The existence of these 'selective' areas allowed a detailed pharmacological characterization of these sites to be made in a more precise manner than has been attained in membrane-binding studies. While 5-[3H]HT labeled with nanomolar affinity all the 5-HT<sub>1</sub> subtypes, the other 3H-labeled ligands labeled selectively 5-HT<sub>1A</sub> (8-OH-[3H]DPAT), 5-HT<sub>1C</sub> ([3H]mesulergine) and both of them ([3H]LSD). Very high concentrations of 5-HT<sub>1</sub> receptors were localized in the choroid plexus, lateroseptal nucleus, globus pallidus and ventral pallidum, dentate gyrus, dorsal subiculum, olivary pretectal nucleus, substantia nigra, reticular and external layer of the entorhinal cortex. The different fields of the hippocampus (CA1-CA4), some nuclei of the amygdaloid complex, the hypothalamic nuclei and the dorsal raphe, among others, also presented high concentrations of sites. Areas containing intermediate densities of 5-HT<sub>1</sub> receptors included the claustrum, olfactory tubercle, accumbens, central grey and lateral cerebellar nucleus. The nucleus caudate-putamen and the cortex, at the different levels studied, presented receptor densities ranging from intermediate to low. Finally, in other brain areas--pons, medulla, spinal cord--only low or very low concentrations of 5-HT<sub>1</sub> receptors were found. From the areas strongly enriched in 5-HT<sub>1</sub> sites, dentate gyrus and septal nucleus contained 5-HT<sub>1A</sub> sites, while globus pallidus, dorsal subiculum, substantia nigra and olivary pretectal nucleus were enriched in 5-HT<sub>1B</sub>. The sites in the choroid plexus, which presented the highest density of receptors in the rat brain, were of the 5-HT<sub>1C</sub> subtype. The distribution of 5-HT<sub>1</sub> receptors reported here is discussed in correlation with the distribution of serotonergic neurons and fibers, the related anatomical pathways and the effects which appear to be mediated by these sites.

#### ~67 Citings

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### 114. Comparison of buspirone in two separate studies

By Goldberg H L; Finnerty R

From The Journal of clinical psychiatry (1982), 43(12 Pt 2), 87-91, English, Database: MEDLINE

Two double-blind studies are described in which buspirone was compared with placebo and diazepam (Study A) or clorazepate (Study B) in outpatients with moderate to severe anxiety. Results, assessed on the Hamilton Rating Scales for Depression and Anxiety, the SCL-56, the Profile of Mood States, and the Covi and Raskin scales, indicated that buspirone consistently relieved both anxiety and associated depression. In Study B, trends in favor of buspirone were seen on several SCL-56 items and the Hamilton somatic factor; significant differences in this direction were found for several POMS items. Sedation was seen less often with buspirone than either diazepam or clorazepate.

#### ~2 Citings

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### 115. Olfactory projection systems, drugs and behaviour: a review

By Cairncross K D; Cox B; Forster C; Wren A F  
From Psychoneuroendocrinology (1979), 4(3), 253-72, English, Database: MEDLINE

~0 Citings

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**116. Association and commissural fiber systems of the olfactory cortex of the rat**

By Haberly L B; Price J L  
From The Journal of comparative neurology (1978), 178(4), 711-40, English, Database: MEDLINE

The association and commissural fiber systems arising in the olfactory cortical areas caudal to the olfactory peduncle (the piriform cortex, nucleus of the lateral olfactory tract, anterior cortical nucleus of the amygdala, periamygdaloid cortex and entorhinal cortex) have been studied utilizing horseradish peroxidase as both an anterograde and a retrograde axonal tracer. In the piriform cortex two sublaminae within layer II (IIa and IIb) layer III have been found to give rise to distinctly different projections. Retrograde cell labeling experiments indicate that the association fiber projection from layer IIb is predominately caudally directed, while the projection from layer III is predominantly rostrally directed. Cells in layer IIa project heavily to areas both caudal and rostral to the piriform cortex. The commissural fibers from the piriform cortex are largely restricted in their origin to layer IIb of the anterior part of the piriform cortex and in their termination on the contralateral side to the posterior part of the piriform cortex and adjacent olfactory cortical areas. A projection to the olfactory bulb has also been found to arise from cells in layers IIb and III of the ipsilateral piriform cortex, but not in layer IIa. In addition to those from the piriform cortex, association projections have also been found from other olfactory cortical areas. The nucleus of the lateral olfactory tract has a heavy bilateral projection to the medial part of the anterior piriform cortex and the lateral part of the olfactory tubercle (as well as a lighter projection to the olfactory bulb); both the anterior cortical nucleus of the amygdala and the periamygdaloid cortex project ipsilaterally to several olfactory cortical areas. The entorhinal cortex has been found to project to the medial parts of the olfactory tubercle and the olfactory peduncle. The olfactory tubercle is the only olfactory cortical area from which no association fiber systems (intrinsic or extrinsic) have been found to originate. A broad topographic organization exists in the distribution of the fibers from several of the olfactory areas. This is most obvious in the anterior part of the olfactory cortex, in which fibers from the more rostral areas (the anterior olfactory nucleus and the anterior piriform cortex) terminate in regions near the lateral olfactory tract, while those from more caudal areas (the posterior piriform cortex and the entorhinal cortex) terminate in areas further removed, both laterally and medially, from the tract. Projection to olfactory areas from the hypothalamus, thalamus, diagonal band, and biogenic amine cell groups have been briefly described.

~18 Citings

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**117. Biochemical correlates in mouse-killing behavior of the rat: prolonged isolation and brain cholinergic function**

By Yoshimura H; Ueki S  
From Pharmacology, biochemistry, and behavior (1977), 6(2), 193-6, English, Database: MEDLINE

After 30 days of isolation, 45% of the rats exhibited mouse-killing behavior. The killing response was suppressed by atropine (5 mg/kg and 8 mg/kg, IP) and scopolamine (8 mg/kg, IP), whereas methylatropine was ineffective. Acetylcholine (ACh) content and acetylcholinesterase (AChE) activity were measured in 5 discrete areas of rat brain. As compared with the aggregated rats only the killer rats exhibited higher ACh levels in the diencephalon. The activity of AChE in all brain areas was unchanged by isolation; no significant difference was found between the killer and nonkiller rats. These results suggest that central cholinergic mechanisms participate in the mediation of mouse-killing behavior in the rat.

~0 Citings

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**118. THE CONNEXIONS OF THE AMYGDALA**

By COWAN W M; RAISMAN G; POWELL T P  
From Journal of neurology, neurosurgery, and psychiatry (1965), 28137-51, English, Database: MEDLINE

~9 Citings

