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Review

The possible role of 5-$HT_{1B/D}$ receptors in psychiatric disorders and their potential as a target for therapy

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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) is implicated in several psychiatric diseases. Is this also true for 5-$HT_{1B/D}$ receptors? These receptors are found in high density in substantia nigra, globus pallidus, striatum and basal ganglia and in other brain regions. This ubiquity makes 5-$HT_{1B/D}$ receptors responsible for many physiological and behavioural functions. This review focuses on the role of 5-HT_{1B} receptors in the regulation of 5-HT release and synthesis. Microdialysis experiments performed on freely moving animals are an interesting in vivo model to study the function of the terminal 5-HT_{1B} autoreceptor. Synthesis of 5-HT, estimated by the measurement of the accumulation of 5-hydroxytryptophan (5-HTP) ex vivo or in vitro, is modulated by the 5-HT_{1B} autoreceptors. Many reports have shown that chronic administration with selective serotonin reuptake inhibitors leads to the desensitisation of the terminal 5-HT_{1B} autoreceptors. With the help of some animal models of depression and anxiety and with some data from clinical studies it has been hypothesised that 5-HT_{1B} receptors may be supersensitive in depression, anxiety and obsessive compulsive disorder. Thus, since the dysfunction of 5-HT_{1B} receptors may be involved in some pathological states, particularly in the psychiatric field, these receptors represent important potential targets for drugs to treat mental diseases.

Keywords: 5-$HT_{1B/D}$ receptor; Psychiatric disorder; 5-HT (5-hydroxytryptamine, serotonin) release; 5-HT (5-hydroxytryptamine, serotonin) synthesis; Depression; Anxiety; Obsessive compulsive disorder; Desensitisation; Supersensitive; Target

1. Introduction

In the early 1950s, Twarog and Page (1953), by using a sensitive bioassay to detect the presence of serotonin (5-hydroxytryptamine, 5-HT) in the cerebral tissue, began to study the compound in the brain. The psychotomimetic activity of lysergic acid diethylamide (LSD), which had been shown to antagonise the effects of serotonin on smooth muscle, led to the suggestion of a possible central role for serotonin in mental illness (Wooley and Shaw, 1954). Since then, an intense research effort has shown that serotonin is implicated in many functions of the central nervous system (CNS), including neuronal development (Lauder, 1983), thermoregulation (Feldberg and Myers, 1964), pain (Tenen, 1967), motor regulation (Jacobs, 1991), sleep (Jouvet, 1967), appetite (Fernstrom and Wurtman, 1971), sexual behaviour (Gorzalka et al., 1990), aggression (Sheard, 1969; Soubrié, 1986), anxiety (Chopin and Briley, 1987) and mood (Golden and Gilmore, 1990).

The implication of serotonin in such a variety of functions is not surprising considering the overall structure of the serotonergic systems in the brain. Anatomically, these systems consist of groups of neurons whose cell bodies are located in the brainstem and raphe nuclei and complex axonal systems which project to almost all regions of the CNS, but with particularly dense innervation of the cerebral cortex, limbic structures, basal ganglia, many parts of the brainstem and the grey matter of the spinal cord. Furthermore, many neurons are branched which means that a single cell frequently projects to more than one brain area. Consequently, serotonin is released from nerve terminals in virtually all brain regions, which explains why this neurotransmitter is involved in functions of such widely different anatomical origins as emotion (associated with the limbic nuclei), feeding, sexual activity and thermoregulation (hypothalamic origin), or memory (linked to hippocampal activity). Therefore, in view of this multiplicity

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of actions, serotonin has also been implicated in a variety of pathological conditions in the psychiatric field. Animal models for predicting the potential therapeutic effects of drugs interfering with serotonergic transmission in the CNS have allowed considerable progress in psychopharmacology (Willner, 1991). Clinical correlates of the effects of the serotonergic system in animal studies exist in anxiety, depression, psychosis, obsessive–compulsive disorders (OCD) and aggressivity, sexual dysfunction and eating disorders.

Two principal classifications of 5-HT receptors have been based on either their pharmacology (Bradley et al., 1986) or their molecular biology, the latter identifying seven families, 5-HT_{1-7}, comprising a total of 14 structurally and pharmacologically distinct mammalian 5-HT receptor subtypes (for reviews see Hoyer et al., 1994; Barnes and Sharp, 1999). Hartig et al. (1996) proposed a new classification of the previously termed "5-HT_{1B}" and "5-HT_{1D}" receptor subtypes based on molecular biology data. They suggested that the term "5-HT_{1B}" be used for the rodent 5-HT_{1B} and human 5-$HT_{1D\beta}$ subtypes (see Hoyer et al., 1994), and that "5-HT_{1D}" should be employed for the rodent 5-HT_{1D} and human 5-$HT_{1D\alpha}$ subtypes (Hoyer et al., 1994). This nomenclature is followed hereafter in this review. A high density of 5-HT_{1B} sites is found in the basal ganglia (particularly the substantia nigra, globus pallidus, caudate putamen, ventral pallidum and entopeduncular nucleus), but also many other regions such as hippocampus and cortex (Bruinvels et al., 1993). Data from many studies suggest that 5-HT_{1B} receptors are located on terminals presynaptically and postsynaptically relative to the 5-HT neurons where they play the role of both 5-HT autoreceptors and 5-HT heteroreceptors. The former control the release of 5-HT while the latter control the release of non-serotonin neurotransmitters. Some 5-HT_{1B} receptors might be located also postsynaptically on cell bodies of non-serotonergic neurons, however to our knowledge, no proven demonstration has been presented so far. Some reports have suggested the presence of 5-HT_{1B} receptors in the dorsal raphe nucleus (Davidson and Stamford, 1995; Roberts et al., 1998), which could play a modulatory role in 5-HT release in this brain region (Moret and Briley, 1997a).

5-HT_{1B} knockout mice have been produced by specific ablation of the 5-HT_{1B} receptor gene by homologous recombination (Castanon et al., 1997). Although these animals, lacking the 5-HT_{1B} receptor, may undergo adaptation during and after development, they represent an interesting model for studying the function of the 5-HT_{1B} receptor. The 5-HT_{1B} knockout mice have greater aggression and impulsivity, as well as increased alcohol and cocaine consumption compared to normal animals (Huang et al., 1999; Scearce-Levie et al., 1999). In addition studies in these mice suggest that 5-HT_{1B} receptors participate in the regulation of paradoxical (rapid-eye movement, REM) sleep (Boutrel et al., 1999).

The present review focuses on the function of 5-HT_{1B} autoreceptors in the regulation of serotonin release and synthesis, and of 5-HT_{1B} heteroreceptors in the regulation of the release of non-serotonin neurotransmitters. With the help of data from experiments on animal models and human clinical data, the possible implication of 5-HT_{1B} receptor subtypes in the etiology of different psychiatric diseases is discussed.

2. 5-HT_{1B} autoreceptors

2.1. Release of 5-HT

The release of 5-HT from nerve terminals is under the control of inhibitory 5-HT autoreceptors in animal and human brain (for reviews see Briley et al., 1997; Göthert and Schlicker, 1997). Results of in vitro release experiments have shown that these receptors belong to the 5-$HT_{1D\beta}$ (Fink et al., 1995) or human 5-HT_{1B} according to the classification proposed by Hartig et al. (1996) based on molecular biology (see above). The same characterization of 5-HT_{1B} subtype has been found in the cerebral cortex of the guinea pig (Bühlen et al., 1996). Another in vitro study using SB-236057 (1′-ethyl-5-(2′-methyl-4′-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4′-piperidine]), which has high affinity for human 5-HT_{1B} receptors, has recently confirmed that in both the guinea pig and human cerebral cortex, the terminal 5-HT autoreceptor is of the 5-HT_{1B} subtype (Middlemiss et al., 1999).

The direct in vivo study of 5-HT autoreceptor function has become more accessible since the advent of intracerebral microdialysis, a technique which allows direct in vivo sampling and measurement of neurotransmitters and their metabolites in the extracellular fluid of the brain (Di Chiara, 1990) of anaesthetised or freely moving animals.

The relatively non-selective 5-HT_{1B} receptor agonist, 5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (RU 24969), has been reported to decrease extracellular 5-HT levels in the hippocampus of anaesthetised rat when administered systemically (Martin et al., 1992). A similar reduction of dialysate 5-HT has also been obtained with this compound in the frontal cortex of anaesthetised rats (Sleight et al., 1989) and in the diencephalon of awake rats (Auerbach et al., 1991) following systemic administration of this compound. In addition, local administration of RU 24969 through the microdialysis probe via the perfusion medium directly into the terminal regions induced a decrease in extracellular 5-HT in the hippocampus of anaesthetised rat (Hjorth and Tao, 1991; Bosker et al., 1995) and in the diencephalon of awake rats, where locally applied *m*-trifluoromethyl-phenylpiperazine (TFMPP) also decreased dialysate 5-HT levels (Auerbach et al., 1991). The effect of the local infusion of RU 24969 was attenuated by

simultaneous infusion of the non-selective 5-HT autoreceptor antagonist methiothepin into the hippocampus (Martin et al., 1992).

Hjorth and Tao (1991) have shown that 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrolol[3,2,6]pyrid-5-one (CP 93129), a 5-HT_{1B} receptor agonist with about a 100-fold higher affinity for 5-HT_{1B} than for 5-HT_{1A} binding sites (Koe et al., 1990; Macor et al., 1990), when administered via the dialysis perfusion medium, caused a reduction of 5-HT output in the hippocampus of anaesthetised rats. This effect was significantly antagonised by co-infusion of the non-selective 5-HT_{1B} receptor antagonist, methiothepin. From the above results it would appear that 5-HT release in terminal areas in vivo is modulated by 5-HT_{1B} autoreceptors in the rat.

In the rat hypothalamus, methiothepin, when applied locally via the microdialysis probe, increased the extracellular levels of 5-HT both in the absence and in the presence of the 5-HT uptake inhibitor citalopram, suggesting that in awake animals 5-HT autoreceptors in the terminal projection areas are tonically activated and exert a potent inhibitory tone on the release of 5-HT (Moret and Briley, 1996a).

Guinea pigs are suitable animals to study terminal 5-HT_{1B} autoreceptors since their receptors have a similar pharmacology to those in humans (Bühlen et al., 1996). Local (via microdialysis probe) administration of the 5-$HT_{1A/B}$ agonist, 5-carboxyamidotryptamine (5-CT), into the frontal cortex of the freely moving guinea pig decreased extracellular 5-HT levels (Lawrence and Marsden, 1992). Sumatriptan, a 5-$HT_{1B/D}$ agonist, when added to the perfusion medium, similarly reduced extracellular levels of 5-HT in the frontal cortex of anaesthetised guinea pigs (Sleight et al., 1990; Roberts et al., 1997) presumably via an activation of 5-HT_{1B} autoreceptors. In guinea pig hypothalamus, local, through the probe, administration of naratriptan, which is more selective for 5-$HT_{1B/D}$ receptors compared to 5-HT_{1A} receptors than sumatriptan, also decreases the extracellular levels of 5-HT, an effect which is attenuated by the non-selective 5-HT_1 receptor antagonist, methiothepin at 1 μM, a concentration which does not by itself modify the outflow of 5-HT (Moret and Briley, 1996b; Briley et al., 1997). In guinea pig frontal cortex, sumatriptan-induced inhibition of 5-HT release has been shown to be reversed by the 5-HT_{1B} receptor antagonist, 1′-methyl-5-[[2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo-[2,3-f]indole-3,4′-piperidine] (SB-224289) (Gaster et al., 1998; Fig. 1). The extracellular levels of 5-HT measured by microdialysis in hypothalamus of freely moving guinea pigs are increased by methiothepin when the concentrations of 10–100 μM are used (Moret and Briley, 1996b). Similarly, in vivo microdialysis measurements in guinea pig hypothalamus show a prolonged increase in extracellular levels of 5-HT following s.c. administration with the 5-HT_{1D} receptor antagonist, 1-methyl-4-[7-(4-chlorophenyl)methylaminocarbonyl] napththyl-piperazine (CP-291, 952) (Tingley et al., 1998). This suggests that, as in the rat, in the hypothalamus of freely moving guinea pig 5-HT autoreceptors are tonically activated and exert a potent inhibitory tone on the release of 5-HT. When this inhibition is removed by an antagonist, such as methiothepin or CP-291,952, there is a major increase in 5-HT release. A similar effect has been found with methiothepin in guinea pig substantia nigra (Briley and Moret, 1993).

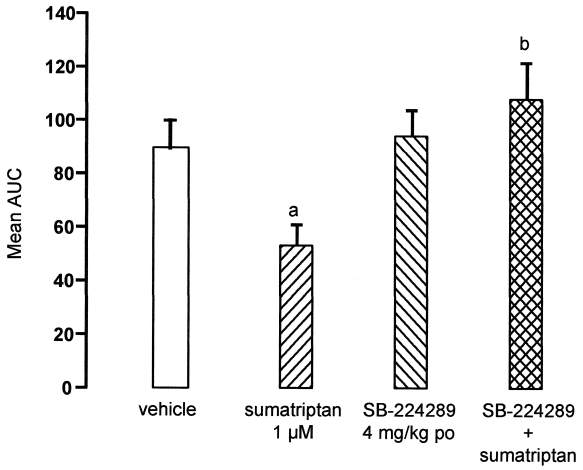

Fig. 1. Effect of SB-224289 on sumatriptan-induced inhibition of 5-HT release in the frontal cortex of the freely moving guinea pig as measured by microdialysis. Ordinate refers to the mean area under the curve (AUC). Each column represents mean ± S.E.M. from at least four animals. [a]$P < 0.05$ compared to vehicle; [b]$P < 0.05$ compared to sumatriptan. Redrawn from Gaster et al., 1998.

More recently, Roberts et al. (1998) have suggested a new hypothesis concerning the distribution of 5-$HT_{1B/D}$ autoreceptors. In the frontal cortex and striatum which are principally innervated by the dorsal raphe nucleus, *N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl] 2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (GR 127935), a 5-$HT_{1B/D}$ receptor antagonist, decreases extracellular levels of 5-HT after acute administration. The authors explain this decrease by antagonism of inhibitory 5-$HT_{1B/D}$ receptors on raphe cell bodies, leading to a local increase in 5-HT, which, in turn, stimulates 5-HT_{1A} receptors to decrease cell firing, and hence 5-HT release from terminals. In contrast, the 5-HT_{1B} receptor antagonist, SB-224289, has no effect on 5-HT levels in either region. The authors explain the SB-224289 absence of effect by the less important 5-HT_{1B} receptor antagonism than when both 5-HT_{1B} and 5-HT_{1D} receptors are blocked at the level of the dorsal raphe nucleus. Or it is also thought that it may be possible that there is an alternative projection from the 5-HT_{1D} receptors of the dorsal raphe nucleus to the frontal cortex, mediating inhibition of terminal 5-HT release. In the dentate gyrus, a region principally innervated by the median raphe nucleus, GR 127935 and SB-224289 increase extracellular levels of 5-HT, result suggesting a

lack of 5-$HT_{1B/D}$ receptors in the median raphe nucleus (Roberts et al., 1998).

These studies underline the complexity of the control of 5-HT neurotransmission and the role of 5-HT autoreceptors which is clearly more sophisticated than originally suspected.

In spite of this complexity it has been successfully demonstrated by Rex et al. (1996) that 5-HT_{1B} receptors are involved in cortical release of extracellular 5-HT in guinea pigs when exposed to the elevated plus maze. Non-handled guinea pigs remain in a state of reflexive freezing for the entire 20 min observation period when subjected to the aversive conditions of the plus-maze (Rex et al., 1993). However, guinea pigs handled twice a day from birth do not exhibit reflexive freezing on exposure to the plus-maze but show behaviour similar to that of rats (Pellow et al., 1985; Barth et al., 1993). Under the mild aversive conditions of the elevated plus maze, the release of extracellular 5-HT is increased, an effect abolished by the non-selective 5-HT_1 receptor agonist, 5-carboxamidotryptamine. Pre-treatment with the selective 5-HT_{1B} receptor antagonist, GR 127935, blocks this effect of 5-CT. These results indicate that the 5-HT_{1B} autoreceptor in the frontal cortex is functional under aversive conditions. However, more work is needed to establish with certainty in which direction, pro- or anti-anxiety, it plays in this role.

5-HT-Moduline is an endogenous tetrapeptide (Leu–Ser–Ala–Leu, LSAL) characterised by its non-competitive binding to 5-HT_{1B} receptors. By inducing structural changes in these receptors, this peptide prevents 5-HT binding, thereby desensitising the receptors and inhibiting serotonergic function (Sarhan and Fillion, 1998). As already mentioned above, several experimental studies have shown that an acute stress, which is assumed to induce anxiety, increases 5-HT release in various brain areas, as measured by microdialysis (Kawahara et al., 1993; Vahabzadeh and Fillenz, 1994; Pei et al., 1990; Clement et al., 1993). Bolaños-Jiménez et al. (1995) have shown that 5-HT_{1B} receptors are desensitised following an acute immobilisation stress and Seguin et al. (1997) demonstrated that rats receiving 5-HT-moduline via intracerebroventricular injection exhibit a similar desensitisation of their 5-HT_{1B} receptors. In rats subjected to the acute immobilisation stress, a major increase of 5-HT-moduline tissue content is observed in various brain areas. They hypothesised that 5-HT-moduline induces a desensitisation of 5-HT_{1B} receptors, resulting in an excess of 5-HT activity which has been proposed to be closely related to anxiety, thus implying a role for 5-HT-moduline in the pathophysiology of anxiety.

There are thus numerous suggestions of the involvement of the terminal 5-HT_{1B} autoreceptor dysfunction in the development of anxiety. Further studies probably linking microdialysis with behavioural studies are required to clarify this relationship.

2.2. Synthesis of 5-HT

Activation of somatodendritic 5-HT_{1A} autoreceptors decrease 5-HT neuronal firing and, in turn, the synthesis, metabolism and release of 5-HT (see Moret and Briley, 1997b). However, studies in the rat (Hjorth et al., 1995) have shown that the 5-$HT_{1B/2C}$ receptor agonist, TFMPP, suppresses 5-HT synthesis in vivo as estimated by the accumulation of 5-hydroxytryptophan (5-HTP) after the inhibition of the amino acid decarboxylase, i.e. an index of tryptophane hydroxylation. This suppression of synthesis which is seen in terminal projection areas such as the limbic forebrain and striatum, is also observed in axotomized animals, indicating that it is independent of neuronal firing (Hjorth et al., 1995; Fig. 2). Furthermore, a similar inhibitory effect of TFMPP on 5-HT synthesis is found in vitro in slice preparations in the presence of depolarising concentrations of potassium. In vitro the effect of TFMPP is attenuated by the non-selective 5-HT receptor antagonist, methiothepin, as well as the 5-HT_{1B} receptor antagonists, propranolol or cyanopindolol (Hjorth et al., 1995). By comparison, the decrease of 5-HT synthesis in forebrain regions induced in vivo by 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT) is prevented by transection of the brain. In addition, 8-OH-DPAT does not decrease 5-HT synthesis in vitro (Hjorth et al., 1995). These data thus suggest that the reduction of rat brain 5-HT synthesis by TFMPP is mediated by 5-HT autoreceptors located on the serotonergic terminals, and that this effect is independent of 5-HT neuronal firing (Hjorth et al., 1995).

This finding confirms an earlier suggestion of the possible involvement of 5-HT_{1B} autoreceptors in the modulation of 5-HT synthesis. Indeed a study using a similar ex vivo protocol (Moret and Briley, 1993, 1997b) found that sys-

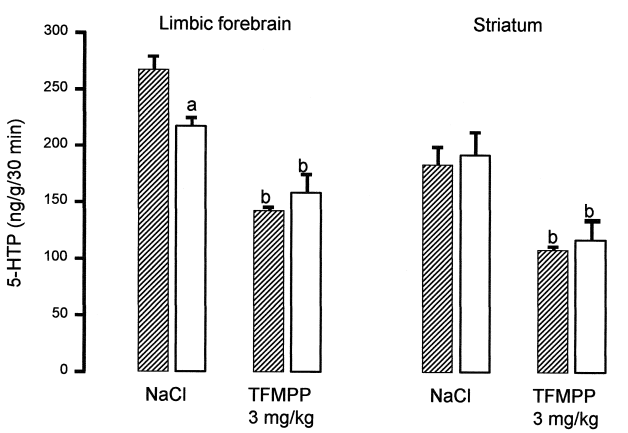

Fig. 2. Effect of TFMPP on rat brain 5-HT synthesis after unilateral axotomy. Ordinate refers to the 5-HTP formation (ng/g brain tissue/30 min) in limbic forebrain and striatal regions on the intact (cross hatched columns) and transected sides (open columns), means ± S.E.M. of five to seven observations. Control animals received NaCl. [a] $P < 0.05$ transected vs. intact side; [b] $P < 0.01$ TFMPP-treated groups vs. controls. Redrawn from Hjorth et al., 1995.

temically administered methiothepin increased the synthesis of 5-HT in rat frontal cortex, while the 5-HT_{1A}/5-HT_2 receptor antagonist, spiperone, had no effect.

In guinea pig brain, systemic administration of GR 127935, a reportedly selective 5-$HT_{1B/D}$ receptor antagonist (Roberts et al., 1994) increases 5-HT synthesis in the frontal cortex (maximum effect 233% of control). Smaller, but significant increases (55–60%) in 5-HT synthesis have also been found in other regions such as the hypothalamus, hippocampus and substantia nigra following systemic administration of similar doses of GR 127935 (Moret and Briley, 1996b).

Tingley et al. (1998) reported that the high affinity 5-HT_{1D} receptor antagonist CP-291,952 produces increases in 5-HT turnover (ratio of 5-hydroxyindole acetic acid (5-HIAA)/5-HT) in guinea pig cortex and other brain regions following oral administration and reverses the decrease in 5-HT turnover caused by the 5-HT_{1D} receptor agonist, [3-(*N*-methylpyrrolidin-2 *R*-ylmethyl)-5-(3-nitropyrid-2-yl)amino-1H-indole] (CP-135,807), in these regions. Taken together, these findings observed in both rat and guinea pig strongly suggest that the terminal 5-$HT_{1B/D}$ autoreceptors can play a role in the regulation of 5-HT synthesis.

There are few studies on the association of stress or anxiety and changes of 5-HT synthesis. Chaouloff et al. (1998) used the Wistar–Kyoto (WKY) rat strain which displays high emotivity (e.g. "anxiety") in stressful environments to assess the neurochemical bases of emotivity in comparison to Wistar rats. They observed that WKY rats, when compared with Wistar rats, display a lower hyperlocomotor response to the acute administration of the non-selective 5-HT receptor compound, RU 24969. Since RU 24969-induced hyperlocomotion has been proposed to be a postsynaptic 5-HT_{1B} receptor-mediated response in rats (Chopin et al., 1994; Martinez and Geyer, 1997), they examined whether such a genetic difference in a 5-HT_{1B} receptor-mediated response extends to 5-HT_{1B} receptor-mediated function, such as the inhibition of 5-HT synthesis at serotonergic nerve. In the midbrain 5-HT turnover, as indicated by the accumulation of 5-HTP, is higher in WKY rats than in Wistar rats and the pretreatment of WKY rats with GR 127935 increases midbrain 5-HTP levels (Chaouloff et al., 1998). These interesting findings need to be extended to other brain regions and confirmed with more selective agents. However, the use of these emotive or "anxious" strains of rats promises to be a fruitful model to study the involvement of receptor subtypes in affective disorders.

3. 5-HT_{1B} heteroreceptors

As noted above, 5-HT_{1B} receptors also serve as heteroreceptors on non-serotonergic neurons. In vitro studies have demonstrated an inhibitory influence of these receptors on acetylcholine release in rat hippocampus (Maura and Raiteri, 1986; Cassel et al., 1995), dopamine release in rat striatum (Sarhan et al., 1999) and glutamate release in various brain regions of the rat (see review of Barnes and Sharp, 1999). Finally and most importantly from the point of view of this review, 5-$HT_{1B/D}$ receptors inhibit the release of γ-aminobutyric acid (GABA) (Feuerstein et al., 1996). The importance of this effect is suggested by the high density of 5-HT_{1B} binding sites located on striatonigral GABAergic afferents in the substantia nigra (Waeber et al., 1990a,b).

Pharmacological challenge tests provide a method of assessing the functional responsiveness of 5-HT receptor subtypes in the human brain. Such tests require identification of the particular response believed to be mediated by the receptor concerned. Ideally, a pharmacological challenge should employ a selective agonist ligand. If this is not available, it is possible to use a less selective agent, and the response blocked by selective receptor antagonists in order to show that the action is mediated through activation of the specific receptor (Cowen, 1993). Studies of the possible role of 5-$HT_{1B/D}$ receptors in psychiatric disorders in humans have benefited from the availability of sumatriptan, the first relatively selective compound for 5-$HT_{1B/D}$ receptors used clinically for the symptomatic treatment of migraine attacks. Sumatriptan only penetrates the blood–brain barrier to a limited extent, nevertheless it has proven to be a useful clinical research tool, especially for neuroendocrine and behavioural challenge studies. Although sumatriptan increases plasma prolactin (Franceschini et al., 1994), the most specific neuroendocrine response induced in humans by the administration of sumatriptan is a major, greater than fivefold, increase in plasma levels of growth hormone (GH) (Franceschini et al., 1994). This effect, which is prevented by prior administration of the non-selective 5-HT_1 receptor antagonist cyproheptadine, has been suggested to result from an inhibition of the release of somatostatin via stimulation of 5-$HT_{1B/D}$ heteroreceptors (Mota et al., 1995).

4. Possible role of 5-HT_{1B} receptors in depression

As already mentioned above, 5-HT is involved in the physiological processes of feeding, sleep, sexual behaviour, mood, vigilance and learning, all of which are modified to varying extents in human depression. However, the involvement of precise 5-HT receptor subtypes in depression, and in the action of antidepressant drugs, is still far from clear. Little information is available on the possible effects of direct 5-HT_{1B} receptor stimulation.

Many reports have demonstrated that chronic administration of tricyclic antidepressant or selective serotonin reuptake inhibitors to rats results in a down-regulation of the terminal 5-HT_{1B} autoreceptor (see review of Briley et al., 1997). In guinea pigs this autoreceptor also appears to

be desensitised after a long-term blockade of 5-HT uptake (Briley et al., 1997). These findings are particularly interesting in the context of depressive illness. In spite of the rapid onset of uptake blockade in humans (within a few hours in platelets), the earliest signs of therapeutic improvement in depressive symptoms appear only after 2 weeks of treatment with selective serotonin reuptake inhibitors (see review of Feighner and Boyer, 1991). The latency of the therapeutic effects has been attributed to the need for adaptive changes to be brought about by long-term treatment (for review, see Briley and Moret, 1993). One of these adaptive changes may be the desensitisation of the terminal 5-HT_{1B} autoreceptor, with the subsequent rise of synaptic levels of 5-HT and the stimulation of one or more postsynaptic receptors, which is thought to be an essential long-term action of these antidepressants. Thus, rather than waiting for the desensitisation of the 5-HT_{1B} autoreceptor which can take 2 to 3 weeks, a 5-HT_{1B} receptor antagonist acting at the terminal autoreceptor should be rapidly efficacious (Briley and Moret, 1993). Using in vivo microdialysis on freely moving rats, Moret and Briley (1996a) have found that extracellular levels of 5-HT are increased by both acute and repeated administration with the selective serotonin reuptake inhibitor, citalopram, without washout. In rats treated chronically without washout, methiothepin (administered locally via the probe) has a greater maximal effect on 5-HT outflow than in rats receiving acute citalopram treatment (Moret and Briley, 1996a). This study shows that a 5-HT uptake inhibitor and an autoreceptor antagonist are both capable of increasing extracellular levels of 5-HT. Furthermore, these two effects are additive or possibly synergistic, suggesting that a terminal 5-HT autoreceptor antagonist or a combination of such a drug with a 5-HT uptake inhibitor would produce a greater increase in extracellular levels of 5-HT in hyposerotonergic states and thus, be potentially useful in the treatment of depressive disorders resistant to therapy by a single drug (Briley and Moret, 1993; Matzen et al., 2000).

Does this mean that 5-HT_{1B} receptors are supersensitive in depressed patients? At this time we have no direct answer but indirect responses are provided by some studies carried out in animal model of depression.

In the learned helplessness (LH) paradigm, some (but not all) rats that are exposed to uncontrollable footshocks fail to learn an escape response, such as a lever press in an operant cage or to move into another compartment in a shuttle box apparatus. In learned helpless rats, exposure to uncontrollable stress produces a number of signs seen in depressed patients such as weight loss, changes in sleep pattern, decreased locomotion as well as performance deficits in learning tasks (Sherman et al., 1979). These symptoms and specifically the performance deficits are reduced by a variety of clinically effective antidepressant drugs (Martin et al., 1990). In addition, the density of serotonin uptake sites as measured by [^{3}H]-imipramine binding (in the cortex) (Sherman and Petty, 1984) or [^{3}H]-paroxetine binding (in the hypothalamus) (Edwards et al., 1991) are reduced in learned helpless rats as compared to controls. This closely resembles the clinical situation, where there have been numerous reports (for review see, for example, Owens and Nemeroff, 1994) of decreases in serotonin uptake sites labelled by [^{3}H]-imipramine (and other more selective ligands) in platelets of depressed patients and in the post-mortem brain of suicide victims.

In learned helpless rats, 5-HT_{1B} receptors are up-regulated (increased receptor binding) in the cortex, hippocampus and septum and down-regulated in the hypothalamus (Edwards et al., 1991), compared to control animals. These results suggest that a change in 5-HT_{1B} receptor responsiveness might be related to the escape deficit. 5-HT release measured in vivo by microdialysis in the cortex of learned helpless rats is decreased (Petty et al., 1992), which is compatible with 5-HT_{1B} autoreceptors being up-regulated. More recently Neumaier et al. (1997) have found that presynaptic 5-HT_{1B} mRNA hybridization signal in the dorsal raphe nucleus of helpless rats is 25% higher than control values. This result suggests that an increased capacity to synthesise presynaptic 5-HT_{1B} receptors could account for diminished serotonin neurotransmission in LH. All these findings are coherent with a supersensitivity (or greater density) of 5-HT_{1B} receptors in this LH model of depression (Table 1).

Another rodent model which has been developed to detect antidepressant activity and which simulates certain aspects of the disease state is the olfactory bulbectomised rat. Bilateral olfactory bulbectomised animals have characteristic hyperactivity in a stressful novel environment, which is reversed only by chronic antidepressant treatment (McNamara et al., 1995). This rat model is highly selective for detecting the activity of both typical and atypical antidepressants (Van Riezen and Leonard, 1991). It shows that the non-selective 5-HT_{1B} receptor antagonist, methiothepin, reduces the hyperactivity in olfactory bulbectomised rats at doses where it does not modify the behaviour of control animals, suggesting that methiothepin exhibits antidepressant-like activity in this model of depression. This finding suggests that 5-HT_{1B} receptor antagonists may have antidepressant properties (Table 2).

Data are also available from challenge studies in human volunteers. Sumatriptan and more recent 5-$HT_{1B/D}$ receptor agonists such as, rizatriptan and zolmitriptan, have

Table 1
Biochemical parameters in rats with a behavioural deficit resulting from uncontrollable shocks (LH) expressed as percentage of control animals

Cortex	5-HT_{1B} B_{max}	+119%	(Edwards et al., 1991)
Dorsal raphe	5-HT_{1B} mRNA	+25%	(Neumaier et al., 1997)
Cortex	5-HT release	−54%	(Petty et al., 1992)

5-HT_{1B} B_{max} represent the maximum of 5-HT_{1B} binding sites in cortical membranes. 5-HT_{1B} mRNA is 5-HT_{1B} in situ hybridization signal in the dorsal raphe nucleus. 5-HT release from frontal cortex was measured by microdialysis.

Table 2
Effect of 3 mg/kg methiothepin on ambulation scores in the open field (group median) in the olfactory bulbectomised (OB) rat model of depression

	Open field ambulation counts
Sham + vehicle	70
Sham + 3 mg/kg methiothepin	75
OB + vehicle	112[a]
OB + 3 mg/kg methiothepin	85[b]

Results are expressed as ambulation counts over a 3 min observation period.
[a] $P < 0.01$ as compared with sham control.
[b] $P < 0.05$ as compared with OB control. Taken from McNamara et al. (1995).

been shown to increase plasma GH in humans (see review of Whale and Cowen, 1998).The GH response to sumatriptan was found to be blunted during winter depression in 10 seasonal affective disorder patients and normalised in these patients after mood improvement by light therapy (Yatham et al., 1997a). A blunted GH response to sumatriptan was also found in two studies of non-medicated patients with acute unipolar major depression (Yatham et al., 1997b; Cleare et al., 1998). These studies suggest that 5-$HT_{1B/D}$ receptors are down-regulated in depression, which contrasts to the supersensitivity of these receptors found in the LH animal model of depression. Clearly further studies are required to clarify this apparent contradiction.

5. Possible role of 5-HT_{1B} receptors in anxiety

In general, compounds that decrease 5-HT neurotransmission tend to decrease the level of anxiety, whereas those that increase 5-HT stimulation tend to increase the level of anxiety (Chopin and Briley, 1987; Briley and Chopin, 1991, 1994). Broekkamp et al. (1989) have discussed that particular animal models are relevant only for the study of a particular type of anxiety disorder, and they concluded that the 5-HT_{1B} or 5-HT_{1D} receptors play a role in the "defensive burying" anxiety model and probably mediate the anti-anxiety effects of serotonin uptake inhibitors. Various agonists that exhibit a certain selectivity for 5-HT_{1B} receptors, such as RU 24969, TFMPP and eltoprazine show anxiogenic-like activity in animal models (Briley et al., 1997) such as the shock probe conflict procedure, the social interaction test and the elevated plus-maze test both in rats (Pellow et al., 1987) and in mice (Benjamin et al., 1990; Rodgers et al., 1992), although results in conflict tests in rodents are more variable (Deacon and Gardner, 1986). The rat ultrasonic vocalisation (USV) model (Olivier et al., 1998), is an animal model reflecting anxiety, where ultrasonic vocalisation emitted by rat pups isolated from their mother and littermates are recorded as an index of anxiety. This model has been used to study ligands with different selectivity for various subtypes of serotonin receptors. TFMPP stimulates ultrasonic vocalisation at a low dose but suppresses it at a high dose. The more selective 5-$HT_{1B/D}$ receptor agonist, (-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]-pyridine) (CP 94,253), dose-dependently supressed ultrasonic vocalisation, an effect attenuated by the 5-$HT_{1B/D}$ receptor antagonist, GR 127935 (Fish et al., 2000).

By using recently available more selective antagonists, Chopin et al. (1998) have shown the possible implication of 5-HT_{1B} receptors in anxiety. The 5-$HT_{1B/D}$ and 5-HT_{1B} receptor antagonists, respectively, GR 127935 and SB 224289, increase the amount of time spent in the light chamber in the two-compartment paradigm in mice, suggesting the drugs to exert anxiolytic-like activity in this anxiety model.

The benzodiazepine receptor antagonist, flumazenil, attenuates the anxiolytic-like effects of both diazepam and of GR 127935 in this model. The anxiolytic-like effects of both diazepam and GR 127935 are also inhibited by the 5-HT_{1B} receptor agonist GR 46611 which is inactive when given alone. A combination of an inactive dose of diazepam with an inactive dose of GR 127935 increases the time spent in the light compartment, suggesting a potentiation of anxiolytic effects between these two compounds. These findings suggest that complex interactions can occur between benzodiazepine and 5-HT_{1B} receptors in the regulation of anxiety states, supporting a suggestion made earlier by Rex et al. (1993). It is possible that this interaction may involve the GABA system since 5-HT_{1B} receptors have been shown to regulate GABA release.

Using a murine genetic model, Clément et al. (1996) have studied variations in the density of 5-HT_{1B} receptor subtype measured in the brains of parental strains and two other genetically modified populations by quantitative autoradiography in relation to modifications of anxiety-related behaviours. The results have shown that chromosomal fragments, previously shown to be involved in anxiogenic processes, are mainly associated with a variation in the density of the 5-HT_{1B} receptors.

From studies using anxiety tests it thus appears that 5-HT_{1B} receptor agonists induce or exacerbate an anxiety state while antagonists are anxiolytic. Is the 5-HT_{1B} autoreceptor implicated? Theoretically the stimulation of the autoreceptor by an agonist decreases 5-HT release and would be expected to be anxiolytic. Antagonists, on the contrary, by blocking the autoreceptor, enhance 5-HT release and would be expected to be anxiogenic. Thus it seems unlikely that the autoreceptor is implicated in the action of 5-HT_{1B} receptor drugs controlling anxiety, but rather the 5-HT_{1B} heteroreceptor. These receptors, present on non-serotonin terminals, modulate the release of other neurotransmitters. Feuerstein et al. (1996), for example, have demonstrated that 5-HT_{1D}-like receptors inhibit

GABA release in human neocortex. Thus an enhanced activation of 5-HT_{1D}-like heteroreceptors decreases the release of GABA, leading to an anxiogenic state. On the contrary a blockade of these receptors should enhance the release of GABA thus reducing anxiety.

5-HT_{1B} "knockout" mice have been produced by specific ablation of the 5-HT_{1B} receptor gene by homologous recombination (Castanon et al., 1997). Although these animals, which lack the 5-HT_{1B} receptor, may undergo adaptation during and after development, they represent an interesting model for studying the function of the 5-HT_{1B} receptor (see review by Stark and Hen, 1999). Ramboz et al. (1996) have found that there is no difference in the level of anxiety between mutant and wild-type mice as judged by their activity in the light/dark model. In contrast, 5-HT_{1B} knockout mice are less "anxious" compared to wild-type mice in the open-field (Zhuang et al., 1999), the ultrasound vocalisations (Brunner et al., 1999), the burying behaviour (personal communication) models with no difference or a decrease in anxiety seen in the elevated plus-maze (Brunner et al., 1999). These data in general lend support to the notion that a 5-HT_{1B} receptor antagonist is likely to exert an anxiolytic activity.

6. Possible role of 5-HT_{1B} receptors in OCD

Serotonergic pathways are thought to be involved in the pathophysiology of OCD since selective serotonin reuptake inhibitors are useful in therapy (Zohar et al., 1992; Pigott et al., 1992). In addition, in some studies the acute administration of the non-selective 5-HT receptor agonist, *m*-chlorophenylpiperazine (*m*CPP) as a probe to study OCD, produces an acute symptomatic worsening in untreated OCD patients (Zohar et al., 1987; Fig. 3) which normalises in patients successfully treated chronically with clomipramine (Zohar et al., 1988; Fig. 3). The more selective 5-$HT_{1B/D}$ receptor agonist, sumatriptan, has also been shown to exacerbate symptoms in OCD patients (Dolberg et al., 1996), although this effects has not been observed in all studies (Pian et al., 1998). The two challenges, *m*CPP and sumatriptan (Zohar, 1996), associated with an exacerbation of obsessive–compulsive symptoms, appear to be related to 5-HT_{1D} receptors and it has been suggested that 5-$HT_{1B/D}$ receptors may be supersensitive in OCD patients (Zohar et al., 1988; Dolberg et al., 1995). In addition, functional brain imaging with single photon emission computed tomography combined with symptom provocation with sumatriptan further supports the role of the 5-HT_{1D} receptor (Stein et al., 1999; Stern et al., 1998). In a pilot study in severe drug resistant OCD patients, chronic treatment with sumatriptan resulted in a modest reduction of the OCD symptoms in this highly resistant group (Stern et al., 1998). Since OCD symptoms are unaltered by modification of synaptic 5-HT levels, through tryptophane loading (Charney et al., 1988) or depletion

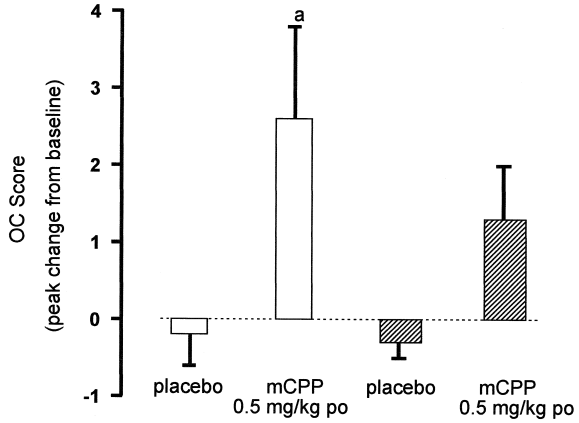

Fig. 3. Effect of *m*CPP (0.5 mg/kg p.o.) in obsessive compulsive disorder the same patients, untreated (open columns) and treated with clomipramine (150 mg/day) for 4 months (cross hatched columns). Ordinate refers to obsessive compulsive score as peak change from baseline). [a] $P < 0.05$ compared to placebo. Data taken from Stern et al., 1998.

(Pigott et al., 1993), the receptors involved appear not to be 5-HT release-controlling autoreceptors but more probably 5-$HT_{1B/D}$ heteroreceptors.

7. Conclusion

In spite of the lack of selective ligands, especially antagonists, available pharmacological data suggest the probable involvement of 5-$HT_{1B/D}$ receptors in the control of a certain number of animal behavioural activities (Briley et al., 1997) and in psychiatric diseases.

Increased levels of anxiety appear to be associated with increased serotonergic activity (Briley and Chopin, 1994). The frequent co-existence of high levels of anxiety with depression, often considered to be a hyposerotonergic state is, therefore, somewhat of a paradox. Interestingly, rats exposed to repeated inescapable shocks, such as the "learned helpless rats" not only show a number of "depressive" signs (Sherman et al., 1979), but also exhibit behaviour associated with high levels of anxiety (Vandijken et al., 1992a,b). Increased sensitivity of both 5-HT_{1B} autoreceptors and 5-HT_{1B} heteroreceptors could explain this paradoxical situation. Increased feedback regulation (through supersensitive autoreceptors) would result in lower levels of 5-HT release, while up-regulated 5-HT heteroreceptors (on GABA terminals for example) could lead to increased anxiety through decrease levels of GABA (Briley et al., 1997).

By associating behavioural studies of depression, stress and anxiety state with neurochemical changes of 5-HT using, for example, the microdialysis technique, it will be possible with the availability of new selective drugs to identify exactly the target implicated and the underlying biochemical mechanism.

The accumulated evidence suggests that the 5-HT_{1B} receptor may play a key role in the control of anxiety and

other disorders. The control of 5-HT_{1B} receptors through endogenous peptide, 5-HT-modulin, offers an interesting therapeutic target for the treatment of anxiety and possibly depression (Sarhan and Fillion, 1998).

Recent studies in OCD (Dolberg et al., 1995) suggest that 5-HT_{1D} receptors (probably heteroreceptors) may be supersensitive and that their desensitisation through long-term administration of 5-HT reuptake inhibitors is related to a therapeutic improvement. A significant gain in the delay of onset of action and possibly greater efficacy might therefore be expected by the use of specific direct-acting 5-HT_{1D} receptor antagonists in the treatment of OCD.

In conclusion, 5-$HT_{1B/D}$ receptors are clearly involved in a number of basic behavioural activities in animals. Several lines of evidence suggest that changes in the sensitivity of 5-$HT_{1B/D}$ auto- and/or heteroreceptors may be fundamental to psychiatric disorders such as depression, anxiety, OCD and other diseases. Further investigation into 5-$HT_{1B/D}$ receptor function in psychopathology would appear to be potentially rewarding. In addition the development of new selective compounds, particularly antagonists, will provide therapeutic agents which may be more efficacious and more rapidly acting than current medication.

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