Behavioural consequences of selective activation of 5-HT receptor subtypes
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Chapter 10

Interaction between 5-HT receptor subtypes: Is a disturbed balance contributing to the symptomatology of depression in man?
SUMMARY

The consequences of our findings for understanding the effects of antidepressant treatments are described in this chapter. The following topics come up for discussion. In a summary table the involvement of 5-HT receptor subtypes in inducing behavioural effects is described. It is emphasized that these effects are not always exclusively linked to serotonergic functions nor that they are always initiated by central 5-HT receptors. Hereafter the complex mutual inhibitory effects of 5-HT receptor subtype mediated processes are discussed by interpreting effects of antagonists and describing the different effects of low and high doses of mixed 5-HT\textsubscript{1C}/5-HT\textsubscript{2} receptor agonist. Mutual influences are seen particularly with 5-HT\textsubscript{1A}, 5-HT\textsubscript{1C} and 5-HT\textsubscript{2} but not with 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D} or 5-HT\textsubscript{3} mediated effects. It is shown that the behavioural consequences of 5-HT\textsubscript{1A}, 5-HT\textsubscript{1C} and 5-HT\textsubscript{2} receptor stimulation may be changed by brain lesions or chronic treatment with drugs. Among these drugs are the antidepressants. Finally, 5-HT receptor functioning in depressed patients is discussed and the hypothesis is proposed that an important function of antidepressants is to restore a disturbed balance between 5-HT\textsubscript{1A}, 5-HT\textsubscript{1C} and 5-HT\textsubscript{2} receptors in depressed patients.

10.1 INTRODUCTION

The first signs of behavioural changes after increasing synaptic 5-HT availability have been described by Hess and Doepfner (1961) and later by Grahame-Smith (1971). They described the so-called “serotonin-syndrome” after injection of L-tryptophan in rats that were pretreated with a monoamine oxidase (MAO) inhibitor. Thus, reciprocal forepaw treading, head weaving, hindlimb abduction, flat body posture, Straub tail and piloerection, were seen. The same syndrome could also be induced by a variety of other 5-HT agonists such as 5-methoxy N,N-dimethyltryptamine (5-MeODMT), quipazine and the 5-HT releasing compound fenfluramine (Grahame-Smith, 1971; Green et al., 1976; Green and Kelly, 1976; Green and Heal, 1985). However, these compounds do not have selectivity for 5-HT receptor subtypes (Hoyer, 1988). With the synthesis of more selective agonists and antagonists, it became possible to identify behavioural changes related to one particular serotonin receptor subtype. These behavioural changes will be reviewed and the effect of antidepressant treatment on these behaviours will be discussed. It should be noted however that the described behavioural changes are not viewed as models of physiological or pathological conditions. Those are used merely as markers of serotonin function. According the behavioural changes induced by the psychoactive compounds allow a prediction of alterations that occur in the function of the transmitter after drug administration. If, for example, a response is changed after chronic treatment with an antidepressant drug as seen in chapter 9 than this was taken as indication how a serotonin function was changed by an antidepressant. A concept can then be formulated concerning changes involved in the therapeutic mechanism of action of the drug. Again it is emphasized that these behavioural effects are not viewed as models for depression. Rather those are considered as a kind of bioassay for specific receptor functioning.
10.2 BEHAVIOURAL CHANGES MEDIATED BY 5-HT RECEPTOR SUBTYPES

In table 1 the different behavioural changes mediated by 5-HT receptor subtypes are summarized. The majority of these behaviours are not influenced exclusively by one particular 5-HT receptor subtype, nor are the changes necessarily caused by an action within the brain.

10.2.1 Non-selectivity of 5-HT mediated behaviour

Body temperature is influenced by many drugs. The 5-HT¹A agonist 8-OH-DPAT, the α-adrenergic agonist clonidine, the dopamine agonist apomorphine, but also the dopamine antagonist haloperidol can induce hypothermia. Hyperthermia induced by the 5-HT agonist MK 212 seems to be mediated by central 5-HT² receptors (Gudelski et al., 1986), whereas similar effect of high doses of the 5-HT antagonist mianserin might be mediated by noradrenergic mechanisms (Berendsen et al., 1978).

Hypolocomotion can be the result of activation of 5-HT¹A or 5-HT¹C and 5-HT² receptors. 8-OH-DPAT but also mCPP and TFMPP can reduce locomotor activity (chapter 5; Lucki and Frazer, 1985; Lucki et al., 1989). Reduced locomotor activity is also seen after injection of 5-HT antagonists like mianserin, dopamine antagonists like haloperidol and low doses of dopamine agonists like apomorphine (Cuomo et al., 1983; Megens et al., 1988; Costall et al., 1981). Thus, hyper- or hypothermia and inhibition of locomotor activity are not selective for a single receptor system. Research for more selective and simple behavioural changes was thus needed in order to study more thoroughly the functions of the various receptor subtypes. In chapters 2, 3, 4 and 6 such selective behaviours were described.

Table 1.

Behavioural changes mediated by the different 5-HT receptor subtypes.

<table>
<thead>
<tr>
<th>Behaviour mediated by:</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>5-HT¹A receptors</strong></td>
<td></td>
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<tr>
<td>5-HT syndrome (rat)</td>
<td></td>
</tr>
<tr>
<td>Hyperphagia (rat and mice)</td>
<td>Tricklebank et al., 1984</td>
</tr>
<tr>
<td>Head shakes (pig)</td>
<td></td>
</tr>
<tr>
<td>Lower lip retraction (rat)</td>
<td>Goodwin and Green, 1985; Hjorth, 1985, Gudelski et al., 1986; Goodwin et al., 1986</td>
</tr>
<tr>
<td>Attentuation of 5-HT¹C and 5-HT² mediated behaviour (rat)</td>
<td>Lüscher et al., 1990.</td>
</tr>
</tbody>
</table>

Chapter 3; Berendsen et al., 1989.
5-HT_1B receptors

5-HT_1C receptors
Hyperphagia (antagonists, rat) Dourish et al., 1989
Penile erections Attenuation of 5-HT_1A and 5-HT_2 mediated behaviour (rat) Chapter 5; Berendsen et al., 1989.

5-HT_1D receptors
Hindlimb scratching (rat) Chapters 6 and 7.

5-HT_2 receptors
Head twitches (mice) Corne et al., 1963; Heal et al. 1985; Goodwin and Green, 1985.
Head shakes (rat) Bedard and Pycock, 1977; Yap and Taylor, 1984; Peroutka et al., 1981.
(wet dog shakes)
Attenuation of 5-HT_1A mediated lower lip retraction, hypothermia and hypoactivity Chapter 5
Attenuation of 5-HT_1C mediated penile erections Chapter 2
Potentiation of 5-HT_1A mediated forepaw treading Berendsen et al., 1989; chapter 5.

5-HT_3 receptors
Antagonists active in
- anticancer treatment-induced emesis Costall et al., 1987a.
- Chronic dopamine-induced hyperactivity Tricklebank 1989; Barnes et al., 1989.
- Anxiety models Costall et al., 1987b; 1989.
- Cognition models Barnes et al., 1990; Jones et al., 1990.
- Place conditioning Papp, 1988.

10.2.2 Behaviour in which peripheral 5-HT receptors play a role

Main symptoms of the 5-HT syndrome may also be mediated outside the blood brain barrier. Activation of the 5-HT_1A receptor induces a number of symptoms of the behavioural syndrome, like forepaw treading (Tricklebank et al., 1984; Arvidsson et al., 1981; Hjorth et al., 1982). This 5-HT syndrome is not only induced by 8-OH-DPAT or 5-MeODMT but also by the serotonin precursor 5-hydroxytryptophan (5-HTP). If rats are pretreated with a peripheral decarboxylase inhibitor, which prevents the formation of serotonin from 5-HTP in peripheral tissue but not in the central nervous system, the
induction of forepaw treading, hindlimb abduction and Straub tail is prevented or postponed. Thus, by excluding the formation of 5-HT from 5-HTP in the periphery, the induction of a number of symptoms of the 5-HT syndrome is absent.

10.3 FUNCTIONAL INTERACTIONS BETWEEN 5-HT RECEPTOR SUBTYPE ACTIVATION

The behaviours induced by selective activation of 5-HT receptor subtypes like the lower lip retraction via 5-HT1A receptors (chapter 3), the induction of penile erections through 5-HT1C receptors (chapter 2) and the head shake response after activation of 5-HT2 receptors (Bedard and Pycock, 1977; Yap and Taylor, 1983; Peroutka et al., 1981) are influenced by concomitant activation of other 5-HT receptor subtypes (chapter 5). These functional interactions may explain why compounds that activate certain 5-HT receptor subtypes do not induce the behaviour ascribed to activation of that particular 5-HT receptor subtype. These functional interactions may also explain why antagonists not always block a certain behaviour, but potentiation occurs instead.

10.3.1 Functional 5-HT1A agonistic effects of 5-HT antagonists

Lower lip retraction is the result of selective activation of 5-HT1A receptors. However, this behaviour can also be induced by certain 5-HT antagonists. In chapter 4, it was explained how 5-HT antagonists like ritanserin, cyproheptadine or metergoline, may induce lower lip retraction. These compounds have a higher affinity for 5-HT1C and/or 5-HT2 than for 5-HT1A receptors. The functionally agonistic effect at 5-HT1A receptors may be due to the preferential reduction of the tone on 5-HT1C and 5-HT2 receptors.

This functional agonistic effect of mixed 5-HT1C/5-HT2 antagonists may also explain why the antagonists metergoline, ritanserin and ketanserin potentiate the 8-OH-DPAT induced hypothermia (Green and Goodwin, 1987; Aulakh et al., 1988; Gudelski et al., 1986).

Food intake is increased after application of cyproheptadine, methysergide, mianserin and metergoline in man (Pawlowski, 1975; Silverstone and Schuyler, 1975; Hopman, 1980; Silverstone and Goodall, 1986) and in rats (Dourish et al., 1989). Stimulation of 5-HT1A receptors is also followed by an increase in food intake in rats (Dourish et al., 1985a,b; Bendotti and Samanin, 1986; Wong and Reid, 1987; Neill and Cooper, 1988) and mice (Shepherd and Rodgers, 1990). A functional 5-HT1A agonistic effect may also explain this hyperphagic effect.
10.3.2 Functional interactions involving 5-HT_{1C} receptor activation

An effect that is selectively mediated by 5-HT_{1C} receptors is the induction of penile erections (PE) (chapter 2). Penile erections can be induced by direct 5-HT_{1C} agonist. Indirect 5-HT agonists like the 5-HT precursor 5-HTP, 5-HT releasing compounds like fenfluramine, 5-HT reuptake inhibitors and MAO inhibitors also induce penile erections (Berendsen and Broekkamp, 1987; chapters 2 and 9). Thus, each increase in synaptic availability of 5-HT in the central nervous system of the rat causes an activation of 5-HT_{1C} receptors and enhances the induction of penile erections. However, the dose response curves for PE induced by the agonists MK 212, mCPP and TFMPP are bell shaped (chapter 2). This is apparently due to the low selectivity of these compounds for the 5-HT_{1C} over 5-HT_{2} receptors. Concomitant activation of 5-HT_{2} receptors attenuates the response mediated by the 5-HT_{1C} receptors. Selectivity for 5-HT_{2} over 5-HT_{1A} receptors also plays a role (chapter 2). Some examples of the dominating role of behaviours mediated by other than 5-HT_{1C} receptor subtypes over the 5-HT_{1C} receptor mediated penile erections were described in chapter 5. In the literature, Clineschmidt et al. (1977) reported that i.v. injection of 1.5 mg/kg of MK 212 in rats elicits the 5-HT syndrome, and injection of 3 mg/kg in mice results in the 5-HT_{2} receptor mediated head twitches. Up to 1 mg/kg we saw penile erections but above this dose the appearance of PE was strongly decreased (chapter 2). Thus, after relatively high doses of MK 212, 5-HT receptors other than 5-HT_{1C} and possibly also peripheral 5-HT receptors are activated thereby causing an attenuation of 5-HT_{1C} receptor mediated behaviour. A similar change in behaviour after low and high doses of fenfluramine was also seen. Treatment (s.c.) with a relatively low dose, this compound induces penile erections (Berendsen and Broekkamp, 1987), but after i.p. treatment with higher doses the 5-HT syndrome has been seen (Trulson and Jacobs, 1976). Despite the mutual inhibitory effects of 5-HT receptor subtype activation, a small increase in synaptic availability of 5-HT e.g. by 5-HT releasing or 5-HT reuptake inhibiting compounds, induces penile erections. After a strong increase of synaptic 5-HT also 5-HT_{1A} and 5-HT_{2} receptors are activated. This suggests that the 5-HT_{1C} receptor is the most sensitive one among the central 5-HT receptor subtypes for the endogenous ligand.

10.3.3 Functional interactions involving other 5-HT receptor subtype activation

Activation of 5-HT_{1B} receptors apparently does not interfere with 5-HT_{1A}, 5-HT_{1C} and 5-HT_{2} receptor mediated behaviours (chapter 5). Evidences are as follows: RU 24969, which binds to 5-HT_{1A} and 5-HT_{1B} receptors, appeared to induce 5-HT_{1A} mediated lower lip retraction. The putative 5-HT_{1B} agonist CGS 12066B hardly affected 5-HT_{1A}, 5-HT_{1C} or 5-HT_{2} mediated behaviours, when injected concomitantly with an agonist for these receptors. Closely related to the 5-HT_{1B} receptors are the 5-HT_{1D} receptors (see Introduction). Activation of these receptors in the periphery induced hindlimb scratching in rats (chapter 6), but only in young rats (chapter 7). Apparently this behaviour is very sensitive to alterations in other 5-HT receptor
subtypes or of other neurotransmitter agonists or antagonists. Effects mediated by central 5-HT\textsubscript{1D} receptors are not known. It is even uncertain that these receptors are present in the brains of rats. Injection of the 5-HT\textsubscript{1D} receptor agonist 5-methoxytryptamine (5-MeOT) concomitantly with 8-OH-DPAT does not change neither the 5-HT\textsubscript{1A} mediated lower lip retraction in rats nor the hypothermia or hypolocomotion response in mice. However, 8-OH-DPAT induced forepaw treading was attenuated by 5-MeOT. Forepaw treading may be mediated by peripheral 5-HT receptors (see above). Thus it is possible that peripheral 5-HT\textsubscript{1A} mediated effects are affected by 5-MeOT, whereas central effects are apparently not. The 5-HT\textsubscript{1C} receptor mediated penile erection and the 5-HT\textsubscript{2} receptor mediated head shake responses are not changed if the rats are treated with 5-MeOT concomitantly with an agonist for the 5-HT\textsubscript{1C} or 5-HT\textsubscript{2} receptor respectively, (Berendsen, unpublished observations). 5-HT\textsubscript{3} antagonists do not affect 5-HT\textsubscript{1A} or 5-HT\textsubscript{1C} mediated behaviours (chapters 2 and 3). Thus, it appears that only 5-HT\textsubscript{1A}, 5-HT\textsubscript{1C} and 5-HT\textsubscript{2} receptor mediated behaviours are subject to functional interactions.

### 10.4 MODULATION OF 5-HT RECEPTOR SUBTYPE MEDIATED BEHAVIOUR

In rats in which the presynaptic 5-HT nerve terminals are destroyed with the neurotoxin 5,7-DHT or in which the synthesis of 5-HT is inhibited after repeated treatment with PCPA, the induction of lower lip retraction by 8-OH-DPAT and the induction of head shakes by DOI was not affected (chapter 8). This suggests that 5-HT\textsubscript{1A} and 5-HT\textsubscript{2} receptor functions are not changed after denervation. However, the behavioural response mediated by activation of 5-HT\textsubscript{1C} receptors by direct agonists was strongly enhanced in denervated rats whereas the same response induced by indirect agonists was attenuated. Thus, 5-HT\textsubscript{1C} receptor function changes after denervation. A different change in behavioural response of the 5-HT\textsubscript{1A} and 5-HT\textsubscript{2} versus the 5-HT\textsubscript{1C} mediated behaviours has also been seen after chronic treatment with agonists for these receptors. The dose response curves of 5-HT\textsubscript{1A} receptor mediated 8-OH-DPAT-induced lower lip retraction, and of 5-HT\textsubscript{2} receptor mediated DOI-induced head shakes, were shifted to the right if the rats were 10 days pretreated with 8-OH-DPAT or DOI respectively. In contrast, the dose response curves for the 5-HT\textsubscript{1C} receptor mediated penile erections remained unchanged both after induction of PE by the direct agonist MK 212 or by a 5-HT reuptake inhibitor (Org 6997) after 10 days of pretreatment with these compounds. Also a 10 days pretreatment with the mixed 5-HT\textsubscript{1C}/5-HT\textsubscript{2} antagonist mianserin did not change the 5-HT\textsubscript{1C} mediated PE response whereas the 5-HT\textsubscript{2} receptor mediated head shake response again was attenuated (chapter 9). In later experiments it was found that after chronic treatment with the 5-HT releasing compound fenfluramine the induction of PE by fenfluramine was strongly diminished. Also the PE response of the 5-HT\textsubscript{1C} agonist MK 212 was attenuated after 10 days fenfluramine treatment. A similar tolerance to the effect of fenfluramine was found in
the muricidal rat test. The effects of mianserin and imipramine, however, were stable after treating the animals with these compounds for 10 days (Berendsen et al., in preparation). Thus, the \(5\text{-HT}_{1C}\) mediated response failed to change after chronic treatment with a \(5\text{-HT}\) reuptake inhibitor, a \(5\text{-HT}_{1C}\) agonist or antagonist but could be changed after chronic treatment with a \(5\text{-HT}\) releasing compound.

10.5 5-HT RECEPTORS, ANTIDEPRESSANTS AND DEPRESSION

Up and down regulation of 5-HT receptors seems to play an important role in the mechanism of action of antidepressant. It has been shown that the different types of chronic antidepressant treatments have different effects on 5-HT receptor binding properties. In a review, summarized in table 2, Willner (1985) showed that 5-HT\(_1\) receptor binding is reduced after chronic treatment with a monoamine oxidase (MAO) inhibitor. 5-HT\(_2\) receptor binding is reduced after treatment with all kinds of antidepressants, except of chronic electroconvulsive treatment. The latter increases 5-HT\(_2\) binding sites. The effect of chronic antidepressant treatment on 5-HT\(_3\) receptor binding is not known. Some antidepressants have high affinity for 5-HT\(_2\) receptors within the CNS whereas others have low affinity (Schmidt and Peroutka, 1989).

In patients suffering from major depressive disorders the number of 5-HT\(_2\) and 5-HT\(_1A\) receptors were found to be increased (see for review Mann et al., 1989). An increased 5-HT\(_1A\) receptor binding was also found in postmortem analysis of the brains of depressed patients who committed suicide in a non violent way (Meltzer, 1990). In contrast, in brains of depressives that committed suicide in a violent way 5-HT\(_2\) receptor binding was found to be increased (Mann et al., 1986; Arora and Meltzer, 1989). An increased 5-HT\(_2\) binding has also been found on blood platelets of depressed patients (Biegon et al., 1987; 1990a,b; Arora and Meltzer, 1989) and a direct correlation between increased 5-HT\(_2\) activity and the severity of depression may exist (Biegon et al., 1990b). In line with this are the findings of Pandey et al. (1990). They found that the 5-HT\(_2\) binding sites on platelets were more increased in depressive patients with a recent history of suicide attempt or suicide ideation as compared with non-suicidal depressed patients. The 5-HT\(_2\) binding sites from the last group were also higher than those of normal controls. An increased 5-HT\(_2\) receptor function in depressed patients was found by Mikuni et al. (1991) using the serotonin-stimulated phosphoinositide hydrolysis in platelets as the index of functioning.

After a low dose of mCPP (0.25 mg/kg), probably stimulating only 5-HT\(_{1C}\) receptors, no hormonal or behavioural changes were seen (Kahn et al. 1990). However, after a higher (0.75 mg/kg) dose Mueller et al. (1986) found an increase in prolactin and ACTH plasma level, and an increased body temperature. This latter effect points to a 5-HT\(_2\) mediated effect. It may thus be that the increase in prolactin and ACTH is a 5-HT\(_2\) rather than a 5-HT\(_{1C}\) receptor mediated response. This idea is supported by the findings reported in chapter 2. At low doses of mCPP only the 5-HT\(_{1C}\) receptors are activated but if the dose is increased also 5-HT\(_2\) receptor related activities were observed.
Patients suffering from atypical depression or seasonal affective disorder may have increased $5$-HT$_{1A}$ function due to hypersensitive or upregulation of $5$-HT$_{1A}$ receptors. They show some symptoms that were seen in rats after stimulation of $5$-HT$_{1A}$ receptors, namely hypersomnia and hyperphagia (Quitkin et al., 1979; Meltzer, 1990). MAO inhibitors have the best therapeutic efficacy in this type of depression (Liebowitz et al., 1988; Quitkin et al., 1979). The MAO inhibitors attenuate the effects of $5$-HT$_{1A}$ receptor stimulation in the rat.

Table 2

<table>
<thead>
<tr>
<th>Antidepressent treatment</th>
<th>Effect on receptor binding</th>
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<tr>
<td></td>
<td>$5$-HT$_1$</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>=</td>
</tr>
<tr>
<td>Atypical antidepressants</td>
<td>=</td>
</tr>
<tr>
<td>Uptake inhibitors</td>
<td>=</td>
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<tr>
<td>MAO inhibitors</td>
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</tr>
<tr>
<td>ECS</td>
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= no effect; ▼ decreased binding; ▲ increased binding.

To date nothing is known about changes in $5$-HT$_{1C}$ receptor binding in depressives. Low dose of mCPP, fenfluramine and L-tryptophan, compounds that activate $5$-HT$_{1C}$ receptors, have been reported to have mood elevating properties in healthy volunteers (Mueller et al., 1985; Charney et al., 1982; Ward et al., 1985). A decreased availability of tryptophan, by restricting the tryptophan intake, can induce a mild depression (Delgado et al., 1990; Young et al., 1985). $5$-HT reuptake inhibitors which are clinically effective antidepressants (Hyttel and Larsen, 1985) also induce in rats $5$-HT$_{1C}$ receptor mediated penile erections. Only if they are injected in combination with a MAO inhibitor they induce the $5$-HT syndrome (Hwang and Van Woerd, 1980). In chapter 9 it has been shown that the $5$-HT$_{1C}$ receptor mediated effect could not be attenuated by neither chronic treatment with an agonist for this receptor, nor by chronic treatment with a $5$-HT reuptake inhibitor, nor by chronic treatment with mianserin, an atypical antidepressant and $5$-HT$_{1C}$/5-HT$_2$ antagonist. The $5$-HT$_{1C}$ mediated behaviour was also not affected after chronic treatment with the tricyclic antidepressant imipramine. However, after chronic treatment with fenfluramine the $5$-HT$_{1C}$ mediated behaviour disappeared (Berendsen et al., in preparation). In man, fenfluramine may mimic long term antidepressant effects after a single treatment (Ward et al., 1985) but it has never been proven to be an effective antidepressant after repeated treatment. It appears that antidepressants do not change the $5$-HT$_{1C}$ receptor related behavioural response but attenuate the $5$-HT$_2$ receptor mediated phenomena. Thus, it might be concluded that compounds that cause an attenuation of $5$-HT$_2$ but not of the $5$-HT$_{1C}$ receptor mediated response after chronic treatment have antidepressant properties. These compounds may be active in major depressive disorders. MAO inhibitors are probably an exception. It has been shown in chapter 9 that chronic treatment with
tranylcypromine affects MK 212 induced PE. Functional interactions between 5-HT$_2$ and 5-HT$_1C$ receptors may also take place in depressed men. It has been observed that nocturnal penile tumescense was decreased in these men (Thase et al., 1987). It is tempting to speculate that in men penile erections are also mediated by 5-HT$_1C$ receptors, as has been seen in rats and in non-human primates (chapter 2; Szele et al., 1988). An increased 5-HT$_2$ activity in these depressed men may than suppress the nocturnal penile tumescense.

It has been described above that an imbalance of the tone on 5-HT$_{1A}$, 5-HT$_{1C}$ and 5-HT$_2$ receptors induces the behaviour that is related to the receptor which is mostly activated. Restoration of the balance by activation of the other receptor subtypes, or by down regulation of the hyperactive receptor, attenuates the behaviour mediated by that receptor subtype. Since depression is a heterogeneous disease it is possible to have a situation in which some patients the 5-HT$_{1A}$ receptor is supersensitive whereas in others the 5-HT$_2$ receptor is supersensitive or subsensitive. However, disturbances in other neurotransmitter systems such as the dopamine and noradrenergic system may also contribute. In conclusion the hypothesis advanced in this thesis is that serotonergic antidepressant treatments and MAO inhibitors restore a disturbed balance between the different 5-HT receptor subtypes and especially between 5-HT$_{1A}$, 5-HT$_{1C}$ and 5-HT$_2$ receptors.

Thus a disturbed balance of the tone to the 5-HT$_{1A}$, 5-HT$_{1C}$ and 5-HT$_2$ receptors may contribute to a depressed state. The type of depression depends on which 5-HT receptor subtype is hyperactive or hypoactive. Further studies, specially studies on 5-HT$_{1C}$ receptor binding after chronic treatment with antidepressants and studies on the balance between 5-HT$_{1A}$, 5-HT$_{1C}$ and 5-HT$_2$ receptor binding in healthy volunteers in comparison to depressed patients are needed to confirm or reject this hypothesis.

In animals, studies on the effect of chronic treatment with non serotonergic antidepressants like bupropion or maprotiline on 5-HT receptor subtype mediated behaviours are needed in order to see to what extend these treatments may change the function of a 5-HT receptor subtype.

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