CHAPTER 7

Summary and general discussion
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A meta-analysis of clinical studies involving the six most widely prescribed antidepressants approved between 1987 and 1999 by the FDA suggested that antidepressant treatment is only marginally more effective than placebo (Kirsch et al., 2002). Other worrying aspects of antidepressant treatments are the considerable non-response rates (30-40%) and the late onset of action (2-5 weeks). According to the World Health Organization major depression is likely to become the most frequently occurring disabling disease of the western world in the coming decade. It can therefore hardly be disputed that there is an urgent need for improved antidepressant treatment. There are, however, no signs that a major breakthrough in pharmacotherapy is to be expected in the near future. Serendipitous findings aside, such breakthrough would need a revolutionary new and scientifically verified framework of depression. Neuroimaging, genomics and proteomics are likely to form important building blocks for such a framework, but as yet our level of insight into the pathophysiology of affective disorders is insufficient to realistically expect major advances in rational drug design. Besides major depression may be too heterogeneous a disease to expect miracles from a single novel pharmacological mechanism. A more realistic approach to improve antidepressant treatment may be found in further exploring the existing hypotheses regarding major depression. Development of the majority of antidepressant drugs has been inspired by the monoamine hypothesis, which was based on serendipitous findings more than forty years ago. The hypothesis has been challenged in the past, but recent evidence from neuroimaging and DNA research support the idea that it still has considerable potential.

An approach to improve antidepressant treatment by further exploring the monoamine hypothesis is augmentation strategies. As detailed in chapter one several forms of augmentation are imaginable, but the present thesis mainly concerns those strategies that are aimed to further increase the effect of SSRIs on extracellular serotonin levels, by making use of antagonists of 5-HT receptors involved in inhibitory feedback mechanisms. One may question the relevance of further increasing 5-HT levels for antidepressant activity. However, striving for increased 5-HT levels is a logical consequence of Blier’s desensitization hypothesis and it also fits in the monoamine hypothesis of depression. On the other hand, direct evidence for a relation between increased 5-HT levels and antidepressant activity is as yet missing. Confounding factors are the unavailability of selective and potent 5-HT receptor antagonists for use in humans and the fact that we are not yet able to estimate 5-HT levels in humans accurately. However, such problems do not arise with studies in laboratory animals.
In the present thesis an attempt has been made to address a number of important questions that can be raised with augmentation strategies. For instance, does SSRI augmentation lead to increased neuronal activity in brain areas that have been associated with major depression? In **chapter two** the expression of the immediate early gene c-fos is used to assess the neuronal activation pattern elicited by a single dose of the SSRI citalopram both in absence and presence of the 5-HT<sub>1A</sub> receptor antagonist WAY 100635. However, the results did not exactly meet the expectations. For instance, the pattern of c-Fos expression in the rat brain following the administration of citalopram did not correspond with the distribution of a particular 5-HT receptor type (Kilpatrick et al., 1987; Morilak et al., 1993; Pazos et al., 1985; Pazos and Palacios, 1985; Ward et al., 1995) or with the density of 5-HT containing nerve terminals (Steinbusch, 1981). In retrospect, however, this could be an important finding indicating that the activation of various brain areas by an SSRI does not critically depend on the activation of particular 5-HT receptor subtypes. Or to put it bluntly: What would be the use of SSRI augmentation strategies when the 5-HT receptor antagonist concomitantly inhibits the neuronal activation of brain areas involved in the antidepressant effect of SSRIs? The study also failed to demonstrate an augmented c-Fos response with WAY 100635 in several important brain areas such as prefrontal cortex, hippocampus, dorsal raphe nucleus and median raphe nucleus, which is at variance with 5-HT microdialysis studies. On the other hand, a significant augmentation was seen in the amygdala, nucleus accumbens and paraventricular nucleus of the hypothalamus, key areas of the limbic-hypothalamic-pituitary-adrenocortical system. This could indicate that, in contrast to prefrontal cortex and hippocampus, activation of postsynaptic 5-HT<sub>1A</sub> receptors in these areas does not play a decisive role in the effects of SSRIs. It is also noteworthy that the mood-stabilizing effect of antidepressants has been hypothesized to result from their action on the limbic-hypothalamic-pituitary-adrenocortical system (Barden et al., 1995).

The desensitization hypothesis by Blier et al. provides a firm basis for connecting onset of action of antidepressants to a loss of 5-HT autoreceptor function. The idea that antidepressant response might be hastened by blocking the autoreceptors sounds convincing, but one may question whether it is realistic to expect enhanced efficacy when autoreceptor function is also disabled following chronic treatment with SSRIs. Many studies have reported desensitization of 5-HT<sub>1A</sub> autoreceptors following chronic antidepressant treatment, indicating that there may be little to gain in terms of efficacy. In contrast to 5-HT<sub>1A</sub> autoreceptors, chronic antidepressant treatment via osmotic mini-pumps did not lead to desensitization of 5-HT<sub>1B</sub> autoreceptors (Cremers et al., 2000). An in situ-hybridization study has, however, shown a decreased expression of the 5-HT<sub>1B</sub> receptor gene following chronic treatment, but also a rapid reversal of the effect after
discontinuation of the antidepressant (Neumaier et al., 2002). In chapter three it is shown that augmentation with 5-HT$_{1B}$ receptor antagonists does not change during chronic antidepressant treatment, while stress markers such as corticosterone, adrenaline and noradrenaline in blood were significantly decreased (Jongsma et al., 2005). The latter effect is in accordance with both preclinical data (Jensen et al., 1999; Reul et al., 1993) and the clinical observation that chronic treatment with antidepressants restores HPA-axis hyperactivity in depressive patients (Barden et al., 1995; Inder et al., 2001) The study also indicates that 5-HT$_{1B}$ autoreceptors do not desensitize during chronic antidepressant treatment, which makes it rather unlikely that they are actively involved in the altered stress-hormone response. This might be clinically relevant, because it suggests that the therapeutic effect of ongoing antidepressant treatment could be further improved by co-administration of a 5-HT$_{1B}$ receptor antagonist. A confounder could be the role of postsynaptic 5-HT$_{1B}$ receptors in the treatment of depression. It can be argued, however, that chronic antidepressant treatment desensitizes postsynaptic but not presynaptic 5-HT$_{1B}$ receptors. Because the in situ-hybridization is not likely to discriminate between pre and postsynaptic 5-HT$_{1B}$ receptors, and 5-HT microdialysis studies measure presynaptic effects only, this might explain the different outcome of these studies. If postsynaptic 5-HT$_{1B}$ receptors do indeed desensitize following chronic treatment it would be rather unlikely that their activation contributes to the antidepressant effect.

Blier’s desensitization hypothesis is based on data from electrophysiology studies into presynaptic 5-HT$_{1A}$ receptors located in the dorsal raphe nucleus. However, dynamic changes of 5-HT$_{1A}$ receptor function may not be restricted to the presynaptic receptors. Previous studies have shown that postsynaptic 5-HT$_{1A}$ receptors located in the central nucleus of the amygdala do not only control presynaptic release but also desensitize upon chronic SSRI treatment (Bosker et al., 1997; Bosker et al., 2001). In chapter three it is shown that postsynaptic 5-HT$_{1A}$ receptors in the prefrontal cortex control local release as well as 5-HT release in the serotonergic dorsal raphe nucleus, suggesting a long loop type of feedback from the prefrontal cortex to the dorsal raphe nucleus. Whereas presynaptic 5-HT$_{1A}$ receptors in the dorsal raphe and postsynaptic 5-HT$_{1A}$ receptors in the amygdala desensitize, the sensitivity of 5-HT$_{1A}$ receptors in the prefrontal cortex appears to increase upon chronic SSRI treatment, which is in agreement with the observed trend toward increased [$^3$H]-8-OH-DPAT binding in the prefrontal cortex. Importantly, opposite effects on pre and postsynaptic 5-HT$_{1A}$ receptors following chronic antidepressant treatment have also been reported by a recent study wherein an increased and decreased agonist stimulated GTP$\gamma$S binding was found in hippocampus and raphe nucleus, respectively (Castro et al., 2003). Such opposite effects on pre and postsynaptic 5-HT$_{1A}$ receptor-mediated feedback would imply a

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shift in control of terminal 5-HT release from the autoreceptors to their postsynaptic counterparts, which could be a factor in the clinical efficacy of antidepressants.

The release of 5-HT and hence also the SSRI induced increases of extracellular 5-HT levels depend on 5-HT autoreceptor control, but also on the availability of the serotonin precursor tryptophan. The latter is in accordance with the clinical observation that depressed patients that were successfully treated with antidepressants suffer from a relapse following tryptophan depletion. In chapter five, it is shown that depletion of tryptophan or inhibition of serotonin synthesis by NSD 1015 strongly reduces the effect of an SSRI on extracellular 5-HT levels, indicating that the effect of SSRIs largely depends on precursor availability and thus de novo synthesis of serotonin. It is therefore conceivable that insufficient synthesis of serotonin, for instance caused by an unfavorable tryptophan hydroxylase gene polymorphism (Zhang et al., 2004; Zhang et al., 2005; Zill et al., 2004), can contribute to the high non-response rates with SSRI treatment. The importance of de novo serotonin synthesis is further emphasized by the additional increase of extracellular 5-HT levels observed when tryptophan is co-administered with an SSRI (van der Stelt et al., 2004, this thesis). While in most clinical studies rather high dosages of tryptophan are used, the results from the present study indicate that even modest increases of tryptophan plasma levels markedly augment the effect of an SSRI on extracellular 5-HT levels. Arguably, a lower dose of tryptophan may have a comparable effect on antidepressant activity, but it could be less prone to causing serious side effects such as the serotonergic syndrome.

It is also conceivable that SSRI augmentation with a 5-HT receptor antagonist has little effect if the lack of therapeutic effect originates from insufficient levels of tryptophan. However, while the concept of antagonist-based augmentation has been applied clinically by co-administration of an SSRI with the mixed β-adrenergic and 5-HT1A receptor antagonist pindolol (Ballesteros and Callado, 2004) or the 5-HT2C receptor antagonist mianserin (Maes et al., 1999; Ferreri et al., 2001), no attention has been paid in those studies to the circulating tryptophan levels. In chapter five the effect of tryptophan supplementation on 5-HT1A, 5-HT1B and 5-HT2C receptor antagonist based augmentation strategies is also investigated. While tryptophan further increased all three forms of 5-HT antagonist-based SSRI augmentation, only antagonism of 5-HT1B receptors was capable to significantly enhance the augmentation observed with tryptophan. Apparently, when the precursor is sufficiently present, 5-HT1B receptor-controlled processes like synthesis and release become the limiting factor. Summarizing, it should be taken into account that if treatment with serotonergic antidepressants is insufficient even following augmentation, additional tryptophan might be required to attain the therapeutic effect.
Release of 5-HT and the effect of SSRIs on extracellular 5-HT levels are limited by the availability of tryptophan, but otherwise depend on intracellular serotonin stores. These stores rely both on synthesis and reuptake of previously released serotonin. So theoretically, under conditions of prolonged reuptake inhibition, synthesis needs to adjust in order to prevent depletion of intracellular serotonin stores. In chapter six it is shown that as a result of continuous reuptake inhibition and decreased synthesis (through the activation of the autoreceptors) intracellular serotonin stores are steadily depleted. Future research should reveal whether this could be part of the mechanism of action or must be regarded as an unwanted side effect of SSRIs.

Another worrying aspect of chronic antidepressant treatment is the clinical phenomenon called rebound depression. When antidepressant therapy is suddenly discontinued, patients have been reported to relapse into a depressive state, emphasizing the need to slowly phase out SSRI treatment. An analogy may be found with the washout period in preclinical chronic treatment studies, which is commonly used to avoid interference with the pharmacological probes. Arguably, the effects of a sudden discontinuation of treatment are more prominent than the effect of the treatment itself. The latter possibility is also investigated in chapter six by comparing the effects of chronic SSRI treatment on total serotonin content, synthesis and metabolism in presence and absence of a washout period.

The data suggest that the washout period has caused a strong increase of 5-HT metabolism, which could not be compensated by de novo synthesis resulting in a rather dramatic depletion of serotonin stores. Interestingly, the most marked effects were measured in brain areas with a high density of 5-HT\textsubscript{1B} receptors. Arguably, the sudden discontinuation of the SSRI leads to a strong decline in 5-HT\textsubscript{1B} autoreceptor activation thereby dramatically increasing 5-HT release and metabolism. This would also imply that 5-HT\textsubscript{1B} receptors do not desensitize following chronic treatment, which is in line with the study in chapter three. The effects of the washout period on all tested parameters are indeed considerable and it is tempting to causally relate a sudden decline in 5-HT\textsubscript{1B} autoreceptor activation to the phenomenon of rebound depression. Finally, the washout study clearly supports the clinical practice to gradually phase out antidepressant treatment in order to prevent rebound effects.
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References


