The effects of selective serotonin reuptake inhibitors on the function of distinct serotonin receptor subtypes in the rat

Ph.D. thesis

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Introduction

The discovery of selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs) has emerged as a major therapeutic advance in psychiatry and marked a milestone in psychopharmacology. In addition to being established treatments for depression, SSRIs have well-documented efficacy in the anxiety disorders, panic disorder and OCD [16]. Evidence suggests that SSRIs are effective in the treatment of dysthymic disorder, social phobia, premenstrual syndrome, bipolar disorder depression and bulimia nervosa [16]. The surfeit of biological substrates, receptors and neuroanatomical pathways for 5-HT are candidates to mediate not only the therapeutic actions of SSRIs but also their side effects [12]. Knowledge about serotonergic neurotransmission has been expanding rapidly. Recent research has delineated at least 14 molecularly different serotonin receptor subtypes and multiple, discrete neuronal and nonneuronal pathways and mechanisms that mediate the many functions of serotonin [12]. The immediate actions of SSRIs are mostly side effects such as nausea, anxiety, nervousness and headache [12, 16]. Therapeutic effects of SSRIs usually take weeks to become apparent. The explanation for curative effects characteristic of SSRIs is likely found in delayed neurochemical adaptations. A leading hypothesis explaining the late therapeutic effects as well as the development of tolerance to side effects involves the desensitization of pre- and postsynaptic serotonin receptors [12, 16].

Background and Objectives

1. **Which serotonin receptor subtypes are involved in the effects of SSRIs in anxiety?**

In some patients, SSRIs may precipitate or exacerbate anxiety, jitteriness and agitation and that may cause a decrease in treatment acceptance. In animal models of anxiety, SSRI antidepressants are, in general, characterized by an anxiogenic-like profile after acute administration [13]. A limiting factor in ongoing studies of SSRI-induced anxiety has been the absence of subtype-selective compounds. The purpose of Study One was to explore the role of distinct 5-HT receptor subtypes involved in anxiety through the rat social interaction test, using novel, subtype-selective antagonists.

2. **Which serotonin receptor subtypes mediate excessive grooming behaviour?**

Acute SSRI treatment was reported to induce self-grooming, a stereotype behaviour in rats [13] and correspondingly, the 5-$HT_{2C/2B}$ receptor agonist *m*-CPP is also known to produce dose-dependent self-grooming [1]. Excessive grooming in animals is regarded similar to the symptoms of obsessive-compulsive disorder (OCD) [10]. Furthermore, a growing body of evidence about OCD links this classic psychiatric syndrome to 5-HT_2 receptors [8]. As mentioned before, a restraining aspect of previous inspections on role of the various 5-HT receptors involved in grooming behaviour has been the lack of subtype-selective agents. The purpose of Study Two was to explore the function of 5-HT_{2C} and 5-HT_{2B} receptors in self-grooming in rats observed in single cages, by application of subtype selective antagonists.

3. What are the effects of chronic SSRI treatment on 5-HT_{1A} receptor sensitivity?

Since it generally takes time for the numerous therapeutic actions of SSRIs to develop or for the transient side effects to abate, this has led to a search for delayed neurobiological actions of SSRIs which might explain their late pharmacological actions. Desensitization of 5-HT_{1A} receptor function, a direct consequence of the chronic increase in 5-HT transmission has been proposed as a basic mechanism of action of SSRIs [12]. The objective of Study Three was to compare the effects of chronic fluoxetine treatment on responses to the selective 5-HT_{1A} agonist 8-OH-DPAT. The experiments were conducted in the Fawn-Hooded rat strain, an animal model of depression and anxiety [11], and control Sprague-Dawley rats.

4. What are the effects of chronic SSRI treatment on 5-HT_{2C} receptor sensitivity?

Earlier studies suggested a considerable desensitization of 5-HT_{2C} receptors after long-term SSRI treatment. Chronic treatment with paroxetine and fluoxetine significantly attenuated the effect of the 5-$HT_{2C/2B}$ receptor agonist *m*-CPP on locomotion and rears in rats [5] and chronic fluvoxamine produced matching results [17]. Furthermore, long-term fluoxetine administration significantly reduced the anxiety-like effects of *m*-CPP and other anxiogenic compounds in the social interaction test in the rat [2, 13, 14]. Following chronic paroxetine treatment, both the prolactin and hyperthermic responses to *m*-CPP were significantly attenuated in humans [9]. These effects

of chronic SSRI treatment are suspected to be the consequence of 5-HT_{2C} receptor desensitisation [2, 5, 9, 17].

The aim of Study Four was to test the effects of chronic SSRI treatment on 5-HT_{2C} receptor sensitivity by observing *m*-CPP-induced (and fully 5-HT_{2C} receptor-mediated) behavioural responses.

5. What are the effects of serotonin depletion on 5-HT_{2C} receptor function?

A refinement of the monoamine hypothesis of depression is that depressive illness may arise from decreased brain 5-HT function [16]. One of the factors associated with low levels of 5-HT is altered sensitivity of 5-HT receptors. The sensitization of 5-HT receptors after depletion of brain 5-HT has been described earlier [3]. In Study Five we aimed to inspect changes in 5-HT_{2C} receptor sensitivity in Sprague-Dawley rats after p-CPA-induced serotonin depletion. We used *m*-CPP-induced self-grooming and penile erection as established indicators of 5-HT_{2C} receptor function.

6. What is the effect of SSRI treatment on epileptic activity in WAG/Rij rats?

Rats of the WAG/Rij strain exhibit spontaneously occurring spike–wave discharges (SWDs), accompanied by behavioral phenomena and pharmacological reactivity very similar to human absence epilepsy [15]. Previous studies in this rat strain suggested a modulatory role of 5-HT on epileptic activity. Anticonvulsant effect of the SSRI fluoxetine and its most important metabolite norfluoxetine has been recently reported in a mouse epilepsy model [4]. Based on these data, in Study Six we aimed to explore the effect of the SSRI fluoxetine on seizure generation in WAG/Rij rats.

Methods

1. Animals

All procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. The protocols were approved by the local Ethical Committee. Male Sprague-Dawley (240-330g) and Fawn-Hooded rats (260-330 g) were used in the social interaction and the behavioural studies. Adult male Wistar Albino Glaxo rats from Rijswijk, Netherlands (WAG/Rij rats, 320-420 g) bred in our laboratory, were used in the epilepsy studies. The animals (4 per cage) were kept under standard condition, with standard food and water freely available. The temperature was 21±1^{o}C, the 12 hour light-dark cycle started at 06.00 hour.

2. Study One

Rats were housed in a room adjacent to the testing room at least for two weeks before the tests. The animals were randomly assigned to treatments. In the low light (5 lux), familiar arena conditions animals were individually pre-exposed to the test box and the injections three times on days preceding the test. Rats were tested for social interaction with an unknown test partner that did not differ by more than 15 g in weight. At the end of each test the box was thoroughly wiped with detergent and dried to remove odours. The animals were tested in a random order in an adjacent room for 7.5 min. The evenly illuminated box (60 x 60 x 40 cm), was marked to 10 cm compartments by lines on the floor. The behaviour of animals was recorded on videotape. It was scored later by a person unaware of the drug treatment. The following

behaviours were included in total social interaction: sniffing partner, anogenital sniffing, peaceful following, grooming partner, under-crawling, over-climbing, chasing, aggressive grooming, dominant posture, submissive posture, biting, boxing, kicking, pushing, and wrestling. Rearing, crossing of lines and self-grooming were also scored.

3. Study Two, Four and Five

In these experiments animals were placed to single observation cages immediately after *m*-CPP or vehicle injections. Display of grooming behaviour was scored every 15 s by a trained person, beginning with the injection of the compounds. Vibration, face and head washing, body grooming, scratching, paw licking, head shaking and genital grooming were included as components of grooming behaviour. Animals were scored for 30 min, thus, the maximum available score of self-grooming during the observation period was 120. Penile erections were observed and quantified for 30 mins.

4. Study Three

All studies were performed in rats placed into persplex cylinder restraints. They were previously exposed at least 4 times to the experimental conditions. By the 4th exposure rats were clearly adapted to the situation, thus no hypermotility, struggling or other sign of stress were observed. Body temperature, lower lip retraction and masseter-eyeball syndrome were measured or scored parallel in the same experiments. The animals were placed in plexiglass restrainers which allow partial movement. For body temperature measurements, rectal probes were used.

5. Study Six

Animals were chronically equipped with epidural EEG electrodes (two in frontal- and two in parieto-occipital region) and EMG electrode (sewn in the neck muscle). An electromagnetic transducer activated by cable movements was used to record motor activity. To quantify the occurrence of SWDs, cumulative duration (in seconds) and number of paroxysms were summarized.

6. Statistical analysis

The data were analysed by one- or two-way analysis of variance, analysis of variance for repeated measures and the Kruskal-Wallis test. For post hoc comparisons we used the Tukey-Kramer test, the Mann-Whitney rank sum test, and the Newman-Keuls test.

Results

1. Serotonin receptors mediating acute anxiogenic effects of SSRIs

Fluoxetine caused dose-dependent decrease in time of total social interaction and increase in self-grooming in rats. Pretreatment with SB-242084, a selective 5-HT_{2C} receptor antagonist significantly reversed these anxiogenic effects of fluoxetine in the rat social interaction test. In contrast, pretreatment with the 5-HT_{1A} antagonist WAY-100635 failed to block the anxiety-like effects of fluoxetine. Our studies provide evidence that anxiogenic effects of SSRIs are mediated by activation of 5-HT_{2C} receptors.

2. Serotonin receptors involved in excessive self-grooming

The 5-$HT_{2C/2B}$ receptor agonist *m*-CPP caused dose-dependent increase of self-grooming in rats. The selective 5-HT_{2C} receptor antagonist SB-242084 inhibited *m*-CPP-induced self-grooming, but the selective 5-HT_{2B} antagonist SB-215505 did not alter the effect of *m*-CPP. These results confirm that the selective activation of 5-HT_{2C} receptors induces self-grooming.

3. The effect of chronic fluoxetine treatment on 5-HT_{1A} receptor function

Hypothermia induced by the 5-HT_{1A} receptor agonist 8-OH-DPAT in rats was attenuated after chronic fluoxetine treatment, which supports the hypothesis of 5-HT_{1A} receptor desensitisation as a consequence of long-term SSRI therapy. Interestingly, this effect was faster and more potent in the Fawn-Hooded rat strain, which is considered as an animal model of depression and anxiety.

4. The effect of chronic fluoxetine treatment on 5-HT_{2C} receptor function

5-HT_{2C} receptor-mediated responses, *m*-CPP-induced self-grooming and penile erection diminished following chronic fluoxetine treatment. These findings provide evidence for 5-HT_{2C} receptor desensitisation associated with long-term SSRI treatment.

5. The consequences of serotonin depletion on 5-HT$_{2C}$ receptor responsivity

In Study Five we demonstrated that chemically induced, lasting depletion of brain 5-HT in rats resulted in enhanced responses to *m*-CPP, which indicates an increase in 5-HT$_{2C}$ receptor responsivity. This result supports the theory of increased 5-HT$_2$ receptor sensitivity in connection with low brain serotonin concentration, a phenomenon associated with depressive disorders.

6. The effect of fluoxetine on epileptic activity in WAG/Rij rats: involvement of 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors

In Study Six fluoxetine-induced increase in brain 5-HT neurotransmission produced an upsurge in epileptic activity in WAG/Rij rats; however simultaneous inhibitory and excitatory effects were detected which are exerted through activation of different 5-HT receptor subtypes. Stimulation of 5-HT$_{2C}$ receptors proved to inhibit spike-wave discharges (SWDs) and activation of 5-HT$_{1A}$ receptors promotes the generation of SWDs.

Discussion

In our present work we demonstrated that acute anxiogenic effects of SSRIs in rats are produced by the activation of 5-HT$_{2C}$ receptors. Our research helps to understand the causes underlying SSRI-induced anxiety, an adverse effect often seen in patients treated with selective serotonin reuptake inhibitors [16].

We also proved that 5-HT$_{2C}$ receptor activation induces self-grooming in the rat. Based on our experiments, along with other previous animal and human studies, it can be assumed that the 5-HT$_{2C}$ receptor plays an important

role in the pathomechanism and pharmacology of obsessive-compulsive disorder [8].

Our studies provide evidence for the desensitisation of 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors as a consequence of chronic SSRI treatment. These findings can help to clarify the mode of action of SSRIs producing the late therapeutic effects as well as the long-term side-effects (e.g. sexual dysfunction) [12].

Reduced brain 5-HT function and increased sensitivity of certain 5-HT receptors have been proposed as mechanisms associated with depressive disorders [6, 7]. In our animal experiments, the chemically-induced depletion of brain 5-HT produced an increased sensitivity of 5-HT$_{2C}$ receptors. These results could facilitate the understanding of neurotransmitter and receptor alterations lying beneath the pathogenesis of depression.

Studies conducted in the WAG/Rij rat strain offer a great potential to understand human absence epilepsy [15]. Our investigations on the effects of SSRIs in WAG/Rij rats present additional evidence for the central modulatory role of the serotonergic system in absence epilepsy. Based on recent literature, this role appears to be increasingly relevant considering the close correlation between the circadian pattern of 5-HT neurotransmission and vigilance states. The growing number of drugs affecting a wide range of 5-HT receptors renders our studies even more pertinent.

In conclusion, we can truly expect that our results may provide valuable clues for the pharmacotherapy of anxiety disorders, depression and epilepsy, and progress the development of novel anxiolytic, antidepressant and antiepileptic medications.

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