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The effect of chronic selective serotonin reuptake inhibitor treatment on serotonin$_{1B}$ receptor sensitivity and HPA axis activity

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Abstract

The authors have investigated 5-HT$_{1B}$ receptor function in prefrontal cortex and dorsal hippocampus as well as the HPA axis response after subchronic (24 h) and chronic (15 days) treatment with the SSRI citalopram. All experiments were carried out in presence of citalopram to prevent rapid resensitization of the 5-HT$_{1B}$ receptors. Moreover, this more closely resembles the clinical situation. The concentration of citalopram was measured in both brain areas to ensure comparable levels in the different treatment groups. Using microdialysis, the authors found that under those conditions the effect of the 5-HT$_{1B}$ receptor antagonists SB 224289 and the mixed 5-HT$_{1B/1D}$ receptor antagonist GR 127935 on extracellular levels of 5-HT was unaltered by duration of treatment. Basal levels of 5-HT, however, were increased in the dorsal hippocampus following chronic treatment. In addition, plasma levels of the catecholamines adrenaline and noradrenaline and the HPA axis hormones ACTH and corticosterone were all decreased after chronic treatment.

Keywords: Desensitization; HPA axis; Microdialysis; 5-HT $_{1B}$ receptor; Serotonin

1. Introduction

Antidepressants are clinically effective only after prolonged treatment, indicating that adaptive mechanisms are involved in the therapeutic effect. This delayed response may be linked to a gradual desensitization of firing rate and release controlling 5-HT autoreceptors (Blier et al., 1987). This idea was based on electrophysiological experiments in rats, wherein acute administration of antidepressants decreased the firing rate of 5-HT neurons, which normalized after prolonged administration (Blier et al., 1987; Chaput et al., 1986).

Using 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor antagonists, microdialysis studies in rodents have demonstrated that acute administration of an SSRI activates both types of autoreceptors (Cremers et al., 2000a; Hjorth, 1993; Invernizzi et al., 1997; Rollema et al., 1996). Both electrophysiology and microdialysis have revealed a reduction of 5-HT$_{1A}$ receptor functionality following chronic administration (Cremers et al., 2000b; Invernizzi et al., 1994; Kreiss and Lucki, 1995; Le Poul et al., 1995). In contrast with single unit recordings, changes in 5-HT$_{1B}$ receptor functionality following chronic antidepressant treatment could not be demonstrated using microdialysis (Auerbach and Hjorth, 1995; Bosker et al., 1995; Chaput et al., 1986; Cremers et al., 2000b; Davidson and Stamford, 1997; Moret and Briley, 1996).

Levels of 5-HT$_{1B}$ mRNA, on the other hand, are decreased following chronic treatment with antidepressants, but rapidly return to normal after discontinuation of the antidepressant (Anthony et al., 2000; Neumaier et al.,

Abbreviations: ACTH, adrenocorticotropic hormone; dHC, dorsal hippocamus; HPA, hypothalamic–pituitary axis; 5-HT, serotonin; PFC, prefrontal cortex; SSRIs, selective serotonin reuptake inhibitors.

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1996). Arguably, a loss of presynaptic 5-HT_{1B} receptor function may be retrieved within a few days after discontinuation of the drug. Hence, the possibility that presynaptic 5-HT_{1B} receptors rapidly resensitize is worth investigating. This is further emphasized by the common practice in microdialysis studies to use a washout period (2–7 days) to minimize pharmacological interference by residual antidepressant.

Next to these central serotonergic adaptations, peripheral alterations of stress hormone release might also play a role in the therapeutic effect of long-term treatment with SSRIs. Stress activates many physiological systems, such as the sympathetic system, resulting in rapid release of the catecholamines adrenaline and noradrenaline from the adrenal medulla. This is followed by activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in release of ACTH from the pituitary which induces the release of cortisol (corticosterone in rats) from the adrenal cortex. Prolonged elevation of catecholamines and cortisol by chronic stress could be a factor in stress related pathology, including depression. Pharmacological intervention in stress-related processes might therefore help to slow down exacerbation of depressive symptoms. This is supported by the observation that the HPA axis hyperactivity in depressed patients is normalized after clinical remission due to chronic antidepressant treatment (Barden et al., 1995; Holsboer and Barden, 1996).

In this study, the authors have investigated whether presynaptic 5-HT_{1B} receptors become less responsive during chronic treatment with the SSRI citalopram. Citalopram was administered via osmotic minipumps to obtain steady-state levels within the clinically effective range (Cremers et al., 2000b). To circumvent resensitization of presynaptic 5-HT_{1B} receptors, all microdialysis experiments were performed in the presence of the drug. Extracellular levels of 5-HT and citalopram were measured in prefrontal cortex and dorsal hippocampus, brain areas that have been implicated in depression and anxiety, respectively. Responsiveness of presynaptic 5-HT_{1B} receptors was measured by the ability of the 5-HT_{1B} antagonists GR 127935 and SB 224289 to augment the effect of citalopram. In addition, the authors have measured plasma levels of catecholamines, ACTH and corticosterone to investigate the effect of treatment duration on peripheral levels of stress hormones.

2. Materials and methods

2.1. Animals

Male Harlan rats (Zeist, The Netherlands) weighing 285–320 g were housed eight per cage under standard conditions (22–24 °C, 12/12 light/dark cycle, food and water ad libitum). Following implantation of the minipump, rats were housed in pairs. After stereotaxic surgery and during the microdialysis experiments, the rats were housed separately. All animal experiments were according to the governmental guidelines for care and use of laboratory animals and were approved by the Committee for Animal Research of the Medical Faculty of the Groningen University.

2.2. Drugs

The following drugs were used: Citalopram hydrobromide (kindly donated by Lundbeck (Denmark) courtesy of Dr. Sanchez), GR 127935 (*N*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazole-3-yl)[1,1′-biphenyl]-carboxamide, synthesised in our own laboratory, courtesy of Dr. Y. Liao and Dr. M. Mensonides) and SB 224289 (2,3,6,7-tetrahydro-1′-methyl-5-(2′-methyl-4′-[(5-methyl-1,2,4-oxqadiazole-3-yl)-biphenyl-4-yl]carbon-yl)furo[2,3-f]indole-3-spiro-4′-piperidine oxalate, purchased from Sigma-Aldrich). GR 127935 was dissolved in saline with a drop of acetic acid and administered at a dose of 1 μmol/kg, SB 224289 was dissolved in a 10% dimethylsulfoxide (DMSO)–saline solution and administered at a dose of 4 mg/kg. Both substances were injected subcutaneously in a volume of 1 ml/kg. Both dosages were chosen for their ability to augment SSRI induced increase of 5-HT to the same extent (Cremers et al., 2000a; Roberts et al., 1999).

2.3. Surgery

2.3.1. Minipumps

Osmotic minipumps (2ML2 Alzet, USA, 5 μl/h, 2 weeks) were either filled with saline or 50 mg/ml citalopram hydrobromide dissolved in saline under aseptic conditions. During isoflurane anaesthesia (2.5%, 400ml/min N_2O, 600 ml/min O_2), minipumps were implanted subcutaneously on the left side of the back of the rat.

After 14 days, all minipumps were replaced with citalopram filled minipumps. Hereafter, the microdialysis probes were implanted.

2.3.2. Probes

During isoflurane anaesthesia (2.5%, 400 ml/min N_2O, 600 ml/min O_2), a home-made concentric microdialysis probe (i.d. 220 μm, o.d. 310 μm, AN 69, Hospal, Italy), made of polyacrylonitrile/sodium methyl sulphonate copolymer dialysis fiber was stereotaxically implanted in the prefrontal cortex (PFC) or the dorsal hippocampus (dHC) using the following coordinates: PFC; inscisorbar at −3.3 mm (posterior: +3.5 mm, lateral: +0.9 mm, ventral from dura: −6.0 mm), exposed tiplength was 4 mm. DHC; incisorbar at +5.0 mm (posterior: −4.0 mm, lateral: −1.2 mm, ventral from skull: −5.5 mm), exposed tiplength was 2 mm. (Paxinos and Watson, 1982). The probes were secured in place with dental cement.