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Acute and repeated treatment with the 5-HT_7 receptor antagonist SB 269970 induces functional desensitization of 5-HT_7 receptors in rat hippocampus

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Abstract:
Background: SB 269970, a 5-HT_7 receptor antagonist may produce a faster antidepressant-like effect in animal models, than do antidepressant drugs, e.g., imipramine. The present work was aimed at examining the effect of single and repeated (14 days) administration of SB 269970 on the 5-HT_7 receptor in the hippocampus.
Methods: The reactivity of 5-HT_7 receptors was determined using 5-carboxamidotryptamine (5-CT), which increased the bursting frequency of spontaneous epileptiform activity in hippocampal slices. Additionally, the effects of SB 269970 administration on the affinity and density of 5-HT_7 receptors were investigated using [^{3}H]-SB 269970 and the influence of SB 269970 and imipramine on mRNA expression levels of $G\alpha_s$ and $G\alpha_{12}$ mRNA were studied using RT-qPCR.
Results: Acute and repeated treatment with SB 269970 led to attenuation of the excitatory effects of activation of 5-HT_7 receptors. Neither single nor repeated administration of SB 269970 changed the mean affinity of 5-HT_7 receptors for [^{3}H]-SB 269970. Repeated, but not single, administration of SB 269970 decreased the maximum density of [^{3}H]-SB 269970 binding sites. While administration of imipramine did not change the expression of mRNAs for $G\alpha_s$ and $G\alpha_{12}$ proteins after both single and repeated administration of SB 269970, a reduction in $G\alpha_s$ and $G\alpha_{12}$ mRNA expression levels was evident.
Conclusions: These findings indicate that even single administration of SB269970 induces functional desensitization of the 5-HT_7 receptor system, which precedes changes in the receptor density. This mechanism may be responsible for the rapid antidepressant-like effect of the 5-HT_7 antagonist in animal models.

Key words:
5-carboxamidotryptamine, adaptive changes, epileptiform activity, hippocampal slice, imipramine, SB 269970

Introduction

Serotonin (5-hydroxytryptamine, 5-HT), which acts as a neurotransmitter and/or a neuromodulator, is involved in a wide spectrum of physiological processes including sleep, cognition, sensory perception, motor activity, temperature regulation, appetite, hormone secretion, nociception, and sexual behavior (reviewed in: [30]). Dysfunctions of the serotonergic system are thought to be involved in the pathomechanism of depressive disorders. Besides other structures, the hippocampus plays an important role as a target for anti-

depressant and anxiolytic drugs [72] (reviewed in: [40, 47]). It has been suggested that a common result of different types of antidepressant therapies is an enhancement of 5-HT neurotransmission within the hippocampus (reviewed in: [9, 19, 27]).

The cellular effects of 5-HT are mediated by up to 14 distinct membrane receptor subtypes that may be expressed in various amounts in single neurons (reviewed in: [28, 29, 55]). Such a diversity permits the occurrence of different effects of 5-HT, including both, inhibitory and excitatory influence on neuronal networks. These mechanisms allow 5-HT to remodel neuronal excitability in a variety of cell types and neuronal circuits in a functionally appropriate manner. In the hippocampus, the most prominent modulatory effect of 5-HT is a 5-HT$_{1A}$ receptor-mediated reduction of the excitability of pyramidal cells [1]. Another 5-HT receptor subtype which effectively modulates neuronal activity is the 5-HT$_4$ receptor whose activation increases excitability of hippocampal pyramidal cells [12, 15]. Adaptive modifications of serotonergic mechanisms modulating the functions of forebrain structures provide an effective mechanism of antidepressant therapies (reviewed in: [8, 36, 39]). In rats, repeated administration of tricyclic antidepressants (TCAs) enhances the inhibitory effect of 5-HT$_{1A}$ receptor activation on the excitability of hippocampal pyramidal neurons [6, 13, 17, 35]. Adaptive changes induced by treatment with the TCA imipramine in rat hippocampus involve attenuation of the excitatory effect of 5-HT$_4$ receptor activation [7, 74]. Repeated administration of selective serotonin reuptake inhibitors (SSRIs) reduces the effectiveness of hippocampal 5-HT$_4$ receptor activation as well; however, at variance with the effects of TCA, the sensitivity of hippocampal 5-HT$_{1A}$ receptors remains unchanged after treatment with SSRIs [7, 13, 14, 62] (reviewed in: [27]).

The 5-HT$_7$ receptor is the latest 5-HT receptor subtype to be identified [4, 54]. In the brain, the 5-HT$_7$ receptor is predominantly expressed in the thalamus, hippocampus, hypothalamus [48] and raphe nuclei [37]. This receptor has been implicated in mood regulation, circadian rhythmicity and sleep, the disturbances of which are evident in the course of affective disorders (reviewed in: [26, 61]). It has been well established that neuronal 5-HT$_7$ receptors activate adenylate cyclase through Gα_s protein [34, 56]. Interestingly, it has been shown that activation of the 5-HT$_{7A}$ receptor stimulates AC1 and AC8 Ca^{2+}/calmodulin-dependent isoforms of adenylate cyclase which are insensitive to Gα_s *in vivo* [3]. Moreover, it has been found that 5-HT$_7$ receptors may also activate Gα_{12} protein [32]. On a cellular level, activation of the 5-HT$_7$ receptor decreases potassium conductances and increases the hyperpolarization-activated current I_h, and thus enhances the excitability of hippocampal pyramidal cells [2, 5, 65]. All these effects contribute to the 5-HT$_7$ receptor-mediated facilitation of hippocampal population spikes *in vivo* [38], as well as to the enhancement of epileptiform activity in disinhibited hippocampal slices *in vitro* [20, 49, 64].

It has been suggested that the modification of 5-HT$_7$ receptor activity resulting from chronic treatment with antidepressants may represent a mechanism underlying the therapeutic effect of these drugs [57] (reviewed in: [24, 26]). It is noteworthy that several psychotropic drugs exhibit high affinity for 5-HT$_7$ receptors [50, 52, 56, 59] (reviewed in: [33]). It has also been shown that certain antidepressants may exert some effects by acting directly on the 5-HT$_7$ receptor [46].

Recent studies have demonstrated a synergistic interaction between serotonin receptors antagonists and several antidepressant drugs [53, 67], including the specific 5-HT$_7$ receptor antagonist SB 269970 [11, 70]. In animal models, inactivation or blockade of the 5-HT$_7$ receptor has been shown to induce antidepressant-like behavior [21, 25, 69]. Chronic treatment with antidepressants has also been shown to modify the reactivity of 5-HT$_7$ receptors. The downregulation of the 5-HT$_7$ receptor has been found to take place in rat suprachiasmatic nucleus of the hypothalamus after chronic treatment with TCAs including imipramine, and the SSRI – fluoxetine [46, 58]. Our earlier study indicated attenuation of the effects of activation of rat hippocampal 5-HT$_7$ receptors after treatment with the TCA imipramine and the SSRI citalopram [64]. These findings support the hypothesis that the 5-HT$_7$ receptor may be a target for the action of antidepressants drug. Moreover, blockade of this receptor opens up good possibilities for the treatment of depression [43] (reviewed in: [24, 40, 44]). It is widely known that the response to treatment with conventional antidepressants may be delayed for several weeks.

Previously, our electrophysiological study showed that repeated (14 times), but not single, imipramine administration diminished the reactivity of the 5-HT$_7$ receptor [64]. We also demonstrated that chronic treatment with imipramine modified neither the affinity of 5-HT$_7$ receptors to [^{3}H]-SB 269970 nor the density of those receptors [63].