



Effects of repetitive administration of tianeptine, zinc hydroaspartate and electroconvulsive shock on the reactivity of 5-HT₇ receptors in rat hippocampus

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Abstract:

The influence of repeated administration of tianeptine, an atypical antidepressant, which was administered twice daily (10 mg/kg) for 14 days and zinc hydroaspartate, a compound exhibiting antidepressant-like activity, which was administered twice daily (65 mg/kg) for 14 days, and the effects of electroconvulsive shocks (ECS) delivered once daily for 10 days, were investigated *ex vivo* in rat hippocampal slices. Slices were prepared 2 days after the last session of treatment of animals, and spontaneous epileptiform bursts were recorded extracellularly from the CA3 area. 5-HT₇ receptor-mediated increase in bursting frequency was induced by bath application of 5-carboxamidotryptamine (5-CT; 0.025–1 μM) in the presence of N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide (WAY 100635; 2 μM), an antagonist of the 5-HT_{1A} receptor. The data indicate an enhancement of the excitatory effect of the activation of 5-HT₇ receptors after ECS repeated ten times, but not by a single ECS. Neither tianeptine nor zinc, administered for 14 days, altered the reactivity of 5-HT₇ receptors.

Key words:

5-HT₇ receptors, adaptive changes, ECS, epileptiform activity, hippocampal slice, tianeptine, zinc

Introduction

Repetitive administration of antidepressants exerts a pronounced influence on the function of the brain serotonergic system. These effects, however, still remain incompletely understood. Among serotonin receptors, 5-HT₇ receptors represent the most recently identified subtype [2, 53, reviewed in: 26]. 5-HT₇ receptors have been implicated in such processes as

phase-shifting of circadian rhythms and induction of sleep, disturbances of which often accompany affective disorders [32, 59]. In behavioral tests, the 5-HT₇ receptor knockout mice show decreased immobility, which occurs after the administration of antidepressant drugs to normal animals [25]. In line, the selective 5-HT₇ receptor antagonist SB 269970 shows antidepressant-like activity [67] and enhances the action of antidepressant drugs [68]. Localization studies in rodent brain indicated the highest abundance of

5-HT₇ receptors in the hippocampus, thalamus and hypothalamus [42]. Down-regulation of 5-HT₇ receptors occurs in rat suprachiasmatic nucleus after chronic treatment with a number of antidepressants [41]. However, there is still little knowledge of how antidepressant treatments influence the 5-HT₇ receptor-mediated functions in forebrain structures, in particular in the hippocampus.

Electrophysiological studies have shown that the activation of 5-HT₇ receptors increases excitability of the neuronal membrane. In rat hippocampus, 5-HT₇ receptors enhance spontaneous bursting in the CA3 area [17]. The 5-HT₇ receptor-mediated increase in the excitability of hippocampal pyramidal cells results from a reduction of the slow afterhyperpolarization (sAHP) due to a reversible blockade of the Ca²⁺-activated K⁺ channel [1, 17, 63]. Moreover, in CA1 pyramidal neurons, the activation of 5-HT₇ receptors increases the hyperpolarization-activated nonselective cation current, I_h [3].

Our previous study demonstrated that treatments with imipramine, a tricyclic antidepressant, or citalopram, a selective serotonin reuptake blocker, both lasting 14 days, decreased the responsiveness of rat hippocampal CA3 circuitry to the activation of 5-HT₇ receptors [61]. However, effects of other classes of antidepressant treatments with distinct modes of action on the function of hippocampal 5-HT₇ receptors remain unexplored. One of those, an atypical antidepressant, tianeptine, facilitates 5-HT uptake, in contrast to the effects of a majority of antidepressant drugs which block the uptake of amine neurotransmitters [15]. Tianeptine differs from classical antidepressants in its lack of interaction with many receptors [70]. It also reduces activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress [38]. Another clinically effective means of treating depression is the therapy based on electroconvulsive shock (ECS) [57], but the mechanisms underlying its effect are unclear. As with drug treatment, ECS is only efficacious after repetitive administration. Several biochemical correlates of chronic ECS have been identified in animal models but the most research focused on components of G protein-coupled receptor signaling cascades, in particular the cAMP pathway [48]. Recent data suggest an important role of zinc in the psychopathology and therapy of depression (reviewed in [46]). It has generally been assumed that endogenous zinc is involved in the modulation of glutamate ionotropic receptors [21] but it may also influ-

ence the reuptake of serotonin [16]. Administration of zinc salts results in antidepressant-like effects in rodent models of depression [28, 45, 47]. It has also been shown that zinc enhances the action of imipramine [71].

In the present study, we set out to evaluate the influence of repeated administration of tianeptine, ECS and zinc on 5-HT₇ receptor-mediated modulation of epileptiform activity in *ex vivo* hippocampal slices.

Materials and Methods

Animals and experimental procedure

Male Wistar rats, weighing approximately 80 g at the beginning of the experiment, were housed under a controlled light/darkness cycle (light on from 7.00–19.00) and had free access to standard food and tap water. In the first experimental group, tianeptine, dissolved in 2 ml of water, was administered *po* (10 mg/kg) twice daily, for 14 days. Control animals received water. The second experimental group received ECS (130 mA, 0.3 s, 50 Hz; *via* earclip electrodes) or sham treatment (handled identically but without electrical stimulation) once daily for 10 days. Additional acute ECS group received sham treatment once daily for 9 days followed by a single ECS on the 10th day. In all animals, ECS induced a tonic-clonic seizure, lasting about 30 s. The third experimental group of rats received zinc hydroaspartate dissolved in 2 ml of 0.9% NaCl at a dose of 65 mg/kg (11.3 mg/kg of zinc) *po*, twice daily for 14 days. Control rats received vehicle. Control groups were investigated concurrently with treated animals.

Experimental procedures were approved by the Animal Care and Use Committee of the Institute of Pharmacology and were carried out in accordance with the European Community guidelines for the use of experimental animals and with national law.

Slice preparation and electrophysiological recording

Rats were decapitated two days after the last drug or ECS administration. Their brains were rapidly removed and immersed in an ice-cold artificial cerebrospinal fluid (aCSF) containing (in mM): NaCl (124), KCl (5), CaCl₂ (2.5), MgSO₄ (1.3), KH₂PO₄ (1.25),

NaHCO₃ (24) and D-glucose (10), which was bubbled with the mixture of 95% O₂/5% CO₂. After dissection, the hippocampus was cut into transverse slices (450 μm thick) using a vibrating microtome (Vibratome, USA). Slices were kept in a holding chamber at room temperature for 1–6 h.

Recording was performed in the chamber of a submerged type. Slice was superfused at 2.5 ml/min with warmed (32 ± 0.5°C), modified aCSF, in which (NaCl) was raised to 132 mM and (KCl) was lowered to 3 mM. Modified aCSF was devoid of Mg²⁺ ions and it contained 2 μM WAY 100635, a specific 5-HT_{1A} receptor antagonist. Glass micropipettes filled with 0.9% NaCl (1–4 MΩ) were inserted in the pyramidal layer of the CA3 area.

Spontaneous epileptiform bursts (Fig. 1) were amplified (Axoprobe 2, Axon Instruments, USA), band-pass filtered (1 Hz – 10 kHz), A/D converted, stored on a PC and analyzed off-line. Activity was also displayed on chart recorder (TA240, Gould, USA).

Data analysis

Bursting frequency was determined as the number of events per 1-min bins. 5-CT-induced effects were assessed in terms of a change in bursting frequency, by comparing the average frequency over 6–10 min after beginning of 5-CT application (Fig. 1) to baseline values.

Dose-response data were fitted to the Hill equation using the Sigma Plot software (SPSS Inc., USA) and compared using two-way ANOVA followed by *post-hoc* LSD Fisher's test. Data from treated and control rats were compared using paired *t*-test.

Drugs

5-Carboxamidotryptamine maleate (5-CT) was purchased from Tocris. N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide (WAY 100635) was purchased from Sigma and zinc hydroaspartate was from Farmapol, Poznań. Tianeptine was generously donated by Servier Polska.

Results

Spontaneous epileptiform bursting of stable frequency occurred within 15–20 min of perfusion of

slices with a nominally Mg²⁺-free aCSF. Similarly to previous findings [61, 62], bursting events consisted of an initial, population spike-like waveform, reaching 3–4 mV in amplitude, which was followed by small spikes, superimposed on a slower, positive-going wave. In the presence of 2 μM WAY 100635 in the aCSF, the application of 5-CT resulted in an increase in the bursting frequency which reached maximum between 6 and 10 min after the beginning of 5-CT application (Fig. 1). It has previously been demonstrated that this effect is mediated by 5-HT₇ receptors [63].

Repeated administration of tianeptine did not affect the mean basal bursting frequency, which did not differ from the frequency of bursts recorded in slices obtained from control animals (0.111 ± 0.005 Hz, n = 57 vs. 0.114 ± 0.007 Hz, n = 35, respectively; *p* > 0.05). The 5-HT₇ receptor-mediated, 5-CT-induced increase in the bursting frequency was not different in slices prepared from animals treated repeatedly with tianeptine compared to slices obtained from control rats at any of the tested concentration of 5-CT (Fig. 2).

Chronic ECS did not change the mean basal bursting frequency, which did not differ from that recorded in slices obtained from the sham group of animals (0.126 ± 0.005 Hz, n = 36 vs. 0.133 ± 0.007 Hz, n = 26; *p* > 0.05, *t*-test). However, the 5-CT-induced increase in the bursting frequency was significantly enhanced in slices prepared from animals treated re-

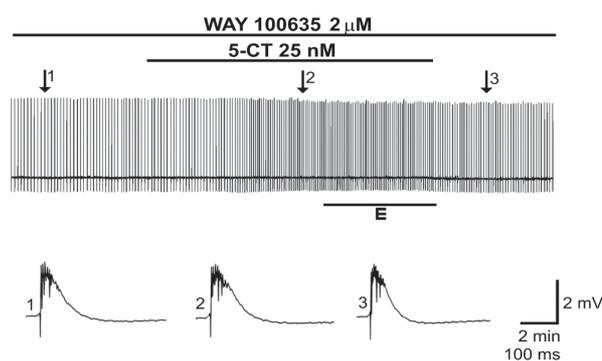


Fig. 1. The excitatory effect of 5-CT. The graph shows a chart recording from a representative experiment. Time of 5-CT (25 nM) application is indicated by the shorter horizontal line. WAY 100635 (2 μM) was present in the aCSF throughout the experiment to block 5-HT_{1A} receptors (longer horizontal line). The traces below the graph (labeled: 1, 2, 3) represent examples of bursting events (indicated in the graph by arrows with respective numbers) at an expanded timescale. A part of the recording (labeled: E) represents the period used for the measurement of the 5-CT-induced effect (note an increased bursting frequency)

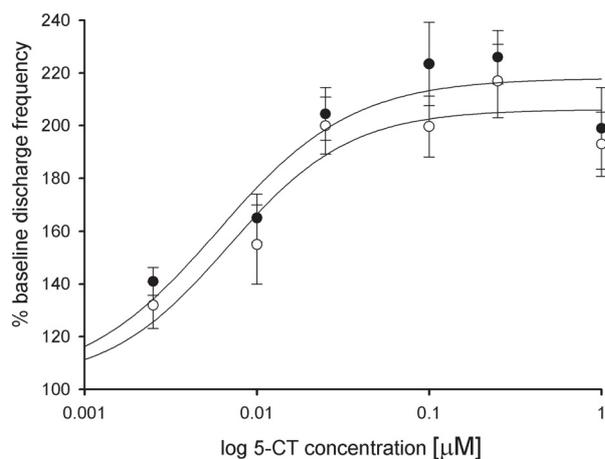


Fig. 2. Dose-response curves for the effect of 5-CT on the bursting activity in slices obtained from tianeptine-treated and control rats. The figure shows mean increases in bursting frequency (\pm SEM) in slices from rats treated with tianeptine for 14 days (filled circles) and from control animals (open circles). The solid lines are fitted to the Hill equation which yielded EC_{50} values of 6 and 7 nM for the tianeptine-treated and control group, respectively. The calculated values of maximum discharge frequency are 218% and 206% for the tianeptine-treated and the control group, respectively. For each point: $n = 9$ to 15. Two-way ANOVA: $F(5, 81) = 0.1778$, $p = 0.97$

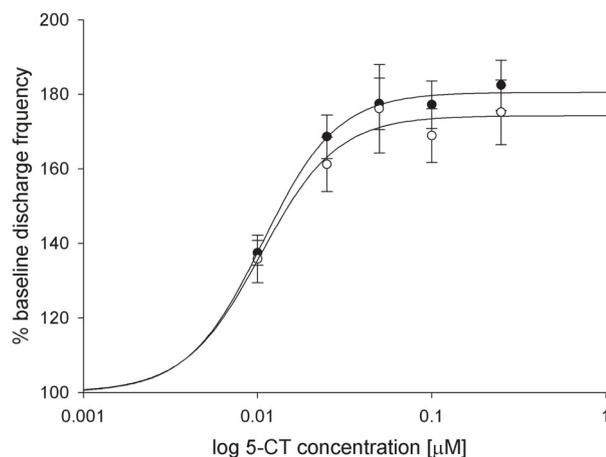


Fig. 4. Dose-response curves for the effect of 5-CT on the bursting activity in slices obtained from zinc hydroaspartate-treated and control rats. The figure shows increases in bursting frequency (\pm SEM) in slices from rats receiving zinc for 14 days (filled circles) and from control animals (open circles). The solid lines are fit to the Hill equation which yielded EC_{50} values of 11 and 10 nM for the chronic zinc-treated group and the control group, respectively. Calculated values of maximum discharge frequency are 180% and 174% for the zinc-treated group and the control group, respectively. For each point: $n = 12$ –20. Two-way ANOVA: $F(4, 187) = 0.1185$, $p = 0.97$

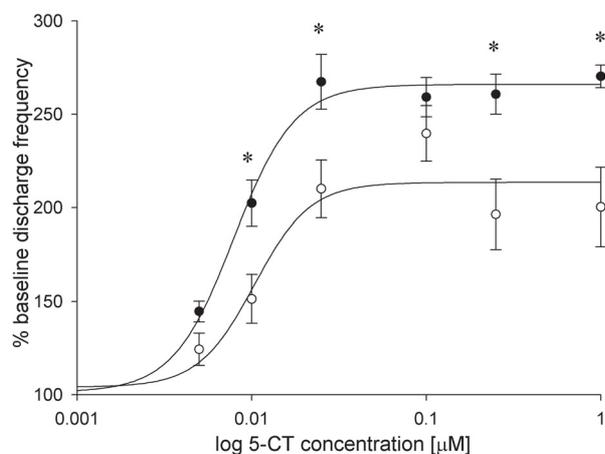


Fig. 3. Dose-response curves for the effect of 5-CT on the bursting activity in slices obtained from ECS-treated and control rats. The figure shows mean increases in bursting frequency (\pm SEM) in slices obtained from rats subjected to ECS for 10 days (filled circles) and from control animals (open circles). Fitting to the Hill equation (solid lines) yielded EC_{50} values of 8 and 10 nM for the ECS group and the control group, respectively. The calculated values of maximum discharge frequency are 266% for the ECS group and 214% for the control group. For each point: $n = 8$ to 17. Two-way ANOVA: $F(5, 57) = 1.3019$, $p = 0.28$. * denotes *post-hoc* Fisher's test: $p < 0.01$

peatedly with ECS (Fig. 3). In contrast, a single ECS did not modify the effect of 5-CT (data not shown).

Repeated administration of zinc hydroaspartate did not affect the mean basal bursting frequency (treated animals: 0.176 ± 0.006 Hz, $n = 26$; control rats: 0.153 ± 0.056 Hz, $n = 19$; $p > 0.05$, *t*-test). The treatment did not influence the effect of 5-CT on the bursting frequency, either (Fig. 4).

Discussion

A number of studies demonstrate that different antidepressive treatments affect the serotonergic system in the brain by inducing adaptive changes in various 5-HT receptor subtypes (for review see [9, 36, 40]). Our earlier work indicated that repetitive treatment with antidepressant drugs (both tricyclic and selective 5-HT reuptake inhibitors) increased the responsiveness of hippocampal pyramidal neurons to the 5-HT_{1A} receptor agonist 8-OH-DPAT and decreased the responsiveness to the 5-HT₄ receptor agonist zacopride [5, 6, 34]. Similar adaptive changes were also produced by repeated, but not single, ECS [7]. We have also presented evidence that repetitive administration of citalopram or imipramine resulted in a reduced ef-

fectiveness of rat hippocampal 5-HT₇ receptor activation [61]. Together with a reduced excitatory effect of the 5-HT₄ receptor activation induced by several antidepressant treatments in the CA1 area [6, 7, 72] and an increased 5-HT_{1A} receptor-mediated inhibition induced by tricyclic antidepressants in the CA1 and CA3 areas [12, 60], it seems that antidepressant therapies result in an enhancement of the inhibitory action of 5-HT in the hippocampus *via* changing the responsiveness of at least three 5-HT receptors.

However, the results of the present study demonstrate that neither tianeptine nor zinc hydroaspartate treatments resulted in a change in the responsiveness of CA3 hippocampal circuitry to the activation of 5-HT₇ receptors. Moreover, the responsiveness of 5-HT₇ receptors was even enhanced as a result of repetitive ECS administration.

Currently available data on the cellular and neurochemical effects of tianeptine are difficult to reconcile with a monoamine hypothesis of depression, although the drug possesses clear clinical efficacy [65]. Tianeptine is a serotonin-uptake enhancer whose antidepressant effectiveness is based on its ability to reduce rather than to increase serotonin availability in the extracellular space [51] and unlike tricyclic antidepressant drugs, tianeptine does not appear to be associated with adverse cognitive, psychomotor, sleep, cardiovascular or body weight effects and has a low propensity for being abused [65]. Tianeptine differs from most antidepressants in that it is not primarily metabolized by the hepatic cytochrome P450 system [65]. The results of the present study show that repetitive tianeptine administration does not produce any changes in the reactivity of 5-HT₇ receptors when tested in slices prepared 2 days after the last administration of the drug. These results are consistent with a lack of changes in the recovery time of hippocampal CA3 neuronal firing following 5-HT application after chronic tianeptine administration [52]. This lack of changes in the responsiveness of 5-HT₇ receptors is supported by data showing that basal 5-HT levels are unchanged by tianeptine treatment [15]. Additionally, it has been shown that prolonged administration of tianeptine does not modify the reactivity of hippocampal 5-HT_{1A} receptors [52] in contrast to tricyclic antidepressants [12]. Recent studies have provided evidence that tianeptine interferes with the effects of stress on glutamatergic transmission. Tianeptine prevents the alterations in the electrophysiological properties of glutamatergic synapses after acute and chro-

nic stress (for review see [37]). We have recently found that repetitive tianeptine administration results in the reduction of glutamatergic transmission in the rat frontal cortex (unpublished results). Collectively, the data suggest that the antidepressive action of tianeptine is not linked to the effect on the 5-HT receptors in the hippocampus but it rather normalizes glutamatergic functions which undergo alterations due to prodepressive stimuli and may, therefore, have distinct clinical advantages when compared with other antidepressant treatments [27].

Zinc ions exhibit antidepressant-like effects when tested in the rat forced swim test [28, 47] and in rat olfactory bulbectomy model of depression [47]. Moreover, zinc supplementation has been shown to enhance antidepressant-like effects in rat chronic unpredictable stress model of depression [13]. It has been demonstrated that human depression might be accompanied with lower serum zinc concentrations [30, 33, 39]. A beneficial role of zinc supplementation on antidepressant therapy has been found in patients with unipolar depression [44]. The enhancement of 5-HT uptake by zinc [16] and an important role zinc plays in the synthesis of the serotonin from L-tryptophan (as a component of decarboxylase) (reviewed in [54]) imply that antidepressant efficacy of zinc ions might be connected with alteration of the serotonergic transmission. However, in the present study, we have not detected any changes in reactivity of 5-HT₇ hippocampal receptor in zinc-treated rats. Recent work provides compelling evidence for a dysfunction of the glutamate system in major depressive disorder and the involvement of NMDA receptors in the mechanism of antidepressant activity of various treatments. We have recently found that repetitive zinc hydroaspartate administration decreases glutamatergic transmission in the rat frontal cortex (unpublished data). NMDA antagonists mimic the effects of clinically effective antidepressants in both preclinical tests predictive of antidepressant action and procedures designed to model aspects of depressive symptomatology (for review see [50]). Since zinc is an antagonist of the NMDA receptor complex, the potential mechanisms of antidepressant activity of zinc ions might be related to their direct antagonism of NMDA receptor or the antagonistic action on group I metabotropic glutamate receptors [46] than to their direct influence on 5-HT transmission. Yet, interactions between the antidepressant efficacy of zinc ions, by modulation of glutamatergic transmission, and 5-HT system are not unlikely. Glu-

tamate receptors may modulate the extracellular 5-HT level by participating in serotonin release [58, 69]. A complex serotonergic-glutamatergic interaction exists in the raphe nuclei where the release of glutamate is modulated by presynaptic 5-HT₇ heteroreceptors. The activation of these receptors inhibits glutamate release, which results in a reduction of excitatory input to serotonergic neurons and an attenuation of 5-HT release [22].

The results of the present study indicate that repeated ECS may increase the affinity and/or density of hippocampal 5-HT₇ receptors, in contrast to the outcome of the treatment with imipramine or citalopram [61]. It has generally been assumed that the serotonergic system is involved in the mechanism of the therapeutic action of the ECS, however, many findings (both experimental and clinical) are contradictory. Long-term ECS did not change the firing of dorsal raphe neurons, cortex and hippocampus [8]. However, long-term ECS reduces 8-OH-DPAT-induced hypothermia in both mice and rats [8, 18, 56] and leads to up-regulation of 5-HT_{1A} receptors in the dentate gyrus [24]. Long-term ECS was reported by some studies to increase 5-HT_{1A} receptor sensitivity in the hippocampus [7, 12, 14], and receptor binding in the cortex [43] and in the hippocampus [24], while other studies have reported no change in 5-HT_{1A} receptor binding in the hippocampus and a decrease in the cortex [49, 56]. ECS treatment has been shown to increase the density of 5-HT_{2A} receptors [10, 20, 64] localized in superficial layers of frontal cortex, septum and the CA1 region of the hippocampus, to increase 5-HT_{2A} mRNA levels [10, 11] and to enhance behavioral and functional responsiveness to serotonergic agents [31, 64]. Treatment with antidepressants causes a decrease in abnormally elevated 5-HT_{2A} receptor number on blood platelets to the normal level in depressive patients who show clinical improvement [4]. However, ECS treatment increases the number of platelet 5-HT_{2A} receptors [55] and 5-HT transporter sites [29, 35]. Thus, the effects of ECS on 5-HT receptors often differ from those of antidepressant drugs. Therefore, it seems that the therapeutic effect of ECS is not related to a direct influence on 5-HT transmission but rather it involves multiple interactions with other neurotransmitter systems and/or changes in intracellular signal transduction pathways (for review see [19]).

We have previously found that treatment with imipramine or citalopram decreased the reactivity of hip-

poampal 5-HT₇ receptors [61]. On the other hand, the present results indicate that repeated ECS increased the 5-HT₇ receptor-dependent response in the hippocampus while treatments with tianeptine and zinc did not alter it. Although it cannot be excluded that an increased dose and administration time would eventually affect the 5-HT₇ receptor-dependent response, these results suggest that there is no common mechanism of various antidepressant treatments on hippocampal 5-HT₇ receptors. Nevertheless, the finding that the blockade of hippocampal 5-HT₇ receptors exerts anxiolytic and antidepressant effects [66] warrants further studies.

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