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Repeated administration of citalopram and imipramine alters the responsiveness of rat hippocampal circuitry to the activation of 5-HT_7 receptors

Krzysztof Tokarski [a], Agnieszka Zahorodna [a], Bartosz Bobula [a], Malgorzata Grzegorzewska [a], Patrycja Pitra [a], Grzegorz Hess [a,b,*]

[a] *Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Kraków, Poland*
[b] *Institute of Zoology, Jagiellonian University, Ingardena 6, 30-060 Kraków, Poland*

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Abstract

The effects of a selective serotonin reuptake inhibitor, citalopram, and a tricyclic antidepressant drug, imipramine, administered repetitively for 14 days, were investigated ex vivo in rat hippocampal slices. Spontaneous epileptiform bursts were recorded from the CA3 area in nominally Mg^{2+}-free incubation conditions. 5-carboxamidotryptamine (5-CT) dose-dependently increased bursting frequency in the presence of *N*-[2-[4-(2-methoxyphenyl)-1 piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY 100635). This effect could be dose-dependently blocked by (2*R*)-1-[(3-Hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine hydrochloride (SB 269970), thus implicating the involvement of 5-HT_7 receptors. Repeated treatment with citalopram or imipramine resulted in an attenuation of the excitatory effects of the activation of hippocampal 5-HT_7 receptor.
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Keywords: 5-carboxamidotryptamine; Adaptive change; Epileptiform activity; Hippocampal slice; WAY 100635; SB 269970

1. Introduction

A dysfunction of the serotonergic system of the human brain has been implicated in the pathomechanism of depressive disorders and adaptive modifications of the serotonergic modulation of the functions of forebrain structures are thought to provide one important outcome of antidepressant therapies (reviewed in: Mann, 1999; Middlemiss et al., 2002; Blier, 2003). It has been suggested that a common result of different types of antidepressant therapies is an enhancement of serotonin (5-hydroxytryptamine; 5-HT) neurotransmission within the hippocampus (reviewed in: Blier and de Montigny, 1998; Dremencov et al., 2003; Hensler, 2003). The most prominent neuromodulatory effect of 5-HT on hippocampal CA1 and CA3 neurons is a 5-HT_{1A} receptor-mediated hyperpolarization (Andrade and Nicoll, 1987; Beck et al., 1992). Repeated administration of tricyclic antidepressants results in an enhancement of the inhibitory effect of the 5-HT_{1A} receptor activation on the excitability of rat CA1 (Bijak et al., 1996; Maj et al., 1996) and CA3 hippocampal pyramidal neurons (de Montigny and Aghajanian, 1978; Chaput et al., 1991). Repeated administration of a selective serotonin reuptake inhibitor (SSRI), fluoxetine, enhanced the effects of 5-HT_{1A} receptor activation in CA1, but not in CA3, pyramidal neurons (Beck et al., 1997). The sensitivity of 5-HT_{1A} receptors located on CA3 neurons remains also unchanged after treatments with other SSRIs, citalopram and paroxetine (Chaput et al., 1986, 1991).

Another 5-HT receptor subtype, effectively modulating hippocampal pyramidal cells, is the 5-HT_4 receptor, whose activation increases excitability of CA1 neurons (Colino and Halliwell, 1987; Chaput et al., 1990). Adaptive changes induced in rat hippocampus by treatment with a tricyclic antidepressant, imipramine, involve an attenuation of the excitatory effect of 5-

* Corresponding author. Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Kraków, Poland. Tel.: +48 12 662 3212; fax: +48 12 637 4500.
E-mail address: Hess@if-pan.krakow.pl (G. Hess).

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HT_4 receptor activation (Bijak et al., 1997; Zahorodna et al., 2002). Repeated administration of a selective serotonin reuptake inhibitor (SSRI), citalopram, results in a reduced effectiveness of 5-HT_4 receptor activation in CA1 cells as well (Tokarski and Bijak, 1996; Bijak et al., 1997), however, it has been reported that treatment with another SSRI, fluoxetine, did not modify the 5-HT_4 receptor-mediated effect in CA1 neurons (Beck et al., 1997).

The 5-HT_7 receptor is the latest 5-HT receptor subtype to be identified (Bard et al., 1993; Ruat et al., 1993). Within the brain, the 5-HT_7 receptor is present predominantly in the thalamus, hippocampus and hypothalamus (Neumaier et al., 2001). It has been implicated in various functions including mood regulation, circadian rhythmicity and sleep, disturbances of which are related to affective disorders (reviewed in: Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004). On the cellular level, activation of the 5-HT_7 receptor results in an increased excitability of hippocampal cells mediated via a decrease of potassium conductance underlying slow afterhyperpolarization, as demonstrated in CA3 pyramidal neurons (Bacon and Beck, 2000). In CA1 pyramidal cells the effects of 5-HT_7 receptor activation involve a decrease of slow afterhyperpolarization (Tokarski et al., 2003) and an increase of hyperpolarization-activated current I_h (Bickmeyer et al., 2002). These effects contribute to 5-HT_7 receptor-mediated facilitation of CA1 and CA3 hippocampal population spikes in vivo (Matsumoto et al., 2002) as well as to modulation of epileptiform activity recorded in the CA3 area of disinhibited hippocampal slices in vitro (Gill et al., 2002). Downregulation of the 5-HT_7 receptor has been found to occur in rat suprachiasmatic nucleus of the hypothalamus after chronic treatment with tricyclic antidepressants, including imipramine, and a SSRI, fluoxetine (Sleight et al., 1995; Mullins et al., 1999). However, it is not known whether antidepressant treatments modify the 5-HT_7 receptor-mediated responses in forebrain structures. Therefore, in the present study we set out to evaluate the influence of repeated administration of two antidepressants, a SSRI, citalopram and a tricyclic antidepressant, imipramine, on 5-HT_7 receptor-mediated modulation of epileptiform activity in ex vivo hippocampal slices. Modulation of the frequency of spontaneous epileptiform bursting has been shown to provide a sensitive measure of the activation of 5-HT receptor subtypes, in a manner not dependent on the strength of external stimuli (Salgado-Commissariat and Alkadhi, 1997; Gill et al., 2002; Tokarski et al., 2002). Our data indicate an attenuation of the effects of the activation of hippocampal 5-HT_7 receptor after antidepressant treatments.

2. Materials and methods

2.1. Treatment of animals and slice preparation

Experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology and were carried out in accordance with the European Community guidelines for the use of experimental animals and national law. Male Wistar rats, weighing approx. 100 g at the beginning of the experiment, were housed in groups under a controlled light/dark cycle (light on: 7.00–19.00) and had free access to standard food and tap water. Citalopram or imipramine, dissolved in 2 ml of water, were administered per os (10 mg/kg) twice daily, for 14 days, since maximum adaptive effects on modulation of population spike amplitude by 5-HT have been shown to occur after 14 days of treatment (Bijak et al., 2001). Citalopram and imipramine treatments were conducted at different times of the year using rats purchased from two different licensed dealers. Each treated group had a matched control group, receiving water, but otherwise treated identically and investigated simultaneously with treated animals. Rats were killed by decapitation two days after the last drug administration. Their brains were rapidly removed and immersed in an ice-cold artificial cerebrospinal fluid (aCSF) of the following composition (in mM): NaCl (124), KCl (5), $CaCl_2$ (2.5), $MgSO_4$ (1.3), KH_2PO_4 (1.25), $NaHCO_3$ (24) and D-glucose (10), which was bubbled with the mixture of 95% O_2/5% CO_2. After dissection, the hippocampus was cut into transverse slices (400 μm thick) using a vibrating microtome (FHC, Brunswick, USA).

2.2. Recording and data analysis

Slices were left to recover in a holding chamber at room temperature for 1–6 h. A single slice was then transferred to the recording chamber of a submerged type, which was superfused at 1.5 ml/min with warmed (32±0.5 °C), modified aCSF, in which [NaCl] was raised to 132 mM and [KCl] was lowered to 2 mM, devoid of Mg^{2+} ions. Glass micropipettes filled with 2 M NaCl (1–4 MΩ) were used to record activity from the pyramidal layer of the CA3 area. Spontaneous epileptiform bursts were amplified (Axoprobe 2, Axon Instruments, USA), band-pass filtered (1 Hz–10 kHz), A/D converted, stored on a PC (1401 interface with SIGAVG software, CED, UK) and analysed off-line. Discharges were also displayed using a chart recorder (TA240, Gould, USA). Bursting frequency was determined as a number of events per 1 min bins. Drug effects were assessed in terms of change in bursting frequency (±S.E.M.), by comparing average frequency over 6–10 min after beginning of 5-carboxamidotryptamine maleate (5-CT) application to baseline values (see Fig. 2A). Dose-response data were fitted to Hill equation using SigmaPlot software (SPSS Inc., USA) and compared using two-way analysis of variance followed by post hoc LSD Fisher's test. Data from treated and control rats were also compared using paired *t*-test.

2.3. Drugs

5-carboxamidotryptamine maleate (5-CT), (2*R*)-1-[(3-Hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine hydrochloride (SB 269970) and citalopram hydrobromide were obtained from Tocris. *N*-[2-[4-(2-methoxyphenyl)-1 piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY 100635) and imipramine hydrochloride were obtained from Sigma.

3. Results

Spontaneous epileptiform bursting of stable frequency occurred within 10–15 min of perfusion of slices with nominally Mg^{2+}-free aCSF. Bursting events, representing primary bursts (e.g. Köhling et al., 2001), consisted of a prominent initial population spike-like waveform, reaching 3–4 mV in amplitude, which was followed by a variable number of small spikes, superimposed on a slower, positive-going wave, lasting 60–100 ms (Figs. 1–3). While the application of 5-CT alone resulted in a decrease in the bursting frequency, after addition of WAY 100635, a selective 5-HT_{1A} receptor antagonist (Newman-Tancredi et al., 1996), an increase in the bursting frequency was evident (Fig. 1A_1). In the continuous presence of 1 μM WAY 100635 in the aCSF, this effect reached maximum between 6 and 10 min after the beginning of 5-CT application (Fig. 2A). As illustrated in Fig. 3C and D, the excitatory effect of 5-CT was dose-dependent. SB 269970, a specific antagonist of the 5-HT_7 receptor (Lovell et al., 2000), dose-dependently blocked the excitatory effect of 5-CT in the presence of WAY 100635 (Fig. 2C). SB 269970 and WAY 100635 alone exerted no effect on epileptiform activity.

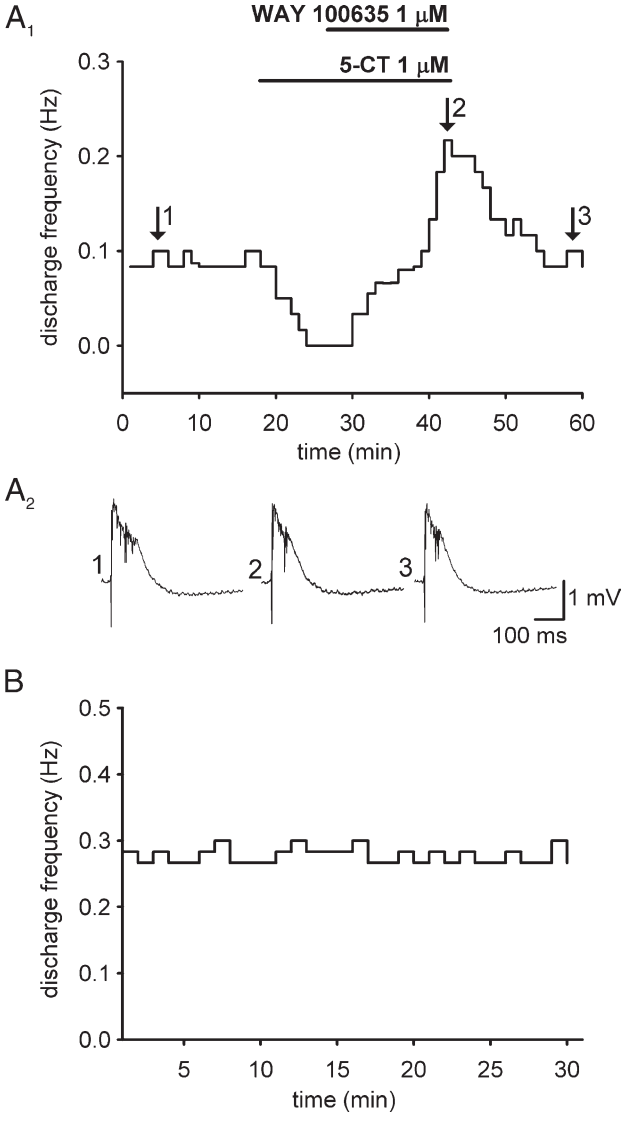

Fig. 1. Modulation of spontaneous epileptiform activity by 5-CT in the CA3 area of rat hippocampal slice. A_1: The net inhibitory effect of 5-CT application could be turned into excitatory after addition of the selective 5-HT_{1A} receptor antagonist, WAY 100635. *Graph* illustrates changes in the discharge frequency in a representative experiment. In this and in the following figure *bars* denote the time-period of perfusion with the substances. A_2: The traces labeled 1, 2, 3 represent examples of single bursting events, recorded at times indicated in the graph in A_1 by *arrows*. B: A representative example of control recording demonstrating the stability of bursting frequency.

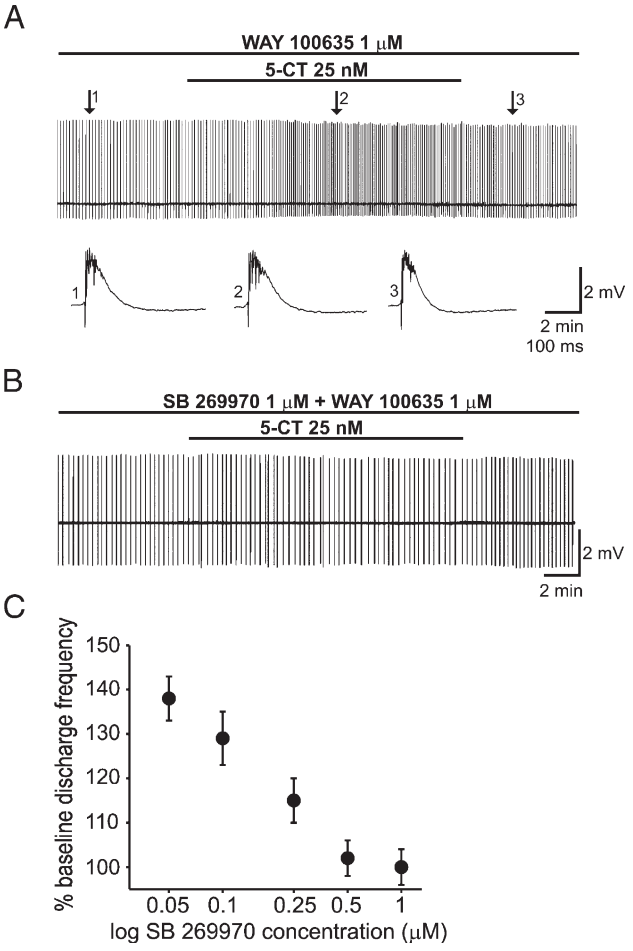

Fig. 2. Modulation of spontaneous epileptiform activity by the 5-HT_7 receptor in the CA3 area of the hippocampal slice. A: The excitatory effect of 5-CT. *Graph* shows chart recording from a representative experiment. WAY 100635 was present in the aCSF throughout the experiment to block 5-HT_{1A} receptors. The traces below graph (1, 2, 3) represent examples of bursting events (*indicated in graph by arrows*) at expanded timescale. B: The excitatory effect of 25 nM 5-CT could be blocked by the specific 5-HT_7 receptor antagonist SB 269970 present in the aCSF throughout the experiment in addition to WAY 100635. C: Dose-dependence of the inhibition of the excitatory effect of 100 nM 5-CT by SB 269970, in the presence of 1 μM WAY 100635. For each point: $n=6$.

Repeated administration of citalopram did not affect the mean basal bursting frequency (0.138±0.037 Hz, $n=37$), which was not different from the activity recorded in slices obtained from the control group of animals (0.120±0.047 Hz, $n=24$; $P>0.05$, *t*-test). In the imipramine-treated group the mean basal bursting frequency was lower than in the citalopram-treated group (0.066±0.003 Hz, $n=82$), however, it was not different from the activity recorded in slices obtained from the control

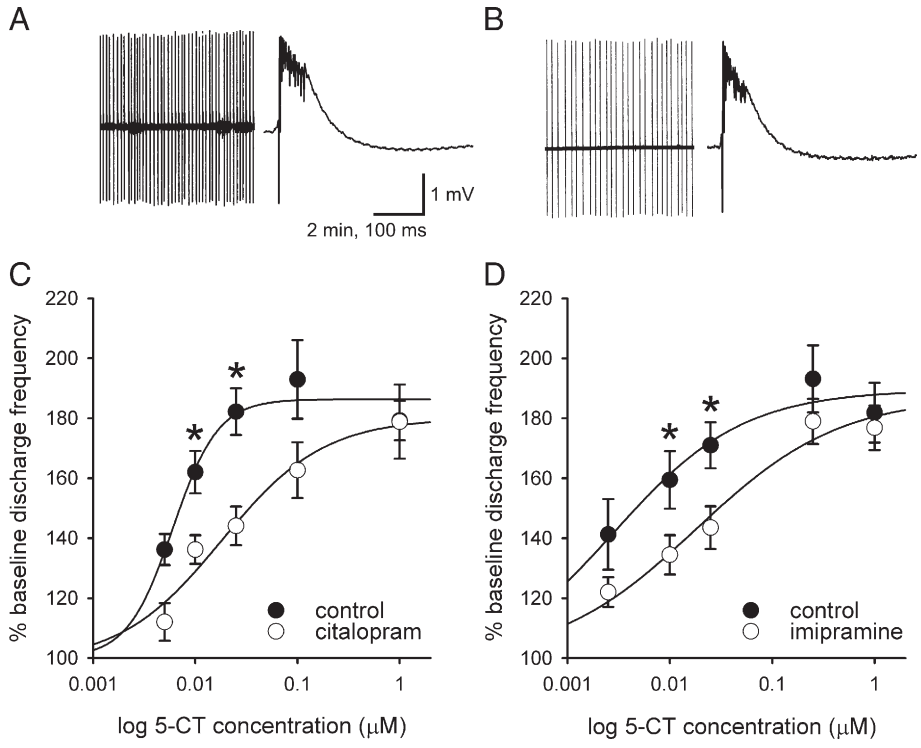

Fig. 3. Attenuation of the excitatory effect of 5-CT by an earlier treatment with citalopram or imipramine for 14 days. A, B: Representative examples of recordings from slices obtained from animals treated with citalopram (A) or imipramine (B). Single events shown to the right at the expanded timescale correspond to the last of the bursts in the chart recordings, shown to the left at compressed timescale. C, D: Dose-response curves for the effect of 5-CT on the bursting activity in ex vivo slices. Shown are mean increases in bursting frequency (±S.E.M.) in slices obtained from control animals (filled circles) and from citalopram-treated rats (C, open circles) and imipramine-treated rats (D, open circles). The solid lines are fits to the Hill equation which yielded EC_{50} values of 6 and 18 nM for the control and citalopram-treated group, respectively (C), as well as 3 and 18 nM for the control and imipramine-treated group, respectively (D). For each point: $n=4–15$. *$P<0.01$, ANOVA.

group, receiving water (0.061±0.003 Hz, $n=67$; $P>0.05$, *t*-test). The difference in the mean basal bursting frequency between imipramine- and citalopram-treated groups was, most likely, a result of seasonal variability and different origins of the two groups of animals (see Materials and methods). The 5-CT-induced increase in the bursting frequency was significantly attenuated in slices prepared from animals treated repeatedly with citalopram (Fig. 3C) or imipramine (Fig. 3D). The overall shape of epileptiform bursts was not affected by antidepressant treatments (compare Fig. 3A, B with Figs. 1A2 and 2A).

4. Discussion

Incubation of hippocampal slices in a nominally Mg^{2+}-free aCSF results in an increase in NMDA receptor conductance and in an occurrence of spontaneous bursting activity (Walther et al., 1986; Mody et al., 1987). It has been established that primary bursts are initiated by CA3 pyramidal neurons (Miles and Wong, 1983) and they propagate within slice in recurrent excitatory connections (Traub et al., 1994). 5-HT exerts two opposite effects on epileptiform activity recorded from the area CA1 of hippocampal slices in Mg^{2+}-free conditions, the early-inhibitory and the late-excitatory. While the inhibitory effect is mediated by the 5-HT_{1A} receptor, the excitatory effect of 5-HT has been attributed to the 5-HT_4 receptor (Tokarski et al., 2002). The present results, obtained from hippocampal CA3 area with intact synaptic inhibition, are consistent with data of Gill et al. (2002), who demonstrated that spontaneous epileptiform activity, which develops in the CA3 area during blockade of gamma-aminobutyric A ($GABA_A$) and $GABA_B$ receptor-mediated synaptic inhibition, may be enhanced by the application of either 5-CT or 8-hydroxy-2-dipropylaminotetralin hydrobromide (8-OH-DPAT), in the presence of WAY 100635, i.e. in conditions allowing for the selective activation of the 5-HT_7 receptor, and that this effect may be blocked by the selective 5-HT_7 receptor antagonist SB-269970. 5-CT does not interact with the 5-HT_4 receptor, however, it is an agonist of 5-HT_5 receptors, but the effects of the activation of these receptors on neuronal excitability are currently unknown (Nelson, 2004). Since 5-HT_5 receptors inhibit adenylyl cyclase activity through $G_{i/o}$ proteins (Nelson, 2004), it is conceivable that the hypothethic effect of 5-HT_5 receptor activation on pyramidal cell excitability would be opposite to known, excitatory effects of 5-HT_4 and 5-HT_7 receptors, which are mediated via G_s protein-coupled stimulation of adenylyl cyclase.

5-HT modulates excitability of hippocampal pyramidal cells through at least three 5-HT receptor subtypes. The activation of 5-HT_{1A} receptors, via opening of G protein-activated K^+ (GIRK) channels, results in a hyperpolarization of CA1 and CA3 pyramidal cells (Andrade et al., 1986; Andrade and Nicoll, 1987; Colino and Halliwell, 1987; Ropert, 1988; Beck et al., 1992; Premkumkar and Gage, 1994). It has been shown in CA1 pyramidal neurons that the inhibitory effect of 5-HT is followed by a slower depolarization, accompanied by a reduction of

calcium-activated afterhyperpolarization and by a decrease in spike frequency adaptation, which have both been attributed to 5-HT_4 receptor-mediated stimulation of cAMP-dependent protein kinase and modulation of potassium conductances (Andrade and Chaput, 1991; Roychowdhury et al., 1994; Torres et al., 1996). The mechanism of the depolarization may involve a cAMP-gated channel (Chapin et al., 2002). Recent work conducted in CA3 (Bacon and Beck, 2000) and CA1 pyramidal cells (Tokarski et al., 2003) has shown that the activation of the 5-HT_7 receptor reduces the slow afterhyperpolarization and spike adaptation as well. Inhibition of the slow afterhyperpolarization results in an increase of the frequency of bursting activity in the CA3 area (Gill et al., 2002). All three 5-HT receptor subtypes may modulate the hyperpolarization-activated cation current, I_h, which affects synaptic integration and firing properties of neurons through a cAMP-dependent, protein kinase A (PKA)-independent mechanism (Chapin and Andrade, 2001; Bickmeyer et al., 2002; but see: Chapin et al., 2002). The effects of the 5-HT_7 receptor activation are generally thought to be mediated through G_s protein-coupled stimulation of cAMP synthesis and PKA, but the 5-HT_7 receptor may also stimulate Ca^{2+}-calmodulin-sensitive isoforms of adenylate cyclase, AC1 and AC8, as well as the extracellular signal-regulated kinase (ERK) cascade through a protein kinase A-independent pathway (reviewed in: Hedlund and Sutcliffe, 2004; Thomas and Hagan, 2004).

Earlier work conducted in vivo demonstrated that repeated administration of imipramine results in an enhancement of the responsiveness of rat hippocampal pyramidal CA3 neurons to microiontophoretic application of 5-HT_{1A} receptor agonists (de Montigny and Aghajanian, 1978; Chaput et al., 1991). Using ex vivo slices, it has subsequently been shown that imipramine treatment, apart from increasing the responsiveness of hippocampal CA1 pyramidal cells to the activation of postsynaptic 5-HT_{1A} receptors, also results in an attenuated responsiveness of the 5-HT_4 receptor (Bijak et al., 1996, 1997). The present data, obtained using recording ex vivo of a type of spontaneous network activity, extend these findings in showing that adaptive effects of imipramine treatment in the CA3 area of the hippocampus involve also an attenuated responsiveness of the 5-HT_7 receptor. Antidepressant-induced modifications of the slow afterhyperpolarization in CA3 neurons are unlikely since it has been shown that imipramine treatment does not change the amplitude of the slow afterhyperpolarization in CA1 pyramidal cells (Bijak et al., 2001). Treatment of rats with citalopram induces a reduction in the effectiveness of the 5-HT_4 receptor activation in CA1 neurons (Tokarski and Bijak, 1996; Bijak et al., 1997). Thus, the effect of citalopram on the function of the 5-HT_7 receptor located on CA3 neurons, seen in this study, resembles that on the function of the 5-HT_4 receptor located on CA1 cells. Altogether, these data point out to the complexity of antidepressant treatment-induced adaptive effects on postsynaptic hippocampal 5-HT receptors.

The present study provides evidence of an attenuation of the excitatory effect of the activation of the 5-HT_7 receptor. This phenomenon may occur either as a result of increased 5-HT_7 receptor activation and/or activation of other receptors by elevated extracellular 5-HT level due by blockade of its reuptake or, alternatively, by interaction of antidepressants with the receptor. It has been shown that imipramine may directly interact with the 5-HT_7 receptor and produce functional Fos immunoreactivity (Mullins et al., 1999). Downregulation of the 5-HT_7 receptor, related to chronic treatment with a variety of antidepressants including imipramine and fluoxetine, has previously been found to occur in the suprachiasmatic nucleus of rat hypothalamus (Sleight et al., 1995; Mullins et al., 1999), where the treatment induced a reduction in 5-HT_7 receptor density by approx. 30%, without changing receptor affinity. However, modifications in 5-HT receptor-mediated responses could either be related to decreased receptor density or may occur independently. For example, repeated administration of imipramine results in an enhanced electrophysiological responsiveness of rat hippocampal pyramidal neurons to the 5-HT_{1A} receptor agonist 8-OH-DPAT (de Montigny and Aghajanian, 1978; Chaput et al., 1991; Tokarski and Bijak, 1996). This effect is uncorrelated with changes in 5-HT_{1A} receptor binding (Bijak et al., 1996), suggestive of an enhancement of cellular effector systems, which potentially may involve modifications in the capacity of the receptor to activate G protein, changes in G protein expression or phosphorylation as well as modifications at the level of effector (reviewed in: Donati and Rasenick, 2003; Hensler, 2003). It has recently been reported that increases in postsynaptic 5-HT_{1A} receptor agonist-stimulated [^{35}S]GTPγS binding occur in rat hippocampus after imipramine and fluoxetine treatments, indicative of a modification of the initial, activation step of receptor/G protein coupling (Shen et al., 2002) although other studies did not confirm this finding (Hensler, 2002). Imipramine-induced decrease in reactivity of rat CA1 hippocampal neurons to the activation of the 5-HT_4 receptor may also be related to modifications of the transduction pathway, involving adenylate cyclase and protein kinase A (Bijak, 1997). It has been shown that antidepressants may induce a reduction of certain cAMP-mediated responses (e.g. Pilc and Legutko, 1995). Since the protein G_s-mediated signal transduction pathway is stimulated also in the case of the 5-HT_7 receptor activation, it is conceivable that the effects seen in the present study may be due to antidepressant-induced reduction of cAMP synthesis or protein kinase A activity. However, numerous studies indicate that the therapeutic action of antidepressants is linked to an increase of the activity in the adenylyl cyclase system, which results in enhancement of cyclic AMP-response element binding protein (CREB)-mediated gene transcription in the hippocampus (reviewed in: D'Sa and Duman, 2002; Dremencov et al., 2003). Further studies are needed to resolve the molecular mechanism of reduced effectiveness of hippocampal 5-HT_7 receptor activation after antidepressant treatments. Interestingly, stress may increase the level of 5-HT_7 receptor mRNA in the hippocampus (Yau et al., 2001). Since the 5-HT_7 receptor has been shown to stimulate hippocampal glucocorticoid receptor expression in cell cultures (Laplante et al., 2002), antidepressant-induced reduction in responsiveness of the 5-

HT_7 receptor may result in reduced level of glucocorticoid receptors.

In conclusion, the results of the present study indicate for the first time that repetitive administrations of citalopram or imipramine result in a reduced effectiveness of rat hippocampal 5-HT_7 receptor activation. This phenomenon has general consequences for the serotonergic modulation of information processing in the hippocampus. Together with a reduced excitatory effect of the 5-HT_4 receptor activation induced by several antidepressant treatments in the CA1 area (Bijak et al., 1997, 2001; Zahorodna et al., 2002) and an increased 5-HT_{1A} receptor-mediated inhibition induced by tricyclic antidepressants in the CA1 and CA3 areas (Chaput et al., 1986, 1991; Tokarski and Bijak, 1996), antidepressant therapies result in an enhancement of the inhibitory action of 5-HT in the hippocampus.

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