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Imipramine but not 5-HT_{1A} receptor agonists or neuroleptics induces adaptive changes in hippocampal 5-HT_{1A} and 5-HT_4 receptors

Agnieszka Zahorodna*, Krzysztof Tokarski, Maria Bijak

Department of Physiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Cracow, Poland

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Abstract

It has been reported that the treatment with a tricyclic antidepressant imipramine induces an increase in the sensitivity of 5-HT_{1A} receptors and a decrease in the sensitivity of 5-HT_4 receptors in the rat hippocampus. 5-HT_{1A} receptor agonists and neuroleptics also affect 5-HT_{1A} receptors in different brain areas; therefore, it was of interest to compare their effects on hippocampal 5-HT receptors with the influence of the well-established antidepressant imipramine. We studied the effects of repeated treatment with imipramine, the 5-HT_{1A} receptor agonists 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT) and buspirone, and the neuroleptics haloperidol and clozapine on the sensitivity of rat hippocampal CA1 neurons to 5-HT_{1A}- and 5-HT_4 receptor activation. Imipramine was administered for 21 days (10 mg/kg p.o., twice daily), 8-OH-DPAT for 7 days (1 mg/kg s.c., twice daily) and buspirone for 21 days (5 mg/kg s.c., twice daily). The rats received haloperidol (1 mg/kg) and clozapine (30 mg/kg) for 6 weeks in drinking water. Hippocampal slices were prepared 2 days after the last treatment with imipramine, 8-OH-DPAT or buspirone, and 5 days after the last treatment with the neuroleptics. Using an extracellular in vitro recording, we studied changes in the amplitude of stimulation-evoked population spikes, induced by 5-HT, 8-OH-DPAT and the 5-HT_4 receptor agonist zacopride. Activation of 5-HT_{1A} receptors decreased, while activation of 5-HT_4 receptors increased the amplitude of population spikes. Imipramine significantly enhanced the inhibitory effects of 5-HT and 8-OH-DPAT, and attenuated the excitatory effect of zacopride. No other treatment used in the present study changed the sensitivity of hippocampal CA1 neurons to 5-HT_{1A} and 5-HT_4 receptors activation. These findings indicate that adaptive changes in the sensitivity of hippocampal neurons to 5-HT_{1A} and 5-HT_4 receptors agonists are specific to imipramine and may thus—at least partly—mediate its effects.

Keywords: 5-HT_{1A} receptor; 5-HT_4 receptor; 8-OH-DPAT (8-hydroxy-2(di-*n*-propylamino)tetralin); Antidepressant; Buspirone; Clozapine; Imipramine; Haloperidol

1. Introduction

A substantial body of evidence suggests that affective disorders stem from the malfunction of the serotonergic (5-hydroxytryptamine, 5-HT) system in limbic regions of the brain (for review, see Leonard, 1995; Maes and Meltzer, 1995). It has been shown in rats that long-term treatment with tricyclic antidepressants or electroconvulsive shocks results in a hypersensitivity of hippocampal postsynaptic 5-HT_{1A} receptors (Blier et al., 1987, 1988; Chaput et al., 1991). We have previously found that repeated treatment with a tricyclic antidepressant imipramine and electroconvulsive shocks enhance the inhibitory effect of 5-HT in the hippocampus, both directly—by increasing 5-HT_{1A} receptor responsiveness (Bijak et al., 1996, 2001), and indirectly—by inducing subsensitivity to the activation of excitatory 5-HT_4 receptors (Bijak et al., 1997, 2001). It is of interest to ascertain whether this effect is specific to tested antidepressant treatments, or whether adaptive changes in hippocampal 5-HT_{1A} and 5-HT_4 receptors are also linked to the action of other drugs, such as 5-HT_{1A} receptor agonists and neuroleptics, which reportedly display the antidepressant activity.

5-HT_{1A} receptor agonists have anxiolytic and antidepressant effects and have also been reported to augment the action of antidepressant drugs (Heiser and Wilcox, 1998). It has been suggested that the rapid antidepressant-like action of 5-HT_{1A} receptor agonists in rats is mediated by their ability to readily desensitize somatodendritic 5-HT_{1A} receptors in the dorsal raphe (Kennett et al., 1987). This is consistent with the reports that chronic antidepressant treatments with monoamine oxidase inhibitors or selective 5-HT reuptake blockers induce progressive desensitization of somatodendritic 5-HT_{1A} receptors (Blier and De Montigny, 1985; Blier et al., 1988). The desensitization of somatodendritic autoreceptors enhances serotonergic transmission,

* Corresponding author. Tel.: +48-12-6623209; fax: +48-12-6374500.
E-mail address: zahoro@if-pan.krakow.pl (A. Zahorodna).

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which may thus induce adaptive changes in postsynaptic 5-HT receptors. In the present study, we examined the effect of repeated treatment with the selective, high intrinsic activity 5-HT_{1A} receptor agonist 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT), and the partial agonist buspirone (Fulton and Brogden, 1997) on the sensitivity of hippocampal 5-HT_{1A} and 5-HT_4 receptors. Agents with a relatively high intrinsic activity at 5-HT_{1A} receptors may have a greater potential therapeutic efficacy and a possibly faster onset of action than relatively weak partial agonists (Schreiber and De Vry, 1993). Buspirone is a representative of a new class of nonbenzodiazepine anxiolytics, known as azapirones. These compounds have a high affinity for 5-HT_{1A} receptors and have been reported to produce antidepressant effects in humans (Fulton and Brogden, 1997).

The ability of antipsychotic drugs to modulate serotonergic function is important for their efficacy and side-effect profiles (Meltzer, 1999). The effects of antipsychotic drugs on the serotonergic system may be responsible for their activity on the negative symptoms of schizophrenia, psychotic depression and cognition. It has been shown that clozapine mediates some of its antianxiety actions by a 5-HT_{1A} receptor-dependent mechanism (Bartoszyk et al., 1996). Clozapine has also been found to be effective as an antimanic agent and a mood stabilizer in treatment-resistant mood disorders (Calabrese et al., 1996). Most atypical antipsychotics are high-affinity antagonists of 5-HT_{2A} receptors (Meltzer et al., 1989). Furthermore, several antipsychotic drugs exhibit a high affinity for 5-HT_6 and 5-HT_7 receptors (Brunello et al., 1995) and a moderate affinity for 5-HT_{1A} receptors (Coward et al., 1989; Schotte et al., 1996; Newman-Tancredi et al., 1998). While some antipsychotic drugs, including clozapine, are partial agonists at 5-HT_{1A} receptors, other antipsychotics, e.g. haloperidol, display an antagonist behavior at 5-HT_{1A} receptors (Newman-Tancredi et al., 1998). It has been reported that antipsychotic drugs may affect extracellular 5-HT levels and metabolism (Ichikawa et al., 1998; Antoniou et al., 2000); they also alter densities of 5-HT transporters and 5-HT_{1A} receptors in different brain areas (Ase et al., 1999).

In the present study, we examined the influence of different classes of drugs with diverse actions on serotonergic transmission on the sensitivity of hippocampal CA1 neurons to 5-HT_{1A} and 5-HT_4 receptors agonists in order to determine whether the previously described effects of chronic imipramine on hippocampal 5-HT receptors are specific to this tricyclic antidepressant, or are common to different therapies which display some antidepressant activity.

2. Materials and methods

2.1. Animals

The study was carried out on male Wistar rats purchased from licensed dealers. The animals weighed approximately 100–120 g at the beginning of the experiment. They were housed in groups of seven per cage on a controlled light/dark cycle (light on: 07:00–19:00) and had free access to standard food and tap water. All the experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences. Every treated group of animals had matched control group (7–10 animals). Both groups were investigated at the same time. Imipramine (10 mg/kg p.o.; dissolved in water) was given twice daily for 21 days; control rats received water (2 ml/kg p.o.). 8-OH-DPAT (1 mg/kg s.c.; dissolved in water) was given twice daily for 7 days; control rats received water (2 ml/kg s.c.). Buspirone (5 mg/kg s.c.; dissolved in water) was given twice daily for 21 days; control rats received water. Clozapine (30 mg/kg per day) and haloperidol (1 mg/kg per day) were dissolved in a small amount of lactic acid and were then diluted with tap water. Both neuroleptics were given in drinking water for 6 weeks. The volume of the consumed liquid was checked every day. Control animals received tap water ad libitum. The rats receiving imipramine, 8-OH-DPAT or buspirone were sacrificed 48 h after the last treatment, while those treated with neuroleptics were sacrificed 5 days after the last treatment.

2.2. Hippocampal slice preparation and recording

The rats were killed by decapitation. Their brains were quickly removed and placed in an ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM): NaCl, 124; KCl, 2; $CaCl_2$, 2.5; $MgSO_4$, 1.3; KH_2PO_4, 1.25; $NaHCO_3$, 24; and glucose 10. After dissection, the hippocampus was cut into 350-μm-thick transverse slices using a tissue slicer (Frederick Haer, Brunswick, ME, USA). The slices were left to recover in ACSF (equilibrated to pH 7.4 with 95% O_2/5% CO_2 at 32 °C) for 1–6 h. A single slice was transferred to a submerged brain-slice recording chamber superfused at 1.5 ml/min with ACSF bubbled with 95% O_2/5% CO_2 at 32 ± 0.5 °C. For extracellular recording of population spikes, a glass microelectrode filled with 2 M NaCl (resistance 1–4 MΩ) was positioned in the stratum pyramidale of the CA1 area. A bipolar, tungsten electrode was placed in the stratum radiatum to stimulate the Schaffer collateral–commissural pathway. Square-wave pulses of 0.1-ms duration were applied at 0.02 Hz. The recorded signals were amplified (Axoprobe, Axon Instruments, Foster City, CA, USA), bandpass-filtered (1 Hz–10 kHz) and stored on a PC hard disk after AD conversion at 5–10 kHz (CED1401 interface and SIGAVG data acquisition software; Cambridge Electronics).

2.3. Chemicals

After stabilization of the baseline response for at least 20 min (defined as no more than 10% variation in the median amplitude of the population spike), the slice was superfused

with the tested drug for 10 min and subsequently washed with a standard solution for 20 min. Stock solutions were prepared in water, and the drugs were diluted in ACSF to the final concentration immediately before application. Only one application per slice was made.

The drugs used were: (±)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (8-OH-DPAT), buspirone hydrochloride, haloperidol base (RBI, Natick, MA, USA), 5-HT creatinine sulphate (Sigma, St. Louis, MO, USA), 4-amino-5-chloro-2-methoxy-substituted benzamide (*R*,*S*)zacopride (generously donated by Delalande, France), clozapine and imipramine hydrochloride (Polfa, Poland).

2.4. Analysis and statistics

Population spike amplitudes were measured as the mean of two amplitudes taken from the peak of the initial positivity to the trough of the initial negativity, and from the trough of the initial negativity to the peak of the second positivity (Spike 2 software, Cambridge Electronics). Input–output curves were generated for each slice before drug application. Population spike which was 30% of the maximum amplitude was chosen to study the effects of 5-HT receptor agonists, because earlier study indicated that the most pronounced effects of 5-HT and 8-OH-DPAT were observed at this value (Bijak et al., 1996). Four responses were evoked, and mean population spike amplitudes were calculated under control (pre-drug) conditions, at 8–10 min of 5-HT receptors agonists application and following a 20-min washout. Each slice was treated as an independent sample. Statistical assessment was carried out using Student's *t*-test.

3. Results

The doses of 5-HT, 8-OH-DPAT and zacopride used in the present study were determined in our previous studies (Bijak et al., 1996, 1997). Similarly, the pharmacological specificity of 5-HT_{1A} and 5-HT_4 receptor-mediated effects was previously determined by the application of selective antagonists, WAY 100135 and DAU 6285, respectively (Bijak et al., 1996, 1997). 5-HT (2.5 μM) reversibly decreased the amplitude of population spikes (Fig. 1). The inhibitory effect of 5-HT reached a steady-state by 1–2 min, remained stable throughout the application and disappeared within 3–6 min following return to the drug-free solution. 8-OH-DPAT of 1 μM also reversibly decreased the amplitude of population but it showed a slow, and often incomplete recovery during the wash-out period of 15–20 min (Fig. 2). Zacopride (5 μM) increased the amplitude of population spikes (Fig. 3). The effect of zacopride reached a steady-state level in 5–7 min and remained stable throughout the application. The reversal was slow (about 20–30-min washout) and often incomplete.

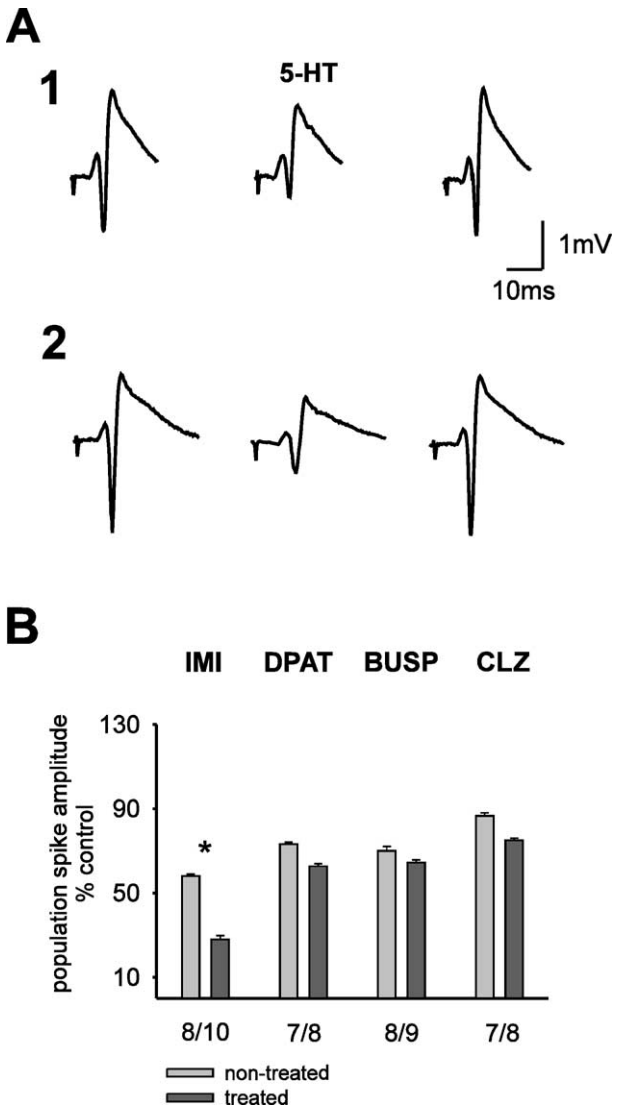

Fig. 1. An example of the inhibitory effect of 5-HT (2.5 μM) on the population spike recorded in the CA1 region of hippocampal slices from control animals and those treated with imipramine (A1 and A2, respectively). Effects of repeated treatment with imipramine (IMI), 8-OH-DPAT (DPAT), buspirone (BUSP) and clozapine (CLZ) on the inhibitory action of 5-HT (B). The results are expressed as the mean (± S.E.M.) percentage change of the baseline population spike amplitude. Numbers below bars represent the number of slices tested in control and treated groups (data from 7–10 rats). * $P \leq 0.05$, Student's *t*-test.

Repeated treatment with imipramine did not affect the mean amplitude of maximum population spikes (9.5 ± 1.5 mV, $n = 24$ in slices from control animals, treated with H_2O; 10 ± 1.4 mV, $n = 30$ in slices from rats treated repeatedly with imipramine) neither did the mean amplitude of 30% of the maximal population spikes (3.2 ± 0.06 mV, $n = 24$ in slices from control animals, treated with H_2O; 3.2 ± 0.08 mV, $n = 30$ in slices from rats treated repeatedly with imipramine). In slices obtained from animals treated repeatedly with imipramine, the inhibitory effects of both 5-HT and 8-OH-DPAT were significantly potentiated (Figs. 1 and 2),

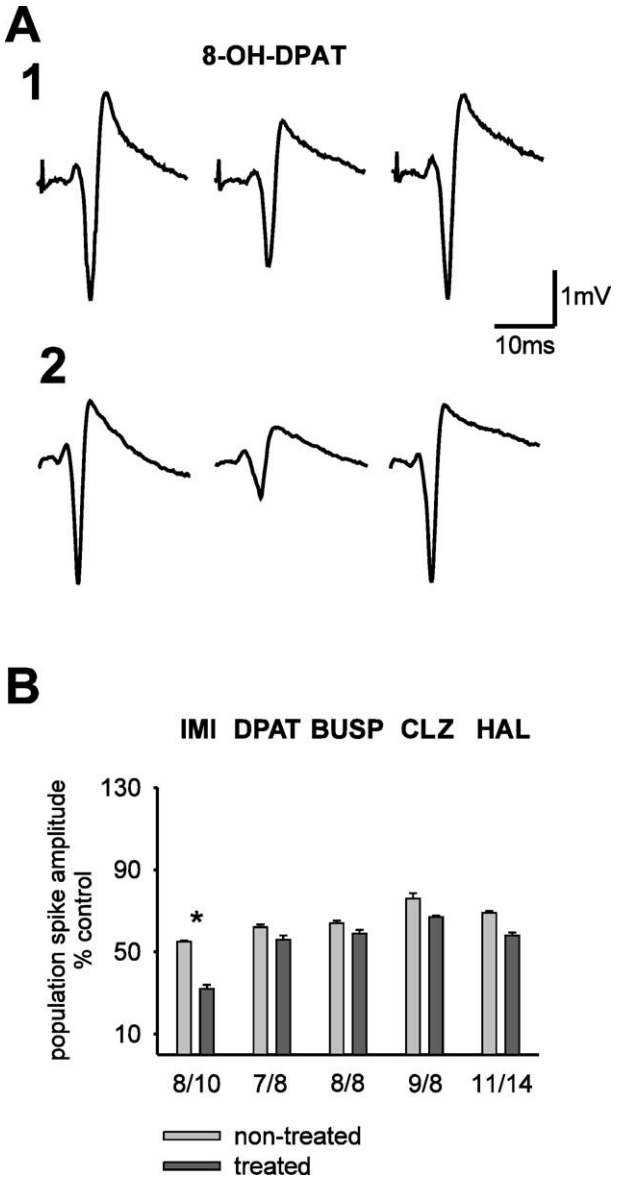

Fig. 2. An example of the inhibitory effect of 8-OH-DPAT (1 μM) on the population spike recorded in the CA1 region of hippocampal slices from control animals and those treated with imipramine (A1 and A2, respectively). Effects of repeated treatment with imipramine (IMI), 8-OH-DPAT (DPAT), buspirone (BUSP), clozapine (CLZ) and haloperidol (HAL) on the inhibitory action of 8-OH-DPAT (B). The results are expressed as the mean (± S.E.M.) percentage change of the baseline population spike amplitude. Numbers below bars represent the number of slices tested in control and treated groups (data from 7–10 rats). * $P \leq 0.05$, Student's *t*-test.

whereas the zacopride-evoked increase in the population spike amplitude was attenuated (Fig. 3).

Neither 8-OH-DPAT nor buspirone treatment affected the mean amplitude of maximum population spikes (9 ± 1.2 mV, $n = 21$ in slices from animals treated with H_2O for 7 days; 9.7 ± 1.4 mV, $n = 25$ in slices from rats treated with 8-OH-DPAT; 8 ± 1.5 mV, $n = 24$ in slices from rats treated with H_2O for 21 days; 7.6 ± 1.4 mV, $n = 25$ in slices from rats treated with buspirone for 21 days) nor mean amplitude of 30% of maximal population spikes (3.3 ± 0.08 mV, $n = 21$ in slices from animals treated with H_2O for 7 days; 3.4 ± 0.07 mV, $n = 25$ in slices from rats treated with 8-OH-DPAT; 2.7 ± 0.1 mV, $n = 24$ in slices from rats treated with H_2O for 21 days; 2.7 ± 0.08 mV, $n = 25$ in slices from rats treated with buspirone for 21 days). Repeated treatment with 8-OH-DPAT and buspirone had no significant effect on the inhibition induced by 5-HT or 8-OH-DPAT (Figs. 1B and 2B). Repeated 8-OH-DPAT induced a small reduction in the excitatory action of

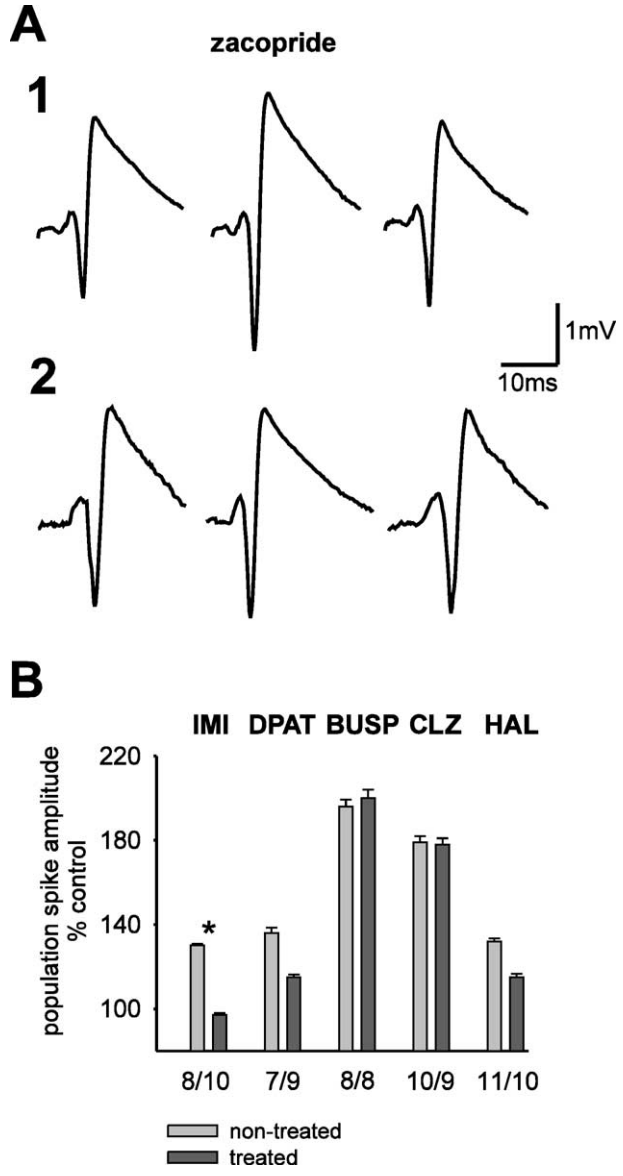

Fig. 3. An example of the excitatory effect of zacopride (5 μM) on the population spike recorded in the CA1 region of hippocampal slices from control animals and those treated with imipramine (A1 and A2, respectively). Effects of repeated treatment with imipramine (IMI), 8-OH-DPAT (DPAT), buspirone (BUSP), clozapine (CLZ) and haloperidol (HAL) on the excitatory action of zacopride (B). The results are expressed as the mean (± S.E.M.) percentage change of the baseline population spike amplitude. Numbers below bars represent the number of slices tested in control and treated groups (data from 7–10 rats). * $P \leq 0.05$, Student's *t*-test.

zacopride, which did not reach statistical significance, while repeated buspirone had no effect (Fig. 3B).

Neither clozapine nor haloperidol treatment affected the mean amplitude of maximum population spikes (8.7 ± 1.5 mV, $n = 26$ in slices from control animals; 8.3 ± 1.3 mV, $n = 25$ in slices from rats treated with clozapine; 8.3 ± 1.3 mV, $n = 22$ in slices from control animals; 8.4 ± 1.2 mV, $n = 24$ in slices from rats treated with haloperidol), similarly, mean amplitude of 30% of maximal population spikes was not affected by clozapine nor haloperidol treatment (2.99 ± 0.09 mV, $n = 26$ in slices from control animals; 2.86 ± 0.1 mV, $n = 25$ in slices from rats treated with clozapine; 2.9 ± 0.07 mV, $n = 22$ in slices from control animals; 3 ± 0.07 mV, $n = 24$ in slices from rats treated with haloperidol). Clozapine did not affect the inhibitory effect of 5-HT (Fig. 1B). In slices prepared from animals treated either with clozapine or haloperidol, there was only a minor, non-significant increase in the inhibition induced by 8-OH-DPAT (Fig. 2B), whereas the excitatory effect of zacopride was not affected (Fig. 3B).

4. Discussion

The 5-HT_{1A} receptor is believed to play a role in a variety of behaviors such as aggression, sexual behavior and appetite control, and in several psychiatric disorders such as mood and anxiety disorders, anorexia nervosa, schizophrenia and alcoholism (Schreiber and De Vry, 1993; Maes and Meltzer, 1995; Barnes and Sharp, 1999; Meltzer, 1999). Several lines of evidence indicate that 5-HT_{1A} receptor agonists have anxiolytic, antiaggressive and antidepressive properties (Newman et al., 1992; De Vry, 1995; Fulton and Brogden, 1997). This study confirms that the tricyclic antidepressant drug imipramine potently increases the sensitivity of hippocampal CA1 neurons to the activation of 5-HT_{1A} receptors. Concurrently, imipramine decreases the sensitivity of hippocampal neurons to the excitatory effect of 5-HT_4 receptor activation. Since inhibitory 5-HT_{1A} receptors and excitatory 5-HT_4 receptors are colocalized on the same pyramidal cells, the net effect of imipramine is a marked enhancement of the 5-HT-induced inhibition of CA1 neurons (Bijak et al., 1996, 1997). Our earlier study showed that also other antidepressant treatment, repeated electroconvulsive shocks, increased the sensitivity of hippocampal CA1 neurons to 5-HT and 8-OH-DPAT and decreased their sensitivity to zacopride (Bijak et al., 2001). These findings are in line with the described enhanced inhibitory tone of 5-HT in the hippocampus of rats treated chronically with imipramine or electroconvulsive shock (Haddjeri et al., 1998). The present study demonstrates that neither 5-HT_{1A} receptor agonists nor neuroleptics alter the sensitivity of CA1 neurons to the activation of 5-HT_{1A} and 5-HT_4 receptors.

5-HT_{1A} receptor agonists have a well-established anxiolytic activity; furthermore, they display some antidepressant efficacy in preclinical and clinical trials (Chojnacka-Wójcik et al., 1991; Schreiber and De Vry, 1993; Fulton and Brogden, 1997). 5-HT_{1A} receptor agonists exert their effect via desensitization of somatodendritic 5-HT_{1A} receptors (Kennett et al., 1987). Since the desensitization of somatodendritic 5-HT_{1A} receptors is also induced by selective 5-HT reuptake blockers and monoamine oxidase inhibitors (Blier et al., 1988; Mongeau et al., 1997), which suggests that the down-regulation of somatodendritic 5-HT_{1A} receptors may be responsible for the antidepressant action of various agents. However, it has been proposed that an interaction with somatodendritic 5-HT_{1A} receptors is responsible for the anxiolytic effects of 5-HT_{1A} receptor agonists, while their antidepressive effects stem from an interaction with postsynaptic 5-HT_{1A} receptors (Schreiber and De Vry, 1993). Postsynaptic 5-HT_{1A} receptors—at least in the hippocampus—are sensitized by repeated tricyclic antidepressants and electroconvulsive shocks (Chaput et al., 1991; Bijak et al., 1996, 2001; Mongeau et al., 1997). Yet, electrophysiological studies indicate that hippocampal 5-HT_{1A} receptors are unaffected by repeated treatment with 8-OH-DPAT and buspirone (this paper) as well as other 5-HT_{1A} receptor agonists (Blier and De Montigny, 1987; Godbout et al., 1991). Therefore, it seems that hippocampal 5-HT_{1A} receptors are not involved in the antidepressant and antianxiety action of 5-HT_{1A} receptor ligands. It cannot be excluded that postsynaptic 5-HT_{1A} receptors in other brain regions, or those coupled to other than K^+ channel transduction pathways, are affected by repeated treatment with 5-HT_{1A} receptor agonists, since regional and cellular specificity of the receptor regulation has been reported for the 5-HT_{1A} receptor expressed in various cerebral areas (Blier et al., 1987; Blier and De Montigny, 1999). Some studies have shown the subsensitivity of a 5-HT_{1A} receptor-mediated biochemical response (the 5-HT-induced inhibition of forskolin-stimulated adenylate cyclase) in rat hippocampal neurons, after treatment with selective serotonin reuptake inhibitors, desimipramine or electroconvulsive shocks (Newman and Lerer, 1988; Newman et al., 1992; but see Varrault et al., 1991) and after repeated treatment with 5-HT_{1A} receptor agonists (Newman et al., 1992; but see Varrault et al., 1991). It still remains to be established whether hippocampal 5-HT_{1A} receptors are coupled to both K^+ channels and adenylate cyclase, or whether two separate pools of 5-HT_{1A} receptors are involved in the electrophysiological and biochemical effects.

Our study also shows that the sensitivity of hippocampal neurons to the 5-HT_4 receptor agonist is not changed by repeated treatment with the 5-HT_{1A} receptor agonists, despite the fact that 5-HT_{1A} receptor agonists can desensitize somatodendritic autoreceptors and thus enhance 5-HT neurotransmission (Kennett et al., 1987).

Although the effects of neuroleptics have been attributed to dopamine receptor blockade, serotonin receptors and alterations in the serotonergic system have also been implicated in their mechanism of action (Meltzer, 1999). The

majority of atypical antipsychotic drugs have a high affinity for 5-HT_{2A} receptors and a moderate affinity for other 5-HT receptor subtypes (Meltzer et al., 1989). Clozapine suppresses the firing rate of 5-HT neurons in the dorsal raphe nucleus, which is likely to be mediated (at least partly) by the blockade of α_1-adrenoceptors (Gallager and Aghajanian, 1976; Sprouse et al., 1999). However, partial agonist properties of clozapine at 5-HT_{1A} receptors (Coward et al., 1989; Schotte et al., 1996) are probably sufficient to activate presynaptic 5-HT_{1A} somatodendritic autoreceptors. Thus, repeated clozapine may induce adaptive changes in serotonergic neurotransmission and in postsynaptic 5-HT receptors. In fact, it has been shown that repeated treatment with clozapine and haloperidol changes the density of 5-HT transporters and 5-HT_{1A} receptors in different areas of rat brain, among others in the hippocampus (Ase et al., 1999). Our study has shown, however, that repeated treatment with clozapine or haloperidol has no effect on the sensitivity of hippocampal neurons to 5-HT_{1A}- and 5-HT_4 receptors agonists. This finding supports the hypothesis that the hypersensitivity of hippocampal 5-HT_{1A} receptors and the hyposensitivity of 5-HT_4 receptors may be specifically linked to the mechanism of action of antidepressant drugs.

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