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European Journal of Pharmacology 305 (1996) 79–85

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Imipramine increases the 5-HT_{1A} receptor-mediated inhibition of hippocampal neurons without changing the 5-HT_{1A} receptor binding

Maria Bijak *, Krzysztof Tokarski, Anna Czyrak, Marzena Maćkowiak, Krzysztof Wędzony

Polish Academy of Sciences, Institute of Pharmacology, Smętna 12, 31–343 Kraków, Poland

Received 23 November 1995; revised 7 February 1996; accepted 16 February 1996

Abstract

The effect of repeated treatment with imipramine on the 5-HT_{1A} receptor-mediated inhibition of a population spike was studied in the rat CA1 hippocampal region ex vivo. Serotonin (5-hydroxytryptamine, 5-HT) and the selective 5-HT_{1A} receptor agonist 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT) decreased dose-dependently the amplitude of population spikes; this effect was blocked by the selective 5-HT_{1A} receptor antagonist (S)-*N*-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide dihydrochloride [(S)-WAY 100135]. Repeated (14 days, twice daily), but not single, administration of imipramine (10 mg/kg) shifted the dose-response curves for serotonin and 8-OH-DPAT to the left. Repeated treatment with imipramine did not change the density of 5-HT_{1A} receptors in the hippocampus as measured by autoradiography using [^{3}H]8-OH-DPAT as a ligand. The latter findings indicate that the imipramine-induced increase in the responsiveness of hippocampal neurons to stimulation of 5-HT_{1A} receptors may not involve an increase in the density of this receptor subtype. To find out whether the efficacy of the postreceptor transduction mechanism is changed by repeated treatment with imipramine, we examined the effect of baclofen. The baclofen-induced inhibition of the population spike was not changed by imipramine. Our results suggest that repeated treatment with imipramine induces sensitization to the inhibitory effects of 5-HT_{1A} receptor agonists in the hippocampus.

Keywords: Antidepressant; Imipramine; 5-HT_{1A} receptor; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); 5-HT (5-hydroxytryptamine, serotonin); Baclofen; Hippocampal slice

1. Introduction

It has been established that central serotonergic systems are involved in the pathophysiology of major depression (for review, see Meltzer and Lowy, 1987). As a result, it has been a matter of considerable interest to investigate adaptive changes in the serotonergic transmission following long-term treatment with antidepressants. 5-HT_{1A} receptors may be involved in the antidepressant action, since 5-HT_{1A} receptor agonists show antidepressant-like effects in some animal models (Kennett et al., 1987; Giral et al., 1988; Benvenga and Leader, 1993) as well as in clinical studies (Amsterdam, 1992; Grof et al., 1993). The localization of the 5-HT_{1A} receptors that mediate the putative antidepressant effect is still a matter of dispute, yet it has been suggested that postsynaptic 5-HT_{1A} receptors may be involved (Martin et al., 1990; Wieland and Lucki, 1990; Chojnacka-Wójcik et al., 1991; Luscombe et al., 1993). The density of postsynaptic 5-HT_{1A} binding sites is particularly high in such limbic areas as the hippocampus, septum or entorhinal cortex (Miquel et al., 1991; Sijbesma et al., 1991). In these areas, activation of 5-HT_{1A} receptors has an inhibitory effect on principal neurons due to a membrane hyperpolarization mediated by an increase in potassium conductance (Andrade and Nicoll, 1987; Andrade, 1992).

Some electrophysiological in vivo and ex vivo studies demonstrate that the inhibitory action of serotonin (5-hydroxytryptamine, 5-HT) on hippocampal pyramidal cells is enhanced after prolonged treatment with antidepressants (Chaput et al., 1991; Dijck et al., 1991; Bijak and Tokarski, 1994; Bijak and Papp, 1995); however, contradictory results have also been reported (Olpe et al., 1984; Rowan and Anwyl, 1985; Beck and Halloran, 1989). These conflicting results of electrophysiological experiments may be due to the fact that in most studies 5-HT was used as an agonist. Although the main effect of 5-HT in the hippocampus is hyperpolarization via activation of 5-HT_{1A}

* Corresponding author. Tel.: (48) (12) 374022; fax: (48) (12) 374500.

PII S0014-2999(96)00151-3

receptors, 5-HT also activates other subtypes of 5-HT receptors which evoke an increase in the excitability of pyramidal cells (Andrade and Nicoll, 1987; Colino and Halliwell, 1987; Andrade, 1992). Some of these 5-HT receptor subtypes may undergo adaptive changes after treatment with antidepressants. Therefore, in order to study the adaptive changes in the 5-HT_{1A} receptor induced by repeated treatment with the tricyclic antidepressant drug imipramine in more detail, we applied the selective 5-HT_{1A} receptor agonist 8-hydroxy-2-(dipropylamino) tetralin (8-OH-DPAT) and the selective antagonist (S)-*N*-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide dihydrochloride [(S)-WAY 100135]. Having found an increase in the response to the 5-HT_{1A} receptor activation after repeated treatment with imipramine, we wanted to ascertain whether the functional changes resulted from an increase in the binding or distribution of 5-HT_{1A} receptors. Furthermore, our investigation was aimed at determining whether imipramine affected the efficacy of postreceptor transduction mechanisms between the G-protein and K^+ channel. To this end, we used baclofen which activates γ-aminobutyric acid-B ($GABA_B$) receptors coupled, like 5-HT_{1A} receptors, to the K^+ channel via a G-protein (Andrade et al., 1986; for review, see Misgeld et al., 1995).

2. Materials and methods

2.1. Animals and drug treatment

The experiments were performed on male Wistar rats (purchased from a licensed dealer), kept on a natural light/dark cycle, with free access to food and water. Imipramine was dissolved in water and administered twice daily for 14 days (10 mg/kg, 2 ml/kg p.o.; repeated treatment). Other animals received water twice daily for 13 days (2 ml/kg p.o.), followed by a single dose of imipramine (10 mg/kg; acute treatment). Non-treated animals served as a control. Each group consisted of 7–8 animals. The rats receiving imipramine were killed 48 h after the last dose.

2.2. Hippocampal slice preparation and recording

Rats (230–250 g) were decapitated and, after dissection, their hippocampi were cut into 350-μm-thick transverse slices using a tissue slicer (FHC Brunswick, USA). The slices were transferred to a recording chamber and superfused at a rate of 1.5 ml/min with a gassed medium (95% O_2 5% CO_2) consisting of (in mM) 124 NaCl, 2 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1.25 KH_2PO_4, 26 $NaHCO_3$ and 10 glucose; at 32°C, pH was 7.4. The response of CA1 neurons to electrical stimulation of the Schaffer collateral-commissural fiber pathway was recorded extracellularly using glass micropipettes filled with 2 M NaCl (2–5 MΩ). For electrical stimulation (Grass S8 stimulator with an isolation unit), a bipolar twisted wire electrode was used. The stimuli were square wave pulses of 0.1 ms duration, applied at a frequency of 0.1 Hz. Following electrode placement, a slice was allowed to equilibrate for 40–60 min. Extracellular signals were amplified (Axoprobe, Axon Instruments), bandpass-filtered (1 Hz–10 kHz) and stored on a PC hard disk after AD conversion at 5 kHz (a CED interface, Cambridge Electronic). The amplitude of the population spike was measured as a 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.

After stabilization of the baseline response (defined as no more than 10% variation in the median amplitude of the population spike), the slice was superfused with the tested drug for 5 min (5-HT and baclofen) or 10 min (8-OH-DPAT), and subsequently washed with a standard solution for 20 min. Each drug was tested on a separate slice. When used, (S)-WAY 100135 was applied for 40 min before the application of either 5-HT or 8-OH-DPAT. The effects of the tested substances on the population spike were expressed as a percentage of the baseline, predrug (control) population spike. Mean effects were calculated and compared between experimental groups. A statistical analysis was performed using an ANOVA followed by Student's *t*-test.

2.3. Autoradiography

The brains were removed and rapidly dissected into coronal blocks (thickness 5 mm) containing the hippocampus. The blocks were immediately frozen by submersion in dry ice-cold isopentane and stored at −70°C. The blocks were cut into coronal sections (10 μm) using a Leitz cryostat LC 3000 (temperature −17°C). The sections were thaw mounted onto subbed glass microscope slides, dried at room temperature and then stored at −20°C. The assay was performed on the following day in 50 mM Tris-HCl (pH 7.4) buffer containing 180 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgCl_2$. The sections were incubated for 60 min at room temperature in the same Tris-HCl buffer (supplemented with ascorbic acid, 10 mg/100 ml, and pargyline, 0.2 mg/100 ml) in the presence of 1.5 nM [^{3}H]8-OH-DPAT (Amersham; spec. act. 137 mCi/mmol). Non-specific binding was determined in adjacent sections by adding 5 μM 5-HT. After incubation, the sections were rinsed, dried and apposed to a Hyperfilm-^{3}H (Amersham) along with a tritium standard (^{3}H-microscale, Amersham) in an X-ray cassette for 3 weeks at 4°C. The films were then developed using a D-19 Kodak developer.

The autoradiograms were quantified by computerized densitometry (Java, Jandel image analysing system). The measured light transmittance values were converted to tissue radioactivity equivalents (with reference to standards), and hence to binding values (fmol/mg tissue, with

reference to the specific activity) for the radiolabeled ligand. The values of non-specific binding were determined directly from film images of the sections incubated in the presence of the displacer 5-HT (5 μM). These values were averaged and subtracted from total binding readings to obtain specific binding values. Cresyl violet staining of tissue sections was used in conjunction with the atlas of Paxinos and Watson (1986) to verify anatomical regions.

2.4. Drugs

The drugs used were: (±)-8-hydroxy-2-(dipropylamino)tetralin [8-OH-DPAT; RBI], (±)-baclofen (RBI), imipramine hydrochloride (Polfa); pargyline (Sigma), serotonin creatinine sulfate (5-HT; Sigma), (S)-*N*-tert-butyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide dihydrochloride [(S)-WAY 100135 synthesized by Dr. J. Boksa, Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland]. Stock solutions of 5-HT and 8-OH-DPAT were prepared in water in the presence of an antioxidant (sodium metabisulfite, Sigma) and were diluted in a standard solution before application.

3. Results

3.1. Effect of 5-HT and 8-OH-DPAT on population spikes

Bath application of 5-HT (5–20 μM) and the 5-HT_{1A} receptor agonist 8-OH-DPAT (1–4 μM) induced a reversible (Fig. 1A) reduction in the amplitude of population spikes recorded in the CA1 cell layer. The inhibitory effect of 5-HT reached a steady-state level by 1 min, remained stable throughout the application, and was reversed within 5–10 min following return to the drug-free solution. The effect of 8-OH-DPAT reached equilibrium by 4–6 min and showed a slow recovery during a washout period of 15–20 min. The 5-HT and 8-OH-DPAT-induced inhibitory effects

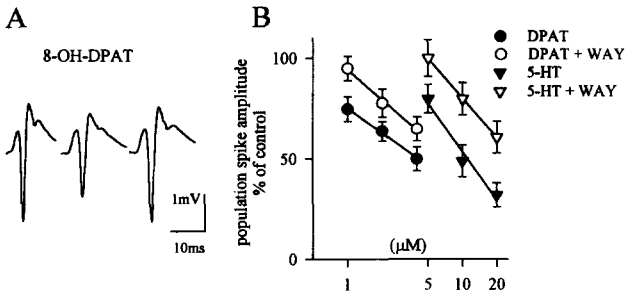

Fig. 1. Inhibition of the population spike by 8-OH-DPAT and 5-HT. An example of the inhibitory effect of 8-OH-DPAT (1 μM) on the population spike recorded in the CA1 cell layer (A). Dose-response curves for 8-OH-DPAT (1, 2 and 4 μM; DPAT) and 5-HT (5, 10 and 20 μM) and their shift to the right by (S)-WAY 100135 (1 μM; WAY; B). Each point represents the percentage (mean ± S.E.M.; $n = 8$ slices) of a predrug (control) population spike amplitude. A population spike that amounted to 50% of the maximum population spike was chosen.

were concentration-dependent (Fig. 1B). The selective 5-HT_{1A} receptor antagonist (S)-WAY 100135 (1 μM) produced a parallel rightward shift of the dose-response curves for 5-HT and 8-OH-DPAT (Fig. 1B); used in a dose of 5 μM (S)-WAY 100135 completely blocked the inhibitory effects of 5-HT and 8-OH-DPAT, having revealed the 5-HT-induced enhancement of the population spike amplitude (not shown). The inhibitory effects of 5-HT and 8-OH-DPAT on the amplitude of population spikes depended on the stimulation intensity, which is shown in Fig. 2A,B. The most pronounced inhibition was observed at low stimulation intensities which evoked threshold population spikes, while there was no, or only a small inhibitory effect when maximum population spikes were evoked by high stimulation intensities.

3.2. Effect of imipramine on the inhibition induced by 5-HT and 8-OH-DPAT

Neither single nor repeated treatment with imipramine affected the mean amplitude of the half-maximum popula-

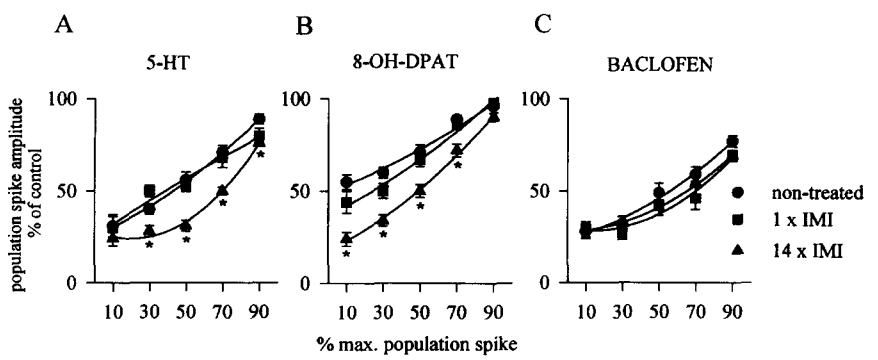

Fig. 2. Effects of single (1 × IMI) and repeated (14 × IMI) administration of imipramine on inhibition of the population spike induced by 5-HT (5 μM; A), 8-OH-DPAT (1 μM; B) and baclofen (1 μM; C). The effects are shown throughout the input–output curves for CA1 cells. Each point shows a percentage change (mean ± S.E.M.) in the predrug (control) population spike against a relative stimulus intensity (percentage of the stimulus intensity which evoked the maximum population spike). In each group, 14 slices from 7 animals were tested. Significance values correspond to a Student's *t*-test, * $P \leq 0.05$ vs. non-treated group.

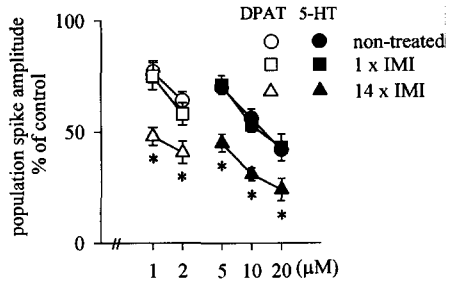

Fig. 3. Repeated (14×IMI), but not acute (1×IMI) treatment with imipramine-induced sensitization of CA1 neurons to the inhibitory effects of 8-OH-DPAT (DPAT) and 5-HT, and shifted the dose-response curves to the left. Significance values correspond to a Student's *t*-test, * $P \leq 0.05$ vs. non-treated and acutely treated groups.

tion spike (5.9 ± 0.33 mV, $n = 33$ in slices from non-treated animals; 5.4 ± 0.27 mV, $n = 32$ in slices from rats treated repeatedly with imipramine). Also the range of stimulation intensities necessary to induce the threshold population spike (7–8 V) and half-maximum population spike (10.3 ± 0.2 V non-treated; 9.9 ± 0.2 V imipramine) did not differ between slices from non-treated animals and those from animals treated repeatedly with imipramine.

A comparison of the inhibitory effects of 5-HT and 8-OH-DPAT in slices from non-treated animals and in those from animals receiving single doses of imipramine did not show any differences. In slices obtained from animals treated with imipramine for 14 days, the inhibitory effects of both 5-HT and 8-OH-DPAT were significantly enhanced (Fig. 2A,B), and the dose-response curves for 5-HT and 8-OH-DPAT were shifted to the left (Fig. 3).

3.3. Effect of imipramine on the inhibition induced by baclofen

Like 5-HT and 8-OH-DPAT, the $GABA_B$ receptor agonist (±)-baclofen (1 μM) decreased the amplitude of the population spike recorded in the CA1 cell layer. Neither acute nor prolonged treatment with imipramine changed this inhibitory effect of baclofen (Fig. 2C).

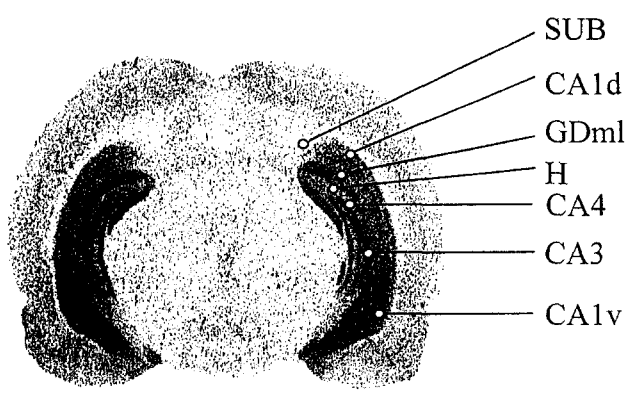

Fig. 4. An autoradiogram showing regional distribution of [^{3}H]8-OH-DPAT-binding sites at the level of the mesencephalon (Ant: −5.3; according to Paxinos and Watson, 1986) in a non-treated rat brain. The darker areas indicate higher binding levels. The areas where the binding density was measured are marked. SUB, subiculum; CA1d, dorsal CA1 field; CA1v, ventral CA1 field; CA3, CA3 field; CA4, CA4 field; GDml, dentate gyrus molecular layer; H, hilar region.

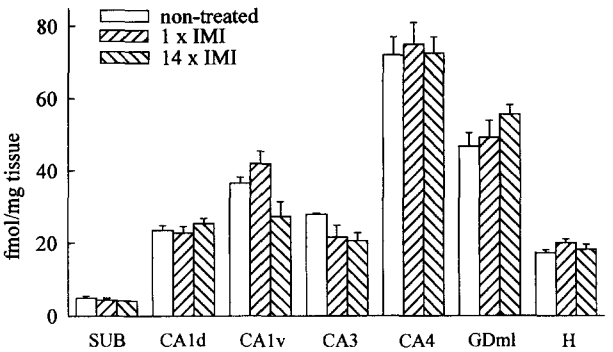

Fig. 5. Distribution of 5-HT_{1A}-binding sites in the hippocampus, as determined by quantitative autoradiography, in non-treated and imipramine-treated rats. Values represent mean ± S.E.M. of 8 measurements/area for each treatment group. Measurements were made on Ant. −5.3 sections (according to Paxinos and Watson, 1986). Abbreviations refer to those used in Fig. 4.

3.4. Effect of imipramine on the density of 5-HT_{1A} receptors in the hippocampus

[^{3}H]8-OH-DPAT produced intensive labeling of subregions of the hippocampus. The highest density of 5-HT_{1A} receptors was observed in the molecular layer of the dentate gyrus and in the dendritic regions of the CA4 subfield. The lowest binding was found in the subiculum, whereas an intermittent density was found in the CA2/CA3 subregions (Fig. 4, Fig. 5), which is in line with previously described autoradiographic data on the hippocampal distribution of 5-HT_{1A} receptors (Miquel et al., 1991; Sijbesma et al., 1991).

[^{3}H]8-OH-DPAT binding was almost totally displaced by 5-HT (5 μM), which indicates that under the experimental conditions used in the present study almost all the binding is due to specific labeling of 5-HT_{1A} receptors. Non-specific binding constituted < 5% of the total binding (data not shown).

The binding of [^{3}H]8-OH-DPAT (measured in one slice from 8 different animals, in all experimental groups) was not changed in any selected region of the hippocampus after single or repeated administration of imipramine (Fig. 5).

4. Discussion

We demonstrated that repeated administration of the antidepressant drug imipramine induced sensitization of postsynaptic 5-HT_{1A} receptors in hippocampal CA1 neurons. The enhancement of the 5-HT_{1A} receptor-mediated functional response, observed electrophysiologically, was not accompanied, however, by an increase in the density of

5-HT_{1A} receptors in the CA1 region, as assessed by autoradiography.

Intracellular recordings from hippocampal pyramidal cells in vitro showed that exogenously applied 5-HT had both inhibitory and excitatory effects (Andrade and Nicoll, 1987; Colino and Halliwell, 1987; Andrade, 1992). Since the inhibition, i.e. hyperpolarization due to an increase in the potassium conductance, was mimicked by the selective 5-HT_{1A} receptor agonist 8-OH-DPAT it has been suggested that this effect is mediated by 5-HT_{1A} receptors. The reduction in the amplitude of the population spike in CA1 cells, induced by 5-HT, is mainly due to a hyperpolarizing action of 5-HT, however, some presynaptic effects of 5-HT on glutamate release, mediated by receptor subtypes other than 5-HT_{1A} receptors, cannot be excluded (Ropert, 1988). Our data demonstrating that the selective 5-HT_{1A} receptor agonist 8-OH-DPAT also decreased the amplitude of the population spike and that the 5-HT_{1A} antagonist (S)-WAY 100135 (Fletcher et al., 1993) shifted the dose-response curve for 5-HT to the right proved that the inhibitory effect of 5-HT on the population spike is mediated by 5-HT_{1A} receptors. The results presented above showing that the inhibitory action of 8-OH-DPAT was enhanced by prolonged treatment with imipramine indicate that supersensitivity of 5-HT_{1A} receptors underlies the imipramine-induced enhancement of the 5-HT-evoked inhibition in CA1 hippocampal neurons. Since our autoradiography experiments did not reveal an increase in the density of hippocampal 5-HT_{1A} receptors after prolonged treatment with imipramine, an increased efficacy of postreceptor transduction mechanisms, such as the G-protein coupling to the K^+ channel, may be postulated. It has been proposed that antidepressants may affect cell signalling by acting directly on G-proteins (Lesch et al., 1992; Yamamoto et al., 1992). If such an effect is induced by imipramine, it seems to be specific to 5-HT_{1A} receptors. The 5-HT_{1A} receptor-activated K^+ channels belong to a general class of inwardly rectifying K^+ channels gated by neurotransmitter receptors through the pertussis toxin-sensitive G-protein (for review, see Misgeld et al., 1995). The inhibitory effect of the $GABA_B$ receptor agonist baclofen, which also hyperpolarizes CA1 neurons by activating the same type of the G-protein-linked K^+ channels as does 5-HT (Andrade et al., 1986; Andrade, 1992; Misgeld et al., 1995), was not affected by treatment with imipramine, though some data suggest an increase in the $GABA_B$ receptor binding after prolonged administration of antidepressants (Lloyd and Pichat, 1987). Furthermore, prolonged treatment with desipramine or mianserin has no effect on the response to baclofen of hippocampal pyramidal cells (Dijck et al., 1991). The inhibitory effect of baclofen on the population spikes, however, cannot be entirely attributed to the postsynaptic action of this compound on K^+ channels, as a presynaptic effect on glutamate release may also be involved (for review, see Misgeld et al., 1995).

Most of the studies in which a quantitative autoradiographic analysis was used revealed no change in [^{3}H]8-OH-DPAT binding in the rat hippocampus following prolonged treatment with tricyclic antidepressant drugs (Watanabe et al., 1993; Hayakawa et al., 1994; and this paper); however, few data showed an increase in the density of 5-HT_{1A} receptors (Welner et al., 1989; Burnet et al., 1994). It has been suggested that the effect of imipramine on the level of hippocampal 5-HT_{1A} receptors and their transcripts is strain-dependent (Burnet et al., 1994).

Imipramine belongs to the group of classic tricyclic antidepressant drugs, which are the most commonly used agents in the treatment of major depression. Antidepressant drugs have a delayed onset of action; therefore, in animal studies adaptive changes which develop only after prolonged treatment with these agents are considered to have relevance to antidepressive effects. Our results show sensitization of hippocampal 5-HT_{1A} receptors in the hippocampus, which is in line with the results of electrophysiological studies in vivo showing that long-term, but not subacute, treatment with tricyclic antidepressant drugs or electroconvulsive shock enhances the sensitivity of rat hippocampal CA3 neurons to the inhibitory effects of the synaptically released and iontophoretically applied 5-HT (for review, see Blier et al., 1987) and 8-OH-DPAT (Chaput et al., 1991). Also ex vivo studies on hippocampal slices showed enhanced responsiveness of pyramidal neurons to 5-HT after prolonged treatment with various antidepressants (Dijck et al., 1991; Bijak and Tokarski, 1994; Bijak and Papp, 1995). This effect, however, was not confirmed by two groups, who reported either a reduction (Rowan and Anwyl, 1985) or no change (Beck and Halloran, 1989) in the 5-HT action on CA1 cells after prolonged treatment with imipramine. Differences in the time lag between the end of treatment and the in vitro experiment may account for the above discrepancies. The two studies in which no sensitization to 5-HT was found were conducted 20–24 h after the last dose of imipramine. It cannot be excluded that, 24 h after prolonged treatment, residual imipramine (Daniel et al., 1981) may block the 5-HT effect by acting at the receptor (Zifa and Fillion, 1992) or the K^+ channel (Wooltorton and Mathie, 1993). In fact, Rowan and Anwyl (1985) demonstrated that inhibition of the population spike by 5-HT can be blocked by imipramine. Also some other variables may be responsible for the apparent discrepancies found in the ex vivo studies. The finding that intracellular recordings from CA1 cells did not reveal any enhancement of the 5-HT-induced hyperpolarization after treatment with imipramine may suggest that the inhibitory effect of 5-HT on population spikes is not only due to a direct membrane hyperpolarization but also involves modulation of the local circuitry by 5-HT, the latter effect probably being affected by treatment with the antidepressant. Synaptic inhibition is crucially involved in modulation of the population spike amplitude. It might be of

interest to determine whether prolonged treatment with antidepressants affects the 5-HT action on synaptic inhibition in the hippocampus, since adaptive changes in 5-HT receptors on inhibitory interneurons may substantially contribute to the effects of 5-HT on population spikes. Such effects are likely to involve not only 5-HT_{1A} receptors which reduce the $GABA_B$ receptor-mediated inhibitory postsynaptic potentials (Segal, 1990), but also other 5-HT receptor subtypes, as it has been shown that inhibitory neurons are excited by 5-HT via 5-HT_3 receptors (Kawa, 1994), and that synaptic inhibition in the hippocampus is enhanced by activation of 5-HT_3, as well as 5-HT_2, receptors (Ropert and Guy, 1991; Piguet and Galvan, 1994). The involvement of synaptic inhibition in modulation of the population spike amplitude may vary, depending on the mode of stimulation. It is noteworthy that in the studies reporting enhancement of the inhibitory effects of 5-HT on population spikes by antidepressant treatment (Dijck et al., 1991; Bijak and Tokarski, 1994; Bijak and Papp, 1995; and the present study) bipolar stimulating electrodes were used, which resulted in gross stimulation of the Schaffer/collateral-commissural pathway, whereas in the study by Rowan and Anwyl (1985) a high resistance microelectrode was used, producing more localized stimulation. In the latter study, a field excitatory postsynaptic potential seemed to dominate the population spike in the recordings and, therefore, possible effects of 5-HT on glutamate release or on the local circuitry were likely to prevail. Such effects may be mediated by receptors other than 5-HT_{1A} ones. In fact, the 5-HT-induced inhibition was blocked by cyproheptadine and ketanserin (Rowan and Anwyl, 1985) which show only very low affinity for 5-HT_{1A} receptors (Zifa and Fillion, 1992).

Our previous studies showed that not only imipramine but also other antidepressants which are more selective uptake inhibitors, e.g. (+)-oxaprotiline (a selective norepinephrine uptake inhibitor) and paroxetine (a selective 5-HT uptake inhibitor), enhance the 5-HT_{1A} receptor-mediated effect in the hippocampus (Bijak and Tokarski, 1994; Maj et al., 1996). The antidepressant-induced sensitization to the inhibitory effect of 5-HT is not restricted to the hippocampus, as it has also been demonstrated in other forebrain areas, such as the lateral geniculate nucleus (De Montigny and Aghajanian, 1978) and amygdala (Wang and Aghajanian, 1980). The therapeutic relevance of the enhanced responsiveness of postsynaptic 5-HT_{1A} receptors remains to be elucidated.

Acknowledgements

This work was supported by a statutory grant from the State Committee for Scientific Research (KBN) given to the Institute of Pharmacology and by the KBN Grant 6 P207 02405 to M.B.

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