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# An antidepressant-induced decrease in the responsiveness of hippocampal neurons to group I metabotropic glutamate receptor activation

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**Abstract**

Imipramine, a serotonin and noradrenaline uptake inhibitor, is the prototypical tricyclic antidepressant. The effects of imipramine on neuronal responsiveness to the group I glutamate metabotropic (mGlu) receptor agonist (*RS*)-3,5-dihydroxyphenylglycine (DHPG) were studied ex vivo, in the CA1 area of rat hippocampus, using extracellular and intracellular recording. DHPG increased the population spike amplitude, depolarized CA1 cells and decreased the slow afterhyperpolarization. Imipramine (20 μM) administered acutely in vitro did not change the effect of DHPG on population spikes. Repeated treatment with imipramine (10 mg/kg, twice daily, for 14 days) significantly attenuated the enhancing effect of DHPG (2.5 and 5 μM) on population spikes, as well as the DHPG-induced depolarization and the decrease in the slow afterhyperpolarization. Repeated treatment with imipramine had no effect on passive or active membrane properties of CA1 pyramidal cells. The results of the time-course experiment demonstrated that the imipramine-induced decrease in the responsiveness of CA1 cells to DHPG was apparent after a 7-day treatment; there was a further decrease after 14 days of treatment to a level which was not changed by longer (21-day) administration of imipramine. The attenuation of neuronal responsiveness to DHPG induced by a 14-day treatment was still detectable 7 days after imipramine withdrawal. It is concluded that repeated treatment with imipramine induces a decrease in the responsiveness of rat CA1 hippocampal neurons to group I mGlu receptor activation with a time course which correlates with the delayed onset of the therapeutic effect of antidepressants in humans. This suggests that alterations in mGlu receptors may contribute to antidepressant efficacy. 

*Keywords:* Antidepressant; DHPG ((*RS*)-3,5-dihydroxyphenylglycine); Glutamate receptor, metabotropic, group I; Hippocampus; Imipramine

## 1. Introduction

Changes in central monoaminergic transmission have been considered to be involved in the mechanism of the therapeutic action of antidepressants, since most of these drugs are known to inhibit the uptake of amines (for review see Caldecott-Hazard et al., 1991). However, a relationship between acute effects of antidepressants and their therapeutic action is disputable, because about 2–3 weeks of administration are usually required to achieve a therapeutic effect. This has encouraged studies of the adaptive changes induced by prolonged treatment with antidepressants.

Most antidepressant drugs affect noradrenaline or/and serotonin (5-hydroxytryptamine, 5-HT) reuptake, and their prolonged administration induces adaptive changes in noradrenergic and 5-HT receptors (Caldecott-Hazard et al., 1991; Mongeau et al., 1997). Moreover, it has been reported that antidepressant treatment also affects other neurotransmitter/neuromodulator systems (Caldecott-Hazard et al., 1991), probably via indirect interactions involving noradrenergic and serotonergic transmission. Noradrenaline and 5-HT can influence, both directly and via regulation of γ-aminobutyric acid (GABA)-mediated synaptic inhibition, the activity of glutamatergic neurons (Nicoll et al., 1990; Bijak and Misgeld, 1995, 1997). Additionally, noradrenaline and 5-HT can regulate glutamate release via presynaptic heteroreceptors (Scanziani et al., 1993; Gereau and Conn, 1994; Muramatsu et al., 1998). Therefore, the adaptive changes in noradrenaline and 5-HT receptors induced by antidepressants may influ-

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ence the synaptic release of glutamate and, as a consequence, result in adaptive changes in postsynaptic glutamate receptors.

Glutamate exerts its action through ionotropic receptors which directly gate ion channels responsible for fast excitatory synaptic transmission and through metabotropic (mGlu) receptors which, via activation of G-proteins and second messenger cascades, influence mainly $K^+$ and $Ca^{2+}$ channels (for review see Pin and Duvoisin, 1995). Metabotropic glutamatergic receptors form a receptor family which is divided into three subgroups according to sequence similarity, signal transduction mechanism and agonist selectivity (Pin and Duvoisin, 1995). Members of the mGlu receptor family play an important role in the modulation of synaptic transmission and neuronal excitability. It has been demonstrated that antidepressant treatments can affect ionotropic NMDA receptors (Skolnick et al., 1996). Moreover, we have shown recently that neuronal responsiveness to mGlu receptor agonists can also undergo adaptive changes during antidepressant therapy (Pilc et al., 1998). We have found that the increase in the population spike amplitude induced by the non-selective mGlu receptor agonist (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid ((1*S*,3*R*)-ACPD) and the selective group I mGlu receptor agonist (*RS*)-3,5-dihydroxyphenylglycine (DHPG) (Ito et al., 1992) is attenuated by repeated treatment with imipramine and electroconvulsive therapy.

The experiments reported here were designed to investigate further the effect of imipramine on CA1 cell responsiveness to activation of group I mGlu receptors by examining the time course of induction and reversal of the imipramine-induced effect. Furthermore, using intracellular recording from CA1 cells, we sought to determine whether any of the direct membrane effects of DHPG underlie the adaptive changes observed in extracellular recordings. In addition, we attempted to find out whether the presence of imipramine altered responses evoked by DHPG.

## 2. Materials and methods

### 2.1. Animals

The experiments were carried out on male Wistar rats (purchased from a licensed dealer) weighing approximately 100–130 g at the beginning of the experiment. The animals were housed in groups of seven per cage on a controlled light/dark cycle (lights on from 0700 to 1900 h) and had free access to standard food and tap water. All experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology.

For each experimental paradigm two groups of animals (7–10 rats per group) were tested: (i) those receiving water (2 ml/kg, p.o.) and (ii) those receiving imipramine (10 mg/kg p.o., dissolved in water) twice daily, for 7, 14 and 21 days. The rats were killed two or 7 days after the last dose, as indicated in the test. In different groups of rats receiving water (7, 14 and 21 days with a 48-h withdrawal, and 14 days with a 7-day withdrawal) the effects of DHPG did not differ, hence the results were pooled.

### 2.2. Hippocampal slice preparation and recording

The rats (250–280 g) were killed by decapitation. Their brains were quickly removed and placed in an ice-cold artificial cerebrospinal fluid (ACSF) containing: NaCl (124 mM), KCl (2 mM), $CaCl_2$ (2.5 mM), $MgSO_4$ (1.3 mM), $KH_2PO_4$ (1.25 mM), $NaHCO_3$ (24 mM) and glucose (10 mM). After dissection, the hippocampus was cut into 350-μm-thick transverse slices using a tissue slicer (Frederick Haer and Co., Brunswick, ME, USA). The slices were left to recover in ACSF equilibrated to pH 7.4 with 95% $O_2$ and 5% $CO_2$ at 32°C for at least 1 h, but were kept for not longer than 6 h postdissection. A single slice was transferred to a submerged brain slice recording chamber, with ACSF bubbled with 95% $O_2$ and 5% $CO_2$, perfused at a flow rate of 1.5 m1/min at $32 \pm 1$°C.

For the extracellular recording of population spikes and field excitatory postsynaptic potentials (EPSPs), two glass microelectrodes filled with 2 M NaCl (resistance 1–4 MΩ) were positioned in the stratum pyramidale and stratum radiatum of the CA1 area, respectively. A bipolar, tungsten electrode was placed in the stratum radiatum for stimulation of the Schaffer collateral–commissural pathway. Square-wave pulses of 0.1 ms duration were applied at a rate of 0.02 Hz. Stimulating and recording electrodes were placed under visual guidance and adjusted to produce a maximal response to a particular stimulus intensity used. For the intracellular recording from CA1 pyramidal cells, microelectrodes (1.5 mm borosilicate glass, pulled on a Flaming Brown puller, Sutter Instruments, USA) were filled with 3 M KCl (resistance 30–80 MΩ). The recorded signals were amplified (Axoprobe, Axon Instruments, USA), bandpass-filtered (1–10 kHz) and stored on a PC hard disk after AD conversion at 5–10 kHz (the CED1401 interface and SIGAVG data acquisition software; Cambridge Electronics).

Only cells with a membrane potential more negative than −55 mV, an input resistance of ≥40 MΩ and overshooting action potentials were used. All the cells were manually clamped at −65 mV by injection of DC current. Input resistance was determined by measuring the voltage response to hyperpolarizing current injection (450 ms, 0.1 nA); membrane non-ohmic behaviour (rectification) was determined by dividing the amplitude of the voltage response to depolarizing current injection by the voltage response to hyperpolarizing current injection of the same amplitude (0.05–0.1 nA). For measurement of afterhyperpolarization the cells were clamped at −60 mV. Afterhyperpolarizations were elicited by a train of action potentials induced by a brief (50 ms) depolarizing current

pulse (1.3–1.5 nA) injected through the recording electrode. The measurement of a slow afterhyperpolarization was taken at its maximum, approximately at 150–200 ms after termination of a depolarizing current pulse.

When the evoked responses were stable for 20 min, or 20 min after a stable baseline recording, DHPG was applied for 10 min via the perfusion medium and slices were subsequently washed with a standard solution for 15–20 min. A stock solution of DHPG was prepared in water and the drug was diluted to the final concentration in ACSF immediately before application. Only one application per slice was made. To test the acute effect of imipramine, slices were perfused for 1–2 h with ACSF containing 20 μM of the drug. The drugs used were: (*RS*)-3,5-dihydroxyphenylglycine (Tocris, UK) and imipramine hydrochloride (Polfa, Poland).

### 2.3. Analysis and statistics

In extracellular recordings we measured population spike amplitudes and initial slopes of field EPSPs (Spike 2 software, Cambridge Electronics). Input–output curves were generated for each slice by adjusting the stimulation intensity to evoke population spikes of 10, 30, 50, 70 and 100% of the maximum amplitude. Four responses were evoked at each stimulation intensity and mean population spike amplitudes/field EPSP slopes were calculated under control (pre-drug) conditions, at 8–10 min of DHPG application and after 15–20 min of washout. Quantitative results are expressed as means ± S.E.M. percent change in baseline pre-drug values. In intracellular recordings passive and active membrane properties of CA1 neurons were evaluated. Quantitative results are expressed as means ± S.E.M. or as means ± S.E.M. percent change in baseline values. Each individual cell or each slice in the extracellular recording was treated as an independent sample. Statistical assessment was carried out using Student's *t*-test.

## 3. Results

### 3.1. Effects of imipramine administered acutely on the action of DHPG

As reported previously (Gereau and Conn, 1995; Zahorodna et al., 1998), the amplitude of population spikes reversibly increased upon application of DHPG (Fig. 1A). The enhancement of population spikes showed a strong dependence on the population spike amplitude (stimulation intensity), being most pronounced at low stimulation intensities which evoked small population spikes, whereas population spikes with the maximum amplitude were not affected (Fig. 1B). The DHPG (2.5–10 μM)-induced increase in the amplitude of population spikes was concentration dependent (Fig 1B). At DHPG 10 μM, the amplitude of population spikes decreased in 7 of the 12 slices, which may reflect a depolarization block (Zahorodna et al., 1998). DHPG (2.5 and 5 μM) had no effect on the initial slope of the field EPSP ($n = 8$) at the time when the amplitude of population spikes was maximally enhanced (Fig. 1A). A decrease in the population spike amplitude was accompanied by a decrease in the field EPSP.

Perfusion of hippocampal slices with imipramine (20 μM) for 1–2 h produced a decrease in the amplitude of population spikes, especially at low intensities of stimulation (Fig. 2A). This effect was accompanied by a small attenuation of the field EPSP slope ($n = 9$). Bath-applied imipramine did not change the relative increase in the amplitude of the population spikes induced by DHPG

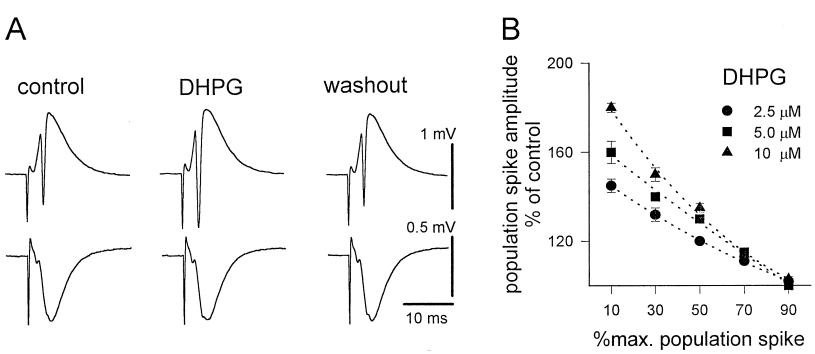


Fig. 1. Effects of DHPG on the extracellularly recorded synaptic responses in the CA1 area of hippocampal slices. (A) Application of DHPG (5 μM for 10 min) reversibly increased the amplitude of the population spike (upper panel) recorded in the stratum pyramidale, but had no effect on the field EPSP (below) recorded simultaneously in the stratum radiatum of the CA1 area. Each trace is an average of four consecutive recordings. Stimulation intensity was adjusted to elicit a population spike of 30% of the maximum amplitude. (B) Dose dependence of the DHPG action on the amplitude of population spikes, tested throughout the input-output curve. The amplitude of the population spike, expressed as a percentage of the control (pre-drug) population spike, was plotted against the relative intensity of stimulation expressed as a percentage of the maximum control population spike. Each point represents a mean % (±S.E.M.; $n = 26$, 8 and 5 for 2.5, 5 and 10 μM DHPG, respectively). The effects evoked by different concentrations of DHPG were significantly different for population spikes with amplitudes equal to 10, 30 and 50% of the maximum.

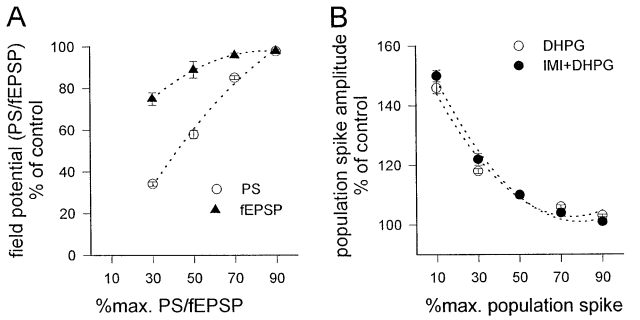


Fig. 2. Effects of acutely applied imipramine (20 μM) on (A) population spikes (PS) and field EPSPs (fEPSP) and (B) on the excitatory action of DHPG (2.5 μM) on the population spike amplitude.

(Fig. 2B). Intracellular recording showed no effect of imipramine on passive and active properties of CA1 cells ($n = 5$).

### 3.2. Effects of repeated imipramine administration on the action of DHPG on field potentials

The same pattern of responses to DHPG was observed in slices from rats receiving water and from animals treated with imipramine (for 14 days, at 48 h after the last injection), however, there was a significant reduction in the DHPG (2.5 and 5 μM)-mediated increase in the amplitude of population spikes in slices prepared from rats treated with imipramine (Fig. 3). This decrease in neuronal responsiveness to DHPG was apparent already after 7 days of imipramine administration. There was a further decrease after 14 days of treatment, whereas no significant difference was observed between groups treated for 14 and 21 days (Fig. 4A). The reduction of the DHPG (2.5 μM)-mediated increase in the population spike amplitude in rats treated with imipramine for 14 days was still noticeable 7 days after imipramine withdrawal (Fig. 4B).

Treatment with imipramine (14 days) did not change the maximum population spike amplitude ($9 \pm 1$ mV in slices from $H_2O$-treated rats; $7.8 \pm 1$ mV in slices from imipramine-treated rats, at 48 h after the last dose).

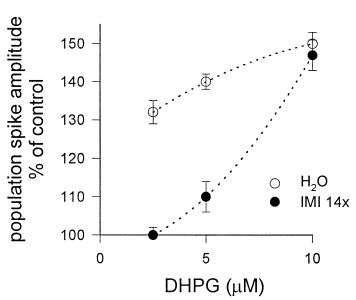


Fig. 3. Repeated treatment with imipramine (14 days, 48 h withdrawal) shifted to the right the dose-response curve for the enhancement of the population spike amplitude induced by DHPG (a population spike of 30% of the maximum amplitude). The values represent the mean percentage of the baseline control ($n = 5$-26).

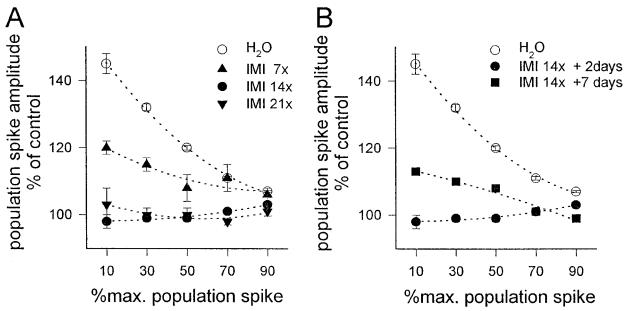


Fig. 4. The time course and persistence of the imipramine-induced decrease in the excitatory effect of DHPG (2.5 μM) on population spikes. (A) Mean input–output curves, presenting the effect of DHPG expressed as a mean percentage of the baseline control, are shown for groups treated with imipramine for 7, 14 and 21 days (with a 48 h withdrawal). (B) Effects of 2- and 7-day withdrawal after 14-day imipramine treatment.

### 3.3. Effects of repeated imipramine administration on the action of DHPG on the intracellularly recorded cell properties

The results reported in this section are based on intracellular recordings from 57 CA1 pyramidal cells in slices prepared from control ($H_2O$-treated) and imipramine-treated rats (14 days, slices prepared 48 h after the last dose). The passive membrane properties of cells did not differ between the two groups (Table 1).

As observed previously in rat CA1 pyramidal neurons (Gereau and Conn, 1995; Zahorodna et al., 1998), application of DHPG (2.5–10 μM) produced a dose-dependent and reversible depolarization of the membrane potential, usually associated with an increase in the resting input resistance and a decrease in the slow afterhyperpolarization. After a 14-day treatment with imipramine, the inhibitory effect of DHPG on the slow afterhyperpolarization

Table 1
Membrane characteristics of pyramidal cells from control animals (treated with $H_2O$ for 14 days) and animals treated with imipramine (14 days, with a 48 h withdrawal), and the effects of DHPG on membrane potential (Δ MP) and resistance (% $R_{in}$) in both groups. RMP resting membrane potential, $R_{in}$ input resistance

| | $H_2O$ | Imipramine |
|---|---|---|
| RMP (mV) | $-63.4 \pm 1.06$ | $-64.2 \pm 0.9$ |
| $R_{in}$ (MΩ) | $72.5 \pm 3.6$ | $78.4 \pm 3.4$ |
| rectification | $1.6 \pm 0.05$ | $1.5 \pm 0.06$ |
| sAHP (mV) | $7.2 \pm 0.4$ | $7.7 \pm 0.4$ |
| | $n = 29$ | $n = 28$ |
| DHPG 2.5 μM | $n = 18$ | $n = 15$ |
| Δ MP (mV) | $4.1 \pm 0.9$ | $3.4 \pm 0.7$ |
| % $R_{in}$ | $105 \pm 5.5$ | $112 \pm 4$ |
| DHPG 5 μM | $n = 11$ | $n = 13$ |
| Δ MP (mV) | $11.2 \pm 0.5$ | $6.8 \pm 0.7$[a] |
| % $R_{in}$ | $116.4 \pm 5.8$ | $118.8 \pm 3.1$ |

[a] Denotes a statistically significant difference, according to the Student's $t$-test ($P < 0.05$).

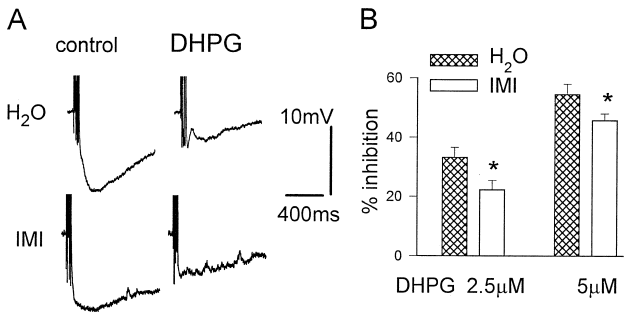


Fig. 5. Repeated administration of imipramine (14-day treatment) decreased the DHPG-induced attenuation of the slow afterhyperpolarization. (A) DHPG (5 μM) diminished the slow afterhyperpolarization in hippocampal slices prepared from $H_2O$- and imipramine (IMI)-treated rats. To measure the slow hyperpolarization amplitude the membrane potential was held at -60 mV. (B) The effect of imipramine on the DHPG-induced inhibition of the slow afterhyperpolarization; pooled data. The values represent the mean percent inhibition ($n = 11–18$). * denotes a statistically significant difference, according to the Student's *t*-test ($P < 0.05$).

was attenuated (Fig. 5); the depolarization induced by DHPG 5 μM was also decreased (Table 1).

## 4. Discussion

The main finding of the present study is that repeated treatment with imipramine causes a decrease in the excitatory response of hippocampal CA1 pyramidal neurons to the selective group I mGlu receptor agonist DHPG. This decrease in the excitatory response to DHPG took 1 to 2 weeks to develop, a time course which correlates with the delayed onset of a therapeutic antidepressive effect in humans. Moreover, the effect was long lasting after discontinuation of treatment with imipramine.

Our previous findings showing that electroconvulsive treatment is as effective as imipramine in inducing desensitization of CA1 neurons to the excitatory effect of the nonselective mGlu receptor agonist ACPD (Pilc et al., 1998) suggest that the decrease in the responsiveness of hippocampal pyramidal cells to group I mGlu receptor activation cannot be attributed solely to the acutely expressed effect of imipramine on the uptake of the amine. It is not very likely either that the antagonistic action of the remaining imipramine on group I mGlu receptors could account for the reduced excitatory effect of DHPG observed in the present study, since it has been shown that the excitatory effect of DHPG is not changed in slices perfused with imipramine. Furthermore, attenuation of the DHPG-induced excitation was still apparent 7 days after discontinuation of treatment. Nonetheless, imipramine decreased the population spike amplitude, probably via its direct action on ion channels (O'Connor et al., 1993; Pancrazio et al., 1998).

Theoretically, any of the components required for the generation of the excitatory response to DHPG — from membrane receptors to ionic channels — may be involved in the observed effect of imipramine. The number of group I mGlu receptors may decline as a result of adaptation to the increased synaptic concentration of glutamate. In fact, biochemical responses to group I mGlu receptor activation desensitized in the presence of glutamate (Catania et al., 1991). The level of synaptically released glutamate may change due to imipramine-induced adaptive changes in the presynaptic monoamine heteroreceptors (such as $\alpha_2$-adrenoceptors and 5-$HT_{1B/D}$ receptors) located on glutamatergic terminals and/or in the postsynaptic monoamine receptors (such as $\alpha_1$- and β-adrenoceptors and 5-$HT_{1A}$ receptors) influencing the activity of glutamatergic neurons (Nicoll et al., 1990; Scanziani et al., 1993; Gereau and Conn, 1994; Muramatsu et al., 1998). Several studies indicate that the number or function of these receptor types is altered by antidepressant therapy (Beck and Halloran, 1989; Bijak, 1989; Bijak et al., 1996, 1997; Caldecott-Hazard et al., 1991; Mongeau et al., 1997).

Long-term antidepressant treatment may also lead to a sustained alteration in the intracellular signal transduction cascades which mediate the actions of G-protein-coupled receptors and which influence receptor desensitization (Rosby and Sulser, 1997). This may result in alterations in the functional sensitivity of diverse metabotropic receptors which themselves are not directly regulated by the antidepressant treatment. Group I mGlu receptors have been shown to be coupled to the phospholipase C and the inositol trisphosphate ($InsP_3$)/$Ca^{2+}$ pathways (Pin and Duvoisin, 1995). It has been proposed that in hippocampal granule cells the mGlu receptor-initiated production of $InsP_3$ mobilizes intracellular $Ca^{2+}$ and leads to an increased protein tyrosine phosphorylation, which is responsible for the inhibition of the $Ca^{2+}$-activated $K^+$ current underlying the slow afterhyperpolarization (Abdul-Ghani et al., 1996). It has been shown that antidepressant drugs can affect calcium mobilization from intracellular stores, as well as the $Ca^{2+}$ and calmodulin-regulated protein kinase system (Silver et al., 1986; Helmeste and Tang, 1998). Moreover, acute and repeated administration of some antidepressant drugs suppresses the basal activity of protein kinase C in the hippocampus (Mann et al., 1995).

Activation of mGlu receptors reduces potassium currents in hippocampal neurons (Charpak et al., 1990), thereby causing a depolarization associated with an increase in the resting input resistance. Treatment with imipramine decreased the depolarizing action of DHPG on CA1 cells without affecting the increase in the input resistance. DHPG potently enhanced spontaneous inhibitory synaptic potentials impinging on CA1 cells (not shown), probably via excitation of inhibitory neurons (Miles and Poncer, 1993). The increase in membrane conductance due to enhanced synaptic activity may contribute to rather minor changes in the input resistance induced by DHPG and may underlie the lack of effect of imipramine treatment on the input resistance increase.

One of the main effects of group I mGlu receptor agonists in the hippocampus is attenuation of the slow afterhyperpolarization. The slow afterhyperpolarization, which is observed in many neurons following depolarization, provides an intrinsic inhibitory influence that plays a pivotal role in regulating neuronal excitability. The slow afterhyperpolarization is an important target of modulation by many neurotransmitters and the neurotransmitter-mediated inhibition of the slow afterhyperpolarization has been linked to activation of a variety of kinases (Nicoll et al., 1990; Pedarzani and Storm, 1993). In hippocampal CA1 cells the slow afterhyperpolarization is inhibited, among others, via β-adrenoceptors, 5-$HT_4$ and group I mGlu receptors (Nicoll et al., 1990; Pedarzani and Storm, 1993). It is of interest that the response of CA1 neurons to the excitatory effects of norepinephrine, the 5-$HT_4$ receptor agonist zacopride and DHPG was attenuated by prolonged treatment with imipramine (Beck and Halloran, 1989; Bijak 1989; Bijak et al., 1997). These data may indicate that imipramine affects some common step in the signal transduction cascade beyond the receptor. While the excitatory effects are decreased by antidepressant treatment, the inhibitory action of 5-$HT_{1A}$ receptor and $\alpha_1$-adrenoceptor activation is enhanced by such treatment in the hippocampus (Bijak 1989; Bijak et al., 1996; Mongeau et al., 1997). This suggests that the antidepressant response could well be linked to an enhanced inhibitory action in this brain structure.

It is difficult to ascertain the possible clinical importance of the effect described above. In animal studies, activation of group I mGlu receptors results in enhancement of CA1 cell excitability. Furthermore, this receptor type has been implicated in synaptic plasticity (long-term potentiation) in the hippocampus, which may underlie learning (Nakanishi, 1994; O'Leary and O'Connor, 1997). Therefore, the antidepressant-induced alterations in hippocampal long-term potentiation (Bernard et al., 1994) may be partly due to what was reported here as decreased activation of group I mGlu receptors.

Although it has been accepted that the primary mechanism by which tricyclic antidepressants relieve symptoms of depression involves inhibition of monoamine reuptake, these drugs also exert additional effects on a variety of other neurotransmitter systems. Our data point to metabotropic glutamate receptors as a target of antidepressants and thus encourage speculation that alterations in mGlu receptors may contribute to antidepressant efficacy.

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