Involvement of GABAergic Systems in Manifestation of Pharmacological Activity of Desipramine

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ABSTRACT—We have conducted this study to elucidate the influence of GABAergic systems on manifestation of pharmacological activity of desipramine using both pharmacological and electrophysiological methods. Desipramine (20 mg/kg, i.p.) significantly blocked the adjuvant-induced thermal hyperalgesia, which was facilitated by treatment with the GABA_A antagonist picrotoxin (2 mg/kg, i.p.) or the GABA_B antagonist saclofen (2 mg/kg, i.p.). This analgesic effect of desipramine was antagonized by post-treatment with picrotoxin or saclofen. However, none of these compounds showed any effect in normal animals without adjuvant-induced inflammation. In a slice preparation of the hippocampus, treatment with GABA (10^{-5} – 5 \times 10^{-4} M), baclofen (10^{-5} – 10^{-4} M) or muscimol (10^{-5} – 10^{-4} M) inhibited the field potential evoked in pyramidal neurons by Schaffer collateral stimulation. The inhibitory effect of GABA was facilitated by concurrent application of desipramine, carbamazepine or diazepam at a concentration of 5 \times 10^{-5} – 2 \times 10^{-4} M. The rank of order of facilitation is: desipramine > carbamazepine > diazepam. Desipramine also enhanced the inhibitory effect of baclofen and muscimol. These results suggest that desipramine causes GABAergic systems to activate still more, and this phenomenon appears to be involved in manifestation of the pharmacological activity of desipramine such as antinociception.

Keywords: GABA, Desipramine, Analgesia, Hippocampus, Field potential

Desipramine, carbamazepine and diazepam are clinically used as antidepressive, antiepileptic and antianxiety drugs, respectively. These three drugs belong to the family of benzazepine derivatives and have similar molecular structures.

It has been accepted that the most commonly discussed mechanism of tricyclic antidepressant drugs is blockade of biogenic amine uptake into brain synaptosomes (1, 2). There are, however, some problems with regard to this mechanism of action of antidepressant drugs, namely, i) although the action on monoamine uptake is immediate, the onset of clinical effect is delayed by more than 10 days (3, 4); ii) the repeated administration of antidepressants is associated with a delayed alteration in monoamine receptors or their second messengers (5, 6), and these receptor alterations are not consistent between antidepressants (7); and iii) compounds, which apparently are devoid of activity on either 5-HT or norepinephrine (NE) synapses, exert antidepressant activity (8, 9). In addition to these inconsistencies regarding antidepressant action, there is evidence that tricyclic antidepressants can relieve chronic pain (10 – 12). These findings suggest the possibility that biochemical mechanisms (13, 14) other than the diverse actions of antidepressants on 5-HT, NE and dopamine synapses may be involved in their clinical effects, including antidepressant activity and pain relief.

In this connection, GABA is one of the neurotransmitters, which is thought to be involved in the pathophysiology of many neuropsychiatric disorders and in endogenous antinociceptive processes. Many previous studies showed that an interaction of antidepressant drugs with GABAergic systems plays an important role in their therapeutic effects. Thus, the repeated administration of antidepressant drugs at clinically effective doses produced changes in GABA-recognition sites (15 – 19). These findings indicate the possibility that GABAergic systems may be one of the important mechanisms for manifestation of the pharmacological actions of desipramine.

The present study was conducted to investigate whether or not GABAergic systems are associated with general pharmacological action induced by administration of desi-
pramine. For this purpose, we measured the withdrawal latency to heat stimulation as a behavioral experiment. Furthermore, because the neuronal networks of hippocampus containing GABAergic pathways are relatively well known, we also measured field potentials in the hippocampal in vitro slice preparations as an electrophysiological experiment.

MATERIALS AND METHODS

Experimental animals

Male Sprague-Dawley rats (body weight of approx. 150–200 g; Nihon Doubutu, Osaka) were used. Food and water were supplied ad libitum, and the animals were kept on a 12-h light-dark cycle.

All surgical and experimental procedures were reviewed and approved by the Osaka University Graduate School of Dentistry Intramural Animal Care and Use Committee and conformed to the guidelines of the International Association for the Study of Pain (20).

Behavioral assessment

Complete Freund’s adjuvant (CFA, containing Mycobacterium butyricum) was used as the inflammatory substance for behavioral experiments. Rats received a subcutaneous (s.c.) injection of 0.15–0.2 ml (75–100 μg Mycobacterium) CFA into the plantar surface of the right hind paw.

We determined the effect of drugs on the withdrawal latency to heat stimulus by using the Plantar Test (Model 7370; Ugo Basile, Varese, Italy) according to a previously described method (21). In brief, prior to testing, animals were placed in a small cage on a glass plate. They were not restrained and could move about and explore freely. While the rat stood still with all paws placed on the ground, an infrared (I.R.) generator was positioned directly under a hind paw and switched on to activate both an I.R. generator and a reaction time counter. The intensity of the light beam was controlled and adjusted to provide a reflex withdrawal latency of approximately 10 s in control animals that received saline injections.

Electrophysiological experiments

Rats were killed by decapitation, and their brains were quickly removed and placed into ice-cold Krebs-Ringer solution (124 mM NaCl, 5 mM KCl, 1.24 mM KH₂PO₄, 1.3 mM MgSO₄, 2.6 mM CaCl₂, 26 mM NaHCO₃ and 10 mM glucose). Parasagittal slices containing the hippocampus were cut at a thickness of 300 μm. They were preincubated in Krebs-Ringer solution for 90 min at 35°C and then used in the electrophysiological experiment.

Slices were transferred to a recording chamber and perfused with Krebs-Ringer solution (35°C) at a rate of 1.3 ml/min. Krebs-Ringer solution was bubbled with a mixture of 95% O₂ and 5% CO₂ during electrophysiological experiments. Schaffer collaterals were stimulated by a bipolar stainless steel electrode with a frequency and duration of 0.5 Hz and 50 μs, respectively. Field potentials were recorded from pyramidal cells in the cornu ammonis (CA1) with glass micropipettes (3–5 Mohm, filled with Krebs-Ringer solution). The summed evoked potentials obtained by adding 5 responses were averaged by a data analyzing calculator (ATAC-350; Nihon Kohden, Tokyo). The effects of drugs were examined by measuring the amplitude of the first peak height (see Fig. 3).

Agents

The following compounds were used: GABA, picrotoxin, desipramine, carbamazepine and diazepam (Wako Pure Chemical Industries, Ltd., Osaka); saclofen (Research Biochemicals International, Natick, MA, USA); CFA (Difco Laboratories, Inc., Detroit, MI, USA).

Statistical analyses

Results are expressed as the mean ± S.E.M. Difference in mean values was first evaluated by Bartlett’s test for variance and then one-way analysis of variance (ANOVA), followed by Dunnett’s test to determine significance among treatments. Differences at P<0.05 were considered statistically significant.

RESULTS

Development of hyperalgesia

Before injection of CFA, the average values of withdrawal latencies for the right and left hind paws were not significantly different (S.E.M., n = 6, 10.1 ± 0.5 s (right), 9.9 ± 0.5 s (left)). The withdrawal latencies of the saline-treated paw and the contralateral paw (untreated) in all groups remained near baseline values throughout the testing sessions. The s.c. injections of CFA into the plantar surface of the right hind paw rapidly produced hyperalgesia as evaluated by the thermal withdrawal test. A significant decrease in withdrawal latencies was observed during the period of 4 h to 5 days after induction of inflammation, followed by a gradual return to the control level by 15 days.

Influence of drugs related to GABA on CFA-induced thermal hyperalgesia

As mentioned above, all animals treated with CFA exhibited a marked hyperalgesia from 4 h through 5 days. Therefore, the behavior experiments were conducted 2 days after induction of inflammation to determine whether or not GABAergic systems are involved in the antinociceptive actions of desipramine. At 2 days, the latencies for the...
CFA-treated paw and the contralateral paw were 7.2 ± 0.81 and 11.3 ± 0.84 s (n = 6), respectively. As shown in Fig. 1, the i.p. administration of picrotoxin (2 mg/kg, i.p.), a GABA$_A$ antagonist, or saclofen (2 mg/kg, i.p.), a GABA$_B$ antagonist, significantly shortens both the ipsilateral and contralateral paw withdrawal latency 30 min after adminis-

![Graph](image)

Fig. 1. Time-course of thermal response latencies following the i.p. injection of picrotoxin (PCX, 2 mg/kg) or saclofen (SAC, 2 mg/kg) in control rats (A) and CFA-treated rats (B and C). Effects of these drugs were measured 2 days after intraplantar injection of CFA. The arrows designated the time (0 min) of i.p. injection of the drugs. The data for each group (N = 6) are presented as the mean ± S.E.M. In the ipsilateral and the contralateral hind paw of the CFA-treated group, thermal response latencies were significantly shortened at 30 min post-GABA antagonists’ injection compared to that of pre-drug injection (−20) (*P<0.05, Dunnett’s test). −20 represents 20 min before injection. Note that the withdrawal latency per animal at each time point is the average of latencies obtained from 3 consecutive stimuli applied at intervals of 2 min. Closed circle and open circle represent the withdrawal latency of ipsilateral hind paw (A: right side, B and C: adjuvant side) and contralateral hind paw (A: right side, B and C: normal side), respectively.

Influence of desipramine on CFA-induced thermal hyperalgesia

Desipramine (20 mg/kg, i.p.) significantly blocked the CFA-induced thermal hyperalgesia at day 2 of inflammation. This antinociceptive effect of desipramine reached a maximum at 1 h after the injection (n = 6, 7.9 ± 0.57 s (before injection), 11.9 ± 0.36 s (1 h after injection)); that is, the withdrawal latency of the inflamed paw 1 h after administration was increased ca. 50% when compared with that before administration. However, the uninflamed contralateral hind paw, as well as the hind paws of control rats, showed no significant change in thermal hyperalgesic response following desipramine administration (Fig. 2A).

The paw-withdrawal latency evoked by desipramine in the inflamed hind paw was never prolonged over the withdrawal latency of the contralateral paw. The desipramine-induced antinociceptive effect was antagonized by treatment with picrotoxin (2 mg/kg, i.p.) or saclofen (2 mg/kg, i.p.) given 10 min after administration of desipramine, as shown in Fig. 2, B and C, respectively.

The effects of desipramine, carbamazepine and diazepam on the inhibitory effect of GABA to the field potentials

Stimulation of Schaffer collaterals evoked responses in CA1 pyramidal neurons consisting of two or three negative population spikes (0.5 – 1.5 mV). Drugs at various concentrations were perfused, and their effects on the field potentials were examined by measuring the first peak height. GABA at a concentration of 5 × 10$^{-4}$ M reduced the amplitude of the field potentials to ca. 70%.

To examine the effect of desipramine, carbamazepine and diazepam on the inhibitory action of GABA, various concentrations of GABA (10$^{-5}$ – 5 × 10$^{-3}$ M) were perfused with concentrations of 5 × 10$^{-5}$ – 2 × 10$^{-4}$ M of each drug (Figs. 3 – 5). Single application (without GABA) of desipramine, carbamazepine and diazepam at these concentrations did not show any effect on the field potentials. Concomitant perfusion of these drugs with GABA significantly shifted the concentration-inhibition curve to the left. The rank of order of facilitation obtained from the concentration-inhibition curve in the presence of 10$^{-4}$ M GABA is as follows; desipramine > carbamazepine > diazepam (Fig. 6).

The effects of desipramine on the inhibitory effect of muscimol and baclofen to the field potentials

Both muscimol and baclofen at concentrations of 10$^{-5}$ and 10$^{-4}$ M reduced the amplitude of the field potentials in a dose-dependent manner. When a concentration of 2 × 10$^{-4}$ M of desipramine was concomitantly perfused with various concentrations of muscimol or baclofen (10$^{-5}$ –
In this connection, GABA is one of the neurotransmitters, which is thought to be involved in the pathophysiology of many neuropsychiatric disorders and in endogenous antinociceptive processes. In the current study, withdrawal latencies of the ipsilateral paw and the contralateral paw in inflamed rats, but not in control rats, were significantly shortened by treatment with the GABA_A antagonist picrotoxin or the GABA_B antagonist saclofen suggesting that the persistence of altered sensations subsequent to tissue injury may cause an enhancement of GABAergic transmission in compensation for inflammatory pain syndromes with the persistence of hyperalgesia and allodynia. In such a situation, desipramine significantly blocked the CFA-induced thermal hyperalgesia, and this inhibitory effect was antagonized by picrotoxin and saclofen at the adjuvant side, but not at the normal side. The reason why only the inhibitory effect of desipramine at the adjuvant side was antagonized is not known. In addition, none of these antagonists related to GABA showed any effect in control animals without adjuvant-induced inflammation. These results led to the hypothesis that the activation of GABAergic neurons may be required for manifestation of the pharmacological activity of desipramine.

The current finding that desipramine-induced analgesia was antagonized by both GABA_A and GABA_B antagonists was similar to the previous results obtained by Ballal et al. (22). They observed that the analgesic activity of imipramine, an analog of desipramine, was enhanced by muscimol (GABA_A agonist), baclofen (GABA_B agonist) or aminoxyacetic acid (GABA transaminase inhibitor), whereas pretreatment with bicuculline (GABA_A antagonist), δ-amino-n-valeric acid (GABA_B antagonist) or thiosemi-carbazide (GABA synthesis inhibitor) attenuated the imipramine analgesia. Furthermore, Sabetkasai et al. (23) reported that the tricyclic antidepressants including in desipramine induced antinociception in both phases of the formalin test, and this response was reduced by the GABA-receptor antagonist. These findings and our present results obtained from the behavioral experiment strongly support the hypothesis that GABAergic systems may play a role in the action of tricyclic antidepressant drugs.
Fig. 3. Effect of GABA in combination with desipramine on the field potentials evoked in CA1 pyramidal cells in hippocampal slices obtained from rats. A and B: Field potentials recorded in Krebs-Ringer solution (A) and 15 min after the perfusion of $10^{-4}$ M GABA plus $2 \times 10^{-4}$ M desipramine in Krebs-Ringer solution (B). C: Dose-response curve of GABA to the field potentials in the absence (closed circle) and in the presence ($5 \times 10^{-5}$ M open circle), $10^{-4}$ M (closed triangle) and $2 \times 10^{-4}$ M (open triangle)) of desipramine. Krebs-Ringer solution containing various concentrations of GABA ($10^{-3}-5 \times 10^{-3}$ M) were perfused with desipramine. The data for each group (N = 6) are presented as the mean ± S.E.M. The amplitude of the field potentials was determined by measuring the first peak height (see panel A) and expressed as % of the control recorded in the absence of drug. Concomitant perfusion of desipramine with GABA significantly shifted the concentration-response curve to the left side. *P < 0.05, when compared with the amplitude obtained in the absence of desipramine in each concentration measured (Dunnett’s test).

Fig. 4. Effect of GABA on the field potentials evoked in CA1 pyramidal cells in hippocampal slices obtained from rats in the absence (closed circle) and in the presence ($5 \times 10^{-5}$ M open circle), $10^{-4}$ M (closed triangle) and $2 \times 10^{-4}$ M (open triangle)) of carbamazepine. Krebs-Ringer solution containing various concentrations of GABA ($10^{-3}-5 \times 10^{-4}$ M) were perfused with carbamazepine. The data for each group (N = 6) are presented as the mean ± S.E.M. The amplitude of the field potentials was determined by measuring the first peak height and expressed as % of the control recorded in the absence of drug. Concomitant perfusion of carbamazepine with GABA significantly shifted the concentration-response curve to the left side. *P < 0.05, when compared with the amplitude obtained in the absence of carbamazepine in each concentration measured (Dunnett’s test).

Fig. 5. Effect of GABA on the field potentials evoked in CA1 pyramidal cells in hippocampal slices obtained from rats in the absence (closed circle) and in the presence ($5 \times 10^{-5}$ M open circle), $10^{-4}$ M (closed triangle) and $2 \times 10^{-4}$ M (open triangle)) of diazepam. Krebs-Ringer solution containing various concentrations of GABA ($10^{-3}-5 \times 10^{-4}$ M) were perfused with diazepam. The data for each group (N = 6) are presented as the mean ± S.E.M. The amplitude of the field potentials was determined by measuring the first peak height and expressed as % of the control recorded in the absence of drug. Concomitant perfusion of diazepam with GABA significantly shifted the concentration-response curve to the left side. *P < 0.05, when compared with the amplitude obtained in the absence of diazepam in each concentration measured (Dunnett’s test).
support the idea that the pharmacological activity evoked by acute administration of tricyclic antidepressant drugs may be mediated by functional alteration of GABAergic mechanisms and subsequent stimulation of non-specific GABA binding sites.

Furthermore, we investigated the influence of desipramine to the field potentials in hippocampal slice preparations, which are valuable materials for physiological and pharmacological experiments (24–26), because the neuronal networks including GABAergic systems are relatively made clear. In this connection, it has been shown that the field potentials evoked in CA1 pyramidal cells by stratum radiatum stimulation is inhibited through the release of GABA from basket cell terminals (27, 28). In the present study, the inhibition of the field potentials by GABA was significantly facilitated by concurrent application of desipramine, carbamazepine or diazepam. The effect of desipramine was especially remarkable. The results of the electrophysiological study on the effect of desipramine to the GABAergic systems confirmed the result obtained from the behavioral study; that is, desipramine remarkably enhances the inhibitory action of GABA in a situation in which GABAergic transmission is facilitated.

Concerning the mechanisms by which desipramine enhances the activity of GABA, it has been reported that chronic (more than 10 days), but not acute, treatment with antidepressant drugs, including desipramine, significantly enhanced the activity of a hippocampal GABA_A receptor-related system (29) and up-regulated GABA_B binding in a dose-and time-dependent manner (15, 16). In the current study, however, the effect of desipramine on CFA-induced thermal hyperalgesia and field potential was observed in acute, but not chronic, administration. Therefore, further experiments are needed to elucidate whether or not single administrations can produce a rapid effect on the GABA receptor. In addition to an alteration of GABA binding sites, there is the possibility that antidepressant drugs modify GABA release. In this connection, Korf and Venema reported that desipramine produce a reversible increase in the release of endogenous GABA from the exposed rat thalamus, and this effect of desipramine was Ca-dependent (30). Furthermore, desipramine markedly increases the GABA concentration in whole mouse brain (31). These previous findings and our present results strongly support the idea that desipramine produce a variety of pharmacological effects, including antidepressive action and analgesic action, through activating GABAergic systems. However, the extent of the action of antidepressant drugs on GABAergic systems may differ among cases, such as antidepressive action and analgesic action, and pathological stages, such as acute and chronic. Namely, repeated treatment may be needed to reveal an antidepressant effect, whereas acute treatment may be enough to relieve pathological pain evoked with chronic inflammation.
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