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Baclofen-impairment of memory retention in rats: possible interaction with adrenoceptor mechanism(s)

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Abstract

This study concerned the influence of adrenoceptor agonists and antagonists on baclofen-induced impairment of memory retention. Intracerebroventricular injection of baclofen (0.25–2 μg/rat) reduced memory retention in rats. The combination of different doses of baclofen with a low dose of clonidine (0.5 μg/rat) elicited a greater decrease in memory retention. Yohimbine (1 μg/rat) potentiated the response to a low dose, but decreased the response to higher doses of baclofen. Single administration of clonidine (0.5–2 μg/rat) but not yohimbine (1–4 μg/rat) itself decreased memory retention. The combination of clonidine with yohimbine did not show any interaction. The low dose of phenylephrine (0.5 μg/rat) or prazosin (0.5 μg/rat) also potentiated the inhibition of memory retention by baclofen. Phenylephrine (0.5–3 μg/rat) increased, while prazosin (0.5–2 μg/rat) decreased memory retention. The combination of the two drugs showed an interaction. It may be concluded that an adrenoceptor mechanism may interact with the memory retention impairment induced by baclofen.

Keywords: Baclofen; Adrenoceptor agonist; Adrenoceptor antagonist; Memory; (Rat)

1. Introduction

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. GABA acts at various pharmacologically distinct receptor subtypes, $GABA_A$, $GABA_B$ and $GABA_C$ (Hill and Bowery, 1981; Matsumoto, 1989; Malcangio and Bowery, 1996). $GABA_A$ receptors are coupled with Cl^- ionophores whereas $GABA_B$ receptors are associated with Ca^{2+} or K^+ channels via G-protein (Bormann, 1988). A third class of GABA binding sites, the $GABA_C$ sites, resembles the $GABA_A$ receptor but is insensitive to bicuculline (Drew et al., 1984). There is extensive evidence indicating that the administration of GABAergic drugs affects memory retention and learning (Castellano and McGaugh, 1990; Brioni et al., 1989; Nakagawa et al., 1995). It has been shown that GABA receptor agonists impair memory and antagonists facilitate memory (Brioni and McGaugh, 1988; Castellano et al., 1989; Castellano and McGaugh, 1989; McGaugh et al., 1990). There are also data indicating that $GABA_B$ receptor blockade results in suppression of hippocampal long-term potentiation in vivo (Brucato et al., 1996). An interaction between cholinergic systems and the impairment of memory induced by $GABA_B$ receptor activation has also been proposed (Nakagawa et al., 1995). Moreover, the possibility of involvement of monoamines in pharmacological effects of baclofen, a $GABA_B$ receptor agonist, is supported by the results of biochemical studies which have shown significant effects of baclofen on the content, release and turnover of these agents in various brain regions (Sawynok, 1989). Data obtained by some investigators indicate that retention is enhanced by adrenoceptor agonists (Introini-Collison et al., 1992). There is also a report indicating that GABAergic cells are excited via α-adrenoceptors (Kawaguchi and Shindou, 1998). However, there is a view that GABAergic systems modulate memory through an interaction with β-adrenergic mechanisms (Introini-Collison et al., 1994), while the involvement of α-adrenocep-

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tors in the impairment of $GABA_B$ receptor mechanism has not been investigated. Therefore, in the present study, the possible interaction of $\alpha 1$- and $\alpha 2$-adrenoceptor mechanism (s) with the response induced by baclofen in the memory retention in rats was studied.

2. Materials and methods

2.1. Animals

The subjects were male Wistar rats weighing 150–200 g. The rats were kept eight per cage at room temperature (22–24°C) and with a 12-h light/12-h dark cycle (light period, 0700–1900 h). The animals had free access to food and water except during the experiments.

2.2. Cannula guide implantation

The animals were anesthetized with ketamine hydrochloride (50 mg/kg) plus xylazine (4 mg/kg). The skull of the rat was fixed to a stereotaxic frame (David Koft Instruments, USA) and permanent stainless steel guide cannulae (21 gauge, 4 mm) were implanted. The tips were aimed at the following coordinates: AP = −0.8 mm, from bregma, L = 1.6 mm, V = 4 mm from the dura with the nose bar at −3.5 mm from the intraural line. The cannula was fixed to the skull using a screw and dental acrylic cement. A stylet was inserted into the cannula to keep it patent prior to injections. The animals were allowed 1 week of recovery before the start of the experiments.

2.3. Intracerebroventricular injections

The animals were gently restrained by hand, the stylet was removed from the guide cannula and a 27-gauge injection needle (1 mm beyond the tip of the implanted guide cannula) was inserted. The injection needle was attached by a polyethylene tube to a 5-μl syringe. The injection solutions were administered in a total volume of 2 μl. The injection needle was retained in the guide cannula for an additional 60 s after the injection to facilitate diffusion of the drugs.

2.4. Training and testing procedures

2.4.1. Apparatus

The passive avoidance apparatus consisted of two compartments, a lighted box (Plexiglass) and a dark box (Black) of the same size (20 × 20 × 40 cm each) separated by a guillotine door (8 × 8 cm). The floor of the dark compartment was made of stainless-steel rod (0.5 cm diameter) separated by a distance of 1 cm. Intermittent electric shocks (50 Hz, 5 s), 1.5 mA intensity, were delivered to the grid floor of the dark compartment by an insulated stimulator.

2.5. Procedure

The animals were allowed to get used to the laboratory environment 30 min before each of the training or testing sessions. All training and testing was done between 0800 and 1300 h. In the training trial, each animal was gently placed in the light compartment, facing away from the dark compartment. The door between the compartments was opened 10 s later and, as the animal entered the dark (shock) compartment, the door was closed and the 1.5 mA foot shock was administered for 5 s. If an animal waited more than 100 s to cross to the other side, it was eliminated from the experiment. The rat was then removed from the apparatus and immediately injected intracerebroventricularly via the guide cannula. Twenty-four hours after training, a test of retention was performed as in the training session, except that the foot shock was not delivered. If an animal remained in the light compartment and did not cross within 600 s to the dark compartment (where the footshock had been given), the session was ended and a score of 600 was assigned.

2.6. Drugs

The following drugs were used: baclofen (Ciba, Basel, Switzerland), phenylephrine hydrochloride, prazosin hydrochloride, clonidine hydrochloride and yohimbine (Sigma, Poole, England). The drugs were dissolved in saline only and were used intracerebroventricularly in a volume of 2 μl/rat. The control groups received saline. Drugs were injected intracerebroventricularly (i.c.v.) immediately after the shock (during training session).

2.7. Data analysis

Analysis of variance (ANOVA) followed by a Newman–Keuls test was used to evaluate the significance of the results obtained. A difference of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of baclofen on memory retention in rats

Intracerebroventricular (i.c.v.) injection of various doses of the $GABA_B$ receptor agonist, baclofen (0.25, 0.5, 1 and 2 μg/rat) [one-way ANOVA; $F(4,35) = 33$, $P < 0.0001$], immediately after the shock (in the training session) decreased retention latencies in rats. The highest response was obtained with the dose of 2 μg/rat of the drug (Fig. 1).

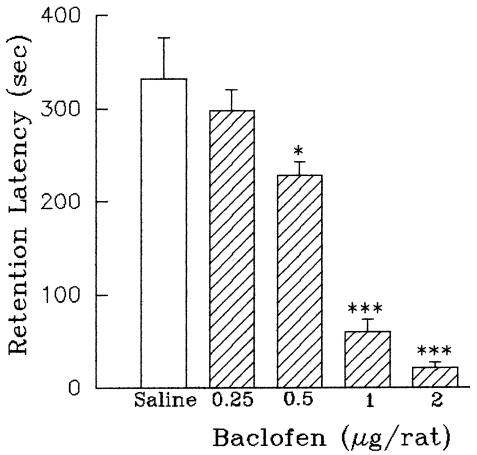

Fig. 1. Effect of baclofen on memory retention in rats. Animals were injected with different doses of baclofen intracerebroventricularly (i.c.v.; 0.25, 0.5, 1 and 2 μg/rat) immediately after the shock, and retention latencies were tested 24 h after the drug injection. Each point is the mean ± SEM for eight rats. $^{*}P < 0.05$, $^{***}P < 0.001$ for differences from saline control group.

3.2. Effects of baclofen in the presence or absence of α-adrenoceptor agonists and antagonists on memory retention in rats

The effects of various doses of baclofen alone or in combination with clonidine or yohimbine are shown in Fig. 2.

Two-way ANOVA indicates that the combination of baclofen (0.25, 0.5 and 1 μg/rat, i.c.v.) [Factor A; $F(3,56) = 88.8$, $P < 0.0001$] with clonidine (0.5 μg/rat, i.c.v.) [Factor B; $F(1,56) = 193.6$, $P < 0.0001$] shows interaction [Factor A × B; $F(3,56) = 24.2$, $P < 0.0001$. Further analysis shows both baclofen and clonidine reduced memory retention and the combination of the drugs potentiated the inhibition of memory retention. Another group of animals received the combination of baclofen with yohimbine. Two-way ANOVA showed that baclofen [$F(3,56) = 27.6$, $P < 0.0001$] but not yohimbine (1 μg/rat) [$F(1,56) = 1.4$, $P > 0.05$] reduced memory retention. However, the

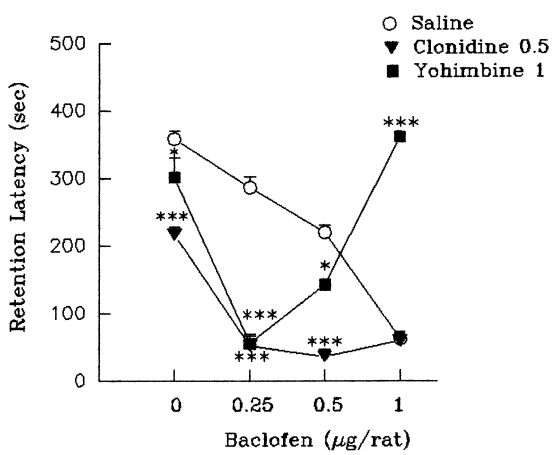

Fig. 2. Effect of baclofen in the presence or absence of clonidine or yohimbine on memory retention. Animals were injected with different doses of baclofen (○; 0.25, 0.5 and 1 μg/rat; i.c.v.) immediately after the shock. Clonidine (▼; 0.5 μg/rat, i.c.v.) 15 min, and yohimbine (■; 1 μg/rat, i.c.v.) was injected 30 min before baclofen administration. Retention latencies were tested 24 h after drug injection. Each point is the mean ± SEM from eight rats. $^{*}P < 0.05$, $^{***}P < 0.001$ for differences from respective baclofen control group.

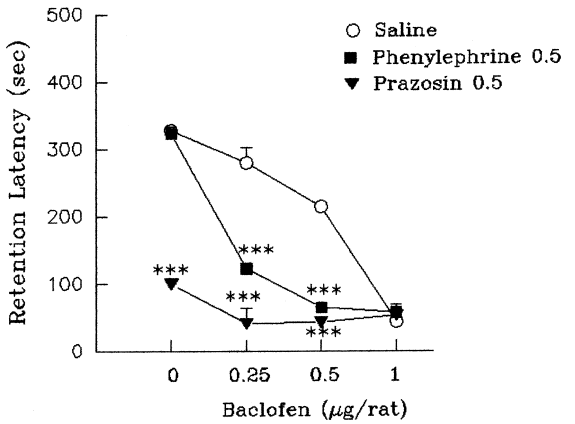

Fig. 3. Effect of baclofen in the presence or absence of phenylephrine or prazosin on memory retention in rats. Animals were injected with different doses of baclofen (○; 0.25, 0.5 and 1 μg/rat, i.c.v.) alone and phenylephrine (▼; 0.5 μg/rat, i.c.v.), 15 min or prazosin (■; 0.5 μg/rat, i.c.v.) 30 min prior to baclofen injection. Baclofen was given immediately after shock was administered. Retention latencies were tested 24 h after drug injection. Each point is the mean ± SEM for eight rats. $^{***}P < 0.001$ for differences from respective baclofen control group.

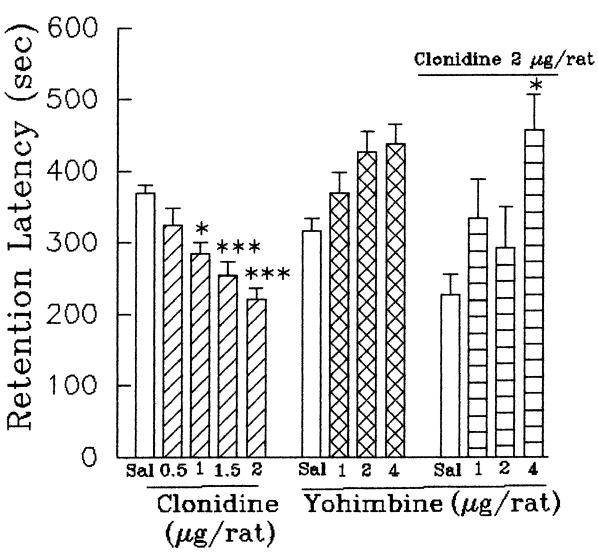

Fig. 4. Effect of clonidine in the presence or absence of yohimbine on memory retention in rats. The animals were injected with saline (2 μl/rat, i.c.v.), clonidine (0.5, 1, 1.5 and 2 μg/rat, i.c.v.) and yohimbine (1, 2 and 4 μg/rat, i.c.v.) alone immediately after the shock was administered. When the combination of yohimbine and clonidine was used, yohimbine was injected 30 min before clonidine. Retention latencies were tested 24 h after drug injection. Each point is the mean ± SEM for eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for differences from respective saline control group.

combination of two drugs showed interaction [$F(3,56) = 64.9$, $P < 0.0001$]. Further analysis indicates that yohimbine potentiated, or decreased the response induced by lower and higher doses of baclofen, respectively.

Fig. 3 shows the effect of baclofen alone or in combination with either phenylephrine (0.5 μg/rat) or prazosin (0.5 μg/rat). Two-way ANOVA showed that both phenylephrine [$F(3,56) = 14.6$, $P < 0.0001$] and prazosin [$F(3,56) = 45.6$, $P < 0.0001$] altered the memory retention induced by baclofen with interaction. Further analysis indicated that both phenylephrine [$F(1,56) = 39.1$, $P < 0.0001$] and prazosin [$F(1,56) = 343.$, $P < 0.0001$] potentiated the baclofen response.

3.3. Effects of adrenoceptor agonist and antagonist on memory retention

The effects of clonidine or yohimbine on memory retention are shown in Fig. 4. Two-way ANOVA showed that there was a significant difference between the response induced by i.c.v. administration of different doses of clonidine (0.5, 1, 1.5 and 2 μg/rat) [$F(1,56) = 8.7$, $P < 0.01$] or yohimbine (1, 2 and 4 μg/rat) [$F(3,56) = 6.6$, $P < 0.01$] from the saline control group. However, the combination of the two drugs showed no interaction [$F(3,56) = 1.1$, $P > 0.05$]. Analysis showed that clonidine but not yohimbine by itself reduced memory retention.

The effects of phenylephrine or prazosin on memory retention are shown in Fig. 5. Two-way ANOVA indicated that i.c.v. administration of different doses of phenylephrine (0.5, 1.5 and 3 μg/rat) [$F(1,56) = 48.0$, $P < 0.0001$] increased, while prazosin (0.5, 1 and 2 μg/rat) [$F(3,56) = 48.9$, $P < 0.0001$] decreased memory retention. However, the combination of different doses of prazosin (0.5, 1 and 2 μg/rat) with phenylephrine (3 μg/rat) showed a lower effect, with no interaction [$F(3,56) = 1.7$, $P > 0.05$].

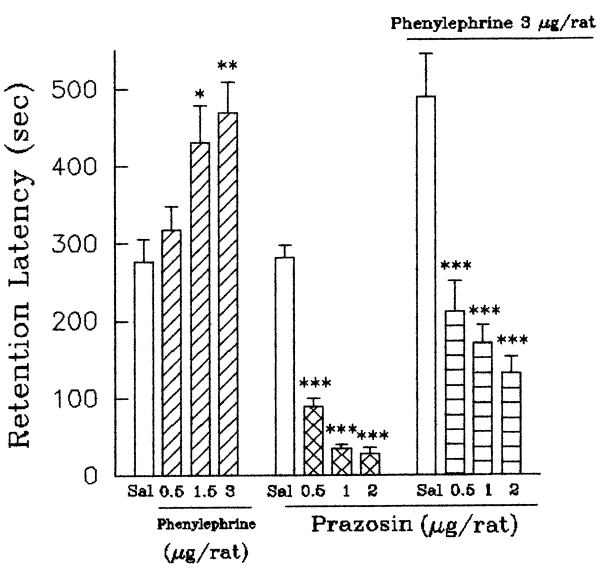

Fig. 5. Effect of phenylephrine in the presence or absence of prazosin on memory retention in rats. Animals were injected saline (2 μl/rat, i.c.v.), phenylephrine (0.5, 1.5 and 3 μg/rat, i.c.v.) or prazosin (0.5, 1 and 2 μg/rat, i.c.v.) immediately after shock administered. When the combination of phenylephrine with prazosin was employed, prazosin was injected 30 min prior to phenylephrine administration. Retention latencies were tested 24 h after the drug injection. Each point is the mean ± SEM of eight rats. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for differences from respective saline control group.

4. Discussion

Passive avoidance learning is now a widely used model of learning (Mondadori et al., 1996; Yu et al., 1997). In the present study, the effects of baclofen, which is a prototypic agonist for $GABA_B$ receptors (Bowery et al., 1985; Bowery, 1993), were evaluated in the presence or absence of adrenoceptor agonists and antagonists on memory retention in a passive avoidance task.

Our findings indicate that post-training administration of the $GABA_B$ receptor agonist, baclofen, in the doses employed produced a dose-dependent impairment of memory retention in the test. The results are in agreement with those obtained by others showing an impairment of memory by baclofen (Stackman and Walsh, 1994; McNamara and Skelton, 1996). The $GABA_B$ receptor mechanisms may have interactions with cholinergic systems (Nakagawa et al., 1995). Furthermore, baclofen inhibits the release of acetylcholine in the rat brain (De Boer and Westerink, 1994), and also reduces the evoked release of [^{3}H] glutamate in guinea pig cortical slices (Potashner, 1979). Since cholinergic systems in the brain and glutamate (Izquierdo and Medina, 1995) may play an important role in learning and memory, baclofen may induce its response through decrease in the activity of the cholinergic and/or *N*-methyl-D-aspartate (NMDA) systems(s).

The possibility of involvement of dopamine, noradrenaline and 5-hydroxytryptamine in the pharmacological effects of baclofen is supported by the results of biochemical studies that have shown significant effects of baclofen on the content, release and turnover of these monoamines in various brain regions (Sawynok, 1989). It has also been shown that, in rats and mice, retention is affected by post-training injection of adrenergic and GABAergic drugs (see Introini-Collison et al., 1994). To examine the influence of the α-adrenergic system on the baclofen response, the effects of α-adrenoceptor agonists and antagonists on the impairment of memory retention were studied.

Previous studies of post-training administration of adrenergic agonists such as epinephrine (Introini-Collison et al., 1992), amphetamine (Martinez et al., 1980) and phenylephrine (Ferry et al., 1999a,b) demonstrated memory enhancing effects, primarily in memory-deficit models. α-Adrenoceptors are assigned to two subtypes: α_1 and α_2

(Coull, 1994). The present data indicate that post-training administration of the α_2-adrenoceptor agonist, clonidine, potentiated the baclofen-induced impairment of memory retention, a finding which may show interaction of the α_2-adrenoceptor mechanism with the baclofen effect. Moreover, clonidine by itself reduced memory retention. α_2-Adrenoceptors can be located both post- and presynaptically on forebrain and hippocampal neurons, and as autoreceptors in the locus coeruleus (Coull, 1994). Thus, the effect of clonidine may be mediated either through pre- or postsynaptic α_2-adrenoceptor sites. The present data indicate that an α_2-adrenoceptor antagonist, yohimbine, potentiated the inhibition of memory induced by a low dose of baclofen, while it decreased the response induced by a higher dose of the GABA receptor agonist. Other investigators showed that α_2-adrenoceptor antagonists potentiate the retention enhancement induced by acetylcholinesterase inhibitor in the rat, through blockade of presynaptic α_2-adrenoceptors (Camacho et al., 1996). Application of yohimbine to the locus coeruleus also dose dependently enhanced memory (Chen et al., 1992). Since activation or inhibition of α_2-adrenoceptors may impair or improve retention respectively, the possibility may exist that an α_2-adrenoceptor mechanism plays a modulatory role in the baclofen response.

Our results also showed that the α_1-adrenoceptor agonist, phenylephrine, potentiated the inhibition of memory retention induced by baclofen, while single administration of phenylephrine increased the memory retention. α_1-Adrenoceptors are predominantly postsynaptic (Coull, 1994). Pharmacological findings indicate that activation of postsynaptic α_1-adrenoceptors potentiates β-adrenoceptor-mediated activation of cAMP formation (Ferry et al., 1999b). Moreover, α_1-adrenoceptors are implicated in mediation of the effects of norepinephrine on storage and their action depends on concurrent β-adrenoceptor activation (Ferry et al., 1999a). Considering the view that GABAergic systems modulate memory through an interaction with β-adrenergic mechanisms (Introini-Collison et al., 1994), one can postulate that postsynaptic α_1-adrenoceptors elicit a modulatory response through such a mechanism. The α_1-adrenoceptor antagonist, prazosin, also increased the baclofen response. The decrease in retention now induced by prazosin may agree with findings of others indicating that prazosin decreases acquisition of memory (Obersztyn and Kostowski, 1983; Riekkinen et al., 1996). There is a report that prazosin elicits α_2-adrenoceptor blocking properties and even releases noradrenaline (Alam, 1994). Whether the present effect of prazosin is elicited by a blockade of an α_2-adrenoceptor mechanism, or whether other mechanism(s) is/are involved, should be clarified. Overall, our findings indicate that α_1- and α_2-adrenoceptors may be involved in modulation of memory. However, more experiments are required to clarify the exact mechanism(s) involved in the interaction between baclofen and adrenoceptors.

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