EFFECT OF PERTUSSIS TOXIN ON BACLOFEN-AND DIPHENHYDRAMINE-INDUCED AMNESIA

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Effect of pertussis toxin on baclofen- and diphenhydramine-induced amnesia

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Abstract The effect of pretreatment with pertussis toxin at the doses of 0.25 and 0.50 μg per mouse ICV on the amnesic effect produced by baclofen (0.1–4 mg kg^{-1} IP), diphenhydramine (15–30 mg kg^{-1} IP) and scopolamine (0.5–5 mg kg^{-1} IP) was investigated in the mouse passive avoidance test. Ten days after a single injection of pertussis toxin, baclofen (2–4 mg kg^{-1} IP) amnesia was prevented. By contrast, pertussis toxin had no effect on diphenhydramine- and scopolamine-induced amnesia. Pretreatment with pertussis toxin at both doses used did not impair motor coordination of the mice, as revealed by the rota-rod test. The present results indicate that the activation of pertussis toxin-sensitive G-proteins represents an important transduction step in memory impairment induced by $GABA_B$ (γ-aminobutyric acid B) agonists, but not by antihistaminic and antimuscarinic drugs.

Key words Pertussis toxin · Baclofen · Diphenhydramine · Scopolamine · Amnesia · Learning and memory · Passive avoidance

Introduction

The role of neurotransmitters in learning and memory has been intensively investigated in recent years. It has become evident that modulation of several neurotransmitter systems, including the GABAergic, influences memory consolidation processes for various learning tasks and in different animal species.

GABA is the main inhibitory neurotransmitter in the brain. It acts on two different types of target receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are coupled with benzodiazepine receptors and Cl^- channels, while $GABA_B$ receptors are coupled with G-proteins (Hill et al. 1984). $GABA_A$ and $GABA_B$ receptors have somewhat different physiological actions. However, they play an important role in learning and memory. Systemic picrotoxin ($GABA_A$ antagonist) administration has long been known to enhance memory facilitation (Breen and McGaugh 1961), whereas the activation of $GABA_A$ receptors impairs memory performances (Jerusalinsky et al. 1994). Similarly, the $GABA_B$ agonist baclofen disrupts memory after systemic, intra-amygdala or intraseptal administration (Swartzwelder et al. 1987; Castellano et al. 1989; Stackman and Walsh 1994). Cognitive processes, including learning and memory, can be ameliorated by $GABA_B$ receptor antagonists (Carletti et al. 1993; Mondadori et al. 1993).

The antihistaminics are known to exert a variety of effects on the central nervous system. The first generation of H_1 antagonists can both stimulate and depress the central nervous system. Stimulation occasionally is encountered in patients given therapeutic doses, but it is a striking feature of poisoning, which can result in convulsions, particularly in infants (Faingold and Berry 1972). Central depression, on the other hand, usually accompanies therapeutic doses of the H_1 antagonists, and appears to be related to occupancy of cerebral H_1 receptors (Simons and Simons 1994). Diminished alertness, slowed reaction times, somnolence or impairment of cognitive functions are common manifestations (Simons and Simons 1994). The ethanolamines, such as diphenhydramine, are particularly prone to cause sedation (Carruthers et al. 1978). Moreover, the administration of diphenhydramine further reduces learning ability in patients with seasonal allergic rhinitis in whom learning performances are already impaired by allergy symptoms (Vuurman et al. 1996).

The first aim of the present study was to investigate the potential amnesic effect of diphenhydramine in the

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mouse passive avoidance test. The $GABA_B$ and histaminergic receptors have been demonstrated to interact with metabotropic receptors coupled to G-proteins (Birnbaumer 1990) leading to the modulation of intracellular effectors, including adenylate cyclase, phospholipase C and ion channels (Simon et al. 1991). Since it has been demonstrated that several actions of $GABA_B$ and histaminergic receptors can be mediated by pertussis toxin-sensitive G-proteins (Bowery 1993; Arrang 1994; Galeotti et al. 1996), we also thought it worthwhile to investigate the role of $G_{i/o}$ proteins in memory processes modulated by GABAergic and histaminergic systems.

Materials and methods

Animals

Male Swiss albino mice (23–30 g) were used. Mice were housed 15 per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. The animals were fed a standard laboratory diet and tap water ad libitum. Mice were randomly assigned to a saline, vehicle (water solution containing 0.01 M sodium phosphate buffer, pH = 7.0, with 0.05 M sodium chloride) or pertussis toxin group (0.25 and 0.50 μg per mouse). Naive animals did not receive any pretreatment, whereas saline, vehicle and pertussis toxin groups received a single intracerebroventricular (ICV) injection on day 0. Pertussis toxin produced, 10 days after administration, 18% and 55% deaths at the doses respectively of 0.25 and 0.50 μg per mouse. All experiments were carried out according to the "Principles of laboratory animal care".

Passive-avoidance test

The test was performed according to the step-through method described by Jarvik and Kopp (1967), modified by us. The apparatus is comprised of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. In the original method, mice received a punishing electrical shock as soon as they entered the dark compartment, while in our modified method, mice, after their entry into the dark compartment, receive a non-painful punishment consisting of a fall into a cold water bath (10°C). For this purpose, the dark chamber was constructed with a pitfall floor. The latency times for entering the dark compartment were measured in the training test and after 24 h in the retention test. Following a single pretreatment with vehicle or pertussis toxin, the effect of baclofen, diphenhydramine and scopolamine was tested 10 days later. Baclofen, diphenhydramine and scopolamine were injected intraperitoneally (IP) immediately after termination of the training session. The maximum entry latency allowed in the retention session was 180 s. The memory degree of received punishment was expressed as latencies recorded in the retention and training sessions.

Rota-rod test

The apparatus consists of a base platform and a rotating rod of 3 cm diameter with a non-slippery surface. The rod was placed at height of 15 cm from the base. The rod, 30 cm in length, was divided into five equal sections by six disks. Thus up to five mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 rpm. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s according to Vaught et al. (1985). The performance time was measured before and 15, 30 and 45 min after subcutaneous administration of saline. The test was performed 11 days after pretreatment with saline, vehicle or pertussis toxin. Naive animals were used as unpretreated controls.

Drugs

The following drugs were used: (±) baclofen (*β-p*-chlorophenyl GABA), scopolamine hydrobromide (Sigma), diphenhydramine hydrochloride (De Angeli) and pertussis toxin (RBI).

All drugs were dissolved in isotonic (NaCl 0.9%) saline solution immediately before use, except for pertussis toxin, which was dissolved in a water solution containing 0.01 M sodium phosphate buffer, pH = 7.0, with 0.05 M sodium chloride. Drug concentrations were prepared in such a way that the necessary dose could be administered in a volume of 10 ml kg^{-1} by IP injection or 5 μl per mouse by ICV injection.

ICV administration was performed under ether anesthesia according to the method described by Haley and McCormick (1957). During anesthesia, mice were grasped firmly by the loose skin behind the head. A hypodermic needle (0.4 mm external diameter) attached to a 10 μl syringe was inserted perpendicularly through the skull and no more than 2 mm into the brain of the mouse, where 5 μl were then administered. The injection site was 1 mm to the right or left from the midpoint on a line drawn through to the anterior base of the ears. Injections were performed randomly into the right or left ventricle. To ascertain that the drugs were administered exactly into the cerebral ventricle, some mice were injected with 5 μl of diluted 1:10 India ink and their brains were examined macroscopically after sectioning.

Statistical analysis

Results are given as the mean ± SEM; an analysis of variance (ANOVA) was used to verify significance between two means. P values < 0.05 were considered significant. Data were analyzed with the StatView computer program for the Macintosh (1992).

Results

A comparison between saline- and vehicle-treated mice in the mouse passive avoidance test is reported in Fig. 1. No difference between the entrance latency of retention and training sessions was observed between the two groups.

Amnesic effect of baclofen, diphenhydramine and scopolamine

The dose-response curves for baclofen (0.1–4 mg kg^{-1} IP), diphenhydramine (15–30 mg kg^{-1} IP) and scopolamine (0.5–5 mg kg^{-1} IP) in the mouse passive avoidance test are reported respectively in Figs. 2, 3 and 4. All compounds, injected immediately after the training session, were endowed with amnesic properties. This effect was dose-dependent and the statistical significance was reached, starting from the dose of 2 mg kg^{-1} IP for baclofen (Fig. 2), 20 mg kg^{-1} IP for

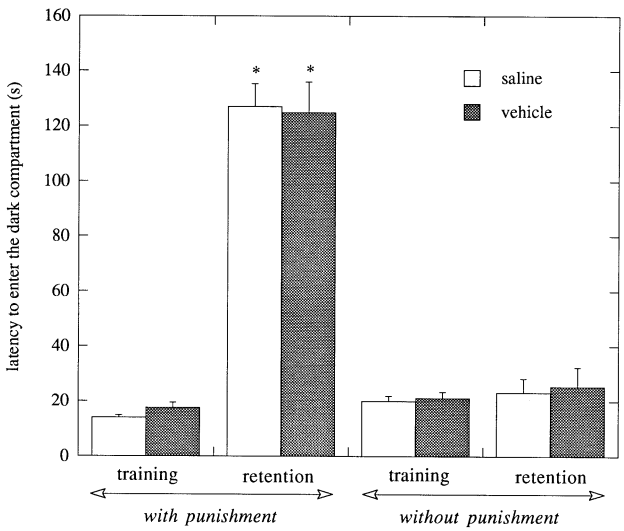

Fig. 1 Comparison between saline (□)- and vehicle (■)-treated mice in the mouse passive avoidance test. Saline and vehicle were injected ICV 10 days before performing the test. All animals were injected with saline IP immediately after the training session. *Vertical lines* give SEM; the number of mice was between 32 and 57. $*P < 0.001$ in comparison with corresponding training session values

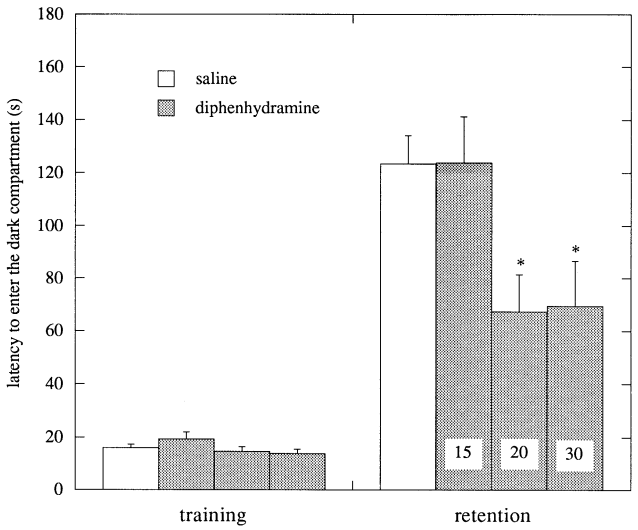

Fig. 3 Effect of diphenhydramine in the mouse passive avoidance test. Diphenhydramine (15–30 mg kg^{-1}) (▩) and saline (□) were injected IP immediately after the training session; *vertical lines* give SEM; in each column is the dose of diphenhydramine administered. The number of mice was between 19 and 32, with the exception of the saline group ($n = 57$). $*P < 0.01$ in comparison with saline-treated mice

diphenhydramine (Fig. 3) and 1 mg kg^{-1} IP for scopolamine (Fig. 4). The maximum amnesic effect was obtained at 4 mg kg^{-1} IP for baclofen (Fig. 2), 30 mg kg^{-1} IP for diphenhydramine (Fig. 3) and 5 mg kg^{-1} IP for scopolamine (Fig. 4) and therefore higher doses were not investigated.

Effect of pertussis toxin on amnesia

The amnesia induced by baclofen (2–4 mg kg^{-1} IP) was prevented, in the mouse passive avoidance test, by pretreatment with pertussis toxin (0.25 μg per mouse ICV) injected 10 days before the training session (Fig. 5). Pertussis toxin pretreatment enhanced the entrance latency in the retention session up to a value comparable to that produced by control animals in both groups of mice treated with baclofen (Fig. 5). By contrast, the administration of pertussis toxin (0.25–0.5 μg per mouse ICV) was not able to prevent diphenhydramine (20 mg kg^{-1} IP, Fig. 6; 30 mg kg^{-1} IP, data not shown) and scopolamine (1 mg kg^{-1} IP, data not

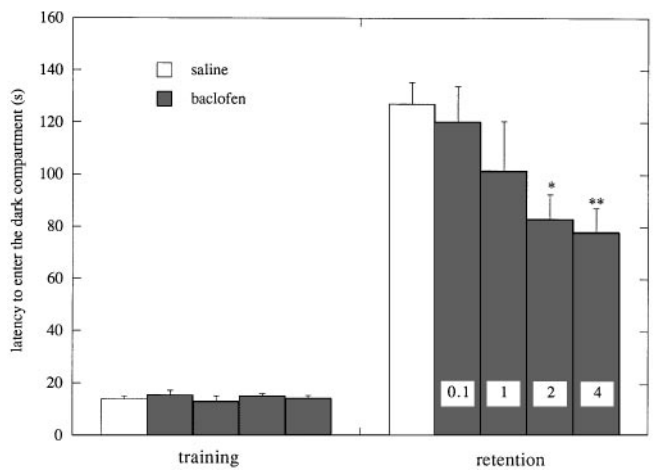

Fig. 2 Dose-response curve of baclofen in the mouse passive avoidance test. Baclofen (■) (0.1–4.0 mg kg^{-1}) and saline (□) were injected IP immediately after the training session; *vertical lines* give SEM; in each column is the dose of baclofen administered. $*P < 0.05$, $**P < 0.01$ in comparison with saline-treated mice

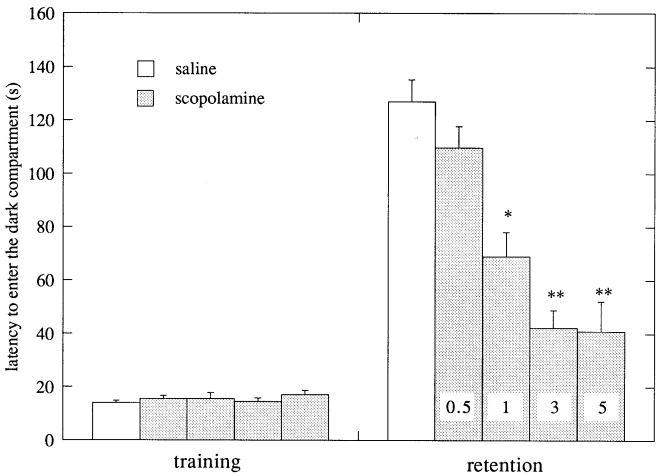

Fig. 4 Dose-response curve of scopolamine in the mouse-passive avoidance test. Scopolamine (0.1–5.0 mg kg^{-1}) (▩) and saline (□) were administered IP immediately after the training session; *vertical lines* give SEM; in each column is the dose of scopolamine administered. The number of mice was between 24 and 48. $*P < 0.01$, $**P < 0.001$ in comparison with saline-treated mice

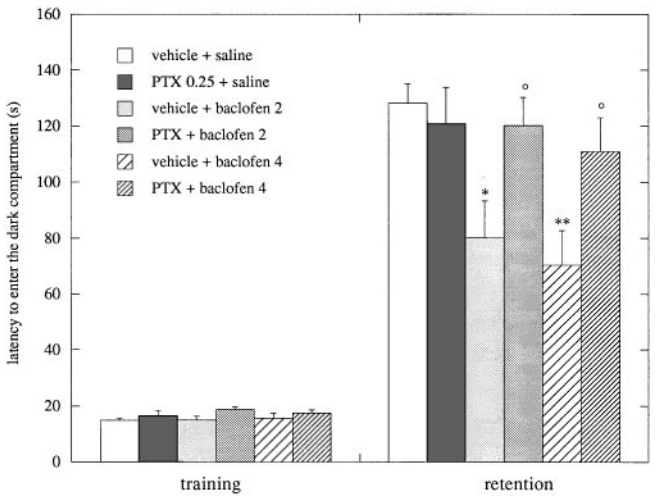

Fig. 5 Effect of pertussis toxin (*PTX*) pretreatment on baclofen-induced amnesia in the mouse passive avoidance test. The test was performed 10 days after a single ICV injection of vehicle or pertussis toxin (0.25 µg per mouse). Baclofen (2–4 mg kg^{-1}) and saline were injected IP immediately after the training session. *Vertical lines* represent SEM; the number of mice was between 20 and 40 with the exception of saline group ($n = 73$). $^{*}P < 0.01$, $^{**}P < 0.001$ in comparison with vehicle-saline treated mice; $^{\circ}P < 0.01$ in comparison with baclofen-treated mice

shown; 3 mg kg^{-1} IP, Fig. 7) amnesia. Pertussis toxin (0.25–0.50 µg per mouse ICV), when given alone, did not enhance the entrance latency in unamnesic mice on the mouse passive avoidance test in comparison with vehicle-treated mice (Figs. 5, 6, 7).

No difference in the entrance latencies of every group in the training session of the passive avoidance test was observed.

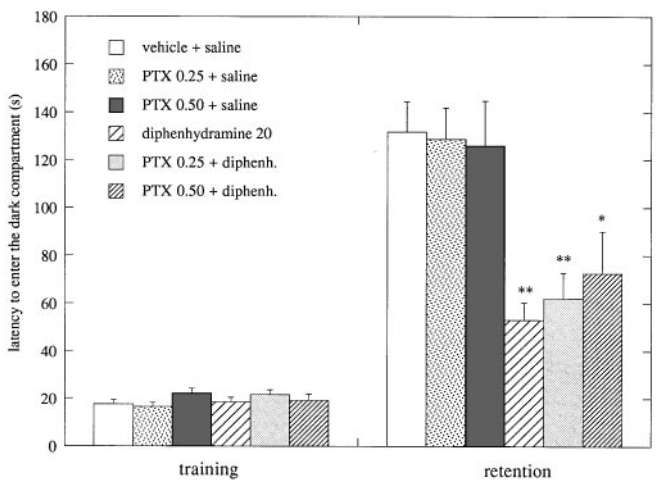

Fig. 6 Effect of pertussis toxin (*PTX*) pretreatment on diphenhydramine-induced amnesia in the mouse passive avoidance test. The test was performed 10 days after a single ICV injection of vehicle or pertussis toxin (0.25 and 0.50 µg per mouse). Diphenhydramine (20 mg kg^{-1}) and saline were injected IP immediately after the training session. *Vertical lines* represent SEM; the number of mice was between 19 and 33. $^{*}P < 0.05$, $^{**}P < 0.01$ in comparison with vehicle-saline treated mice

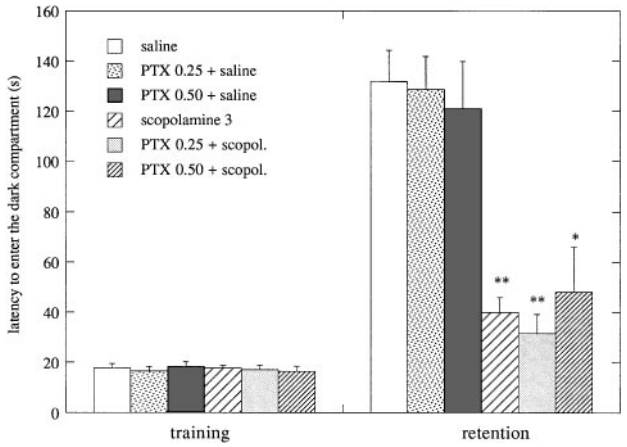

Fig. 7 Effect of pertussis toxin (*PTX*) pretreatment on scopolamine-induced amnesia in the mouse passive avoidance test. The test was performed 10 days after a single ICV injection of vehicle or pertussis toxin (0.25 and 0.50 µg per mouse). Scopolamine (3 mg kg^{-1}) and saline were injected IP immediately after the training session. *Vertical lines* represent SEM; the number of mice was between 15 and 27. $^{*}P < 0.05$, $^{**}P < 0.01$ in comparison with vehicle-saline treated mice

Effect of pertussis toxin on mouse rota-rod test

The motor coordination of mice pretreated with saline, vehicle or pertussis toxin (0.25 and 0.50 µg per mouse ICV), and of naive mice was evaluated by using the rota-rod test (Table 1). Rota-rod performance, tested as number of falls in 30 s, of animals pretreated 11 days before the test with the doses of pertussis toxin investigated, was not significantly impaired in comparison with naive, saline- and vehicle-treated mice according to pretest values (Table 1). Furthermore, the successive IP injections did not elicit any behavioral side effects, since each group progressively reduced the number of falls (Table 1). No difference was observed among vehicle, saline and naive groups (Table 1).

Both of the doses of pertussis toxin tested (0.25 and 0.50 µg per mouse ICV) caused a weight loss 2 days after injection, after which body weight slowly increased. The body weight of naive and vehicle-treated mice progressively increased (data not shown). The

Table 1 Effect of pertussis toxin (PTX) in the mouse rota-rod test. Saline, vehicle and pertussis toxin (0.25–0.50 µg per mouse) were injected ICV 11 days before the test. The number of mice was between 14 and 20

Pretreatment µg/mouse ICV	Number of falls in 30 s			
	Before SC saline injection	After SC saline injection		
		15 min	30 min	45 min
–	2.9 ± 0.5	1.1 ± 0.4	1.0 ± 0.4	0.8 ± 0.4
Saline	2.2 ± 0.3	1.8 ± 0.3	1.4 ± 0.2	0.8 ± 0.2
Vehicle	2.9 ± 0.5	1.6 ± 0.5	0.8 ± 0.4	0.6 ± 0.4
PTX 0.25	2.7 ± 0.3	2.0 ± 0.4	1.2 ± 0.3	1.1 ± 0.3
PTX 0.50	2.3 ± 0.5	1.8 ± 0.5	1.6 ± 0.5	1.2 ± 0.5

gross behavior of pertussis toxin-treated mice was comparable to that of the vehicle-treated group.

Discussion

The present study provides evidence of the involvement of pertussis toxin-sensitive G-proteins in the baclofen amnesic effect, indicating the important role of pertussis toxin-sensitive G-proteins as a transduction step following the activation of $GABA_B$ receptors. Injection of mice with pertussis toxin inhibits the amnesia induced by the $GABA_B$ receptor agonist baclofen. The stimulation of $GABA_B$ receptors provokes an inhibition of adenylate cyclase, the opening of several K^+ channels in central neurons and the reduction of Ca^{2+} currents in cultured sensory neurons by a pertussis toxin-sensitive mechanism (Bowery 1993). Unilateral injection of pertussis toxin in the rat hippocampus resulted in a reduction of baclofen-stimulated GTPase activity and in a reduction of $GABA_B$ receptor binding sites in the rat brain (Knott et al. 1993). It was not unexpected, therefore, that pertussis toxin prevents baclofen amnesia.

Pertussis toxin inactivates several G-proteins ($G_{i/o}$ proteins) by ADP-ribosylation of a specific C-terminal cystein (Hepler and Gilman 1992). The degree of ADP-ribosylation of $G_{i/o}$ proteins was not evaluated by biochemical techniques. However, previous studies in mice reported that baclofen-induced analgesia, obtained at the same doses at which it exerts amnesic effect, was prevented by pertussis toxin pretreatment 11 days before performing the hot-plate test (Galeotti et al. 1996), ensuring that a sufficient level of inactivation of $G_{i/o}$ proteins was reached. Pertussis toxin penetrates brain tissue slowly and incompletely. When the toxin is administered into the cerebral ventricles its distribution is limited to a narrow zone close to the ventricles (Van der Ploeg et al. 1991). This restricted distribution of pertussis toxin suggests that the effects observed in behavioral studies after ICV injection are attributable only to a central action.

The post-training ICV administration of histamine has been reported to cause memory facilitation in rats which is antagonized by the simultaneous treatment with both promethazine and cimetidine (de Almeida and Izquierdo 1986, 1988). In confirmation of the hypothesis of a role of histamine receptors in the modulation of memory processes, we observed that the histamine H_1 receptor antagonist diphenhydramine causes amnesia in the mouse passive avoidance test. The administration of histamine H_1 receptor antagonists produces various inhibitory effects including analgesia, which is prevented by pertussis toxin administration (Galeotti et al. 1996). Histamine exerts its numerous actions through interaction with three pharmacologically distinct receptor subtypes, H_1, H_2 and H_3, which all belong to the superfamily of G-protein coupled receptors (Hill 1990; Arrang 1994). However, taking into account that histamine can modulate the release of several neurotransmitters (Hill 1990), molecules different from histamine, activating $G_{i/o}$ proteins as a signal transduction mechanism, downstream from the initial receptor interaction could be responsible for the diphenhydramine-induced antinociception. On the bases of these data, the involvement of pertussis toxin-sensitive G-proteins in the diphenhydramine amnesic effect was investigated. However, diphenhydramine-induced amnesia does not appear to be related to the activation of a $G_{i/o}$ protein, since it is not prevented by pretreating mice with pertussis toxin. Many of the first generation H_1 antagonists tend to inhibit responses to acetylcholine that are mediated by muscarinic receptors and this anticholinergic property has been proposed as responsible for some of the central actions of the antihistaminics. The mechanism of antimotion sickness effect (Jaju and Wang 1971) and the induction of a sleeplike electroencephalographic activity (White and Boyajy 1960) of diphenhydramine, as well as the ability of several antihistaminics to antagonize isolation-induced fighting in mice (Barnett et al. 1971), have been suggested to be due to their anticholinergic activity. These atropine-like actions are sufficiently prominent in some of the drugs to appear during clinical use. That anticholinergic drugs exert amnesic effects has long been observed. The administration of scopolamine, a muscarinic ACh receptor antagonist, results in impaired learning and memory in humans (Frumier et al. 1976) and animals (Dilts and Berry 1967; Levin and Bowman 1986). Some muscarinic receptor subtypes have been reported to be coupled to pertussis toxin-sensitive G-proteins (the M_2 and m_4 subtypes) modulating adenylate cyclase and several ion channels, whereas others, such as M_1, M_3 and m_5, are linked to G-proteins that activate phospholipase C (Caulfield 1993). The agonist regulation of phospholipase C appears to involve at least two separate mechanisms: the activation of a pertussis toxin-sensitive G-protein or, more commonly, the activation of pertussis toxin-insensitive G-proteins (Park et al. 1993). The muscarinic receptor subtype mainly involved in the modulation of memory processes is the M_1 subtype which, when expressed in Chinese hamster oocytes (CHO), selectively activates pertussis toxin-insensitive G-proteins (G_q and G_{11}) (Mullaney et al. 1993), that in turn activate phospholipase C (Caufield 1993). Furthermore, the activation of the central postsynaptic M_1 receptors produces antinociception (Bartolini et al. 1992) through a molecular mechanism that does not involve $G_{i/o}$ proteins (Galeotti et al. 1996). In our experimental conditions, the amnesia induced by scopolamine is not affected by pretreatment with pertussis toxin, indicating the lack of involvement of $G_{i/o}$ proteins in the inhibition of cognitive performances produced by the blockade of the muscarinic receptors.

The pharmacological profile similarity between diphenhydramine and scopolamine suggests that the amnesia induced by the H_1 antagonist may be related to its antimuscarinic properties.

Studies in the rat (Claro et al. 1986) and mouse (Kendall and Hill 1988) cerebral cortex, and guinea-pig brain slices (Daum et al. 1984), have shown that histamine activates inositol phospholipid hydrolysis which appeared to be mediated by the activation of the H_1 receptor subtype and selectively inhibited by H_1 receptor antagonists. The activation of inositol phospholipid hydrolysis enhanced the levels of several second messengers and protein kinase C, involved in the modulation of memory processes (Tanaka et al. 1993). The same intracellular events can also be obtained after activation of the cholinergic system (Caufield 1993). Therefore, we cannot exclude that diphenhydramine, in inducing its amnesis effect, could be working at histaminergic and/or muscarinic receptors.

Pertussis toxin prevents the activation, by receptor stimulation, of $G_{i/o}$ proteins which are involved in the actions of several inhibitory neurotransmitters. For this reason, ICV injection of the toxin has been reported to produce widespread side effects, which can make interpretation of results from behavioral studies difficult. In our conditions, mice treated with doses of pertussis toxin of 0.50 and 0.25 μg per mouse ICV lost weight, but the motor coordination of mice pretreated with both pertussis toxin doses was not impaired, making the results obtained in the passive avoidance test reliable.

In conclusion, the present data demonstrate that pertussis toxin-sensitive G-proteins represent an essential step in the transduction mechanism underlying the amnesia induced by activation of the GABAergic system. On the other hand, the inhibition of memory processes produced by a block of the histaminergic and cholinergic systems did not appear to be related to the activation of $G_{i/o}$ proteins.

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