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Modulation of rhythmical slow activity, long-term potentiation and memory by muscarinic receptor agonists

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Abstract

We investigated the cholinergic modulation of hippocampal rhythmical slow activity (or θ activity), long-term potentiation and a behavioral memory task. The intravenous administration of the muscarinic receptor agonists, AF102B ((±)-cis-2-methyl-spiro(1,3-oxathiolane-5,3′)quinuclidine hydrochloride hemihidrate) and oxotremorine, induced rhythmical slow activity at doses of 1.0 mg/kg and 0.01 mg/kg, respectively. Long-term potentiation of population spike amplitude in the hippocampal CA1, which was induced by tetanic stimulation to the Schaffer collateral/commissural fiber, was increased by AF102B (1.0 mg/kg i.v.) and oxotremorine (0.01 mg/kg i.v.). Oral administration of AF102B and oxotremorine improved scopolamine-induced memory deficits in a passive avoidance task in mice at doses of 1.0 mg/kg and 0.2 mg/kg, respectively. The correspondence of the effective doses of muscarinic receptor agonists in these three experiments suggested the cholinergic correlation of rhythmical slow activity, long-term potentiation and memory.

Keywords: Learning; Memory; Synaptic plasticity; Cholinergic system; Muscarinic receptor agonist; AF102B; Oxotremorine

1. Introduction

The cholinergic system plays an important role in learning and memory. Muscarinic receptor antagonists such as scopolamine induce a learning deficit (Rush, 1988; Izquierdo, 1989; Lamberty and Gower, 1991). Lesions of the hippocampus, which receives a cholinergic input from the septal nuclei, impair cognitive function, and the impairment is reversed by muscarinic receptor agonists (Nakahara et al., 1988; Fisher et al., 1991; Yamazaki et al., 1991; Inagawa, 1994).

Stimulation of muscarinic receptors reportedly enhances the induction of long-term potentiation in the CA1 area of hippocampal slices (Ito et al., 1988; Hirotu et al., 1989; Blitzer et al., 1990; Boddeke et al., 1992). Long-term potentiation is considered to be a neuronal model of learning and memory (Morris et al., 1986; Doyére and Laroche, 1992; Silva et al., 1992). Therefore long-term potentiation facilitation by the cholinergic system might contribute to improvement of a memory deficit. The facilitation of long-term potentiation by cholinergic activation is probably due to increased cell excitability, since acetylcholine decreases K^+ conductance and induces depolarization in the pyramidal cell membrane (Benardo and Prince, 1982; Nicoll et al., 1990). However, the in vivo physiological mechanisms by which the cholinergic system modulates long-term potentiation remain unclear.

Activation of the cholinergic system induces rhythmical slow activity (or θ activity) in hippocampal electroencephalographs (Vanderwolf, 1975; Rowntree and Bland, 1986; Olpe et al., 1987) and rhythmical slow activity is thought to be involved in the induction of long-term potentiation (Huerta and Lisman, 1993). Hence, the cholinergic system might modulate long-term potentiation through the induction of rhythmical slow activity. Here, we examined the effects of AF102B ((±)-cis-2-methyl-spiro(1,3-oxathiolane-5,3′)quinuclidine hydrochloride hemihidrate), a relatively selective muscarinic M_1 receptor agonist with high bioavailability, and of a non-selective agonist, oxotremorine, on rhythmical slow activity and long-term potentiation in anesthetized rats, as well as on a scopolamine-induced memory deficit in mice, to investigate the correlation between rhythmical slow activity, long-term potentiation and memory.

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2. Materials and methods

2.1. Recording of rhythmical slow activity

Male Wistar rats (270–330 g, Charles River Japan) were anesthetized with sodium pentobarbital (40 mg/kg i.p.). A stainless-steel bipolar electrode with a 0.7-mm tip separation (0.2 mm in diameter) was implanted into the CA1 area of the dorsal hippocampus (3.8 mm posterior to bregma, 2.0 mm lateral to midline, 2.8 mm ventral to dura) and fixed to the skull with stainless-steel screws and dental acrylic cement. After recovery (over 1 week), the hippocampal electrical activities were recorded as follows. The rats were anesthetized with urethane (1.2 g/kg i.p. plus 0.7 g/kg s.c.) and fixed in a stereotaxic frame. The animals were given 2.0 mg/kg i.v. of scopolamine *N*-butyl bromide to block peripheral muscarinic receptors. Hippocampal electrical activity was amplified (time constant of 0.1–0.3 s and high cut filter of 1 kHz) and recorded with a polygraph (Nihon Kohden, RM-600). Before and after drug injection, spectral analyses were performed on 10- or 30-s hippocampal activities with a data analyzing system (band width of 0.098 Hz, sampling rate of 9.77 ms, Nihon Kohden, ATAC-3700). Muscarinic receptor agonists, AF102B (Snow Brand Milk Products Co.) and oxotremorine (Sigma Chemical Co.), were dissolved in physiological saline and injected into the femoral vein. Peak frequencies in spectra before and after injection were analyzed by means of the paired *t*-test.

2.2. Induction of long-term potentiation

Male Wistar rats (280–370 g, Charles River Japan) were anesthetized with 1% halothane in air through a tracheal canula connected to a respirator. The rat was fixed in a stereotaxic frame with the bregma and lambda positioned in the same horizontal plane. A stainless-steel bipolar electrode with 0.5-mm tip separation (0.2 mm in diameter) was lowered into the stratum radiatum of the hippocampal CA1 area (3.0 mm posterior to bregma, 1.5 mm lateral to midline, approximately 2.8 mm ventral to dura) to stimulate the Schaffer collateral/commissural fibers. A monopolar glass-coated silver electrode (tip diameter approximately 20 μm) was placed in the pyramidal cell layer of the ipsilateral CA1 area (5.0 mm posterior to bregma, 3.5 mm lateral to midline, approximately 2.5 mm ventral to dura). Constant-current square pulses (250 μs duration) were used to evoke field responses, which were amplified (Nihon Kohden, MEG-1200, time constant of 2.0 s and high cut filter of 1 kHz) and monitored with an oscilloscope (Nihon Kohden, VC-10). The amplified responses were averaged with a data analyzing system (Nihon Kohden, ATAC-3700) and the amplitude of the population spike height was measured. Test stimulus intensity was set to the level that produced a population spike of about 50% of the maximum response. Single test stimuli were given at 30-s intervals. Five successive responses were averaged and collected every 5 min throughout the experiment. After a 15 min baseline recording, AF102B, oxotremorine or vehicle was injected into the femoral vein. Twenty minutes after the injection of the drug or vehicle, a brief tetanic stimulation (five bursts of four pulses, pulse frequency 200 Hz, inter-burst interval 1 s) was applied at the initial test intensity. The responses to test stimuli were recorded for 60 min following tetanic stimulation. The data were expressed as percentages of the values obtained just before tetanic stimulation. Statistical analysis was performed by means of the unpaired Student's *t*-test or one way analysis of variance (ANOVA) followed by Fisher's LSD.

2.3. Passive avoidance task

Male ddY mice (25–30 g, Japan SLC) were tested in a one-trial step-through passive avoidance task. Scopolamine hydrochloride (0.75 mg/kg) or vehicle (physiological saline) was subcutaneously injected 30 min before the acquisition trial. After 30 s for adaptation to the light chamber of a passive avoidance apparatus (O'Hara, SFK-1), each animal was allowed to enter a dark chamber by removal of a guillotine door separating light and dark chambers. Upon entry into the dark chamber, the mouse received foot shock (80 V, 50 Hz) for 1 s. AF102B, oxotremorine or vehicle was orally administered 20 min before the acquisition trial. Retention of the avoidance task was evaluated 4 h after the acquisition trial. The retention latency of the mice to enter the dark chamber was measured up to a maximum of 300 s. Statistical analysis was performed by means of the Mann-Whitney *U*-test.

3. Results

3.1. Recording of rhythmical slow activity

The hippocampal EEG in anesthetized rats was characterized by predominant irregular slow waves (Fig. 1A and Fig. 2A). Upon injection of AF102B (3.0 mg/kg i.v.) the irregular slow wave was replaced by rhythmical slow activity and a sharp peak near 3 Hz appeared in the spectrum (Fig. 1B). Oxotremorine (0.03 mg/kg) induced similar changes in the hippocampal EEG and the spectrum with a sharp peak near 4 Hz (Fig. 2B). Fig. 3 shows the peak frequencies before and after (1–4 min) an injection of AF102B or oxotremorine. AF102B (1.0–10.0 mg/kg i.v.) and oxotremorine (0.01–0.1 mg/kg) significantly increased the peak frequency in a dose-dependent manner. The agonist-induced rhythmical slow activity was abolished by scopolamine (0.1 or 0.2 mg/kg) and the spectrum was restored to that before the injection of agonists (data not shown).

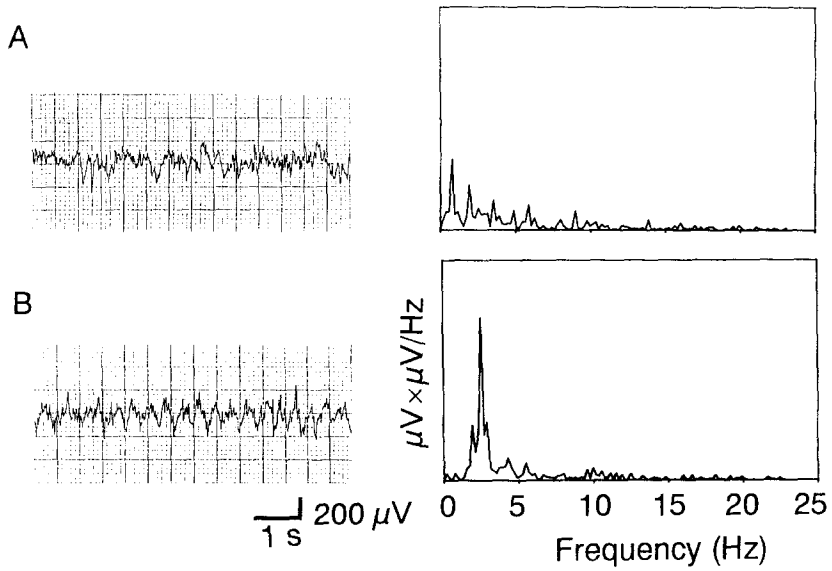

Fig. 1. Effect of AF102B on hippocampal EEG and power spectra in anesthetized rats. A: Before injection. B: After injection of AF102B (3.0 mg/kg i.v.). Left panels: original recordings of EEG. Right panels: power spectra.

3.2. Induction of long-term potentiation

To assess the drug effects on synaptic transmission prior to tetanic stimulation, the evoked responses were recorded for 20 min following drug injection. AF102B at a dose of 5.0 mg/kg slightly reduced the population spike amplitude (Fig. 4). Oxotremorine (0.01 mg/kg) markedly reduced the amplitude (Fig. 5).

Tetanic stimulation (five bursts of four pulses, pulse frequency 200 Hz) induced a short-term potentiation of the population spike amplitude (Fig. 4) which reached about 200% at 5 min after the tetanic stimulation, then gradually decreased to the values obtained before the tetanic stimulation. Stronger stimulation (five bursts of eight pulses, pulse frequency 400 Hz) induced marked long-term potentiation (data not shown). AF102B (1.0 and 5.0 mg/kg) significantly facilitated the weak tetanus-induced potentiation of the population spike in a dose-dependent manner (Fig. 4). Especially at the dose of 5.0 mg/kg, long-term potentiation was marked and the population spike amplitude was maintained above 150% during the measurement period of 60 min. Oxotremorine (0.01 mg/kg) also facilitated long-

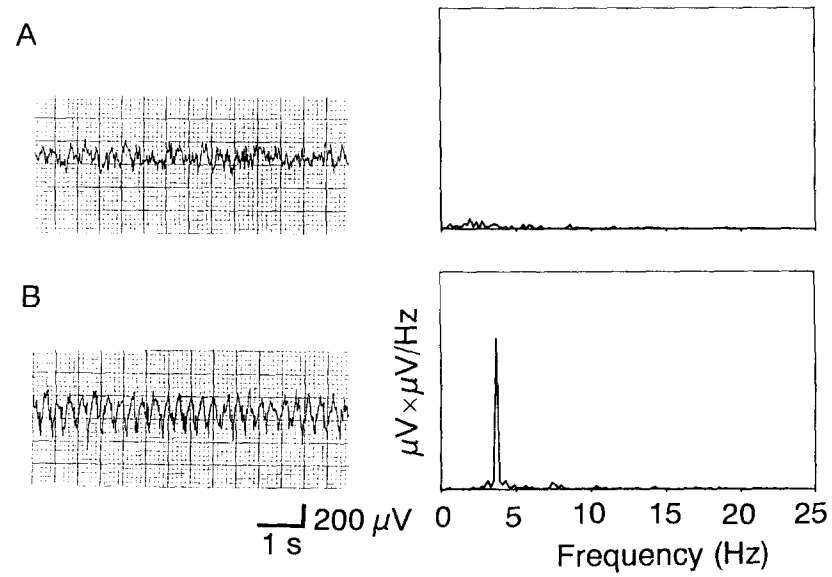

Fig. 2. Effect of oxotremorine on hippocampal EEG and power spectra. A: Before injection. B: After injection of oxotremorine (0.03 mg/kg i.v.). Left panels: original recordings of EEG. Right panels: power spectra.

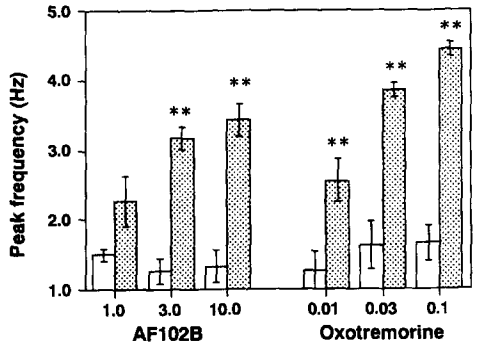

Fig. 3. Dose-dependent effects of AF102B and oxotremorine on peak frequency of RSA. The frequencies were obtained from power spectra before (unfilled column) and after (dotted column) injection of each drug. Each bar represents a mean ± S.E.M. ($n = 4$–6). * *: $P < 0.01$, significantly different from pre-injection values (paired t-test).

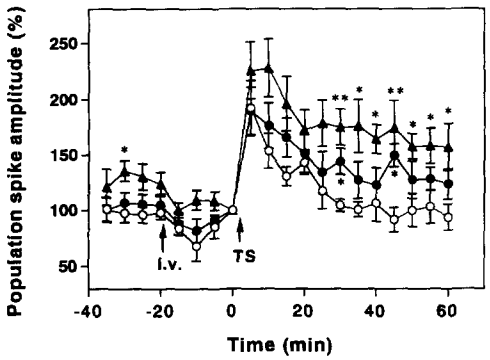

Fig. 4. Facilitative effect of AF102B on LTP in anesthetized rats. AF102B (1.0 mg/kg, ● or 5.0 mg/kg i.v., ▲) or vehicle (○) was injected 20 min before tetanic stimulation (TS). The abscissa indicates the time before and after tetanic stimulation. Values are expressed as percentages of the values at 0 min (mean ± S.E.M., $n = 6$). *: $P < 0.05$; * *: $P < 0.01$, significantly different from vehicle control (one-way ANOVA followed by Fisher's LSD).

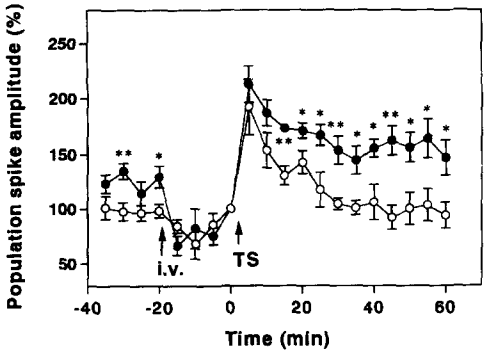

Fig. 5. Facilitative effect of oxotremorine on LTP in anesthetized rats. Oxotremorine (0.01 mg/kg i.v., ●) or vehicle (○) was injected 20 min before tetanic stimulation (TS). Values are expressed as percentages of the values at 0 min (mean ± S.E.M., $n = 6$). *: $P < 0.05$; * *: $P < 0.01$, significantly different from vehicle control (Student's t-test).

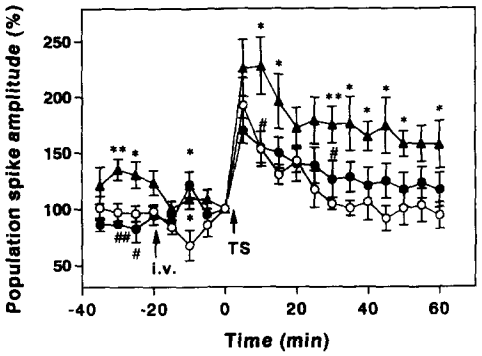

Fig. 6. The effect of scopolamine on AF102B-induced changes in the population spike amplitude before and after tetanic stimulation. ○: vehicle control; ▲: AF102B (5.0 mg/kg i.v.); ●: AF102B and scopolamine (5.0 mg/kg and 0.1 mg/kg, respectively). Values are means ± S.E.M., $n = 5$–6. *: $P < 0.05$; * *: $P < 0.01$, significantly different from vehicle control; #: $P < 0.05$; ##: $P < 0.01$, significantly different from AF102B alone (one way ANOVA followed by Fisher's LSD).

term potentiation (Fig. 5); the values for population spike amplitude were significantly greater than those obtained for the vehicle control.

When scopolamine (0.1 mg/kg) was injected just after AF102B (5.0 mg/kg) the change in the population spike amplitude was similar to that of the vehicle control (Fig. 6). Thus, scopolamine inhibited the actions of AF102B on the long-term potentiation induction and the population spike reduction.

3.3. Passive avoidance task

The mice given scopolamine (0.75 mg/kg s.c.) showed a marked shortening of the retention latency time in the passive avoidance task (Fig. 7). AF102B prolonged the latency time of scopolamine-injected mice in a dose-dependent manner. Significant effects were observed at doses of 1.0 and 5.0 mg/kg p.o. Oxotremorine also significantly restored the scopolamine-induced shortening of the retention latency time at doses of 0.2 and 1.0 mg/kg.

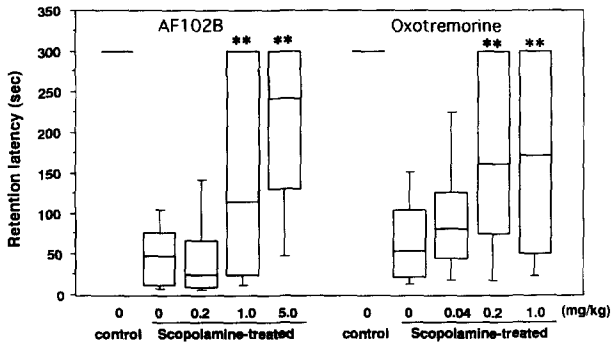

Fig. 7. Restoring effects of the oral administration of AF102B and oxotremorine on retention deficits in mice with scopolamine-induced amnesia in a one-trial passive avoidance task. Values represent means ± S.E.M., $n = 23$–36. * *: $P < 0.01$ significantly different from scopolamine-treated control mice (Mann-Whitney U-test).

4. Discussion

Long-term potentiation is a model of synaptic plasticity and of the neuronal basis of learning and memory (Bliss and Lømo, 1973; Morris et al., 1986; Doyére and Laroche, 1992; Silva et al., 1992). This phenomenon is usually measured by the level of the excitatory postsynaptic potential and/or population spike amplitude. The former expresses synaptic transmission and the latter reflects cell excitability in addition to synaptic transmission (Abraham et al., 1987; Taube and Schwartzkroin, 1988). Since it is reported that behavioral memory functions are correlated with the potentiation of the population spike but not with the excitatory postsynaptic potential (Kleschevnikov and Marchbanks, 1993), we now measured the population spike amplitude as an index of long-term potentiation.

The central cholinergic system, which plays an important role in learning and memory, is suggested to contribute to inducing long-term potentiation in the hippocampal CA1 area in vitro (Ito et al., 1988; Hirotu et al., 1989; Blitzer et al., 1990; Boddeke et al., 1992). In this study, the muscarinic receptor agonists, AF102B and oxotremorine, facilitated long-term potentiation in the CA1 area in anesthetized rats, and the facilitatory effect of AF102B was blocked by scopolamine. These results suggested that the cholinergic system modulates long-term potentiation in vivo. Earlier studies, however, did not elucidate the in vivo physiological mechanisms underlying the cholinergic modulation of long-term potentiation. The present results showed that muscarinic receptor agonists induce hippocampal rhythmical slow activity (or θ activity) at the same doses that facilitate long-term potentiation. The cholinergic system is involved in the generation of rhythmical slow activity (Vanderwolf, 1975; Rowntree and Bland, 1986) and muscarinic receptor agonists increase the frequency of rhythmical slow activity in the urethane-anesthetized rat (Olpe et al., 1987). In addition, rhythmical slow activity may be involved in the induction of long-term potentiation. That is, electrical stimulation with θ frequency induces long-term potentiation (Larson et al., 1986; Tocco et al., 1992) and electrical stimulation synchronized with endogenous θ activity is critical for the induction of long-term potentiation (Huerta and Lisman, 1993). These findings, and our results, suggest the possibility that cholinergic activation induces rhythmical slow activity, then modulates long-term potentiation.

Acetylcholine has a dual action on hippocampal pyramidal cells. It decreases K^+ conductance postsynaptically and then induces depolarization (Benardo and Prince, 1982; Nicoll et al., 1990). The postsynaptic excitatory effects of acetylcholine may contribute to inducing rhythmical slow activity and enhancing long-term potentiation. Acetylcholine also inhibits synaptic transmission presynaptically, reducing the amplitude of the population spike and the field excitatory postsynaptic potential (Hounsgaard, 1978; Valentino and Dingledine, 1981). In the present study AF102B and oxotremorine depressed the population spike amplitude prior to tetanic stimulation. The postsynaptic and presynaptic actions of acetylcholine are probably mediated by muscarinic M_1 and M_2 receptor subtypes, respectively (Müller and Misgeld, 1986; Dutar and Nicoll, 1988; Marchi and Raiteri, 1989). In this study, AF102B (5.0 mg/kg) was as effective as oxotremorine (0.01 mg/kg) to facilitate long-term potentiation, whereas it was less effective than oxotremorine to depress population spike amplitude. While oxotremorine is a non-selective muscarinic receptor agonist, electrophysiological, pharmacological and neurochemical studies have revealed that AF102B is a relatively selective muscarinic M_1 receptor agonist (Fisher et al., 1989, 1991; Mochida et al., 1988; Ono et al., 1988; Gurwitz et al., 1994). AF102B also depolarizes hippocampal pyramidal cells via the muscarinic M_1 receptor (Segal and Fisher, 1992). Therefore, the differences in action profiles for long-term potentiation facilitation and population spike depression may reflect the relative selectivity of these agonists for muscarinic receptor subtypes.

In mice with scopolamine-induced amnesia both AF102B and oxotremorine restored the learning and memory deficits. Hippocampal cholinergic input is closely related to working memory and memory acquisition in passive avoidance tasks (Hagan and R.G.M. Morris, 1988). AF102B ameliorates the working memory deficit and passive avoidance failure induced by hippocampal cholinergic lesions (Nakahara et al., 1988, 1989; Fisher et al., 1989, 1991; Ohno et al., 1994). Oxotremorine also improves the memory impairment in cholinergic deficit models (Lamberty and Gower, 1991; Yamazaki et al., 1991; Inagawa, 1994). The effective doses of AF102B in scopolamine-induced amnesia were similar to those that induced rhythmical slow activity and facilitated long-term potentiation, suggesting cholinergically mediated correlation among rhythmical slow activity, long-term potentiation and memory.

Oxotremorine alleviated the scopolamine-induced amnesia at doses relatively higher than those that enhanced rhythmical slow activity and long-term potentiation. The drugs were administered orally for the behavioral study, but injected intravenously for the other experiments. AF102B is easily absorbed through the duodenum and is distributed to the brain (Iga et al., 1991), and improves memory impairment when given intraperitoneally at doses similar to those in this oral study (Nakahara et al., 1988, 1989; Fisher et al., 1989, 1991; Ohno et al., 1994). On the other hand, oxotremorine is reportedly more effective when given as an intraperitoneal injection (Lamberty and Gower, 1991; Yamazaki et al., 1991; Inagawa, 1994) than it was in this oral study. Thus, the difference in the effective doses of oxotremorine between rhythmical slow activity/long-term potentiation and passive avoidance might reflect its low oral absorption.

In summary and conclusion, the results presented here

showed that muscarinic receptor agonists induced rhythmical slow activity, facilitated long-term potentiation and restored the deficits of learning and memory at corresponding dose ranges. These results provide further support for the hypothesis that the memory and learning enhancing effect of the cholinergic agonists correlate with rhythmical slow activity and long-term potentiation.

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