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Potentiation by DSP-4 of EEG slowing and memory impairment in basal forebrain-lesioned rats

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Abstract

The effects of cholinergic and noradrenergic depletion, alone and in combination, on spatial memory and electroencephalogram (EEG) activity were investigated. Basal forebrain-lesioned rats exhibited a significant decrease in cortical choline acetyltransferase activity and spatial memory impairment. In the cortical EEG, the basal forebrain lesion induced EEG slowing such as an increase in delta power activity and a decrease in beta power activity. Noradrenergic depletion following a treatment with DSP-4 (*N*-2-(chloroethyl)-*N*-ethyl-2-bromobenzylamine) had no effect on cortical choline acetyltransferase activity and spatial memory, but it aggravated the cognitive impairment induced by the basal forebrain lesion. DSP-4 itself increased delta power activity in non-lesioned rats, whereas DSP-4 potentiated the EEG slowing induced by the basal forebrain lesions. Systemic administration of tetrahydroaminoacridine at 1 or 3 mg/kg, i.p., ameliorated the memory deficits and EEG slowing induced by the basal forebrain lesion. However, the drug could not attenuate the EEG slowing and memory impairment in rats that had received a combination of DSP-4 and basal forebrain lesion. These results suggest that noradrenergic depletion aggravated the EEG slowing and the spatial memory impairment induced by cholinergic dysfunction and may decrease the efficacy of an anticholinesterase agent in reversing the cortical cholinergic hypofunction.

Keywords: DSP-4 (*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine); Noradrenaline; EEG (electroencephalogram); Memory; Basal forebrain lesion; Tetrahydroaminoacridine

1. Introduction

It has been proposed that the cholinergic system plays a pivotal role in learning and memory, and in the regulation of the cortical electroencephalogram (EEG) (Deutsch, 1971; Bartus et al., 1985; Winkler et al., 1995). Neocortical EEG and learning behavior have been shown to depend on the proper functioning of cholinergic neurons in the basal forebrain (Ray and Jackson, 1991; Riekkinen et al., 1990). The memory impairment and EEG slowing found in patients with Alzheimer's disease may be attributable to degeneration of the cholinergic neurons in the basal forebrain (Davies and Maloney, 1977; Gordon and Sim, 1967; Gustafson et al., 1987; Hollander et al., 1986; Coben et al., 1990; Schreiter-Gasser et al., 1993). In addition to cholinergic dysfunction, a variety of other neurotransmitter systems such as noradrenergic and serotonergic systems have also been shown to be degenerated in patients with Alzheimer's disease (Palmer et al., 1987; Rossor and Iversen, 1986; Reinikainen et al., 1990; Whitehouse, 1985).

In particular, the noradrenergic system has been shown to be deficient in Alzheimer's disease patients, as evidenced by cell loss in the locus coeruleus, and by reduced noradrenaline content and dopamine-β-hydroxylase activity (Bondareff et al., 1981; Cross et al., 1981). The noradrenergic systems also make a significant contribution to the regulation of the neocortical EEG (Buzsaki et al., 1988b; Morgan and Pfeil, 1979). Furthermore, noradrenergic systems have been reported to influence spatial memory function although the mechanisms remain to be determined (Decker and McGaugh, 1989; Spangler et al., 1990).

These previous reports suggest the EEG slowing seen in Alzheimer's disease patients may be due to concurrent aggravation of both the cholinergic and the noradrenergic innervation of the forebrain (Soininen et al., 1992). Thus, the cortical cholinergic innervation seems to play an important role in mediating memory and EEG activity, but the relationship is not likely to be that simple, with non-

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cholinergic neurons potentially contributing to the EEG and memory function.

In this study, we investigated the effects of combining a basal forebrain lesion with chronic noradrenergic depletion induced by the systemic administration of DSP-4 (*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine), a noradrenergic neurotoxin, in order to compare the disruptive effects of basal forebrain lesion on memory and EEG with the effects of noradrenergic depletion. Furthermore, we examined the effects of tetrahydroaminoacridine, an anticholinesterase agent, on memory impairment and EEG slowing induced by the combination of DSP-4 and basal forebrain lesion.

2. Materials and methods

2.1. Animals

Ten-week-old male rats of the Wistar strain were obtained from Japan SLC. The initial free-feeding weights were 280–300 g. The rats were housed in groups of three per cage at a constant temperature (23 ± 2°C) and maintained under a 12-h ligh/dark cycle with lights on at 7:00 a.m. Experiments were conducted during the light portion of the day.

2.2. Surgery and lesioning

Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and fixed on a stereotaxic apparatus with the incisor bar set 3.3 mm below the interaural line. In all surgical procedures, the stereotaxic coordinates were according to the atlas of Paxinos and Watson (1986). Each rat was surgically implanted with EEG electrodes. Bipolar stainless steel electrodes (0.1 mm in diameter) with an interpolar distance of 0.5 mm were implanted in the left amygdala (2.1 mm posterior to the bregma and 4 mm lateral to midline) and hippocampus (3.8 mm posterior to bregma and 1.8 mm lateral to midline). Bipolar silver electrodes (1 mm) were placed 1 mm apart on the dura mater in the parietal cortex. An integrated circuit socket was attached to the skull with dental cement, and insulated leads were routed from this plug to the electrodes. EEG electrodes connected to female pins were fixed on the skull with dental cement (Polyset; Yata Chemical). The rats were allowed to recover for a minimum of one week before being connected to a flexible tether and slip-ring, and accustomed to the soundproof recording chambers. A stainless steel guide cannula (length = 40 mm; outer diameter = 0.5 mm) was stereotaxically placed 2 mm above the basal forebrain region to allow the infusion of ibotenic acid. The cannula was kept in position by dental cement. Bilateral neurotoxic lesions of the basal forebrain were achieved by the injection of ibotenic acid (Sigma) through the cannula on each side with an interval of 2 days. A stainless steel injection needle (outer diameter 0.25 mm) connected via polyethylene tubing to a 10-μl micro-syringe was inserted into the basal forebrain. The coordinates of the basal forebrain were: 2.6 mm posterior to the bregma, 2.8 mm lateral to the midline and 8 mm ventral from the skull surface. Ibotenic acid was dissolved in 0.1 M phosphate buffer (pH 7.2) at a concentration of 10 μg/μl, and then infused in a volume of 1 μl over a period of 3 min. The injection needles were left in place for a further 5 min to ensure that the drug had diffused away from the needle tip. Sham-operated rats received 0.1 M phosphate buffer in the same way. At the end of the experiments, the placement and size of the lesions were checked.

2.3. Water maze task

A circular pool 178 cm in diameter was used. The tank was filled with water at approximately 23°C. A transparent platform, 10 cm in diameter, was located at a constant position in the center of one quadrant inside the tank, the upper surface of which was 3 cm below the surface of the water. During each trial, we recorded the time it took rats to escape onto the platform within 300 s (latency). If the rat failed to find the platform within 300 s, it was placed on it for 30 s, and the training session was terminated and a maximum score of 300 s was assigned. The behavioral trace, the speed and the distance of swimming in the water maze were monitored with a TV video camera and analyzed using a computer system (AXIS 60, Neuroscience, Tokyo, Japan). The latency to locate the platform was recorded in this experiment. Behavioral tests were performed in rats 21 days after the basal forebrain lesion. Each rat was tested with one trial/day for 5 days.

2.4. EEG recordings

The EEG values of freely moving rats were wire-relay recorded between 9:00 and 16:00 h using a polygraph system (Nihon Kohden). The animals were allowed to adapt for at least 48 h before the test began. The EEG was recorded before and 21–28 days after basal forebrain lesioning. The behavioral states were selected waking-immobility for EEG spectral components monitored with a video camera. On each day of the experiment, the EEG was recorded with an analog tape recorder (XR-310, TEAC) for each rat. Spectral analysis of the EEG was performed by spectral analysis software (DSS98SV, Kanopus). Six consecutive 10-s artifact-free epochs were selected from each tape-recorded EEG sample. The samples of EEG were filtered to pass frequencies below 50 Hz with an analog filter (ASIP-0260; Kanopus), and digitized at a sampling rate of 500 Hz, using an AD converter (ADX98E; Kanopus) connected to the computer (PC-H98, NEC). The digitized EEG was converted to power spectral quantities by fast Fourier transformation. Relative power (power in frequency band/total power) was calculated for the delta

= 1–3.9 Hz, theta = 4–6.9 Hz, alpha = 7–12.9 Hz, and beta = 13–25 Hz bandwidths.

2.5. Choline acetyltransferase activity

Rats were decapitated 21 days after basal forebrain lesion, and the brain was removed rapidly and dissected on ice into the frontal cortex, parietal cortex, occipital cortex and the hippocampus. The tissues were stored at −80°C until choline acetyltransferase assay. Choline acetyltransferase activity was measured according to the radioenzymatic method of Fonnum (1975), using [^{14}C]acetyl coenzyme A (Amersham), and expressed as nmol acetylcholine/h/mg protein. Protein determination (Bradford, 1976) was performed on all samples using a commercially available kit (Bio-Rad, Richmond, CA, USA).

2.6. Noradrenaline level

On the 14th day after the administration of DSP-4, the rats were decapitated and their brains were removed rapidly and dissected on ice into the frontal cortex, parietal cortex, occipital cortex and the hippocampus. Each tissue sample was examined with high-performance liquid chromatography (HPLC) with an electrochemical detector (Eicom, Kyoto, Japan) for analysis of monoamine levels. The working electrode was a WE-3G graphite electrode (Eicom) set at a detector potential of +0.65 V against an Ag/AgCl reference electrode. Monoamines and metabolites were separated on an Eicompack MA-5ODS column (4.6 × 250 mm). The mobile phase consisted of Na_2HPO_4 containing 0.1 mM EDTA, 0.5 mM sodium 1-octanesulfonate, and 20% (v/v) methanol at pH 3.8. The flow rate was set at 1.0 ml/min.

Samples were homogenized on ice in a 0.2 M $HClO_4$/10 M EDTA solution containing a fixed amount of the internal standard isoproterenol. The samples were then centrifuged at 4°C for 10 min (12 000 × *g*), and 20 μl of the supernatant was injected into the HPLC system. Noradrenaline levels are shown as ng/mg protein.

2.7. Drugs

DSP-4 (*N*-2-(chloroethyl)-*N*-ethyl-2-bromobenzylamine; Sigma) and THA (tetrahydroaminoacridine hydrochloride; Nakarai Tesque, Kyoto, Japan) were dissolved in saline. Both drugs were administered intraperitoneally in a volume of 1 ml/kg. Rats were treated with tetrahydroaminoacridine 30 min before each training trial in the water maze. In EEG recordings, this drug was injected 24 h after the last behavioral test.

2.8. Statistics

Data for the water maze task are expressed as medians and were analyzed using the Kruskal-Wallis test, followed by Mann-Whitney's *U*-test. Biochemical data are expressed as means ± S.E. and were analyzed using a one-way analysis of variance (ANOVA) and the Dunnett test. Data for EEG were analyzed by Tukey's test.

3. Results

3.1. Water maze testing

The basal forebrain lesion produced ataxia for 3–20 days after surgery. These behavioral changes were ameliorated after 10 days. On the first day of testing, the escape latency in the sham-operated group did not differ significantly from that in the basal forebrain-lesioned group. However, the escape latencies in the basal forebrain-lesioned group shortened gradually with repeated testing, while those in the sham-operated group shortened rapidly. The swimming speed during the five trials did not differ among groups. The basal forebrain-lesioned rats showed a significant increase in escape latency on the 3rd, 4th and 5th trials of test sessions when compared to the sham-operated group (Fig. 1). DSP-4 at 50 mg/kg, given i.p. 14 days before testing, had no significant effect on the latency of water maze performance in the normal rats, and the swimming speed during the five trial blocks did not differ among experimental groups. However, the basal forebrain-lesioned rats treated with DSP-4 at 50 mg/kg had significantly increased escape latencies on the 3rd, 4th and 5th trials compared with the basal forebrain + vehicle-treated group, indicating that DSP-4 potentiated the memory impairment in basal forebrain-lesioned rats (Fig. 1).

Tetrahydroaminoacridine at 1 and 3 mg/kg dose dependently improved the memory disruption induced by the basal forebrain lesion. Tetrahydroaminoacridine at 1 mg/kg significantly decreased the escape latencies in the 4th trials, while 3 mg/kg produced a significant decrease

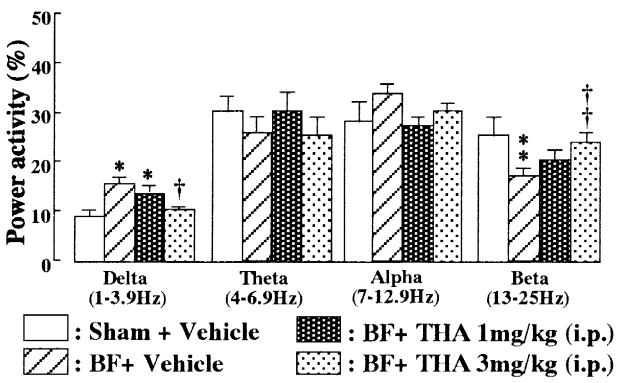

Fig. 1. Effects of DSP-4 plus basal forebrain lesion on acquisition performance in the water maze task. The values are expressed as medians. $n = 7–8$ per group. BF = basal forebrain-lesioned group. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ vs. Sham + Vehicle, $^{*}P < 0.05$, $^{**}P < 0.01$ vs. BF + Vehicle, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. Sham + DSP-4 (Mann-Whitney's *U*-test).

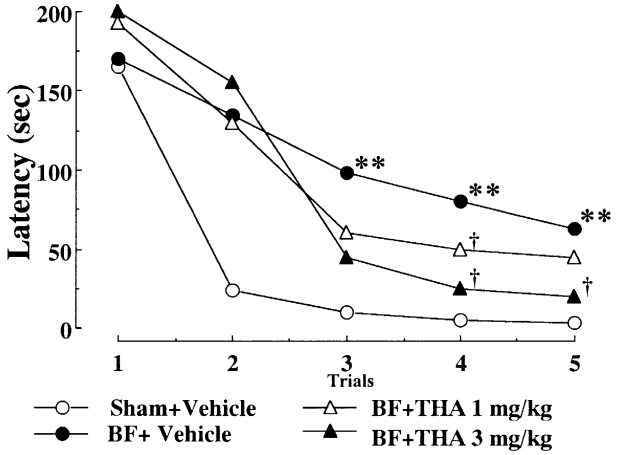

Fig. 2. Effects of tetrahydroaminoacridine (THA) on memory impairment induced by the basal forebrain lesion, as assessed in the water maze. The values are expressed as medians. THA (1 or 3 mg/kg) was injected i.p. 30 min before the training trials. $n = 7–8$ per group. $^{\dagger} P < 0.05$ vs. BF + Vehicle, $^{**} P < 0.01$ vs. Sham + Vehicle (Mann-Whitney's *U*-test).

in the escape latencies in the 4th and 5th trials when compared to those of the vehicle-treated basal forebrain-lesioned group (Fig. 2). However, tetrahydroaminoacridine at 1 or 3 mg/kg had no effect on the memory impairment induced by the combination of DSP-4 and basal forebrain lesion (Fig. 3). No behavioral change was measured in the sham rats after injection of tetrahydroaminoacridine at 1 and 3 mg/kg (data not shown).

3.2. EEG recording

The basal forebrain-lesioned rats showed a significant increase in delta power activity and a decrease in beta power activity, but no significant effects on alpha or theta activity. No recovery of this EEG slowing occurred during

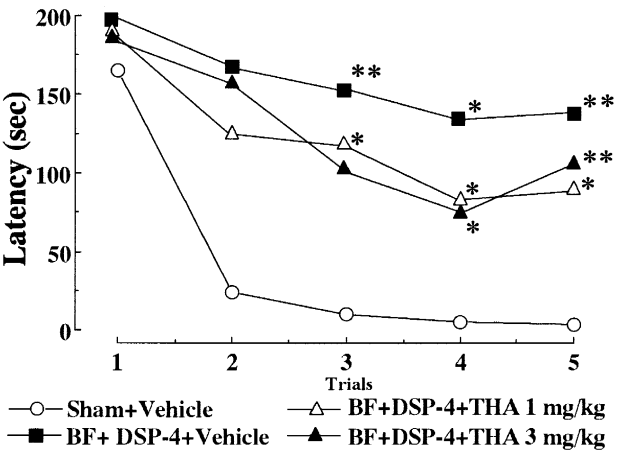

Fig. 3. Effects of tetrahydroaminoacridine (THA) on memory impairment induced by the combination of DSP-4 and basal forebrain lesion, as assessed in the water maze. The values are expressed as medians. THA (1 or 3 mg/kg) was injected i.p. 30 min before the training trials. $n = 7–8$ per group. $^{*} P < 0.05$, $^{**} P < 0.01$ vs. Sham + Vehicle (Mann-Whitney's *U*-test).

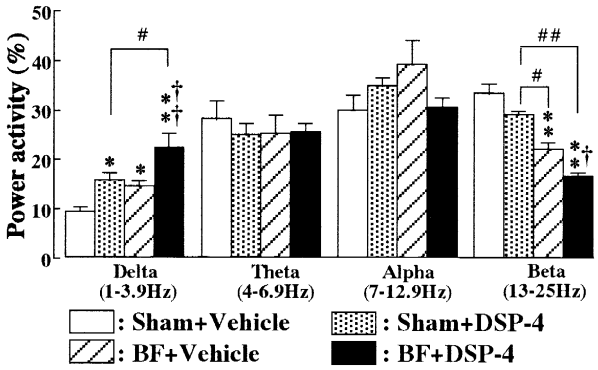

Fig. 4. Effects of DSP-4 plus basal forebrain lesion on cortical EEG power activity in rats. The values (%) are expressed as means ± S.E. $n = 7–8$ per group. $^{*} P < 0.05$, $^{**} P < 0.01$ vs. Sham + Vehicle, $^{\dagger} P < 0.05$, $^{\dagger} P < 0.01$ vs. BF + Vehicle, $^{\#} P < 0.05$, $^{\#\#} P < 0.01$ vs. Sham + DSP-4 (Tukey's test).

the course of the experiment, 49 days. DSP-4 increased only the delta power activity of awake immobility. Furthermore, DSP-4 significantly potentiated the EEG slowing, i.e., it was followed by an increase in delta power activity and a decrease in beta power activity induced by the basal forebrain lesion (Fig. 4). Tetrahydroaminoacridine at 1 mg/kg failed to improve these EEG changes in basal forebrain-lesioned rats compared to their post-lesion baseline values. In contrast, tetrahydroaminoacridine at 3 mg/kg significantly normalized the increase in delta power activity and decrease in beta power activity in basal forebrain-lesioned rats (Fig. 5). However, tetrahydroaminoacridine at 1 and 3 mg/kg had no effect on the cortical EEG slowing induced by the combination of DSP-4 and basal forebrain lesion (Fig. 6).

3.3. Choline acetyltransferase activity

The basal forebrain lesion caused significant reductions in choline acetyltransferase activity in the cortex but not in the hippocampus or striatum, as shown in Table 1. Lesions

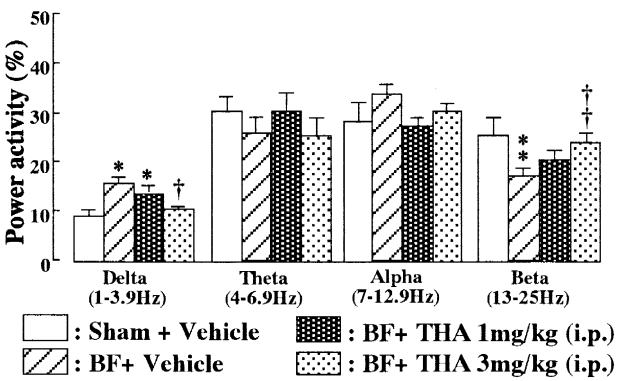

Fig. 5. Effects of tetrahydroaminoacridine (THA) on cortical EEG slowing induced by the basal forebrain lesion in rats. The values (%) are expressed as means ± S.E. $n = 7–8$ per group. $^{*} P < 0.05$, $^{**} P < 0.01$ vs. Sham + Vehicle, $^{\dagger} P < 0.05$, $^{\dagger} P < 0.01$ vs. BF + Vehicle (Tukey's test).

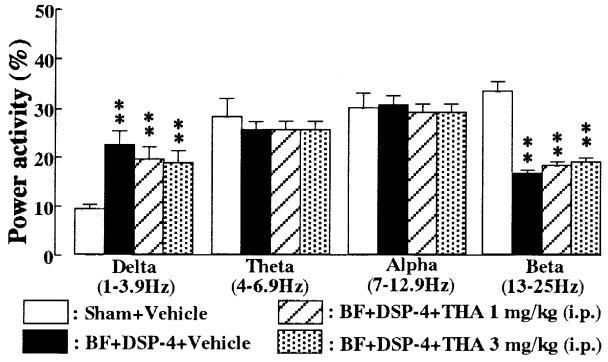

Fig. 6. Effects of tetrahydroaminoacridine (THA) on cortical EEG slowing induced by the combination of DSP-4 and basal forebrain lesion in rats. The values (%) are expressed as means ± S.E. $n = 7–8$ per group. ** $P < 0.01$ vs. Sham + Vehicle (Tukey's test).

of the basal forebrain decreased the choline acetyltransferase activity by an average of 30% in the frontal cortex, 30% in the parietal cortex and 19% in the occipital cortex, as compared to sham-operated animals (Table 1). DSP-4 treatment did not affect the choline acetyltransferase activity in the non-lesioned rats and did not potentiate the decrease in choline acetyltransferase activity in the basal forebrain-lesioned rats.

3.4. Noradrenaline concentration

Noradrenaline levels are shown in Table 2. Noradrenaline content was decreased following basal forebrain lesion only in the occipital cortex. The intraperitoneal injection of DSP-4 at 50 mg/kg significantly reduced noradrenaline levels in all areas sampled. The parietal cortex noradrenaline levels dropped from 0.39 ng to 0.23 ng/mg tissue (56% reduction), and levels in the hippocampal tissue dropped from 0.51 ng/mg tissue to 0.18 ng/mg tissue (65% reduction), compared to sham-operated animals. The rats that received a combination of DSP-4 and basal forebrain lesion showed a decrease in noradrenaline similar to that seen in the DSP-4-treated group.

4. Discussion

Ibotenic acid infusion into the basal forebrain produced a marked reduction in cortical choline acetyltransferase activity. We also confirmed that basal forebrain lesioning induced a memory deficit in the rats, using the water maze task. Further, lesioning the basal forebrain increased cortical delta wave and decreased beta wave activity. This EEG slowing induced by the basal forebrain lesion did not recover spontaneously with the present experimental schedule. The cholinergic deficit induced by basal forebrain lesioning has been previously reported to produce a memory impairment and EEG slowing (Ray and Jackson, 1991; Riekkinen et al., 1990). These findings and those of the present study suggest the importance of cholinergic neuron loss in the memory deficit and EEG slowing induced by basal forebrain lesion.

The present study indicated that noradrenaline depletion, achieved with DSP-4, aggravated the spatial memory deficits induced by basal forebrain lesion. DSP-4 is widely used as a selective noradrenergic neurotoxin (Jonson et al., 1981). Systemic administration of 50 mg/kg DSP-4 has been reported to produce a rapid, marked and selective reduction of noradrenaline levels in various brain regions and in peripheral neurons (Chrobak et al., 1985; Fritschy et al., 1989). In the present study, DSP-4 at 50 mg/kg had no significant effect on spatial memory in the water maze

Table 1
Brain regional choline acetyltransferase (ChAT) activities induced by the combination of DSP-4 and basal forebrain lesion

Brain region	Sham + Vehicle	Sham + DSP-4	BF + Vehicle	BF + DSP-4
Frontal cortex	48.9 ± 1.2	47.8 ± 2.1	34.5 ± 2.5 [a,b]	35.5 ± 1.8 [a,b]
Parietal cortex	50.5 ± 2.3	47.3 ± 3.3	35.3 ± 0.8 [a,b]	32.6 ± 2.1 [a,b]
Occipital cortex	36.0 ± 1.6	39.4 ± 1.5	29.2 ± 1.4 [a,b]	29.6 ± 0.5 [a,b]
Hippocampus	40.7 ± 8.4	47.5 ± 4.3	49.3 ± 1.2	45.2 ± 3.5

ChAT activities (nmol ACh/h/mg protein) were determined 2 weeks after basal forebrain lesioning. Each value represents the mean ± S.E. Eight rats were used in each group. BF = basal forebrain-lesioned group. [a] $P < 0.01$ vs. Sham + Vehicle, [b] $P < 0.01$ vs. Sham + DSP-4 (Dunnett's test).

Table 2
Brain regional noradrenaline contents induced by the combination of DSP-4 and basal forebrain lesion

Brain region	Treatment			
	Sham + Vehicle	Sham + DSP-4	BF + Vehicle	BF + DSP-4
Frontal cortex	0.38 ± 0.01	0.28 ± 0.03 [a]	0.33 ± 0.01	0.30 ± 0.02 [a,b]
Parietal cortex	0.39 ± 0.01	0.24 ± 0.02 [a,b]	0.37 ± 0.01	0.23 ± 0.04 [a,b]
Occipital cortex	0.37 ± 0.01	0.15 ± 0.02 [a,b]	0.31 ± 0.01 [a]	0.17 ± 0.04 [a,b]
Hippocampus	0.51 ± 0.02	0.18 ± 0.04 [a,b]	0.52 ± 0.04	0.15 ± 0.10 [a,b]

Noradrenaline (ng/mg tissue) levels were determined 2 weeks after DSP-4 administration. Each value represents the mean ± S.E. Eight rats were used in each group. BF = basal forebrain-lesioned group. [a] $P < 0.01$ vs. Sham + Vehicle, [b] $P < 0.01$ vs. BF + Vehicle (Dunnett's test).

14 days after treatment, when noradrenaline levels decreased about 40% in the parietal cortex. However, the treatment aggravated the memory deficits induced by the basal forebrain lesion. Noradrenergic depletion induced by DSP-4 has been reported to fail to alter the effects of scopolamine on the acquisition of reference memory in the water maze (Decker and McGaugh, 1989; Spangler et al., 1990). These previous data suggest that such interactions between cholinergic and noradrenergic dysfunctions are not involved in reference memory performance. Indeed, Ohno et al. (1993) recently demonstrated that noradrenergic depletion induced by DSP-4 potentiated the impairment of scopolamine-induced working memory. Thus, these findings suggest that an interaction between cholinergic and noradrenergic dysfunctions is evident only when a working memory procedure is used rather than a reference memory procedure. Our present findings thus indicate that this water maze task may test the working memory procedure involved in attention function rather than reference memory procedure, for the task was performed with one trial per day for 5 days, which is a short period. The firing rates of the neurons in the locus coeruleus have been related to the level of vigilance, and it is possible that the noradrenergic input informs the nucleus basalis cholinergic cells of the appearance of behaviorally important stimuli originating from the external milieu (Aston-Jones and Bloom, 1981; Aston-Jones et al., 1986). Therefore, our data suggest that the central cholinergic, but not the noradrenergic, system plays an essential role in spatial cognition processes, also indicating that the regulation of memory is at least partially controlled by noradrenergic neurons.

A most important finding in the present study was that DSP-4 increased delta power activity in normal rats, and potentiated the increase in delta power and decrease in beta power activity induced by the basal forebrain lesion. Riekkinen Jr. et al. (1990a,b) have demonstrated that the α_2-adrenoceptor antagonists increase fast wave activity, and that an α_2-adrenoceptor agonist increases slow wave activity during periods of immobility and mobility. In the present study, the noradrenergic impairment induced by DSP-4 was accompanied by an increase in cortical delta power activity but it had no effect on spatial memory in the water maze task. These data indicate that EEG slowing, such as an increase in delta power activity induced by noradrenergic impairment, may not be correlated with spatial cognitive disruption. Neocortical choline acetyltransferase activity has been reported to correlate with delta power activity induced by nucleus basalis lesion (Riekkinen et al., 1990; Ray and Jackson, 1991). Our data indicate that DSP-4 has no effect on choline acetyltransferase activity in normal rats and does not potentiate the reduction of choline acetyltransferase activity induced by basal forebrain lesions. Therefore, the increase in delta power activity induced by DSP-4 may indirectly affect the cholinergic impairment associated with cognitive function. Interestingly, DSP-4 potentiated not only the increase in delta power activity but also the decrease in beta power activity, as it aggravated the spatial cognitive disruption induced by the basal forebrain lesion. Previous findings have underscored the involvement of a cholinergic deficit in age-related EEG slowing and that memory deficits are associated with cholinergic deficits. In addition, in aged rats a change was observed in the slow wave (delta, theta) activity, but a large decrease was observed in fast wave (alpha, beta) activity (Buzsaki et al., 1988a). Aged rats have also been reported to show a deficit of working memory in an 8-arm radial maze (Blanco et al., 1994). These data suggest that high frequency activity rather than low frequency activity may be more important for the memory and learning involved in working memory.

We also examined the effect of tetrahydroaminoacridine on memory and EEG activity in the present study. This drug could reverse the memory deficit and EEG slowing induced by basal forebrain lesion, but it could not ameliorate the memory deficit or EEG slowing produced by the combination of DSP-4 and basal forebrain lesion. Riekkinen et al. (1991) have shown that tetrahydroaminoacridine at 7.5 mg/kg partially reverses the increases in delta and theta amplitudes induced by nucleus basalis lesions. In addition, tetrahydroaminoacridine could not reverse the decrease in beta amplitude induced by nucleus basalis lesioning. Our present data show that tetrahydroaminoacridine at 3 mg/kg significantly improved the EEG slowing induced by basal forebrain lesion, although it could not attenuate the memory deficit and EEG slowing induced by the combination of DSP-4 and basal forebrain lesion. Hartounian et al. (1986) also reported that dorsal noradrenergic bundle lesions decreased the efficacy of physostigmine in reversing passive avoidance deficits in rats with basal forebrain lesions. These findings taken together suggest that the presence of noradrenaline within the neocortex is sufficient to ameliorate learning deficits and restore EEG slowing following damage to the basal forebrain. However, the efficacy of tetrahydroaminoacridine in reversing the cortical cholinergic hypofunction induced by noradrenergic depletion may be limited. Furthermore, these data suggest that cognitive impairment accompanied the EEG slowing induced by cholinergic and noradrenergic deficits. The mechanism and generality throughout the cholinergic system of this interaction cannot be determined from the present study. Ray and Cole (1985) stated that it should be noted that changes in fast EEG activity are associated with cognitive and emotional processes. Further studies are required to clarify the correlation to high frequency activity and cognitive functions.

In conclusion, in the present study we observed that noradrenergic deficits aggravate the EEG slowing and the memory impairment induced by cholinergic dysfunction, and we suggest that the noradrenergic deficits may decrease the efficacy of the anticholinesterase agent tetrahydroaminoacridine in reversing the cortical cholinergic hy-

pofunction. The aggravation of memory impairment may be associated with EEG slowing, e.g., decrease in high frequency activity.

5. Missing reference

AUTHOR: please add missing reference to Coben et al. (1990) to Reference list.

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