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Effects of MCI-225 on Memory and Glucose Utilization in Basal Forebrain-Lesioned Rats

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EGUCHI, J., K. IWAI, T. YUASA, M. EGAWA, T. KOMATSU AND K.-I. SAITO. *Effects of MCI-225 on memory and glucose utilization in basal forebrain-lesioned rats.* PHARMACOL BIOCHEM BEHAV 51(4) 935-939, 1995.—The effects of MCI-225 on amnesia, the cerebral glucose metabolism, and choline acetyltransferase (ChAT) activity in basal forebrain (BF)-lesioned rats were studied in comparison with those of tacrine. Bilateral BF lesions with ibotenic acid impaired the performance in passive avoidance (PA) tasks. Single administration of MCI-225 (10 mg/kg, PO) after a 2-week postoperative recovery period, increased the escape latencies in the PA task, but was not statistically significant. Repeated administration of MCI-225 (0.3 and 1 mg/kg, PO for 6 days) significantly reversed the PA failure. The BF-lesioned rat exhibited a marked decrease in the local cerebral glucose utilization (LCGU) in the frontal cortex, parietal cortex, and caudate-putamen. MCI-225 (1 mg/kg, PO for 5 days) significantly ameliorated the reduction of the LCGU in the parietal cortex. MCI-225 did not change the decrease in the cortical ChAT activity induced by the BF lesion. Repeated administration of tacrine reversed the PA failure (0.3 mg/kg, PO) but failed to prevent the decrement in the LCGU and the ChAT activity. These results suggest that MCI-225 could be effective in the treatment of senile dementia of the Alzheimer type, which is accompanied with both deficit in the BF-cortex cholinergic neuron and cerebral glucose hypometabolism.

MCI-225 BF lesion PA LCGU ChAT Tacrine

MCI-225, [4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl) thieno[2,3-d]pyrimidine monohydrate hydrochloride], has been reported to reverse the scopolamine-induced learning deficit in the Morris-type water maze task in rodents and to ameliorate CO_2-induced amnesia in a passive avoidance (PA) task in rats (6,8). MCI-225 has also increased the attentive behavior in midpontine pretrigeminal preparation and reduced the resistance to the extinction of food-rewarded runway response in dorsal noradrenergic bundle-lesioned rats (6,7). From these observations, MCI-225 appears to improve attention and reduce amnesia in experimental animals.

Because MCI-225 clearly reversed the amnesia induced by scopolamine (8), MCI-225 may at least partly ameliorate the learning impairment via the central cholinergic system. As an animal model with damage in the cortical cholinergic neuron, a basal forebrain (BF)-lesioned rat has been widely used (5,27). The BF in rodents is the major source of cholinergic projections to the cortical areas and involves the nucleus basalis magnocellularis, which is thought to be homologous to the nucleus basalis of Meynert (NBM) in human (5). In the NBM, extensive cell loss has been shown in patients with senile dementia of the Alzheimer type (SDAT) (29). Biochemical and histochemical studies provided evidence that neurotoxic or electrolytic lesions of the BF in rodents produced a marked reduction in the activity of choline acetyltransferase (ChAT) and acetylcholinesterase in the cortex (27). Pharmacological studies showed that cholinomimetic drugs, physostigmine, oxotremorine, and tacrine, attenuated performance deficits that results from BF lesions (5,11,18,28). Furthermore, an unilateral BF lesion has been shown to selectively produce a decrease in the local cerebral glucose utilization (LCGU) in the cortex (21). Cerebral glucose hypometabolism and marked decrease in ChAT activity in the cortex and hippocampus of SDAT patients has been reported (13,15,24). Based on these facts, the BF-lesioned rat is currently thought to be a useful experimental animal model that mimics some of the clinical

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symptoms and characteristics that are observed in humans with SDAT (5,27). In this study, the effects of MCI-225 on PA failure, the ChAT activity and LCGU in the BF-lesioned rats were examined and compared with those of tacrine.

METHOD

Animals

Male wistar rats (Japan Laboratory Animals, Inc.), weighing 250–300 g at the beginning of experiments, were used. All rats were housed in groups of five with a 12-h diurnal light cycle.

Drugs

MCI-225 was synthesized in our laboratory. Ibotenic acid (Sigma), tacrine (Janssen), and [^{14}C]DG (Amersham; 11.0 GBq/nmol) were commercially purchased. MCI-225 was suspended in 0.5% Tween 80 and tacrine was diluted in distilled water.

Surgery

Rats were anesthetized with sodium pentobarbital (40 mg/kg, IP) and placed in a stereotaxic apparatus. Bilateral neurotoxic lesions of the BF were produced by injections of ibotenic acid (5 μg/0.5μl/each side), which was dissolved in 50 mM phosphate buffer saline (pH 7.4) using the Paxinos and Watson atlas of the rat brain (1.5 mm posterior, 2.8 mm bilateral to bregma, 7.2 mm below dura) (22). Sham-operated rats only received the vehicle using the same method. Following a recovery period of 2 weeks, rats were subjected to the experiments.

PA Task

A two-compartment step-through PA apparatus was used. The first compartment, an illuminated box (50 × 50 × 45 cm), was separated by a guillotine door (14 × 13 cm) from the second dark compartment (20 × 15 × 13 cm) with a grid floor.

In the acquisition trial, each rat was placed in the light compartment and then allowed to enter the dark compartment. Once the rat entered into the dark compartment, the guillotine door was closed and an electric shock (3.0 mA for 5 s) was delivered via the grid floor. The animal was then put back into the home cage until the retention test. In the retention test, which was carried out 24 h (single administration) or 48 h (repeated administration) after the acquisition trial, the rat was replaced in the illuminated compartment and the latency to enter into the dark compartment was measured up to a maximum cutoff time 300 s.

In single administration test, each compound or vehicle was given 1 h before the acquisition trial. In the 6-day repeated administration test, the fourth and last administrations were carried out 1 h before the acquisition trial and retention test, respectively.

Assay for ChAT Activity

One day after the retention test on the PA task in the repeated administration test, ChAT activity was measured. One hour after the administration of each compound or vehicle, rats were sacrificed by decapitation. The frontal-parietal cortex and hippocampus from each animal were dissected on a cold plate and stored at −80°C until assayed for ChAT activity by the method of Fonnum (10).

Measurement of LCGU

Measurements of the LCGU in the BF-lesioned and sham-operated rats were carried out by the [^{14}C]2-deoxyglucose ([^{14}C]DG) method of Sokoloff et al. (26). Five different brain structures, frontal cortex, parietal cortex, hippocampus, nucleus accumbens, and caudate-putamen were chosen from the regions measured in the previous report (21). Animals received injections for 5 consecutive days. Three hours before the last treatment on day 5, rats had polyethylene catheters inserted into a femoral artery under light ether anesthesia. Sixty minutes after the administration of MCI-225, tacrine, or vehicles, the animals received an IV injection of 1.2 MBq/kg of [^{14}C]DG (11.0 GBq/nmol; Amersham). Blood from the tail artery was sampled at 1, 5, 10, 20, 30, and 45 min after injection of [^{14}C]DG. Plasma glucose concentration in each blood sample was measured by a Blood Sugar-GOD-Perid test (Boehringer-Mannheim Yamanouchi). Aliquots of the plasma sample were solubilized in scintillation vials with 10 ml of ACS-II (Amersham). Radioactivity was counted in a Packard Tri-Carb 4530 scintillation counter.

The rats were decapitated 45 min after injection of [^{14}C]DG; the brains were rapidly removed from the skull and frozen in dry ice. Cerebral sections (20 μm thick) were serially cut from the frozen brains at −20°C, mounted on glass, and dried on a hot plate at 55°C. Autoradiographs of the brain sections were exposed along with calibrated [^{14}C]methyl methacrylase standards (Amersham) to an Imaging Plate (Fuji Film) for 3 days.

The photostimulated luminescence of the autoradiographs corresponding to the calibrated standards and to selected areas of the brain were measured using a Bio Image Analyzer BAS 2000 (Fuji Film) and converted into concentrations of ^{14}C radioactivity. Regional LCGU was calculated according to the equation described by Sokoloff et al. (26) using values for the rate constants and lumped constant reported for normal, conscious rats.

Data Analysis

Data for the PA task were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney's *U*-test. Data for ChAT activity and the LCGU were analyzed by one way ANOVA, followed by Dunnet's *t*-test. All results were expressed as means ± SEM. A 0.05 level of probability was accepted as significant.

RESULTS

Effects of MCI-225 and Tacrine on PA Failure

In a single administration test, injection of ibotenic acid into the BF decreased the escape latencies in the retention test to nearly 50% of the sham-operated group ($p < 0.01$). MCI-225 (10 mg/kg, PO) reversed the PA failure in the BF-lesioned rats, but not significantly. Tacrine (1 and 3 mg/kg, PO) slightly prolonged the escape latencies (Table 1).

In the repeated administration test, the escape latencies in the sham-operated rats and BF lesion + vehicle-treated rats were 281.4 ± 8.0 and 153.9 ± 18.9, respectively (Fig. 1A). MCI-225 (0.1–3 mg/kg) prevented the reduction of latencies in BF-lesioned rats. The mean latencies of MCI-225 (0.3 and 1 mg/kg) treated group were significantly longer than those of the BF lesion + vehicle-treated group ($p < 0.05$, $p < 0.01$, respectively). MCI-225 did not induce any abnormal behaviors within the range of doses used.

As shown in Fig. 1B, repeated administration of tacrine

TABLE 1

EFFECTS OF SINGLE ADMINISTRATION OF MCI-225 OR TACRINE ON THE ESCAPE LATENCY IN PA TASK IN BF-LESIONED RATS

Treatment		n	Step-Through Latency (s)
Sham operation + vehicle		15	237.9 ± 26.9
Ibotenic acid (10 μg/rat)			
+ vehicle		15	134.1 ± 29.3
+ MCI-225 (mg/kg)	1	15	120.1 ± 32.2
	3	15	109.9 ± 31.9
	10	14	167.7 ± 36.9
Sham operation + vehicle		15	279.6 ± 19.0
Ibotenic acid (10 μg/rat)			
+ vehicle		15	146.0 ± 28.0
+ tacrine (mg/kg)	0.3	15	137.3 ± 32.6
	1	15	150.7 ± 34.3
	3	15	159.9 ± 33.4

Mean ± SEM.

(0.3–3 mg/kg) also prolonged the step-through latencies in the BF-lesioned rats. With a dose of 0.3 mg/kg, the latencies of the tacrine treated group were significantly longer than those of the BF lesion + vehicle-treated group ($p < 0.05$).

The minimum effective doses of MCI-225 and tacrine were both 0.3 mg/kg. At the most effective dose, the mean escape latencies were 251.4 ± 18.6 s at a dose of 1 mg/kg of MCI-225 and 209.7 ± 29.4 s at a dose of 0.3 mg/kg of tacrine.

Effects of MCI-225 and Tacrine on Decrement in ChAT Activity

Ibotenic acid in the BF decreased ChAT activity by 27% in the frontal-parietal cortex ($p < 0.01$). However, hippocampal ChAT activity was not affected by ibotenic acid (Table 2).

Figure 2 shows the effects of repeated administration of MCI-225 (A) and tacrine (B) on the cortical ChAT activity in the BF-lesioned rats. There were significant differences in ChAT activity between six groups [A: $F(5, 110) = 22.727$, $p < 0.01$, B: $F(5, 107) = 13.738$, $p < 0.01$]. BF lesion reduced ChAT activity (A, B: $p < 0.01$). Neither MCI-225 or tacrine changed the reduction in cortical ChAT activity.

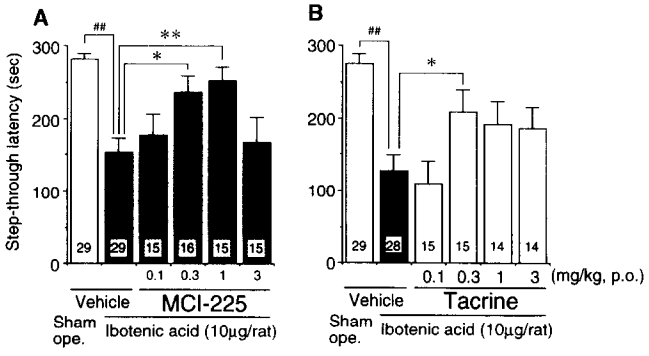

FIG. 1. Effects of repeated administration (6 days) of MCI-225 (A) and tacrine (B) on the escape latency in passive avoidance (PA) task in the basal forebrain (BF)-lesioned rats. Number of animals of each group was shown in the each column. ##$p < 0.01$ vs. sham-operated group; *$p < 0.05$, $p < 0.01$ vs. BF lesion + vehicle-treated group (Mann-Whitney's U-test).

TABLE 2

EFFECT OF BILATERAL LESION OF BF ON ChAT ACTIVITY IN THE FRONTAL-PARIETAL CORTEX AND HIPPOCAMPUS IN RATS

	ChAT Activity		
		nmol/mg Protein/h	% Change
	Sham Operation	Ibotenic Acid (10 μg/rat)	
Frontal-parietal cortex	8.50 ± 0.40 (n = 15)	6.23 ± 0.15 (n = 15)	−26.7%*
Hippocampus	4.90 ± 0.22 (n = 15)	5.08 ± 0.25 (n = 15)	n.s.

Mean ± SEM.
*$p < 0.01$ vs. sham-operated group (Student's t-test).

Effects of MCI-225 and Tacrine on Decrement in LCGU

Figure 3A showed the effects of repeated administration of MCI-225 on the LCGU in BF-lesioned rats. The LCGU was significantly different among three groups tested in the frontal cortex, parietal cortex and caudate-putamen [frontal cortex: $F(2, 11) = 4.169$, $p < 0.05$, parietal cortex: $F(2,10) = 6.612$, $p < 0.05$, hippocampus: $F(2,10) = 2.694$, caudate-putamen: $F(2,10) = 6.629$, $p < 0.05$, nucleus accumbens: $F(2,10) = 3.719$]. In these regions, the LCGU of BF lesion + vehicle-treated group was significantly decreased in comparison with that of sham-operated group (frontal cortex and parietal cortex: $p < 0.05$, caudate putamen: $p < 0.01$).

In the parietal cortex, MCI-225 (1 mg/kg) significantly restored the LCGU to the control level ($p < 0.05$). In other brain regions, MCI-225 attenuated the LCGU reduction, but not significantly. In the sham-operated rats, the LCGU in all regions studied did not change compared to naive rats, and the repeated administration of MCI-225 (1 mg/kg) did not change the LCGU in these regions (data not shown).

In Fig. 3B, comparisons in LCGU for several brain regions are displayed. There were significant differences in LCGU among groups in all regions tested except hippocampus [frontal cortex: $F(2, 6) = 12.683$, $p < 0.01$, parietal cortex: $F(2, 6) = 257.297$, $p < 0.01$, hippocampus: $F(2, 6) = 3.989$, caudate-putamen: $F(2, 6) = 18.456$, $p < 0.01$, nucleus accum-

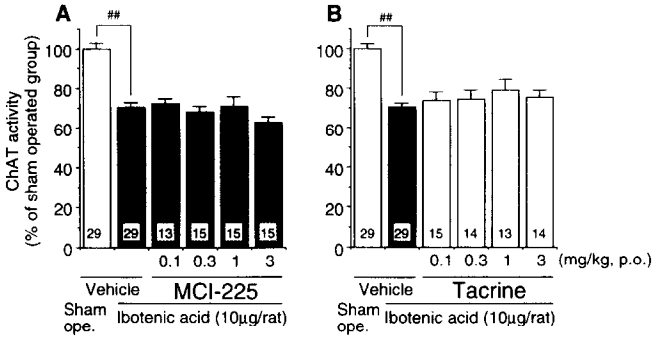

FIG. 2. Effects of repeated administration (7 days) of MCI-225 (A) and tacrine (B) on ChAT activity of the frontal-parietal cortex in the BF-lesioned rats. Number of animals of each group was shown in the each column. ##$p < 0.01$ vs. sham-operated group (Dunnet's t-test).

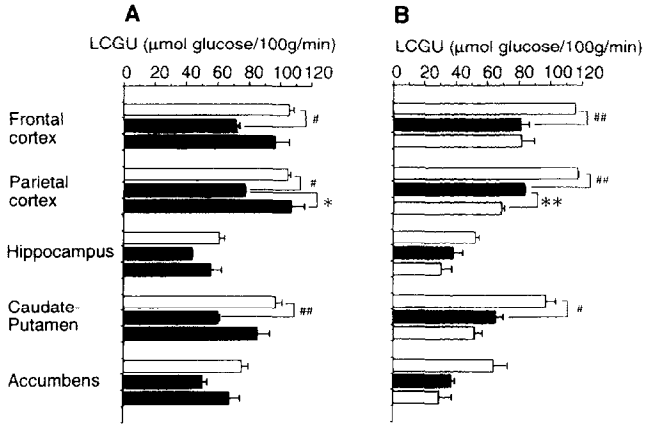

FIG. 3. Effects of repeated administration (5 days) of MCI-225 (A) and tacrine (B) on the local cerebral glucose utilization (LCGU) in BF-lesioned rats. Sham-operated group (open column); BF lesion + vehicle-treated group (closed column); BF lesion + MCI-225 1 mg/kg, PO group (hatched column); BF lesion + tacrine 0.3 mg/kg, PO group (stippled column). $\#\#p < 0.01$, $\#p < 0.05$ vs. sham-operated group; $**p < 0.01$, $*p < 0.05$ vs. BF lesion + vehicle-treated group (Dunnet's t-test). $n = 3$–5.

bens: $F(2, 6) = 6.476$, $p < 0.05$]. BF lesion reduced the LCGU in the frontal cortex ($p < 0.01$), parietal cortex ($p < 0.01$) and caudate-putamen ($p < 0.05$). In the parietal cortex, tacrine (0.3 mg/kg) slightly but significantly worsened the decrement in the LCGU ($p < 0.01$).

DISCUSSION

The bilateral BF lesion with ibotenic acid markedly impaired the retention test performance of the PA task with reduction in both the cortical ChAT activity and the LCGU, which agreed with reported observations (11,18,21). In this study, we found that repeated oral administration of MCI-225 reversed the PA failure at the doses of 0.3 and 1 mg/kg and attenuated the LCGU decrement at a dose of 1 mg/kg without effects on the cortical ChAT activity. On the other hand, tacrine ameliorated the PA failure at a dose of 0.3 mg/kg but failed to reverse the decrement in LCGU and ChAT activity.

In rats with the BF lesion, both magnocellular cells and the cortical cholinergic markers are markedly decreased (5,27). Additionally, the learning impairments in the BF-lesioned rats were reported to be reversed by cholinomimetic drugs such as AChE inhibitors, muscarinic agonists, and acetylcholine (ACh) itself (5). Based on these observations, the changes underlying the learning impairments induced by the BF lesion are most likely the attenuation in the cholinergic neurons (5). Because MCI-225 ameliorates not only the amnesia induced by scopolamine (8), but also that induced by the BF lesion, the antiamnesic effects of MCI-225 may be at least partly attributed to amelioration of the hypofunction in the cholinergic neurons. MCI-225 blocks the binding of [^{3}H]-GR65630 to the serotonin (5-HT)$_3$ receptor in the rat cortex ($IC_{50} = 81$ nM) (9), therefore, MCI-225 may influence the BF–cortex cholinergic neuron through the 5-HT$_3$ receptor. Barnes et al. (3) reported that a selective 5-HT$_3$ receptor antagonist, ondansetron, ameliorates the learning deficit in mice with the BF lesion and that the 5-HT$_3$ receptor mediates the inhibitory effects of 5-HT on ACh release. The ameliorative effects of MCI-225 on cholinergic neurons may be partly due to its 5-HT$_3$ receptor antagonistic action. Within the range of doses used, the cortical ChAT activity was not changed by MCI-225. In normal rats, MCI-225 also does not change ChAT activity (data not shown). MCI-225 seems not to cause the induction or activation of this enzyme.

Furthermore, MCI-225 inhibits the uptake of noradrenaline ($IC_{50} = 69$ nM) in the rat brain synaptosomes (9). Also, the in vivo microdialysis study showed that MCI-225 increased the extracellular noradrenaline content in the rat brain (20). The BF lesion decreased noradrenaline, 5-HT and dopamine levels in the rat brain (16,19), and this hypofunction in monoaminergic neurons was reported to contribute to learning and memory impairments (19). From these results, MCI-225 is thought to reduce the PA failure induced by BF lesions, through the potentiation of both cholinergic and noradrenergic systems.

The unilateral BF lesion is reported to selectively decrease the LCGU in the fronto-parietal cortex, which receives most of the cholinergic projections from BF (21). A cholinomimetic drug, oxotremorine, increased the LCGU in the cortex and ameliorated the PA failure in the BF-lesioned rats (12,17). From these observations, the cortical LCGU decrement may contribute to the amnesia in the BF-lesioned rats. On the other hand, when BF was bilaterally lesioned, LCGU decrements were observed in the whole brain (21). Because the hippocampus and the caudate-putamen are connected to the BF in the primates (1,2), the LCGU decrements in these brain regions by bilateral BF lesion may reflect the innervations.

Schwartz et al. have reported that the LCGU obtained with the [^{14}C] DG technique reflects the glucose metabolism dominantly in the synaptic terminals (25). MCI-225 may act on the synaptic terminals in BF-cortex cholinergic neurons, because MCI-225 potently ameliorate LCGU decrement in the parietal cortex, which is projected by the BF cholinergic neuron. MCI-225 may reverse the deficit in the BF–cortex cholinergic neuron and the recovery of the LCGU decrement by MCI-225 in the parietal cortex may contribute to the improvement in the PA failure in BF-lesioned rats.

In contrast to MCI-225, tacrine slightly worsened the decrement in the LCGU. Thus, tacrine may not ameliorate the glucose hypometabolism in the synaptic terminals at a dose of 0.3 mg/kg, which was the most effective dose in the PA task. Bassant et al. (4) reported that tacrine (10 mg/kg, IP) increased the LCGU in the parietal cortex in normal rats. The difference in the effects of tacrine on the LCGU in two experiments may depend on the difference in the doses of tacrine and/or in the treatments of the BF. High doses of tacrine in their study may produce the potent stimulation to the postsynaptic cholinergic receptors enough to cause an increase in LCGU in postsynaptic neurons in normal rats. In vitro, tacrine is reported to increase or decrease the oxidation of glucose depending on the experimental condition in the cortical slice (23). The different results of MCI-225 and tacrine in the LCGU experiments is thought to be caused by the different pharmacological profiles of the two compounds. That is, MCI-225 inhibits noradrenaline uptake and binds the 5-HT$_3$ receptor without inhibition of AChE activity (data not shown). On the other hand, tacrine dominantly inhibits the activity of AChE. Furthermore, neurochemical studies are necessary to clarify this possibility.

In patients with SDAT, not only a marked loss of cholinergic neurons in NBM (29), but also a decrease in cortical glucose metabolism has been described (13). The magnitude of

the LCGU reductions are closely related to the severity of dementia (13,14). It is interesting that in BF-lesioned rats, MCI-225 potently ameliorated both PA failure and the LCGU decrement in the brain region that is affected in SDAT. These results suggest that MCI-225 could be effective in the treatment of SDAT, which is accompanied by both the deficit in BF-cortex cholinergic neurons and the cerebral glucose hypometabolism.

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