Tacrine Improves Working Memory Deficit Caused by Permanent Occlusion of Bilateral Common Carotid Arteries in Rats

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ABSTRACT—Effect of tacrine, a cholinesterase inhibitor, on spatial acquisition deficit caused by permanent occlusion of bilateral common carotid arteries (2VO) was examined by using the conventional 8-arm and the 4-arm baited radial maze tasks in rats. Daily administration of tacrine (0.1 and 0.3 mg/kg, i.p.) 1 month after 2VO operation significantly improved the impaired spatial acquisition in the conventional maze task. This treatment also ameliorated the 2VO-induced working but not reference memory deficit in the 4-arm baited radial maze task. These results suggest that tacrine improvement of working memory deficit in the 2VO rats is due to stimulation of central cholinergic systems.

Keywords: Permanent occlusion of bilateral common carotid arteries, Spatial acquisition, Tacrine

A variety of animal models have been used to investigate the behavioral and pathophysiological changes observed in human dementia (1, 2) and to pharmacologically elucidate activities of putative anti-amnesiac drugs. Although it is generally accepted that progressive cognitive dysfunction occurs in human dementia, cognitive deficits observed in these animal models are usually transient and recover to a normal level in a time-dependent manner.

Permanent or transient bilateral occlusion of common carotid arteries in the rat is a model for whole brain ischemia and the local cerebral blood flow in anatomically discrete regions reportedly decreases to 25–87% of the sham control at 2.5 hr after permanent occlusion of common carotid arteries (2VO) (3). We previously showed that 2VO caused impairment of spatial acquisition in a conventional 8-arm radial maze task and that this impairment became more marked 1 to 4 months after the 2VO operation (4, 5). Besides these behavioral changes, the 2VO rats exhibited progressive neuronal degeneration and decrease in acetylcholine contents in the brain. Tanaka et al. (6) reported that muscarinic receptor binding ability decreased in 2VO rats. This muscarinic receptor dysfunction appeared to be correlated with discrimination learning disabilities of these animals. Thus, it is likely that changes in the function of central cholinergic systems caused by 2VO are involved in the impairment of learning and memory. In the present study, we examined the effect of tacrine, a cholinesterase inhibitor, on 2VO-induced impairment of spatial acquisition using conventional 8-arm and 4-arm baited radial maze tasks to test whether stimulation of cholinergic systems could improve the learning and memory deficits caused by 2VO.

Male Wistar rats (Japan SLC Inc., Shizuoka) were housed in groups of four per cage in the laboratory animal room maintained at 25 ± 1°C with 65 ± 5% humidity on a 12 hr light/dark cycle (lights on: 07:30 to 19:30). The animals, at the age of 13 weeks, were anesthetized with sodium pentobarbital (45 mg/kg, i.p.), and bilateral common carotid arteries were ligated with silk thread (2VO group). The animals that received the same surgical operation without carotid artery ligation served as the sham-operated controls.

The experimental procedures are the same as those described in our previous report (7). Briefly, prior to the maze training, each animal was handled for 5–10 min daily for 2 days and was given 3 days to adapt to the maze. One month after surgery, one daily training trial of the conventional 8-arm radial maze task or 4-arm baited radial maze task was conducted for each rat. The conventional 8-arm radial maze trial was judged to be complete when the rats had visited all 8 arms or had spent 10 min in the maze. Entry into an arm that the rat had not previously visited was recorded as a correct response and re-entry as an error. The number of errors was used as the index of radial maze performance. Animals received
radial arm maze tasks once daily during a 2 week-training period. Data were expressed as means of two trials.

In a 4-arm baited radial maze task, four arms were randomly assigned to serve as the baited set. This set remained unchanged throughout the experiments for any given rats. Animals received one training trial daily 5 days a week. In the training trial, the first entry into an unbaited arm was regarded as a reference memory error. Re-entry into the baited arm that the rat had previously visited was regarded as a working memory error. Training trials were repeated for 6 weeks. After a 2-week rest period without injecting tacrine and training, the maze performance of the animals in the 4-arm baited radial maze task was reexamed. The rats were kept at 85% of their free-feeding weight throughout a radial maze test period. Water was allowed ad libitum. Data were organized into subject means of five trials.

Tacrine (9-amino-1,2,3,4-tetrahydroacridine HCl; Sigma Chemical Co., St. Louis, MO) was dissolved in saline and injected intraperitoneally (i.p.) in a constant volume of 1 ml/kg body weight 30 min before each trial. The statistical analysis was carried out by the two-way repeated measures analysis of variance (ANOVA) test followed by the Student-Newman-Keuls test. Differences with P<0.05 were considered significant.

Figure 1 shows the spatial acquisition performance of 2VO rats in the conventional 8-arm maze task. Consistent with a previous report from this laboratory (4), the 2VO rats committed more errors than the sham-operated control rats (F(6,114)=0.350, P<0.05). Tacrine, at 0.1 mg/kg but not 0.3 mg/kg (i.p.), significantly decreased the number of errors committed by 2VO in the first block of trials. The daily administration of tacrine (0.1 and 0.3 mg/kg, i.p.) significantly attenuated the permanent 2VO-induced impairment of acquisition performance (F(6,174)=1.61, P<0.05).

In the 4-arm baited radial maze task, both working and reference memory were measured. Working and reference memory errors committed by the permanent 2VO rats during a training period were significantly more than those committed by the sham-operated rats. In the 2VO rats treated daily with tacrine (0.3 mg/kg, i.p.) 30 min before each trial, the number of working memory errors (F(4,72)=0.825, P<0.05) but not reference memory errors (F(4,72)=0.592, P=0.670) was significantly decreased following daily training (Fig. 2).

To elucidate whether tacrine-induced improvement is
due to transient action on cholinesterase or continued enhancement of the central cholinergic systems, the performance of the animals in the 4-arm baited radial maze task was reexamined after a 2-week rest period without administering tacrine. The working memory errors committed by the tacrine-pretreated 2VO rats were slightly less than those committed by the vehicle-pretreated 2VO group, but there was no significant difference in the number of errors between these two groups.

The memory used in the conventional 8-arm radial maze task is generally considered as working memory. This type of memory is analogous to recent memory in humans (1) and appears to be more severely impaired than remote memory in human dementia (8). We previously reported that 2VO causes progressive cognitive impairment of radial maze performance in rats (4) and that the progressive neuronal degeneration and cholinergic dysfunction following the 2VO are partly involved in this cognitive impairment (5). Consistent with a previous report (4), the 2VO rats committed more errors in all sessions than the sham-operated control rats. Moreover, the 4-arm baited radial maze task used in the present study revealed that the 2VO impaired not only working but also reference memory performances and that enhancement of central cholinergic systems by tacrine, a cholinesterase inhibitor, attenuated the deficits in spatial cognitive performance caused by 2VO.

Ni et al. (5) reported that neuronal damage but not decrease in the acetylcholine level in the cerebral cortex was observed at 1 month after permanent 2VO operation of rats, whereas both neuronal damages and decreases in the acetylcholine level became evident in the cerebral cortex and hippocampus at 4 months after 2VO operation. In the present study, when examined at 1 month after 2VO operation, tacrine significantly improved 2VO-induced impairment of working memory in the 4-arm baited radial maze task even if the daily administration of tacrine was started at 1 month after the operation. Considering that central cholinergic systems play important roles in working memory or attention or both (9, 10), it is likely that the deficit in working memory caused by the 2VO is partly due to the progressive impairment of the central cholinergic function and that tacrine ameliorates 2VO-induced working memory by enhancing the activity of central cholinergic systems.

The clinical effects of this compound on cognitive dysfunction of Alzheimer's patients have been attributed to its ability to inhibit the activity of acetylcholinesterase in the brain (11), although tacrine is known to have a variety of pharmacological profiles besides the anti-acetylcholinesterase activity (12, 13). Beninger et al. (10) recently reported that inhibition of acetylcholinesterase attenuates scopolamine-induced working memory error but not reference memory error. Taken together, the present results suggest that tacrine inhibition of acetylcholinesterase activity contributes, at least, to maintain the function of cholinergic systems, resulting in the improvement of working memory impairment in 2VO rats.

The present results also provided evidence that tacrine-induced improvement in the 4-arm baited radial maze task was transient, since no significant difference in the number of errors was observed between vehicle-pretreated and tacrine-pretreated 2VO groups when reexamined 2 weeks after tacrine termination.

It is generally believed that acquired information is consolidated with the passage of time to establish long-term (reference) memory (14). Cerebral ischemia disrupts working and reference memory, indicating that both the information acquisition process and information consolidation process from working memory to reference memory are damaged (15). Tacrine improved only the working memory performance of 2VO rats in the conventional 8-arm radial maze task (working memory task) and the 4-arm baited radial maze task (working/reference memory task), suggesting that this compound may act at the information acquisition stage but not information consolidation in 2VO rats.

In conclusion, the administration of tacrine ameliorated deficits in the spatial acquisition caused by 2VO even after onset of histological and neurochemical damages. These findings raise the possibility that tacrine has a therapeutic potential for the treatment of cerebrovascular dementia.

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REFERENCES


