Facilitation of Memory Retrieval by Pre-Test Morphine and Its State Dependency in the Step-Through Type Passive Avoidance Learning Test in Mice

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Abstract—Amnesia produced by scopolamine and cycloheximide were reversed by morphine given 30 min before the test trial (pre-test), and pre-test morphine also facilitated the memory retrieval in the animals administered naloxone during the training trial. Similarly, pre-test scopolamine partially reversed the scopolamine-induced amnesia, but not significantly; and pre-test cycloheximide failed to reverse the cycloheximide-induced amnesia. These results suggest that the facilitation of memory retrieval by pre-test morphine might be the direct action of morphine rather than a state dependent effect.

Previously, we found that amnesia induced by scopolamine and cycloheximide were reversed by morphine administered 30 min before the test trial (1). However, it is possible that the facilitation of memory retrieval by pre-test morphine might be due to a state dependent effect, namely, the test trial was performed under the same drug state which had been experienced by the animals at the training trial, since it was reported that opioid peptides were released during the training trial in the passive avoidance tasks (2). Thus, the present study was carried out to investigate the involvement of the state dependency in the effect of pre-test morphine.

Male mice, weighing 25–39 g, of the ddY strain were used. They were housed in 42×26×15 cm plastic cages with free access to food and water under a natural day/night regime. Morphine-HCl (Takeda), scopolamine-HCl (Tokyo Kasei) and cycloheximide (Nacalai) were dissolved in saline and administered i.p., in a volume of 0.1 mg/10 g of body weight. The dose of morphine was fixed at the maximum effective dose, 10 mg/kg, based on the result obtained in our previous experiment (3). The step-through type of one-trial passive avoidance task was used. The apparatus consisted of an illuminated and a dark compartment (each 4×13×10 cm) adjoining each other through a small gate (3 cm in diameter) with a grid floor, 2.5-mm stainless steel rods set 7 mm apart. At the training trial, the animal was placed in the illuminated compartment facing away from the dark compartment. When the animal entered into the dark compartment, an electric shock (ES) was delivered through the grid floor until the animal returned to the illuminated compartment. At the test trial, 24 hr after the training trial, the animal was again placed in the illuminated compartment and its latency to enter the dark compartment, maximum 600 sec, was measured. Data were expressed as medians and interquartile ranges, and they were analyzed by Kruskal-Wallis non-parametric one way analysis followed by the 2-tailed Mann-Whitney U-test for the paired comparisons. In all statistical evaluations, P<0.05 was used as the criterion for statistical significance.

A 25-V ES was applied at the training trial in these experiments. Amnesia was induced by 0.1 mg/kg of scopolamine given 30 min before the training trial or by 100 mg/kg of cycloheximide administered immediately after the training trial. As shown in Fig. 1, A and B, pre-test morphine reversed both scopolamine- and cycloheximide-induced amnesia. Pre-test scopolamine, 0.1 mg/kg, also tended to
prolong the step-through latency in the scopolamine-induced amnesic animals, but the effect was not statistically significant (A).

On the other hand, pre-test cycloheximide, 100 mg/kg, failed to reverse the amnesia induced by cycloheximide (B). In the animals treated with saline at the training trial, both scopolamine and cycloheximide did not affect the step-through latency at the test trials by themselves.

The effect of pre-test morphine in the animals administered naloxone pre- and post-training trial. Naloxone was administered pre- ( ) or post- ( ) training trial. *P<0.05, **P<0.01 vs. control group ( ). For other details, refer to the text and the legend of Fig. 1.

Kameyama et al. (4) reported the antagonistic effect of naloxone on cycloheximide-induced amnesia suggesting the involvement of the opioid system in the amnesic action induced by protein synthesis inhibitors. On the other hand, Introini and Baratti (5) reported that the impairment of memory retention induced by post-training 8-endorphin was reversed by oxotremorine or physostigmine and stated that there exists a close relationship between opioid and cholinergic systems. Furthermore, Izquierdo et al. (2) reported that 8-endorphin-like immunoreactivity was reduced in rat brain after the training trial of passive avoidance learning, and they stated that this reduction was attributable to the release of the opioid peptide from its storage site. These facts may suggest the participation of the opioid system in the scopolamine- and cycloheximide-induced
amnesic models, estimated using the passive avoidance learning test, and it may imply that the memory retrieval by pre-test morphine would be due to the state dependency upon endogenous opioid peptide released during the training trial. However, pre-test scopolamine and cycloheximide could not reverse amnesia induced by the respective drugs. Furthermore, in order to exclude the possible involvement of the opioid effect at the training trial, naloxone was administered pre- and post-training, but even in these animals, the facilitation of memory retrieval by pre-test morphine was demonstrated as well. The effect of pre-test morphine could not be attributed to the nonspecific sedative effect of morphine, because the administration of morphine at the training trial did not affect the step-through latency and also in the animals given no foot shock at the training trial, the step-through latency at the test trial was not influenced by the treatment (3). Thus, these results suggest that the facilitation is due to the direct effect of pre-test morphine rather than the state dependent effect.

References
1 Nishimura, M., Shigi, Y. and Kaneto, H.: State dependant and/or direct memory retrieval by morphine in mice. Psychopharmacology (Berlin) 100, 27-30 (1990)