Glutamate Receptor Modulator Dimebon Stimulates Consolidation and Reconsolidation of Weak Memory in Chicks

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Effects of glutamate receptor modulator dimebon on memory consolidation and reconsolidation were investigated in passive avoidance paradigm in newborn chicks. Systemic administration of 0.1 mg/kg dimebon 5 min before or 4 h after "weak" training resulted in formation of long-term memory. Dimebon administration in combination with memory reactivation 24 h after "weak" training recovered the memory decayed by the time of reminder and ensured its subsequent long-term maintenance over 24 h. Thus, we showed the possibility for dimebon-induced recovery of the memory that decayed and had no manifestations in behavior. Dimebon administration potentiated early and late stages of memory consolidation in learning as well as in memory reconsolidation following its reactivation.

Key Words: *memory consolidation; memory reconsolidation; cognitive enhancers*

Pharmacological agent dimebon (9-[2-(2-(dimethylmethylpyridyl-5)-ethyl]3,6-dimethyl-1,2,3,4-tethrahydro-γ-carbolin) is the melatonin analogue and it possesses properties of glutamate and histamine receptor ligand [3]. Dimebon blocks NMDA receptors by binding to NR2B subunit and potentiates activity of AMPA-receptors in low doses [1]. Chronic administration of the agent resulted in enhanced memory in rats trained against the background of cholinergic toxin and β-amiloid fragment administration [3].

The objective of the study was to investigate cognitive enhancer properties of dimebon when it is administered at the time of training as well as at delayed times (4 and 24 h) after training.

MATERIALS AND METHODS

The study was conducted using method of single training of 1-2 day old chicks (*Gallus gallus domesticus*) (n=24) in the "weak" passive avoidance training paradigm [5,7]. The experiments were conducted in accordance with the Order #267 Ministry of Health of Russian Federation (19.06.2003) and "Rules of Studies on Experimental Animals" (approved by the Ethics Committee of the P. K. Anokhin Institute of Normal Physiology; protocol No. 1, 3.09.2005). To train the chicks, animals were presented with "aversive" bead, moistened with pungent substance (10% methyl anthranilate solution in ethanol). This training results in the formation of the memory that lasts no more than 6-12 h in most animals [5,7]. Dimebon was administered intraperitoneally (0.05-1.0 mg/kg in physiological solution 0.1 ml) 5 min before training or 4 or 24 h after training. Control animals were injected with physiological saline in the same volume. Testing was carried out 24 and 48 h later and consisted of 10-sec presentation of the same bead as during training, but dry, and subsequent presentation of neutral bead. Selective avoidance reaction in response to aversive bead was assessed as the presence of long-term memory. The number of animals (in percent) demonstrated avoidance reaction in different experimental groups was compared using χ^2 test.

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RESULTS

Testing in 24 h revealed a U-shaped pattern of the dose-dependence of dimebon effect; the maximum cognition-stimulating effect was observed after dimebon administration in a dose of 0.1 mg/kg (Fig. 1). This dose was used for further experiments aimed to test the possibility to enhance memory not during training, but several hours after that. Synthesis of the effector proteins, which provide morphological reorganization of interneuronal connections in the brain ("second wave" of gene expression), is known to take place 4 h after "strong" passive avoidance training [4]. It is assumed that these processes are less intensive or absent in "weak" training, what results in memory decay. To test the possibility for memory enhancement by effect on "second wave" of protein synthesis, dimebon was administered 4 h after "weak" training. Avoidance levels in animals administered with dimebon were significantly higher than in the control (dimebon: 57% avoidance, n=21; control: 24% avoidance, n=21; p<0.05).

For evaluation of dimebon effects on memory reconsolidation, the possibility for memory recovery under the effect of reactivation stimuli [2] was tested. Memory was reactivated by reminder 24 h after "weak" training, when memory decays in most of animals [6]. Reminder appeared as second episode of "weak" training: the animals were presented with the bead of another color, also moistened with 10% methyl anthranilate solution. The animals received 0.1 mg/kg dimebon intraperitoneally 5 min before reminder and tested 24 h after memory reactivation (*i.e.* 48 h after initial training). Most control animals (trained 48 h before the test and received no additional stimulations) did not avoid the bead used during training. Avoidance level was higher in animals with reminder-reactivated memory; however, these differences did not reach level of statistical significance. Dimebon administration before the reminder significantly increased avoidance level in comparison with the control group and group with reminder only (Fig. 2). Animals exposed to reminder also avoided the bead presented during reminder session: 28% avoidance level in reminder group and 89% avoidance level in the group reminder+dimebon (p<0.0001). This effect can be explained by the effect of dimebon on the new memory formed during the reminder session. Thus, dimebon administration before reminder session (new training) 24 h after the initial training significantly enhanced both the new memory formed during this episode and reactivated memory acquired 24 h before. In order to test selectivity of avoidance, the test with familiar and novel neutral beads was performed. Avoidance level varied from 0 to 17% in all groups without statistically significant intergroup differences. These findings suggest that presentation of reactivation stimuli addressed toward decayed memory against the background of dimebon administration results only in recovery of that memory and in memory development about new experience, rather than in avoidance generalization.

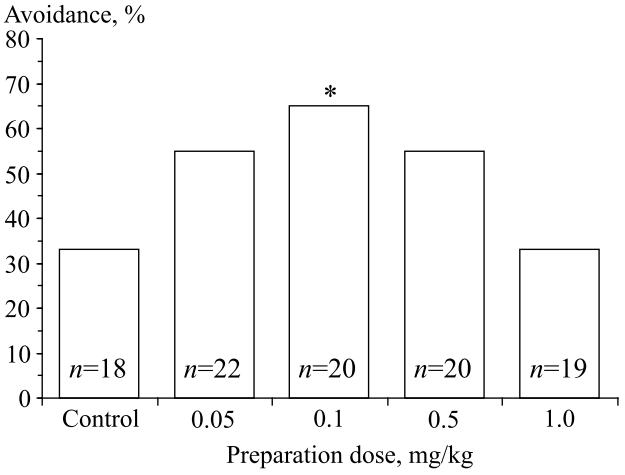

Fig. 1. Effects of systemic dimebon administration 5 min before training on the reproduction of learned behavior 24 h after training. n: number of animals. *p<0.05 in comparison with the control.

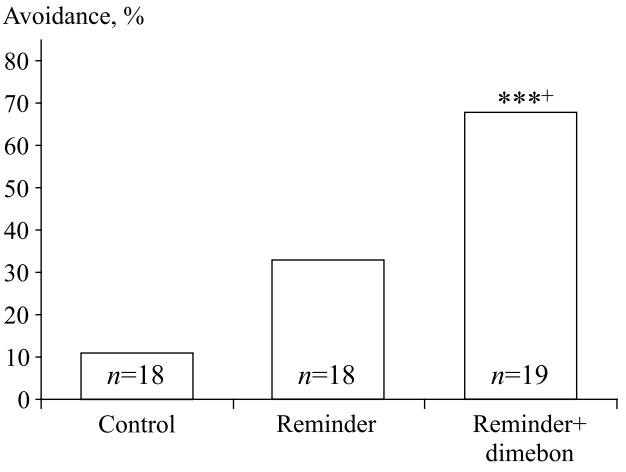

Fig. 2. Effect of systemic dimebon administration in combination with memory reactivation by the reminder on reproduction of learned behavior 48 h after training. ***p<0.001 in comparison with the control, ^{+}p<0.05 in comparison with reminder group.

Additional control group of chicks received dimebon 24 h after training and was presented a neutral bead moistened with water. Testing 48 h later showed aversion level for the "aversive" bead equal 33% (n=18), which was significantly lower than in reminder+dimebon group and had no significant differences from the aversion level in reminder group.

Thus, we showed the possibility for targeted effects on decayed memory with its recovery in a result. Combination of memory reactivation by specific reminder together with administration of cognitive enhancer dimebon resulted in recovery of the decayed memory that had no manifestations in behavior. These

experiments revealed potentiating effects of glutamate receptor modulator dimebon on early and late stages of memory consolidation in the course of it formation, as well as upon the reconsolidation of previously formed memory following its reactivation.

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