PHARMACOLOGY AND TOXICOLOGY

The Effect of a New 9-Aminoacridine Derivative on Working and Long-Term Memory in Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 2, pp. 202-204, February 1999. Original article submitted February 20, 1998.

The effects of Vp, a new 9-aminoacridine derivative, on the radial maze performance of intact and scopolamine-treated rats were compared with those of amiridin and tacrine. In intact rats Vp improved the formation of long-term spatial memory and has a positive effect on working memory at the initial stage of training. In scopolamine-treated rats Vp reduced the amnesic effects of scopolamine on both kinds of memory.

Key Words: *9-aminoacridine derivative; working and long-term memory; radial maze; scopolamine amnesia*

A number of 9-aminoacridine derivatives has been synthesized at the Center for Safety of Bioactive Compounds in the search for drugs with antiamnesic activity and improving cognitive functions. After detailed pharmacological examination of these compounds, we selected Vp (9-butyl-3,3-dimethyl-3,4-dihydroacridine-1(2H)-on hydrochloride) for the development of drug for treating dementia. This substance improves both active and passive avoidance conditioning and reduces scopolamine amnesia. Vp is one order of magnitude less toxic than tacrine and possesses lower anticholinesterase activity [2].

The objective of this study was to investigate the effects of Vp on working and long-term memory in intact and scopolamine-treated rats in the radial maze test. Tacrine and amiridin widely used for the treatment of cognitive dysfunction were used as reference compounds.

MATERIALS AND METHODS

Experiments were carried out on 180 outbred male albino rats weighing 200-300 g. The animals were maintained at 20-22°C and a standard light/dark (12 h:12 h) cycle with free access to water. The experiments were conducted in a sound-proof chamber with artificial illumination.

Intact rats were given 20 sessions of training every other day for 40 days. Scopolamine-treated rats were trained daily (14 days). Before training the rats were placed on a food deprivation schedule until they lost approximately 15% of their initial body weight [1]. During training they were fed immediately after sessions and remained food-deprived to the next session (for about 48 h) [5].

Radial maze consisted of a round central part (50 cm in diameter) connected to eight arms (each 10 cm in diameter and 50 cm length) by the holes. In the preliminary tests without reinforcement the rats were placed in the central part and allowed to investigate the maze for 3 min. Their motor activity, the number of sniffings, freezings, rearings, and arm entries were recorded. The rats visiting less than 3 arms during this period were discarded from further experiments.

On the basis of the preliminary tests the rats were divided into 9 groups. Each group comprised animals with similar horizontal and vertical motor activity and the number of entries. Before the experiments the rats

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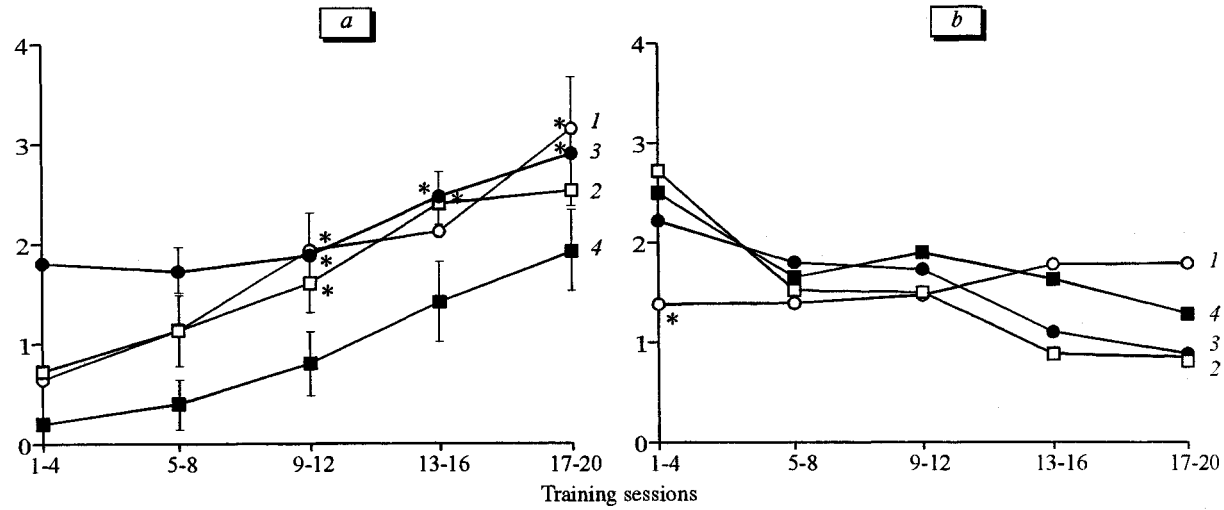

Fig. 1. Effects of Vp, amiridine, and tacrine on long-term (*a*) and working (*b*) memory in intact rats performing the radial maze task. Ordinate: number of consecutive (*a*) and repeated (*b*) entries into reinforced arms. *1*) Vp; *2*) amiridin; *3*) tacrine; *4*) control. *$p<0.05$ compared with control.

were allowed to habituate to the maze (3 min without reinforcement, for 2 consecutive days). After the selection and habituation procedures the training began. The reinforcement (100-220-mg pieces of bread) was placed in the 2nd, 4th, 6th, and 8th arms and the trial was started by placing the rat on the central position facing the 1st arm. After 4 entries into the arms with reinforcement, or any 8 entries, or after 3-min stay in the maze the rat was taken out.

The test drugs were injected in a dose of 0.1 mg/kg intraperitoneally 1 h before the session. The intact animals received them every other day. Scopolamine-treated rats were given daily injections of scopolamine and test drugs. Scopolamine (1 mg/kg) was injected 15 min prior to the session starting from the 5th session. The doses were determined on the basis of our previous studies [3]. To evaluate the effects of the drugs the following indices were used: the number of repeated entries into the reinforced arms (working memory errors); the number of 3 consecutive entries into the reinforced arms (long-term memory) [5]. As the scopolamine-treated rats significantly reduced the number of entries (less than 8 for 3 min), the state of their long-term memory was assessed by the number of entries into the reinforced arms per first 4 entries, including entries into the same arms.

Statistical analysis was performed using Student's *t* test.

RESULTS

When tested on the intact rats, Vp improved the long-term memory to the level of the reference drugs (Fig. 1, *a*). Statistically significant improvement of the long-term memory after Vp, amiridin, and tacrine was observed in sessions 8-12, 5-16 and 5-20, respectively.

At the same time, the number of repeated entries into the reinforced arms (working memory errors) in sessions 1-4 in Vp-treated rats was significantly lower than in control rats (Fig. 1, *b*) implying that unlike amiridin and tacrine, Vp improved also the working memory.

Scopolamine-treated rats showed a significant impairment of long-term memory in sessions 5-10 (Fig. 2, *a*) and a deficit of working memory for the whole period of training (Fig. 2, *b*). These results are in line with previous data on the effects of scopolamine on the radial maze performance [6,7] and justify the use of this model for studying the antiamnesic activity of the new drug.

Vp weakened the amnesic effects of scopolamine. Its antiamnesic activity was comparable to that of amiridin and tacrine. Vp, amiridin, and tacrine significantly improved the long-term memory in scopolamine-treated rats (Fig. 2, *a*). The improvement of working memory by these drugs reached the level of statistical significance during sessions 3-4 (Vp and tacrine) or 1-4 (amiridin), but did not progress with further training. The failure of complete reversal can be explained by irreversible changes in neuronal membranes (increased microviscosity and elevated cholesterol content) induced by chronic scopolamine treatment [4].

In conclusion, Vp improved the formation of long-term spatial memory and reduced the amnesic effects of scopolamine. These effects were comparable to those of amiridin and tacrine. In intact rats, Vp had a positive effect on the working memory at the initial stages of training. All these drugs improved working memory in scopolamine-treated amnesic rats.

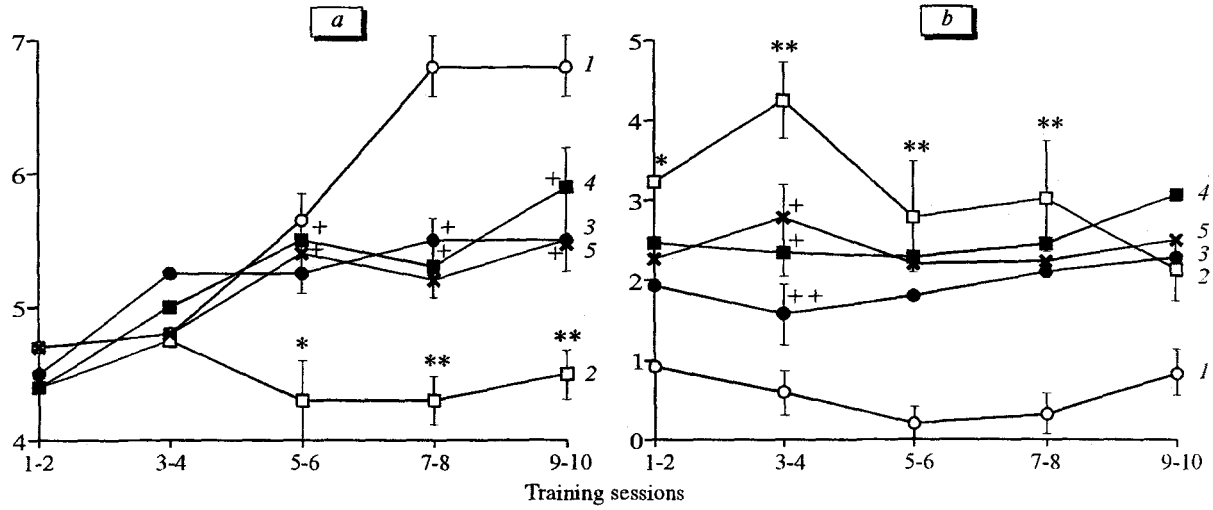

Fig. 2. Effects of Vp, amiridin, and tacrine on long-term (*a*) and working (*b*)memory in the radial maze task in scopolamine-treated rats. Ordinate: number of entries into reinforced arms per the first 4 choices (*a*) and number of repeated entries to reinforced arms (*b*). *1*) control; *2*) scopolamine; *3*) amiridin+scopolamine; *4*) tacrine+scopolamine; *5*) Vp+scopolamine. $^{*}p<0.05$, $^{**}p<0.001$ compared with control; $^{+}p<0.05$, $^{++}p<0.001$ compared with scopolamine-treated rats.

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