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Sustained Aftereffect of the Amnestic Action of Scopolamine in Rats and Its Elimination by Piracetam

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Experiments were carried out on male Wistar rats to assess (1) the effect of chronically administered (for 20 days) scopolamine on their learning capacity and memory 10 days after its last administration and (2) the influence of the nootropic piracetam, given for 10 days after scopolamine and before learning a conditioned passive avoidance response, on cognitive functions of the brain altered as a result of the M-cholinergic receptors being blocked by scopolamine. Scopolamine-dosed rats showed poor reproduction of the conditioned passive avoidance response when tested for this response at 24 h and 30 days after learning it, whereas those treated with piracetam after scopolamine retained the response well both at 24 h and at 30 days. Piracetam also restored the scopolamine-impaired acute extinction of orienting/exploratory activity in the rats.

Key Words: *scopolamine; piracetam; passive avoidance; exploratory activity*

Among the many indications for the use of nootropic drugs are conditions in which cognitive functions as altered as a consequence of age-related changes in the brain. There is convincing evidence that drugs of this group bring benefit to persons whose cognitive functions have become moderately disturbed in the course of natural aging and to patients in the initial stages of senile dementia [7].

Although the biochemical mechanisms of aging are many and varied, they share the common characteristic of reducing the activity of enzymes that synthesize the major neurotransmitters [5]. Compelling evidence has been presented for a deficiency of neurotransmitters for the cholinergic system [7], notably in the case of Alzheimer's disease [5]. An intensive search is underway for suitable animal models of cholinergic deficit that can be used to study the effects of nootropic agents. One such model, developed at the All-Russian Research Center for the Safety of Biologically Active Substances [1], involves long-term administration of the cholinergic receptor blocker scopolamine to rats. This drug has been shown capable of impairing the learning process as well as of altering the fluidity and fatty-acid composition of central nervous system membranes in a manner peculiar to naturally occurring aging. The present study was undertaken to define more precisely certain characteristics of that model by determining the period of time during which cognitive functions remain impaired after scopolamine dosing and how long the standard nootropic drug piracetam can exert a correcting effect on these functions.

MATERIALS AND METHODS

Male Wistar rats aged 6 months at the beginning of the study were used. There were three main

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TABLE 1. Piracetam Correction of Impaired CPAR and Impaired Acute Extinction of OEA in Rats after Their Exposure to Scopolamine

Group and dosing schedule	CPAR: latency of first entry into chamber after conditioning, sec		OEA, 1st min/10th min, ×100
	after 24 h	after 30 days	
Saline, 30 days (control group)	148.5*	180*	21.1
Scopolamine 1 mg/kg, 20 days + saline, 10 days	69.7	95.5	278
Scopolamine 1 mg/kg, 20 days + piracetam 250 mg/kg, 10 days	129.8*	167.3*	10.9
Scopolamine 1 mg/kg, once 30 min before conditioning	62		
Scopolamine 1 mg/kg, once 30 min before conditioning + saline, 10 days	128**		

Note: *$p \leq 0.05$ in comparison with rats dosed with scopolamine for 20 days and then given saline for 10 days; **$p \leq 0.05$ in comparison with rats given scopolamine once 30 min before conditioning.

groups, 13 animals in each. Rats of groups 1 and 2 were given intraperitoneal scopolamine injections at 1 mg/kg once daily for 20 days, while those of group 3 (control group) were injected intraperitoneally with physiological saline in the same dose over the same period. Subsequently, from days 21 to day 30, group 1 rats were given daily intraperitoneal injections of piracetam at 250 mg/kg and rats of the two other groups received saline injections in the same dose also for 10 days. Twenty-four hours after the last piracetam or saline dose, the rats were tested for acute extinction of orienting/exploratory activity (OEA). For this test, they were placed individually for 10 min in the chamber of an Opto-Varimex multichannel locomotor activity recorder (Colomozoo Co.), and the percentage ratio of the number of horizontal movements performed during the 10th minute in the chamber to that during the first minute was calculated as the index of habituation. Immediately after the completion of motor activity recording, a conditioned passive avoidance response (CPAR) was elaborated in the rats using a special device (Lafayette Instruments) [4]. Briefly, each rat was placed on an illuminated platform of the device with the tail facing a square opening leading to a dark chamber with an electrified floor; as soon as the rat was in the chamber, the opening was closed and 5 unavoidable painful electric stimuli of 1 mA and 1 sec in duration each were delivered at 2-sec intervals. The rats were tested for retention of the CPAR at 24 h and 30 days after learning this response, the criterion of retention being the latency of their first entry into the dark chamber.

In addition, two more groups of 10 rats in each were used. These groups received only one scopolamine dose (1 mg/kg) 30 min and 10 days, respectively, prior to CPAR conditioning and both were tested for retention of this response at 24 h after conditioning.

RESULTS

In rats given scopolamine for 20 days followed by saline for 10 days, this drug produced a well-defined amnestic effect, manifested in a shortened latency (as compared to control rats) of their entry into the "dangerous" chamber when they were tested for the CPAR 24 h after learning this response.

Another (previously undescribed) manifestation of impaired cognitive functions after prolonged scopolamine dosing was enhancement, rather than weakening, of OEA (Table 1). It should be stressed that we were dealing here with the scopolamine-altered time course of OEA extinction in the rats rather than with their initial locomotor hyperactivity. As is well known, animals will actively explore a new environment but will stop doing so if they find it to be indifferent to them, i.e., what we have here is an example of "negative conditioning".

Learning and memory were impaired in the present study after a 10-day interval between the last scopolamine injection and CPAR conditioning. In another study [1] rats showed no evidence of CPAR amnesia right after their chronic exposure to scopolamine. However, this M-cholinergic receptor blocker is known to be capable of impairing CPAR reproduction even after a single administration. In our study, too, a shortened latency of the CPAR was observed for rats given scopolamine in a single dose (Table 1), but this effect was not exhibited by rats that learned the CPAR 10 days after receiving a single scopolamine dose: at that time an amnestic effect was exerted by scopolamine only in rats that had been receiving it for a prolonged period (20 days). Such rats also dis-

played a shortened latency of entry into the chamber 30 days after CPAR conditioning. This finding attests to a long-lasting amnestic action of scopolamine after chronic exposure to it.

Piracetam given for 10 days to rats after their 20-day dosing with scopolamine significantly weakened the amnestic effect of the latter, as was evidenced by a prolonged latency of the CPAR both at 24 h and at 30 days after conditioning. We showed earlier [2] that compounds with nootropic activity accelerate the acute extinction of OEA. In this study, piracetam was found to restore the OEA extinction impaired by scopolamine. The nootropic piracetam thus corrected the impaired higher integrative functions of the brain caused by chronic scopolamine exposure, and the protective effect was still evident at day 30 after the discontinuation of piracetam treatment.

Chronically administered scopolamine causes the density and activity of cholinergic receptors to be increased by a feedback mechanism [3,6]. The absence of amnesia immediately after the termination of prolonged scopolamine dosing and its presence 10 days later led Burov *et al.* [1] to suggest that the discontinuation of scopolamine results in a rapid depletion of cholinergic transmission through accelerated binding of the available acetylcholine. The observation that scopolamine withdrawal was followed in rats by the development of changes in brain membranes similar to those occurring during aging prompted the above workers to consider chronic scopolamine exposure as a model of accelerated aging. Our findings permit a more detailed characterization of this rat model. Scopolamine dosing for 20 days followed by 10-day administration of physiological saline resulted, unlike a single scopolamine dose, in a marked and long-lasting deterioration of cognitive functions - not only was the reproduction of the CPAR based on associative learning impaired, but so also was the OEA extinction, which is based on nonassociative learning. Piracetam exerted an antiamnestic effect that persisted for at least 30 days after the termination of the 10-day treatment with this drug.

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