Effect of scopolamine on maze learning performance in humans[1]

D.D. Rasmusson and J.D. Dudar[2]

Department of Physiology and Biophysics, Dalhousie University, Halifax (N.S., Canada B3H 4H7), 3 January 1979

Summary. Scopolamine was administered orally to volunteers who were required to learn a digit memory task and a tactile maze task. Comparison of their performance with that under control drugs suggests that blockage of central cholinergic synapses may have a larger effect on spatial memory than on nonspatial memory. Subjects tended to make more errors under scopolamine and to insert extra turns in drawings of the maze.

Deficits in human memory may involve impairment of a cholinergic component in the hippocampus as indicated by the loss of hippocampal cholinergic enzymes[3,4] and by studies using the cholinergic blocking drug scopolamine[5,6]. A recent hypothesis has attempted to explain the often conflicting data from animal experiments by proposing that the hippocampus is involved in only 1 type of memory, that involving spatial relationships[7]. This proposal has not been contradicted by evaluation of human data[8].

Methods. In order to test the possible involvement of cholinergic mechanisms in spatial memory we tested paid male volunteers on a set of 3 complex finger mazes. Each maze was constructed from plastic building blocks and was placed under a screen so that the subject was not able to see it. Diagrams of the mazes are shown in the figure. They were designed to be of approximately equal difficulty but had to be sufficiently different from one another to reduce interference effects. Mazes R, S and T contained 28, 30 and 32 turns and 17, 23 and 21 blind alleys, respectively.

Each subject was tested under 3 drug conditions: Scopolamine (2 mg) which blocks muscarinic cholinergic synapses; methyl scopolamine (1 mg), a quaternary analogue of scopolamine which is not able to cross the blood-brain barrier and therefore mimics the peripheral effects of scopolamine; and lactose as a placebo. All drugs were administered orally. The order of maze and drug was counterbalanced in a 3×3 Greco-Latin square design, each subject receiving each drug and each maze once. At least 3 days intervened between repetitions on a subject. The experiment was run double-blind and each subject was given a preliminary physical examination to remove subjects who might be adversely affected by scopolamine.

1 h after drug administration the subjects were tested on a supraspan digit test, as described by Drachman[6]. This consisted of the experimenter reading 15 digits which had been randomly selected and asking the subject to repeat as many as possible. The sequence was repeated up to 10 times or until the subject was able to recall them perfectly. Following completion of the digit test, the subjects were required to learn the correct path through the finger maze by touch alone. The experimenter placed the subjects finger at the start of the maze at the beginning of each trial and recorded total time in the maze and entries into blind alleys. Trials were repeated until the subject traversed the maze without error in 4 out of 5 trials or to a maximum of 50 trials. After every 5th trial the subject was asked to draw a diagram of the correct path through the maze. These maps were later scored for the number and direction of correct turns.

Results and discussion. The hypothesis under consideration was whether scopolamine would have a greater effect on maze learning (involving spatial memory) than on the digit test (requiring only nonspatial memory). The results showed that the dosage of scopolamine used did not have any effect on supraspan digit recall. No difference was found between the scopolamine and the control conditions using Drachman's Digit Storage Index[6] or simply the number of correct digits on the 5th trial.

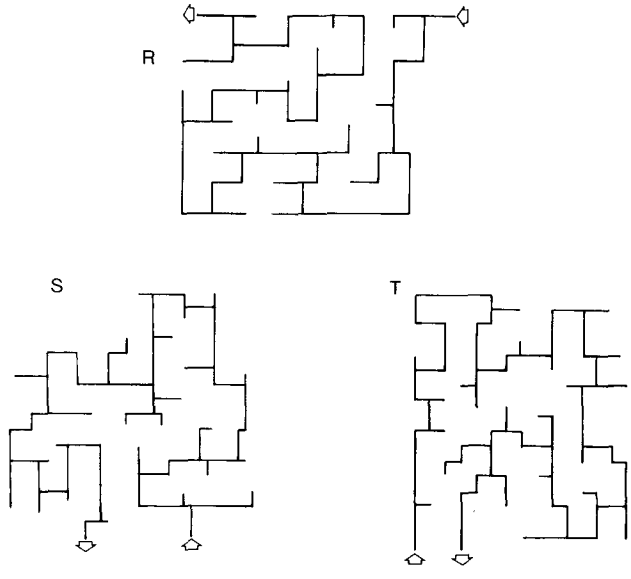
The results obtained from the maze learning conditions were somewhat ambiguous. The number of trials required to reach a criterion of 4 out of 5 perfect trials was not influenced by the drug (table, column 1). However, under scopolamine the subjects tended to make more errors during the course of learning (column 2). Here an error was defined as an entrance into a blind alley, repetitive errors into the same alley on a given trial not being counted.

With respect to the map drawings, the number of turns omitted was the same regardless of drug condition (column 3), but under scopolamine significantly more turns were drawn in the wrong direction and more extra turns were inserted (column 4).

Hartley's test for homogenity of variance showed that in both measures with significant differences (column 2 and 4) the variability in the scopolamine scores was significantly greater than in the other conditions. This corroborates an observation made during the course of the study that scopolamine had widely different effects on different subjects. We feel that this was probably due to variability in the rate of absorption of the drug. The use of i.m. injections

Mean scores on some aspects of maze learning under three drug conditions

Drug	Maze learning		Map drawings	
	Trials to criterion	Total No. of errors	Omitted turns	Extra turns
Scopolamine HBr	27.8	125	31.3	19.4
Methyl scopolamine HBr	27.9	108	32.4	13.9
Lactose	26.4	104	29.1	12.6
	n.s.	$p < 0.05$	n.s.	$p < 0.05$



Diagramatic representation of the 3 finger mazes used. The lines represent the alleyways which were depressions 16 mm wide and 10 mm deep.

in hospitalized subjects[6] would probably reduce this variability.

Large statistically significant practice effects were seen, as subjects invariably performed much better on their 2nd and 3rd mazes than on their first. The effect could have been greatly reduced by presenting the subjects with a practice maze before the initiation of the experiment itself. Also maze T proved to be significantly harder for the subjects to learn than the other 2 mazes.

In summary, we have found evidence to suggest that a low oral dose of scopolamine which did not interfere with storage of a long list of digits interfered with some factors in a spatial learning task. The fact that the overall rate of learning was not impaired makes it unlikely that the impairments observed were due to disruption of attentiveness. The types of impairment produced by scopolamine included entering more blind alleys and the insertion of extra turns in drawings of a 'mental map' of the maze. The large amount of variability in the scopolamine condition indicates the need for a more reliable route of administration.

1 Supported by MRC of Canada.
2 We greatly appreciate the assistance of Dr G.A. Klassen and Mrs J. Crozsman.
3 P. Davies and A.J.F. Maloney, Lancet *2*, 1403 (1976).
4 E.K. Perry, R.H. Perry, P.H. Gibson, G. Blessed and V.E. Tomlinson, Neurosci. Lett. *6*, 85 (1977).
5 D.A. Drachman and J. Leavitt, Archs Neurol. *30*, 113 (1974).
6 D.A. Drachman, Neurology, Minn. *27*, 783 (1977).
7 J. O'Keefe and L. Nadel, The hippocampus as a cognitive map. Oxford University Press, Oxford 1978.
8 J.A. Horel, Brain *101*, 403 (1978).

The postnatal evolution of muscular twitches in the developing rat

G. Lapointe and G. Nosal[1]

Département de Pharmacologie, Faculté de Médecine, Université Laval, Québec, GlK 7P4 (Canada), 16 October 1978

Summary. The reported study concerns the evolution of muscular twitches during the 21 postnatal days of the normal rat pups. The data indicate an age-dependent progression of these twitches in different body regions.

Previous studies on the neurobehavioral evolution of the rat during the postnatal development (Lapointe[2], Lapointe and Nosal[3]) had evidenced a particular developmental feature. During the 21 days of observation, the rat pups exhibited brief and unexpected muscular twitches that were of variable intensity. Such saccadic movements have been previously reported in growing animals: in the rat by Bolles ad Woods[4], Gramsbergen[5], Jouvet-Mounier and Astic[6] and in the mouse by Fox[7]. In addition, Jouvet-Mounier et al.[8] also observed similar movements in rats, mice and guinea-pigs.

However, no systematic study on the body distribution of muscular twitches during the postnatal growth of the rat has been described until now. As we were interested to include this developmental characteristic in our rat model of neurobehavioral evolution (Lapointe, Lin et Nosal[9,10]) we have undertaken a selective investigation on the onset, progression, body distribution and variations of the muscular twitches during the first 3 weeks following birth.

In addition, this behavioral criterion may be useful to appreciate changes in the wake-sleep state of growing rats during the preweaning period of life.

Material and methods. 10 fertile female Sprague-Dawley rats were mated with 10 males of the same strain. They delivered healthy litters which were reduced at birth to 8 pups (4 females and 4 males). A total of 80 pups were used for this study. Controls were performed daily at the time corresponding to the birth hour (±1 h). This daily time has been selected in order to avoid age-related differences between the litters. According to several criteria (morphological and behavioral), which were previously investigated, we found that a few h difference within the first 48 h could be also significant on the neurological state of the neonatal rats. In the case of older pups, identical daily timed controls were applied to all animals with the view to minimize individual variations occurring in the 24-h biological rhythms.

For this specific testing, the pups were placed individually in a plastic cage for a 1-min duration. The body was arbitrarily subdivided into 6 separate zones: the head, the trunk, the dorsoventral region, the tail, the limbs and finally the entire body. The frequency of muscular twitches was recorded by means of a manual counter solely when the animal was at the rest state. However, the same pups were submitted each day to the entire test battery (Lapointe and Nosal[3]) following muscular twitches evaluation. The total time of observation for each pup was of 5–6 min per day.

Experimental results were expressed in twitches/min/animal with the respective SEM for each age from day 1 to day 17. We have chosen the experimental procedure of 1 daily testing on more numerous animals, rather than several twitch tests on a restricted number of animals.

Results. In the postnatally growing rat, muscular twitches are typically characterized by: a) an intermittent occurrence; b) an unexpected sequence of appearance in different regions and c) brief movements of varying magnitude.

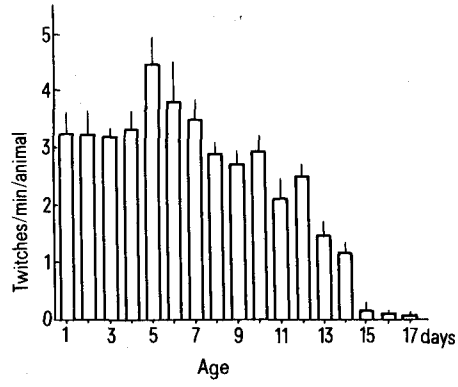


Fig. 1. Evolution of total muscular twitches at different ages (vertical bars represent SEM).