ORIGINAL ARTICLE

INFLUENCING OF SPATIAL MEMORY IN RATS BY DSP-4 AND MESCALINE

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Summary: Behavioural effects of two experimental neurotoxins, mescaline and DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine), on retention of spatial orientation were studied in the T - maze. The stereotaxic administration of both neurotoxins into the selected brain structures was chosen to reveal this effect. The intensity and time course of the neurotoxic effect were dependent on the brain area administered. Nevertheless, the lengthening of the latencies in reaching the goal was generally more marked after mescaline in comparison with DSP-4.

Key words: *DSP - 4; Learning; Mescaline; Stereotaxic administration; T - maze*

Introduction

Selective destruction of relatively homogeneous neuronal populations by means of specific neurotoxins represents an important experimental tool for modelling various pathological conditions of the central nervous system. The neurotoxin DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride, has a predilection for the noradrenergic terminals of the brainstem nucleus of the locus coeruleus. It readily passes the blood - brain barrier when administered systemically to rats and causes a rapid and long-lasting depletion of norepinephrine (NE) in the cerebral cortex, hippocampus, cerebellum and spinal cord (4,6). Although the effect of systemic administration of DSP-4 was studied extensively enough (5,7,9), a lack of information exists on the local „lesion" strategy. That is why we studied retention of spatial orientation in the T-maze with food motivation in rats subjected to DSP-4 lesions of selected brain areas. Effects of DSP-4 and hallucinogen mescaline, administered in the same way, were compared. The action of both drugs tested are possibly mediated via their spontaneously formed cyclic aziridinium ion derivatives in the brain (8,22).

Materials and methods

Fifty four adult male Wistar rats weighing 210 - 250 g were used at the beginning of experiments. The animals were adapted to the conditions of the laboratory vivarium for a period of 14 days. Out of the experimental sessions, the rats were kept in plexiglass cages with three animals in each. During the experiments with appetitive motivation in the T-maze the diet was decreased to 8 pellets for a rat per day, water was accessible *ad libitum.* One group always consisted of six animals.

The T-maze was composed of fine segments (each 12 cm wide, 30 cm long, 11 cm high) fitted on one to another. Both the starting and finishing parts were the same measuring 26 x 26 cm. The experimental conditions utilized the rats ability to find their way along a set of passages. The hungry animal had the task to make its way through the maze, without turning aside into various arms, until it reached the exit, where food awaited it in form of a few pellets.

The rats were trained in the T-maze once a day for 14 days. The longest time spent in the maze was 3 minutes. Those animals which did not reach the exit or took longer than permitted 3 minutes were discarded. Completing their training, the rats were divided into six experimental groups (both drugs administered into three selected brain structures separately) and three groups of control shame-operated rats administered only saline into the same brain structures to check up on effects of anaesthesia and surgery.

Throughout the actual sessions, the time latency taken to reach the target and the number of incorrect turns aside were counted.

Administration of drugs tested was performed by means of permanently introduced cannula. Animals were placed in a stereotaxic frame under sodium thiopental (50 mg/kg Thiopental VUFB inj., intraperitoneally) anaesthesia. After incision and retraction of skin, connective tissue and muscle, trephine openings approximately 1 mm in diameter were placed onto the exposed skull unilaterally to the left with respect to the sagittal suture. The stereotaxic coordinates of the intracerebral cannulae were as follows: the ventriculus lateralis cerebri - 1.0 mm behind the bregma, 3.75 mm below the surface of the skull (V) and 1.6 mm laterally to the

sagittal suture (L), the nucleus basalis of Meynert (nbM) - 0.8 mm behind the bregma, V=8.0 mm, L= 2.6 mm, the nucleus septi medialis (nsm) - 0.75 mm before the bregma, V=5.5 mm, L= 0. Recovery period between surgery and drug administration was 48 hours. DSP - 4 and mescaline were given in a dose of 0.1 mg in a volume of 3 μl of 0.9 % saline.

Effect of mescaline was investigated 60 and 120 minutes after administration and further during 22 succesive days (one trial per day). Effect of DSP-4 was investigated 30 and 90 minutes after administration and then during 9 consecutive days (one trial per day).

At the end of this study, the experimental animals were given a lethal dose of sodium thiopenthal, brains were removed after tracing the cannula pathway with methylene blue for verification of targeted brain structures, frontal brain sections were processed by standard histological method for hematoxyline-eosine stained slides.

The statistical analyses were performed on a PC with the BMDP program P7D: analysis of variance (ANOVA), t-test with Bonfferoni's correction.

Tab. 1: Control and experimental groups, their characterization, number of animals in each group used, concentration of chemicals, site of their administration in the brain structures, and time schedule of examination

Group	*Drugs*	*Structure*	*Time of Examination*
Control	0,9 % saline	v.c.l.	30, 60, 90, 120 min.,
Experiment 1	Mescaline	n.b.M.	1, 2, 3, 4, 5, 6, 7, 8,
Experiment 2	DSP - 4	n.s.m.	9, 10, 14, 15, 16, 19,
n = 6	0,1 mg in 3 l		21, 22 days
	0,9% saline		

Results

Mescaline lengthened time latency of finding the goal in the T-maze 60 and 120 minutes after its administration into the nbM and nsm. At the same time, the effect of intracerebroventricular administration of mescaline did not differ from the control group with saline only. After mescaline administration, the deterioration of spatial orientation was observed in all groups with structures tested on day 1 and day 2. However, decline in time latency outlasted for much longer time in the nbM group, and especially in the nsm group in comparison with rats given the mescaline into the lateral cerebral ventricle (Fig. 1). DSP-4 worsened the performance in the T-maze 30 and 90 minutes after its administration into the lateral cerebral ventricle, this effect lasted only 48 hours. Protraction of time latency was somewhat longer (until day 3) after administration of DSP-4 into the nbM. On the contrary, the lengthening of time latency was lesser in case of DSP-4 administration into the nsm (Fig. 2). Histological verification proved the right placement of the cannula tip into all targeted structures.

Discussion

We have previously demonstrated mescaline capability to impair spatial orientation and movement of experimental animals in an open field after systemic administration (10,11). Attempting to obtain further information on possible sites of intervention of neurotoxins in the brain, we chose a local mode of administration into the selected brain structures in the present study.

The nbM and nsm represent the source of two principal cholinergic systems of the brain (12,19). The role which septum plays for the hippocampus is similar to that of the nbM for the neocortex. At present, the key role of the nbM in the etiopathogenesis of senile dementia of Alzheimers type is recognized: it holds true particularly for early stages of this disease (15,18).

Mescaline showed the most marked supressive effect on spatial behavior of experimental animals after administration into the nbM, and especially into the nsm. On the other hand, the administration into the lateral cerebral ventricle was less effective. These changes make us think of possible participation of monoaminergic neurotransmissíon in its mechanism of action. There are evidences that combined disruption of noradrenergic and cholinergic transmission may result in some cognitive disturbances (1,2,15). At two-phase effect of mescaline was also noted. It consisted of initial prolongation of examined time latency, followed by a certain shortening of it, which was followed by further period of latency prolongation. Similar pattern was observed by Davis and Hatoum (1987) in case of active evasive reaction. This effect could be explained by gradual interference of mescaline with more than only one neuronal mechanism. The first one could react „immediately", i.e., in hours or maximally days after administration of single dose of drug. The second one is „delayed" after latency of more than one week. We suppose that former „immediate" mechanism is based on a direct action predominantly at the receptor level, whereas the „delayed" reaction probably reflects the actual destructive changes of the whole neuronal populations induced by the neurotoxic effect (8).

Also the results of experiments with DSP-4 make us think of participation of a central noradrenergic mechanism. Published data confirm participation of this system in some forms of learning and memory (13,14,16,17,20). Depletion of norepinephrine after DSP-4 administration generally results in a decrease of searching activity, a decreased reaction to novelty, and increased latency of approach behaviour (4).

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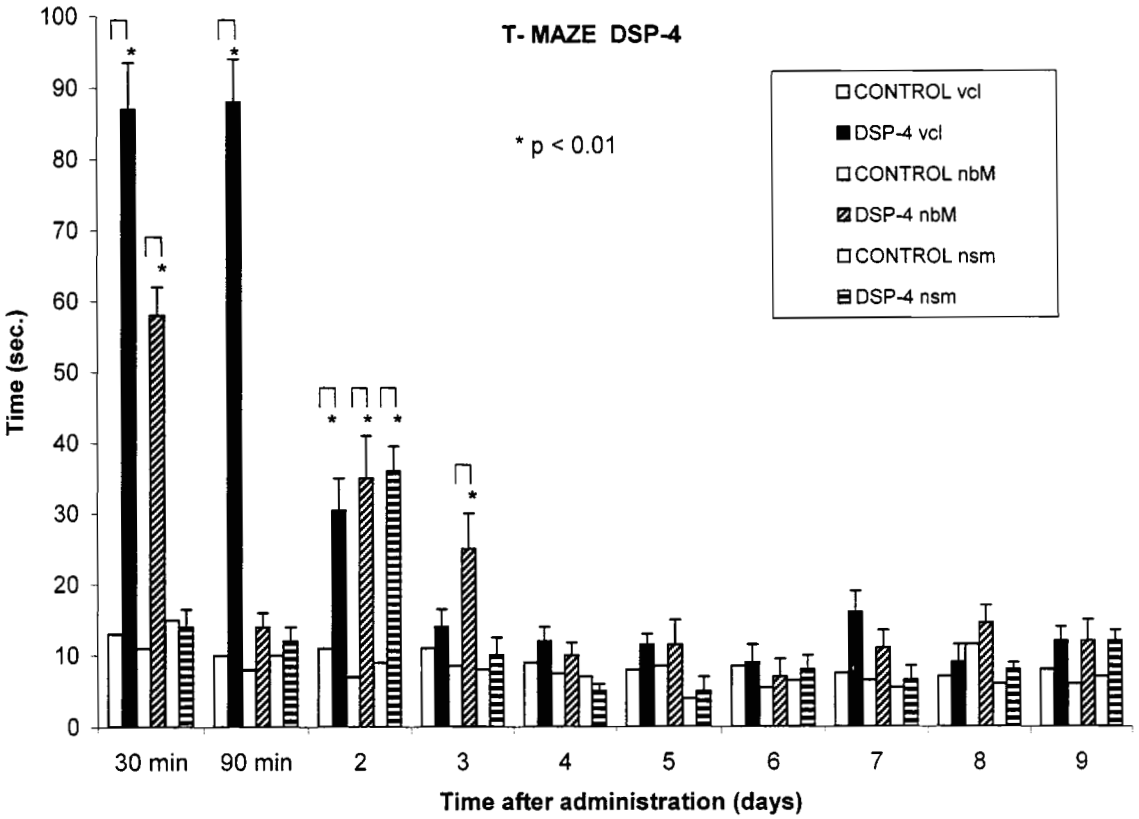

Fig. 1: Effect of mescaline in a dose of 0.1 mg on spatial orientation of animals tested in the T-maze.

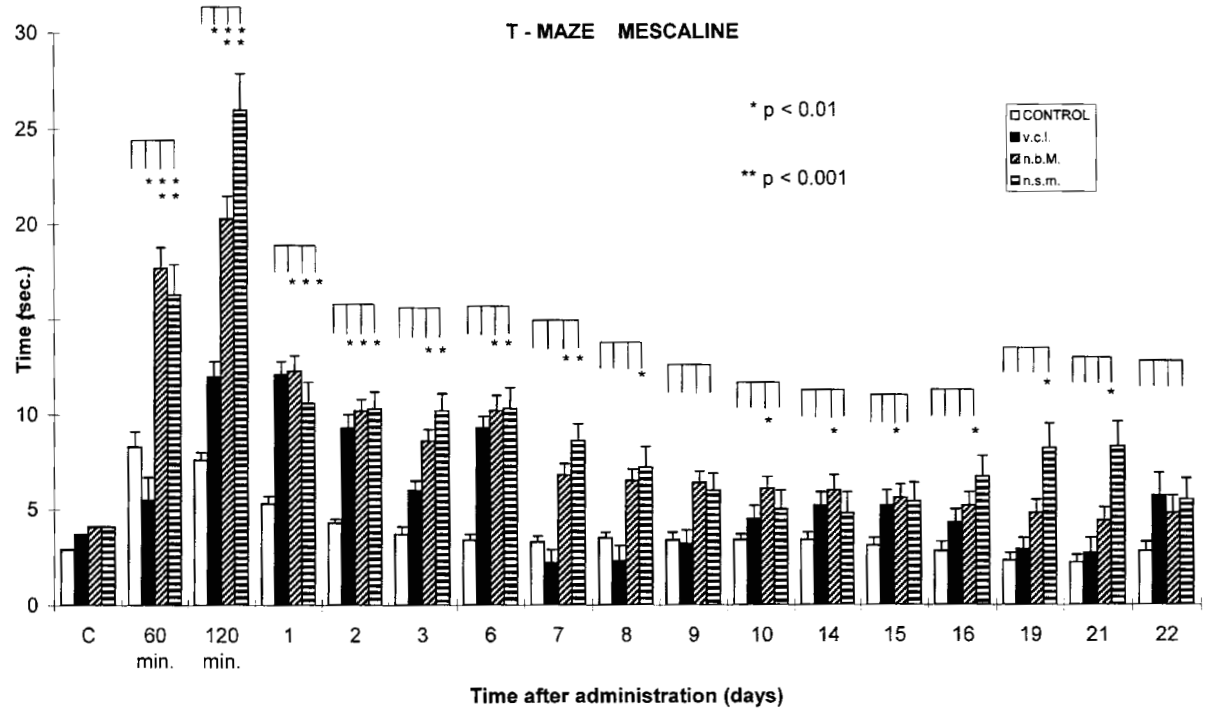

Fig. 2: Effect of DSP-4 in a dose of 0.1 mg on spatial orientation of animals tested in the T-maze.

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