EFFECTS OF SOME DOPAMINE AGENTS ON MODULATION OF MEMORY PROCESSES PERFORMANCE IN RATS

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EFFECTS OF SOME DOPAMINE AGENTS ON MODULATION OF MEMORY PROCESSES PERFORMANCE IN RATS (Abstract) Apomorphine is a potent dopamine receptor agonist which has been used as a neuro-protective agent in the treatment of Parkinson’s disease. SCH-23390 is a synthetic compound that presents selective D1 dopamine receptors antagonist activity and possesses pharmacologic effects similar to standard antipsychotics.

Aim: Experimental researches on the effects of two substances acting on dopamine receptors on the cognitive processes in rats. Material and methods: The experiment was carried out on white male Wistar rats (150-200g) divided into 3 groups of 6 animals each, treated intraperitonealy with the same volume of solution as follows: Group I (Control): saline solution 0.3ml; Group II (coded APO): apomorphine 2mg/kbw; Group III (coded SCH): SCH-23390 0.3mg/kbw. Working memory was assessed using the radial-arm maze. The following measures were recorded: the number of entering an arm containing food, but previously entered (working memory errors); the number of entering an arm that was not baited (reference memory errors); time taken to consume all five baits and the number of arms entered until a repeat entry was made (entries to repeat). The data were presented as mean +/- standard deviation and significance was tested by SPSS Statistics for Windows version 17.0 and ANOVA method. Experimental protocol was implemented according to the recommendations of the “Grigore T. Popa” University Committee for Research and Ethical Issues. Results: In our experimental conditions dopamine agonist apomorphine produced significantly (p<0.05) more novel choices in the first eight-arm entries than the saline vehicle. The animals treated with apomorphine entered significantly (P<0.05) more arms compared to the control group. D1 receptor antagonist SCH-23390 induced a significant decrease (p<0.05) in the number of working memory errors (elements relevant for short-time memory quantification) and average time taken to consume all five baits (p<0.05), but did not modify the number of reference memory errors (for long-time memory quantification) compared to the control group, suggesting a short-time memory retention enhancement and an improvement of discriminative spatial learning. SCH-23390 administration resulted in a not quite significant increase in the number of entries to repeat compared to control rats. Conclusions: The administration of apomorphine also increased the search efficiency in total arm entries, suggesting that it facilitates the response in the test session of secondary reinforcement, more than rewarding, effect combined with a lack of discrimination. Our research revealed that D1 receptor antagonist SCH-23390 influenced short-time memory, without affecting long-time memory of experimented animals. Keywords: APOMORPHINE, SCH-23390, RADIAL ARM MAZE, COGNITIVE
Dopamine is a neurotransmitter with an important role in forming long-lasting memories for some time, especially in episodic memory. Literature data show that dopamine receptor stimulation may be detrimental to the spatial working memory functions in lab animals (1, 2).

Apopomorphine chemically designated as 6αβ-Aporphine-10,11-diol hydrochloride hemihydrate, is a non-ergoline potent dopamine receptor agonist which has been used as a neuro-protective agent in the treatment of Parkinson disease (3).

(R)-(+) 7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride derivative SCH-23390, a synthetic compound acting as a selective, high-affinity antagonist of D1 receptors, possesses pharmacologic effects similar to standard antipsychotics (4).

**MATERIAL AND METHODS**

Male white Wistar rats (150–200g) were used in the study. Animals were housed in plastic cages in an animal room maintained at 23 ± 1°C on a 12-hour dark cycle (light period, 07:00 – 19:00).

Animals received water *ad libidum* and were maintained at 85% of their free feeding weight by controlling the amount of their single daily meal 45 minutes after the experimental session. Before the experiment, rats were placed on a raised wire mesh, under a clear plastic box and allowed 2 hours to acclimate to the testing room.

The animals were divided into 3 groups of 6 subjects each, and treated intraperitoneally as follows:

- **Group I** (Control): saline solution 0.3ml;
- **Group II** (coded APO): apomorphine 2mg/kbw;
- **Group III** (coded SCH): SCH-23390 0.3mg/kbw.

The used drugs, apomorphine, SCH-23390 (Sigma-Aldrich Chemical Company), were dissolved in 0.9% saline, prepared just before use. All drugs were injected intraperitoneally in a constant volume of 1 ml/kg body weight.

The hypothesis that dopamine receptor subtypes are involved in mediation of cognitive pathways is based on a number of experimental reports indicating various activities of different dopamine agents in spatial learning and memory.

To directly prove this hypothesis we investigated the effects of dopamine agonist apomorphine and selective D1 receptor antagonist SCH-23390 on rat memory performance in radial arm maze, a test designed to evaluate lab animals memory processes performances. This standardized test is used as a tool for assessing the neurobehavioral characteristics of memory processes based upon spatial cognition. The substances were administered one hour before the beginning of a behavioral session.

The radial eight-arm maze device consists of central platform (30cm in diameter) elevated from the floor with eight arms (10x80cm) extending radially. The black Plexiglas maze is mounted on an adjustable height tripod (up to 1m). Each arm has lateral walls higher on the proximal side of the arm than on the distal one. On the distal end of each arm, a detachable recessed cup can be installed or replaced by covered up. Food cups for the reinforces were located near the end of each arm.

The design of this device ensures that after checking for food at the end of each arm the animal is forced to return to the central platform before making another choice. The rat always has eight possible options.
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After initial acclimation to the laboratory environment there were two daily sessions of 5 min each in which the rat was placed on the maze without bait in the arms. The subject was then trained to run down a single arm to obtain a piece of cheese as the bait. The animals were assigned to learn either the place task or the cue task. Before each session each of the arm was baited with a reinforcer (piece of cheese), placed in a food cup at the end of the arm. The animal was placed on the central platform of the device, allowed to move freely about the maze, and a digital timer was started for a 5 min period of time.

All eight arms of the maze were accessible but four randomly selected were baited.

The arms were not re-baited during the session. Entries into arms previously entered were counted as errors. The session continued until either the animal entered all eight arms or 5 minutes elapsed. The maze was cleaned between trials.

The following measures were recorded: number of novel arms entered during the first eight choices on an un-baited eight-arm maze as well as the total number of arms entered during 5 min, the number of entering an arm containing food, but previously entered (working memory errors); the number of entering an arm that was not baited (reference memory errors); time taken to consume all five baits, and the number of arms entered until a repeat entry was made (entries to repeat). Facilitation of efficient search behavior required an increase in the number of novel arms entered in the first eight choices, rather than simply an increase in total arms entered during the trial.

A camera set above the maze and connected to a monitor in a neighboring room was used to allow us to score behavior without disturbing the animals. All trials were videotaped and subsequently analyzed by a trained observer who was blind to the treatment condition.

Data for each measure were evaluated separately by analysis of variance for repeated determinations. Results were expressed as arithmetic mean ± SD and represented graphically. All values were processed using SPSS for Windows version 17.0 and ANOVA method. P-values less than 0.05 were considered statistically significant compared with those of controls.

Experimental protocol was implemented following the recommendations of the “Grigore T. Popa” University Committee for Research and Ethical Issues guidelines for handling and use of experimental animals, according to the ethical standards of the European Community.

Each animal was used once only and the duration of the experiments was kept as short as possible. For ethical reasons, all the animals were sacrificed at the end of the experiment.

RESULTS AND DISCUSSION

In our experimental conditions apomorphine administration significantly influenced the data of radial arm maze test compared to control group.

Intraperitoneal injection of dopaminergic agonist apomorphine had an evident effect on increasing search efficiency. It produced significantly (p<0.05) more novel choices in the first eight-arm entries than either the saline vehicle.

Statistical analysis showed that animals treated with apomorphine consistently entered significantly (p<0.05) more arms compared with the control group.

In the behavioral experimental model
used, D1 receptor antagonist SCH-23390 induced a significant decrease (p<0.05) in the number of working memory errors (elements relevant for short-time memory quantification) and average time taken to consume all five baits (p<0.05), but did not modify the number of reference memory errors (for long-time memory quantification) compared to control group, suggesting a short-time memory retention enhancement and an improvement of discriminative spatial learning (fig. 1, 2, 3).

SCH-23390 administration resulted in a quite insignificant increase (p<0.05) in the number of entries to repeat compared to control rats.

**Fig. 1**-Effects of apomorphine and SCH-23390 treatment on the number of working memory errors in radial arm maze test. Values were expressed as mean ± S.E.M of the number of working memory errors. *p<0.05, **p<0.01 vs control.

**Fig. 2**-Effects of apomorphine and SCH-23390 treatment on time (seconds) taken to consume all five baits in radial arm maze test. Values are expressed as mean ± S.E.M of the time taken to consume all five baits. *p<0.05, **p<0.01 vs control.
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**Fig. 3**-Effects of apomorphine and SCH-23390 treatment on the number of reference memory errors in radial arm maze test. Values are expressed as mean ± S.E.M of the number of reference memory errors. *p<0.05, **p<0.01 vs controls.

Different studies using a variety of approaches suggest that the dopamine pathway may be a key component in modulating activity in the central areas to facilitate behavioral flexibility (1, 10).

The central dopamine receptors, especially D1 receptors in the prefrontal cortex, may be very important for mediating dopamine effects on cognitive functioning (11, 12, 13).

Literature data show that apomorphine stimulates post-synaptic dopamine D2-type receptors within the caudate putamen in the brain. Different researches revealed that apomorphine improved motor function in an animal model of Parkinson disease and also attenuated the motor deficits induced by experimental lesions in the ascending nigrostriatal dopaminergic pathway in lab animals (14, 15).

Recent cognitive studies proved that apomorphine dose-dependently impaired recognition memory in animals. It is well known the involvement of dopamine receptors in rodent memory and in spontaneous exploration behavior (16).

Experimental studies suggest that SCH 23390 may prevent the spatial working memory disturbances induced by active substances of marijuana, and block the apomorphine-induced stereotypy and methamphetamine-induced lethality in experimental models (17, 18). Also it presented anti-stereotypic, cataleptogenic, and inhibitory effect onamphetamine circling in different laboratory animal species (19).

**CONCLUSIONS**

The results indicate that facilitation of unconditioned preparatory behavior by dopamine agonist apomorphine applies also to efficient maze search. The administration of apomorphine also increased the search efficiency in total arm entries, suggesting that it facilitates the response in the test session of secondary reinforcement, more than rewarding, effect combined with a lack of discrimination.
Our research revealed that D1 receptor antagonist SCH-23390 influenced short-time memory, without affecting long-time memory of experimented animals. SCH-23390 administration facilitated spatial working memory, as measured by improved choice accuracy in the radial arm maze, when administered to rats.

REFERENCES