STUDY THE EFFECTS OF ARIPIPRAZOLE AND OLANZAPINE ON LEARNING AND MEMORY IN NAÏVE RATS AND RATS WITH APOMORPHINE INDUCED BEHAVIOUR

Topolov M, Getova D
Department of Pharmacology, Medical University Plovdiv, Bulgaria

INTRODUCTION
• Aripiprazole is a new antipsychotic drug, which is an alternative to current antipsychotic drugs that adversely affect cognitive processes [1]. Aripiprazole’s unique pharmacological mechanism of action is different from other atypical antipsychotics and it’s partial dopamine D2 and serotonin 5-HT1A receptor agonist activities have been postulated to confer clinical efficacy and a relatively favorable overall side-effect profile[2].
• Atypical antipsychotic clonazepam acts as dopamine, serotonin and muscarinic antagonist and these transmitters could account for memory impairment in working memory tasks [3].
• Aripiprazole improved short-term memory in mice with a model of Alzheimer’s disease and the effect could be due to dopamine-receptor dependent mechanism [4].

DESIGN OF THE EXPERIMENT
Mice Wistar rats, were divided in 2 series with several groups (n = 8) in each. The animals were treated intraperitoneally with:

First series (naïve rats)
1st group with saline (controls) – 0.1 ml/100g;
2nd group with clonazepam – 1mg/kg;
3rd group with clonazepam – 3mg/kg;
4th group with clonazepam – 5.0mg/kg;
5th group with clonazepam – 1mg/kg;
6th group with clonazepam – 2mg/kg.

Statistical analysis was done by using ANOVA and the mean and the SEM was calculated. The comparison was made using repeated measurement analysis.

RESULTS
First series – naïve rats
On naïve rats the control group significantly increased (p<0.05) the number of avoidance on learning and memory retention, compared to the first day (Fig.1). Rats treated with clonazepam at a dose of 1mg/kg decreased the number of aviances on 4th and 5th days of learning session and on memory retention test, compared to the respective day controls (p<0.05) (Fig.1). Rats treated with clonazepam at a dose of 3mg/kg decreased significantly the number of aviances on 3rd, 4th and 5th days of learning session and on memory re-test as well, compared to the same day controls (p<0.05) (Fig.1).

On naïve rats the control group did not change the number of escapes on learning session and memory retention test (Fig. 2).
Rats treated with clonazepam at a dose of 1mg/kg decreased the number of escapes (p<0.05) on 2nd, 3rd and 4th days of learning session, but did not changed them on memory retention test, compared to the same day controls (Fig. 2). Rats treated with clonazepam at a dose of 3mg/kg decreased the number of escapes on 1st, 2nd, 3rd, 4th and 5th days of learning session and on memory retention test as well, compared to the same day controls (p<0.05) (Fig.2).

Second series (challenged rats)

On naïve rats the control group significantly increased (p<0.05) the number of aviances on learning and memory retention, compared to the first day (Fig.3). Rats treated with clonazepam 0.5mg/kg did not change significantly the number of aviances on the learning session but decreased them (p<0.05) on memory re-test, compared to the same day controls (Fig.3). Rats treated with clonazepam at dosages of 1mg/kg and 2mg/kg decreased significantly the number of aviances on 4th and 5th days of learning session and on memory retention test, compared to the same day controls (Fig.3).

Second series – challenged rats
On naïve rats the control group did not change the number of aviances on learning and memory retention test (Fig. 4). Rats treated with clonazepam at dose of 0.5mg/kg increased the number of aviances on 2nd day of the learning session (p<0.05) but did not changed them on memory retention test, compared to the same day controls (Fig. 4). Rats treated with clonazepam at dose of 5.0mg/kg decreased the number of escapes (p<0.05) only on the 1st day of the learning session, but did not changed them significantly on the memory retest. Rats treated with clonazepam at dose of 1mg/kg did not change significantly the number of escapes neither on the lear-ring session and the memory retest, compared to the same day controls (Fig.4). Rats treated with clonazepam at dose of 2mg/kg decreased the number of escapes during the hole learning session (p<0.05) and on memory re-test as well, compared to the same day controls (p<0.05) (Fig.4).

On naïve rats the control group did not change the number of escapes on learning session and memory retention test (Fig. 2). Rats treated with clonazepam at a dose of 1mg/kg decreased the number of escapes (p<0.05) on 2nd and 3rd days of the learning session, but increased the number of escapes (p<0.05) on the 4th day of the learning session as well as on the memory retention test (p<0.05) (Fig.6). Rats treated with apomorphine 0.5mg/kg and aripiprazole 1mg/kg decreased the number of escapes (p<0.05) on the hole learning session as well as on the memory retention test (p<0.05), compared to the respective day of apomorphine group (Fig.6). Rats treated with apomorphine 0.5mg/kg and clonazepam 1mg/kg decreased the number of escapes (p<0.05) on 1st and 2nd days of the learning session, but did not change the number of escapes on the memory retest (Fig.6).

DISCUSSION
Our data permitted the suggestion that antipsychotic drugs aripiprazole and clonazepam impaired learning and memory in active avoidance test on naïve rats, because the controls showed markedly capability of naïve rats to learn and to memory consolidate the task. The findings reveal that antipsychotic drugs aripiprazole and clonazepam impair the learning and memory.
According to the dopamine hypothesis apomorphine is a direct dopamine receptor agonist in animals and man and exacerbate the behavioral reactions [5, Depoite & Lal 2001]. They propose that this effect derives from the stimulation of presynaptic dopamine receptors, which inhibits dopamine neurotransmission. Probably the impairment of learning and memory in our study by both aripiprazole and clonazepam lead us to suggest that both antipsychotic drugs block the postsynaptic dopamine receptors and apomorphine, acting mainly postsynaptically decreases the dopamine release and the final effect is memory impairment. The suppressed memory effect of aripiprazole is more pronounced than that of clonazepam, probably due to its partial dopamine agonism.

REFERENCES

Acknowledgement:
This work is part of Scientific project HO-03.2012 of MU-Plovdiv, Bulgaria.