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

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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 D(2) and serotonin 5-HT(1A) receptor agonist activities have been postulated to confer clinical efficacy and a relatively favorable overall side-effect profile[2].
- Atypical antipsychotic olanzapine acts as dopamine, serotonin and muscarinic antagonist and these transmitters could account for memory impairment in working memory tasks [3].
- Apomorphine induced conditioning effect by stimulation of dopamine receptors. Apomorphine 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].

The aim of the study was to assess the impact of aripiprazole and olanzapine on behavioral functions of rats with particular emphasis on memory after multiple dosing.

DESIGN OF THE EXPERIMENT

Male 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 aripiprazole – 1mg/kg;
3rd group with aripiprazole – 3mg/kg;
4th group with olanzapine – 0.5mg/kg;
5th group with olanzapine – 1mg/kg;
6th group with olanzapine – 2mg/kg.

Second series (challenged rats)

1st group with saline (controls) – 0.1 ml/100g;
2nd group with apomorphine – 0.5mg/kg
3rd group with apomorphine 0.5mg/kg and aripiprzole 1mg/kg
4th group with apomorphine 0.5mg/kg and olanzapine 1mg/kg

METHODS

1. Two way active avoidance test
Aparatus – automatic reflex conditioner (Ugo Basile)

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Learning session [30 trials, 6s light and buzzer (670Hz and 70dB), followed within 3s 0.4mA foot shock and 10s pause] – 5 consecutive days

⬇

7 days later (after last learning day)
Memory retention session [30 trials, same parameters without foot shock] – 1 day

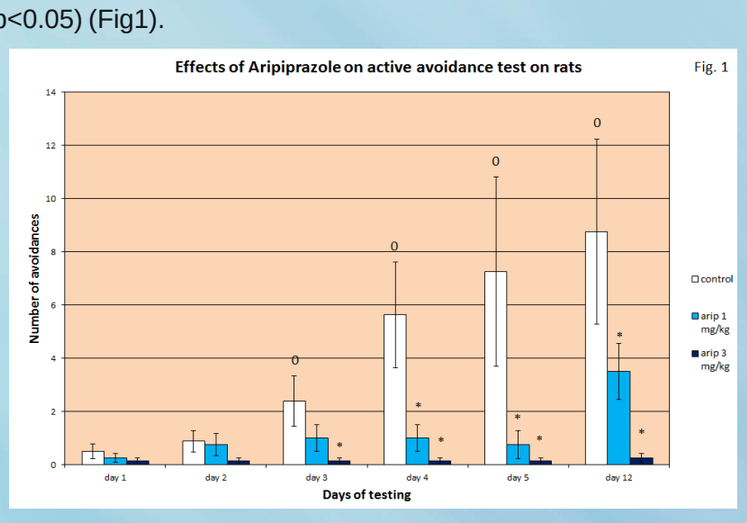
Observation mode: number of
1. conditioned stimuli reactions i.e. avoidances
2. unconditioned stimuli reactions, i.e. escapes

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

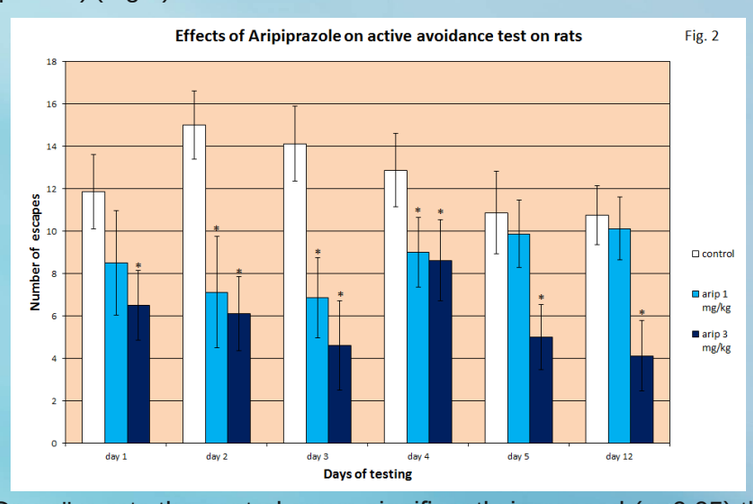
RESULTS

First series – naïve rats

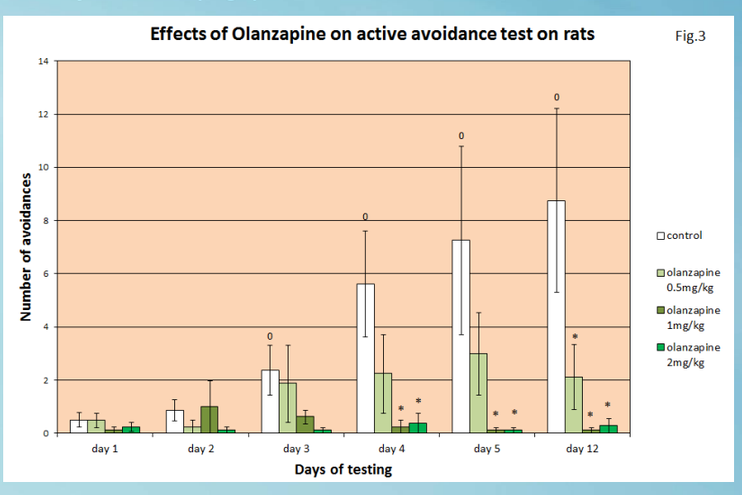
On naïve rats the control group significantly increased (p<0.05) the number of avoidances on learning and memory retention, compared to the first day (Fig.1). Rats treated with aripiprazole at a dose of 1mg/kg decreased the number of avoidances on 4th and 5th days of learning session and on memory retention test, compared to the respective day controls (p<0.05) (Fig1). Rats treated with aripiprazole at a dose of 3mg/kg decreased significantly the number of avoidances 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) (Fig1).



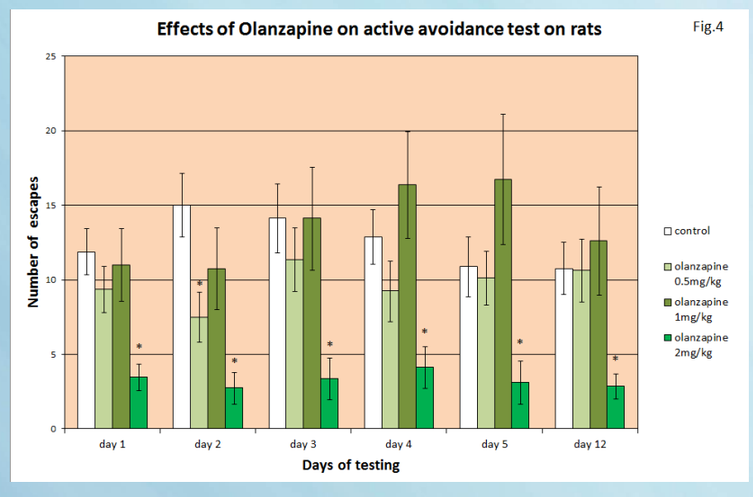
On naïve rats the control group did not change the number of escapes on learning session and memory retention test (Fig. 2). Rats treated with aripiprazole at a dose of 1mg/kg decreased the number of escapes (p<0.05) on 2nd, 3rd and 4th days of learning session, but did not changed them on memory retention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



On naïve rats the control group significantly increased (p<0.05) the number of avoidances on learning and memory retention, compared to the first day (Fig.3). Rats treated with olanzapine 0.5mg/kg did not change significantly the number of avoidances 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 olanzapine at dosages of 1mg/kg and 2mg/kg decreased significantly the number of avoidances on 4th and 5th days on learning session and on memory retention test, compared to the same day controls (Fig3).

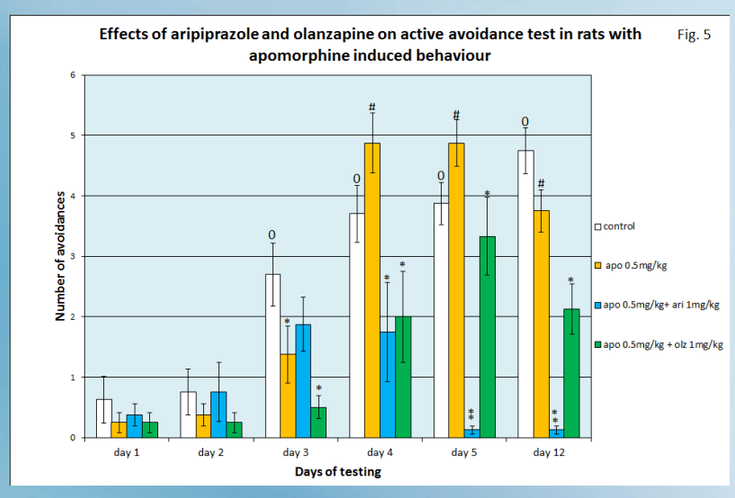


On naïve rats the control group did not change the num-ber of escapes on learning session and memory retention test (Fig. 4). Rats treated with olanzapine at dose of 0.5mg/kg decreased the number of escapes on 2nd day of the learning session (p<0.05) but did not changed them on memory retention test, compared to the same day controls (Fig. 4). Rats treated with olanzapine at dose of 0.5mg/kg decreased the number escapes (p<0.05) only on the 1st day of the learning session, but did not change them significantly on the memory retest. Rats treated with olanzapine at dose of 1mg/kg did not change significantly the number of escapes neither on the lear-ning session and the memory retest, compared to the same day controls (Fig.4). Rats treated with olanzapine at dose of 2mg/kg decreased the number 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)

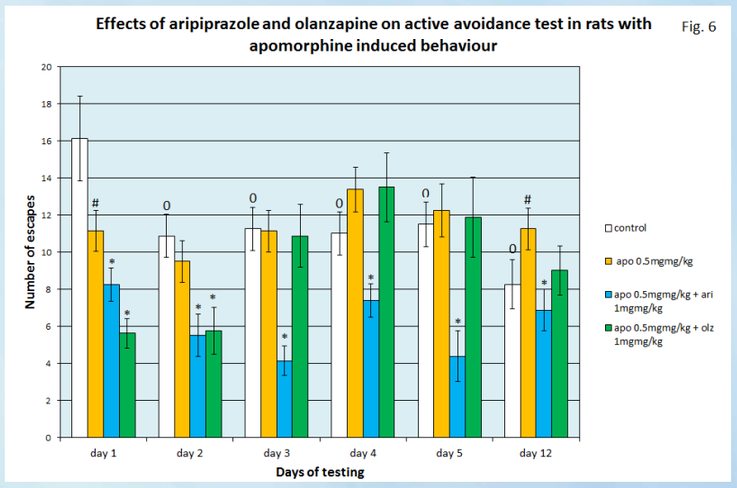


Second series – challenged rats

On challenged rats the control group significantly increased (p<0.05) the number of avoidances on learning and memory retention, compared to the first day (Fig 5). Rats treated with apomorphine 0.5mg/kg increased (p<0.05) the number of avoidaces on 4th and 5th days on learning session, but decreased (p<0.05) them on 3rd day of the learning session and on the memory retention test, compared to the respective day control group. (Fig. 5). Rats treated with apomorphine 0.5mg/kg and aripiprazole 1mg/kg decreased significantly the number of avoidances on 4th day (p<0.05) and 5th day (p<0.01) of the learning session and on memory retention test (p<0.01) compared to the respective days of apomorphine group (Fig.5). Rats treated with apomorphine 0.5mg/kg and olanzapine 1mg/kg decreased the number of avoidances on 3rd, 4th and 5th days of learning session and on memory retention test compared to the respective days of apomorhine group (p<0.05) (Fig.5).



On challenged rats the control group decreased the number of escapes (p<0.05) on 2nd, 3rd, 4th and 5th days of the learning session as well as on the memory retention test (p<0.05). (Fig.6). Rats treated with apomorphine 0.5mg/kg decreased the number of escapes (p<0.05) only on the 1st day of the learning session, but increased the number of escapes (p<0.05) on the memory retention test (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 days of apomorphine group (Fig.6). Rats treated with apomorphine 0.5mg/kg and olanzapine 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 olanzapine 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 olanzapine impair the learning and memory.

According to the dopamine hypothesis apomorphine is a direct dopamine receptor agonist in animals and men and exacerbate the behavioral reactions [5, Depatie & 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 olanzapine lead us to suggest that both antipsychotic drugs blockade the postsynaptic dopamine receptors and apomorphine, acting mainly presynaptically decreases the dopamine release and the final effect is memory impairment. The suppressed memory effect of aripiprazole is more pronounced than that of olanzapine, probably due to its partial dopamine agonism.

Acknowledgement:

This work is part of Scientific project HO-03/2012 of MU-Plovdiv, Bulgaria.

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