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Investigating the Effects of Tolcapone a Catechol-O-Methyltransferase Inhibitor on Learning and Memory in Passive Avoidance Task

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of the present study was to evaluate the effects of tolcapone in haloperidol-challenged rodent models of learning and memory and reserpine-induced parkinsonism in rats.
Methods: The learning and memory enhancing effects of tolcapone (TCP) were assessed in male Wistar rats treated with 5, 15 and 30 mg/kg bw, p.o. The impact of tolcapone on haloperidol challenge and reserpine induced parkinsonism was studied in rodents treated with 5,15 and 30 mg/kg bw TCP p.o. Step-through passive avoidance and loco-motor activity were assessed. The latency reaction time and the number of horizontal and vertical movements were registered, respectively. Statistical analysis was done by SPSS Statistics 19.

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Results: Tolcapone in all studied doses increased latency in short- and long-term memory tests as well as the number of movements in the horizontal and vertical plane. The rats treated with haloperidol and tolcapone in all studied doses showed significant increase in latency during the training days and the two retention tests when compared with the haloperidol treated control but not with saline. In rats with the reserpine model of parkinsonism there was not significant difference in latencies between experimental and saline treated groups neither during the learning session nor during both memory retention tests.
Conclusion: Tolcapone improves incidental memory and delayed recall memory in hippocampus dependent step-through passive avoidance task. The observed effects are probably dopamine mediated but hippocampal noradrenaline might also play an important role.

Keywords: Learning; memory; tolcapone; haloperidol; reserpine; dopamine.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease along with Alzheimer's disease [1,2]. The onset of PD is usually after the age of 50 and a sharp rise of the incidence occurs after the age of 60 [3]. The paramount neuropathological features include: progressive and irreversible loss of 50-70% of dopamine (DA) neurons in substantia nigra pars compacta (SNpc), resulting in striatal dopamine depletion and contextual formation of Lewy bodies [4]. The diagnosis is usually based on its main motor symptoms (MS) such as bradykinesia, muscle rigidity, resting tremor and postural instability [5]. Although PD is essentially a motor disease, patients demonstrate fairly incapacitated non-motor symptoms (NMS). Moreover, these symptoms may occur formerly or concomitantly to the motor hallmarks [6]. The NMS includes autonomic and sensory dysfunction, sleep disturbances, emotional and cognitive decline, learning and memory impairment. The fact that almost all PD patients present with cognitive deterioration at some stage of the disease strengthen the interest in the role of dopamine (DA) in the cortical and hippocampal areas implicated in cognition and memory [7]. The non–motor deficits are of great interest in the last few decades due to their progressive features and escalating deterioration of quality of life [3].

Although the motor symptoms are linked to the progressive degeneration of dopaminergic neurons the pathogenesis of cognitive decline remains unclear [8]. One relatively recent clinical study suggests that cognitive deficiency might be explained with dopaminergic degeneration of SNpc as well as with the essential involvement of prefrontal cortex, hippocampus and amygdala [9]. Dopamine and its regulation play a crucial role in a great number of hippocampal functions, amongst which cognition, learning and memory processes [10]. There are preclinical experimental models which support the above mentioned by demonstrating that impaired behavioral and cognitive tasks are mediated by brain areas such as striatum but also hippocampus and prefrontal cortex [8].

COMT (catechol-O-methyltransferase) enzyme is essential for the dopamine function. It metabolizes dopamine, norepinephrine and other catechol-containing molecules [11]. One of the features of the prefrontal cortex (PFC) is catabolic flux of dopamine via the COMT pathway. Due to a low level of dopamine receptors in PFC, COMT enzyme is crucial for the dopamine degradation in that particular brain region [12]. COMT's influence in other brain areas is yet largely unexplored but the hippocampus is a good candidate for further investigation due to its engagement in learning and memory [13].

Second generation COMT inhibitors, such as tolcapone, are recognized as additional treatment to the standard therapy of PD. Clinical research shows that administration of COMT inhibitors has a robust impact on executive cognition and memory in healthy volunteers and patients with PD [14,15]. Preclinical studies demonstrate that COMT inhibitors increase dopamine levels generally in cortical regions in contrast to psychostimulants which affect all monoamines in the brain [14]. Other experiments with rodents reveal that lower COMT activity, mediated with tolcapone, predicts better performance on cognitive tasks in comparison with saline-treated animals [13].

Present studies with animal models use neurotoxic and genetic approaches to disrupt dopaminergic neurotransmission in the CNS [3]. Reserpine is an alkaloid which inhibits the

vesicular monoamine transporter (VMAT2) and leads to depletion of monoamines, including dopamine [4]. Existing evidence shows that reserpine at doses 1 to 10 mg/kg bw elicit motor impairments [4]. At lower doses 0.1-0.5 mg/kg bw, cognitive decline and memory impairment were described while motor activity was not impaired [16]. Haloperidol is a D2/D3 receptor antagonist ensuing blockage of the dopaminergic neurotransmission. It has higher affinity for dopamine D2 receptors than D3 receptors [17]. Haloperidol administration in doses 0.5-5 mg/kg bw induces muscle rigidity and catalepsy [4].

The aim of our study was to evaluate the effect of the COMT inhibitor tolcapone on learning and memory in naïve rats, haloperidol-challenged rats and rats with reserpine induced monoamine depletion.

2. MATERIALS AND METHODS

2.1 Ethical Statement

All experimental procedures were carried out in accordance with the European Convention for protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. For this study we obtained permission from the Ethics Committee at Medical University of Plovdiv, protocol № 2/19.04.2018 and the Animal Health and Welfare' Directorate of the Bulgarian Food Safety Agency, permit № 4/09.12.2015.

2.2 Animals

Adult male albino rats of Wistar strain (200 ± 20 gr - body weight) were used. They were housed in standard cages under controlled laboratory conditions (08:00-20:00 light-dark cycle, temperature 22 ± 2ºC, humidity 55 ± 5%). Access to food and water were ad libitum. Animals were acclimatized to the laboratory environment before the experiments.

2.3 Drugs and Experimental Design

Tolcapone (TCP), haloperidol (HP) and reserpine (RES) were purchased from Sigma-Aldrich.

To evaluate the effect of TCP on learning and memory in naïve rats they were divided randomly into 4 groups (n=8) as follows: 1st group –saline treated control 0,1 ml/100 g bw; 2nd group – TCP 5mg/kg bw; 3rd group - TCP 15 mg/kg bw; 4th group - TCP 30 mg/kg bw. In all experiments tolcapone was suspended in saline with few drops of Tween 80 and administered orally.

To evaluate the effect of TCP on learning and memory in rats with reserpine induced parkinsonism the animals were randomly divided into 5 groups (n=8) as follows: 1st group – saline treated control 0,1 ml/100 g bw; 2nd group – reserpine 5mg/kg bw; 3rd group - RES + TCP 5 mg/kg bw; 4th group - RES+ TCP 15 mg/kg bw; 5th group - RES + TCP 30 mg/kg bw.

To evaluate the effect of TCP on learning and memory in rats with haloperidol-induced dopaminergic blockage the animals were randomly divided into 5 groups (n=8) as follows: 1st group – saline treated control 0,1 ml/100 g bw; 2nd group – haloperidol 1mg/kg bw; 3rd group - HP + TCP 5 mg/kg bw; 4th group - HP + TCP 15 mg/kg bw; 5th group - HP + TCP 30 mg/kg bw.

All animals were pretreated with TCP for 1 week. Reserpine was administered subcutaneously (s.c.) for 5 consecutive days before performance on memory and loco-motor tasks. Haloperidol was administered intraperitoneally (i.p.) only during the testing days 60 minutes before the tests. TCP was administered 60 minutes before HP.

2.4 Behavioral Tests

2.4.1 One-way step-through inhibitory "passive" avoidance test

We used a two-compartment apparatus (UgoBasile, Italy), with one light and one dark box connected by a sliding automatic door. The training session lasted for 2 days. A short-memory test was performed 24 hours later (on the 3rd day) but the long-term memory retention was tested on the 10th day. Both, learning and retention sessions consisted of 3 trials. The passive avoidance paradigm consisted of the following stages: habituation and acquisition on the 1st day; acquisition on the 2nd day; memory retention test on the 3rd an 10th day. The memory retention test was performed without electrical shock stimulation. The rat is placed in the light box and following a door delay of 7 second it is allowed–access to the dark compartment. When entering the dark chamber (training latency) the door slides down and the rat is subjected to a brief aversive stimulus (UC, electrical foot shock for 9 sec with the intensity of 0.4 mA). The latency of reaction was used as a criterion for learning and retention. The animals that remained in the light chamber for more 178 sec were considered as trained.

2.4.2 Loco-motor activity (activity cage) test

An automatic apparatus (activity cage, UgoBasile, Italy) was used to assess horizontal and vertical spontaneous movements of the animals. The set-up comprises of an electronic unit and an Infra-Red Beam cage complete with two sets of sensor arrays for horizontal and vertical activity. The animal was placed into the plastic cage for 5 minutes. The movement it makes inside the cage interrupts one or more infra-red beam(s). The beam interruptions are counted and recorded by the electronic device.

2.4.3 Test for severity of tremor

The animals were tested 24 hours after the last dose of reserpine. We used the following scale: 0-no tremor; 1-occasional twitches (1 to 2 twitches); 2-moderate/intermittent twitches (3 to 5 twitches); 3-continuous tremor (6 or more twitches). The animal was observed for 5 minutes.

2.4.4 Test for muscle rigidity

The forelimbs of the rat were placed in the middle of a horizontal glass rod, at a height of 25 cm. The required time for falling down from the rod was recorded.

2.4.5 Test for bradykinesia

Bradykinesia was assessed by holding the rat's tail and placing the front paws on a platform and letting the animal walk. The number of steps taken with the forelimbs for 3 minutes was counted [18].

2.5 Statistics

Statistical analysis was performed by using IBM SPSS Statistics 19.0. Data were analyzed by one - way ANOVA, followed by Bonferroni test in case of normal distribution or by Games –Howell test in case of non-notmal distribution. A value of P=.05 was considered to be statistically significant.

3. RESULTS AND DISCUSSION

3.1 Effects of Tolcapone on Learning and Memory in Naïve Rats

3.1.1 Effect of tolcapone on the one-way step-through inhibitory test in naïve rats

The experimental groups treated with 5 mg/kg and 15 mg/kg TCP significantly increased the latency of reaction on the 2nd training day (P<.001) as well as during the memory retention tests (P<.001). The animals with the highest dose of TCP (30 mg/kg) significantly prolonged (P<.001) the time for reaction during the two days of learning and two tests for memory engrams, compared to the respective control group (Fig. 1).

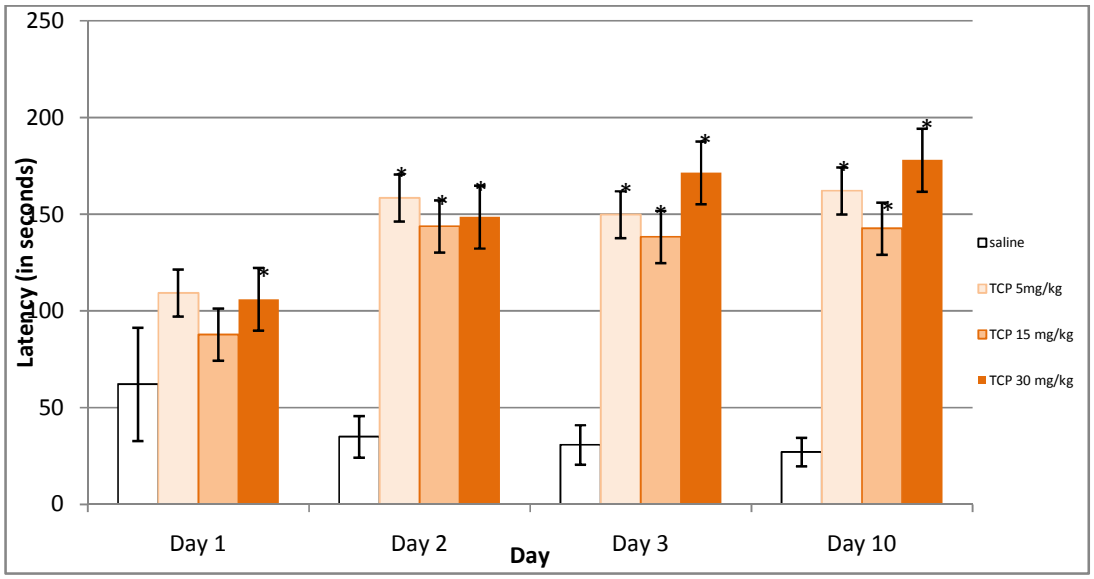

Fig. 1. Effects of tolcapone on the step-through passive avoidance task in naïve rats.
**P<.001 versus the saline control group*

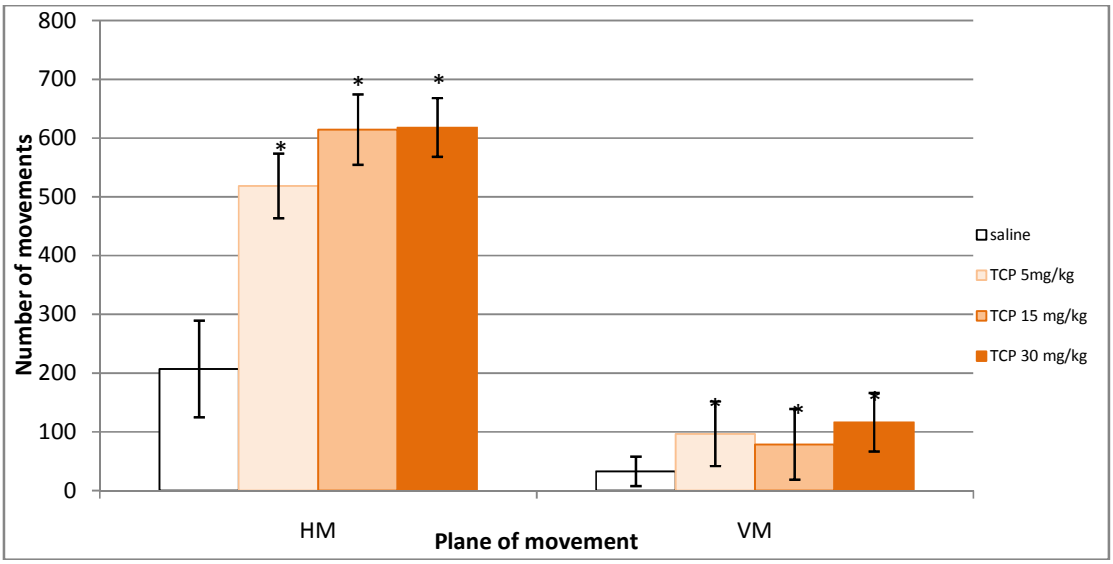

Fig. 2. Effects of tolcapone on locomotor activity in naïve rats.
**P=.05 versus the saline control group*

3.1.2 Effect of tolcapone on locomotor activity in naïve rats

All experimental groups treated with tolcapone significantly increased the number of movements in both planes when compared with saline (*P*=.05) (Fig. 2).

3.2 Effects of Tolcapone on Learning and Memory in Haloperidol-challenged Rats

3.2.1 One-way step-through inhibitory test in haloperidol-challenged rats

Rats treated with haloperidol and the lowest dose of TCP significantly increased the latency on the 1st training day compared with the saline group (*P*<.004) while when compared with haloperidol they significantly increased the latent time during the whole training session as well as the two memory tests (*P*=.05). The other two groups treated with haloperidol and tolcapone in doses 15 and 30 mg/kg did not reach significance in comparison with the saline group but showed significant increase during the two training days and the two retention tests when compared with the haloperidol group (*P*=.05) (Fig. 3).

3.2.2 Locomotor activity in haloperidol-challenged rats

Rats treated with haloperidol 1 mg/kg bw showed a non-significant decrease in the number of horizontal and vertical movements when compared with saline. The animals treated with HP and the lowest dose of TCP (5 mg/kg bw) significantly decreased the movements in both planes ($p<0,05$) when compared with the saline control group. The rats with HP and TCP in doses of 15 and 30 mg/kg bw did not significantly decrease the number of movements when compared to both control groups (Fig. 4).

3.3 Effects of Tolcapone on Learning and Memory in Rats with Reserpine-induced Parkinsonism

3.3.1 Effect of tolcapone on the one-way step-through inhibitory test in rats with reserpine model of parkinsonism

The three experimental groups treated with reserpine and tolcapone non-significantly increased the latency on both training days when compared with the control. There was no significant difference in latencies between the experimental and the saline group in the long- and the short-term memory tests. Reserpine treated control was excluded from the statistical analyses of the results because rats developed severe akinesia and stayed in the light compartment of the apparatus which cannot be analyzed as an improvement in memory functions.

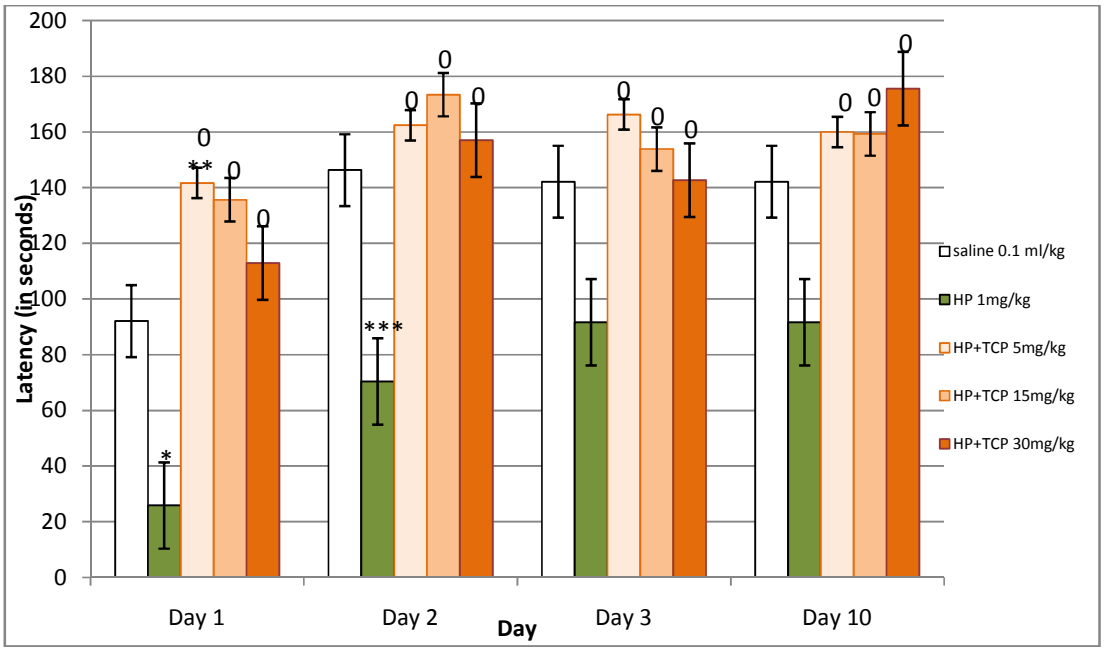

Fig. 3. Step-through passive avoidance task in haloperidol-challenged rats treated with tolcapone 5; 15 and 30 mg/kg bw

**P<.005 versus the1st day saline group*
***P<.004 versus the1st day saline group*
****P<.003 versus the2nd day saline group*
^{0}P=.05 versus the haloperidol group

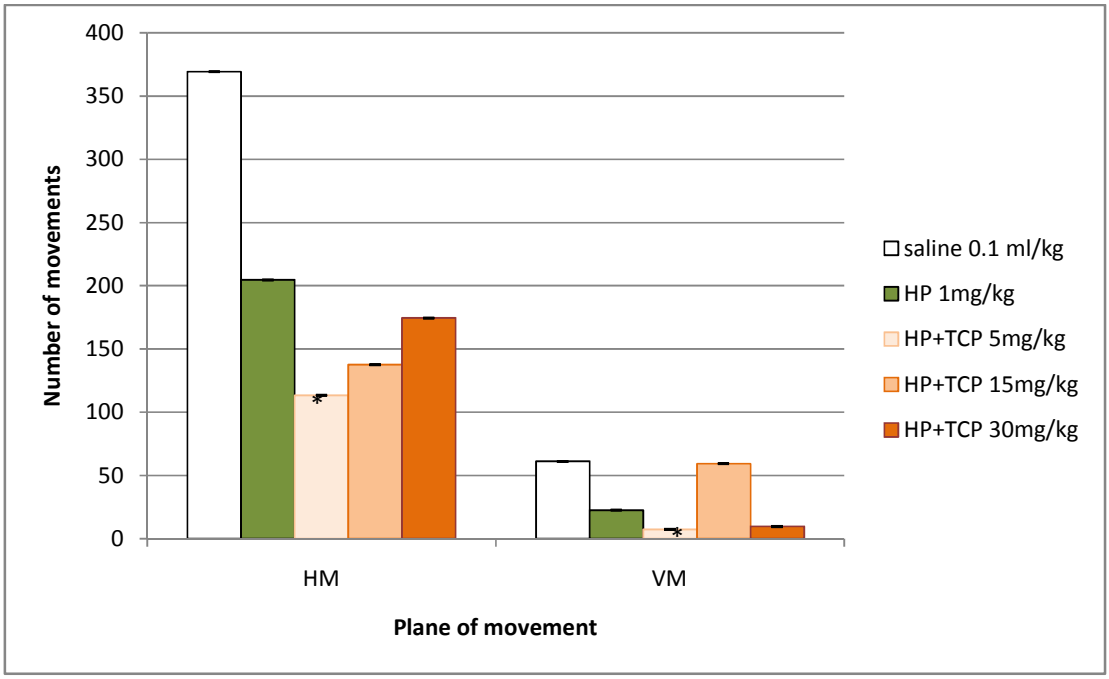

Fig. 4. Effects of haloperidol-challenge on loco-motor activity in haloperidol treated rats

**P=,05 versus the saline control group*

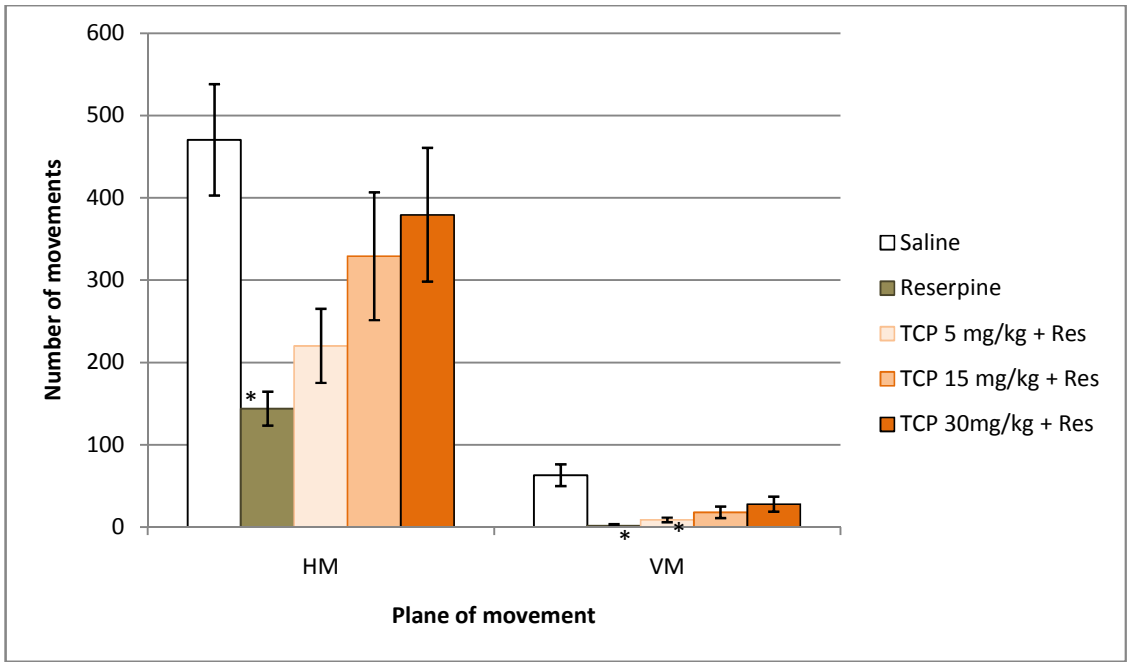

Fig. 5. Effects of reserpine on loco-motor activity in rats with reserpine – induced parkinsonism

**P=,05 versus the saline control group*

3.3.2 Effect of tolcapone on locomotor activity in reserpine model of Parkinsonism

Rats treated with reserpine 5 mg/kg bw showed a significant decrease in the number of horizontal and vertical movements when compared with saline (*P*=.05). The group treated with reserpine and the lowest dose of tolcapone significantly decreased the movements only in the vertical plane (p<0,05) Groups treated with reserpine and TCP in doses of 15 and 30 mg/kg did not show significant decrease of the movements in both planes compared to the saline control group (Fig. 5).

3.4 Effects of Tolcapone on Tests for Rigidity, Bradykinesia and Tremor

Reserpine administration for 5 consecutive days produced twitching, bradykinesia and muscular rigidity when compared with saline (*P*=.05). Tolcapone did not significantly affect rigidity. The highest dose of tolcapone significantly decreased twitching (*P*=.05) and non-significantly improved bradykinesia when compared with reserpine (Table 1).

The hippocampus is a brain structure that is located in the temporal lobe and is involved in processes of learning and memory. It does not have homogeneous morphology. Genetic analysis, differences in anatomic connectivity and behavioral results show that in rodents the hippocampus may be divided into dorsal, intermediate and ventral zones. The dorsal part corresponds to the anterior hippocampus in humans and is more related to cognitive functions whereas the ventral part, which corresponds to the anterior hippocampus in humans is involved in modulation of emotions and reward [19]. Hippocampal dopamine plays an important role in the processes of memory acquisition and consolidation. There are at least two sources of hippocampal dopamine - dopaminergic mesencephalic neurons from the ventral tegmental area and substancia nigra, and noradrenergic neurons from the locus coeruleus. The concentration of dopamine in the hippocampus is lower than in other areas of the brain but neurons of the ventral tegmental area show bursting in reaction to reward which causes an increase in dopamine release in the hippocampus [20]. One of the possible mechanisms by which dopamine regulates learning and memory in the hippocampus is long term potentiation (LTP). It is an activity-dependent modification of synaptic plasticity resulting in the long-lasting potentiation of synaptic transmission [21]. A step-through

Table 1. Effects of tolcapone on reserpine-induced motor signs

Groups	Twitching mean±SD	Bradykinesia mean±SD	Rigidity mean±SD
Saline	0±0	131,750±16,813	38,125±8,515
Reserpine 5 mg/kg bw	29,250±3,806*	12,750±3,063*	60,000±0,000*
Tolcapone 5 mg/kg bw + Reserpine	13,125±2,954*	11,750±3,862*	55,625±4,375
Tolcapone 15 mg/kg bw + Reserpine	19,000±3,133*	9,250±3,539*	60,000±0,000
Tolcapone 30 mg/kg bw + Reserpine	14,857±1,142*0	17,857±7,075*	60,000±0,000

**P =.05 vs saline; 0P =.05 vs reserpine*

passive avoidance task is employed in studies on learning and memory in rats that is based on the fear of electric foot shock. This task is dependent on the integrity of the hippocampus and is used to assess hippocampus-dependent associative memory function in rodents [22]. Since tolcapone crosses the blood-brain barrier [23] and inhibits the activity of COMT it increases dopamine levels in different brain areas including the hippocampus. Matsumoto et al. with *in situ* hybridization techniques demonstrated expression of COMT mRNA in rat hippocampal dentate gyrus and the CA region [24]. Earlier biochemical studies also showed high COMT enzyme activity in rat hippocampus [25]. Tolcapone has been found to modulate dopamine metabolism in the dorsal hippocampus, reducing the levels of homovanillic acid and causing the accumulation of dihydroxyphenylacetic acid [13]. Our study showed that tolcapone in all studied doses significantly improved memory in the step-through passive avoidance task. Based on our results and the aforementioned data for the expression of COMT enzyme in the hippocampus we can therefore speculate that hippocampal dopamine plays a role in tolcapone-induced improvement of short- and long term memory. Our results are consistent with previous preclinical studies using hippocampal dependent tasks. Khromova et al. demonstrated that tolcapone in doses of 3 and 10 mg/kg bw improves memory acquisition and in a dose of 10 mg/kg bw memory extinction in naïve rats, using a single-trial passive avoidance task [26]. Laaticainen et al. also showed that tolcapone improves memory in hippocampus dependent memory tests – delayed rewarded alternation and spatial novelty preference tasks [13].

In order to understand the possible role of dopamine and the involvement of D_2 receptors in the observed effect of tolcapone on learning and memory the rats were challenged with haloperidol. The latter is a dopamine receptor antagonist that has a higher affinity for dopamine D2 receptors than D3 receptors (D2/D3 Ki ratio, 0,195). Occupancy of the dopamine D2 receptor by haloperidol reaches 99.8% 2 h after oral administration [17]. D2 receptors in the presynaptic endings of dopaminergic input fibres play a role in the regulation of hippocampal dependent learning and memory by modulating long-term depression (LTD) in the CA1 region of the hippocampus [27]. Our results showed that the challenge dose of haloperidol in all studied doses of tolcapone greatly decreased the locomotor activity as compared with saline. The haloperidol challenge reduced memory acquisition and retention as tolcapone treated rats did not significantly improved latency when compared with the control. Based on our results we can suggest that D2 mediated LTD in the hippocampus might have been involved in the observed effects of tolcapone on memory functions.

Mechanisms other than dopamine-induced LTD might be responsible for the effect of tolcapone on the improvement of cognitive functions. We used a reserpine-induced model of PD for further investigations on the mechanism by which tolcapone influences learning and memory. Reserpine is an alkaloid that acts through inhibition of the vesicular transporter for monoamines in the CNS. As a result it causes blockage of the storage of monoamines into presynaptic vesicles and depletes cellular content of biogenic amines [3]. Peripherally administered it produces a variety of motor signs that resemble PD. Due to its effects on motor activity reserpine is used to induce a pharmacological model of PD [4]. Although motor impairments are cardinal symptoms of PD and diagnosis is mainly based on them, cognitive deficits have been described in patients with this neurodegenerative disorder. Reserpine is able to produce not only typical motor symptoms of PD but also memory deficits, anxiety-like behavior, depressive-like behavior and anhedonia [3]. It is

able to impair memory at low doses that do not produce motor signs [28]. In the present study reserpine was used in doses that cause both motor and memory impairments [29]. Alves CS et al. have shown that reserpine impairs memory in the passive avoidance task [30]. In this task, as mentioned above, the cognitive function is hippocampal dependent. Results from the present study showed that reserpine did not cause worsening of non-spatial memory assessed by the passive avoidance test since the latency did not decrease significantly in tolcapone + reserpine treated rats compared to the saline group. However, no significant improvement in memory functions was observed neither in the short-term memory nor in the long-term memory.

Reserpine causes depletion of monoamine content not only in the striatum but also in brain areas responsible for cognition such as the hippocampus and cortex [31]. COMT enzyme metabolizes not only dopamine but also other catecholamines e.g. noradrenaline. Noradrenaline is also involved in the hippocampal memory consolidation and retrieval [32] and this mediator is present in larger quantities in hippocampus than dopamine. Laaticainen et al. [13] found that the noradrenaline/dopamine ratio in this brain structure is about 24,9 in naïve rats and 21 in the presence of tolcapone. As reserpine depletes the amount not only of dopamine but also of noradrenaline we can speculate that both mediators might play a role in the effect of tolcapone on cognitive functions. This is supported by the fact that the haloperidol challenge also non-significantly increases the latency when compared with control while reserpine decreases it. Obviously not only dopaminergic mechanisms are involved in tolcapone-induced improvement of memory functions.

4. CONCLUSION

The results of the present study show that tolcapone improves incidental memory (attention) and delayed recall memory in the step-through passive avoidance task probably by a hippocampus dependent mechanism. D2 receptors mediated LTD and hippocampal noradrenaline might play an important role in the observed effect. However, further investigations are needed to figure out the exact mechanism by which tolcapone improves memory functions.

CONSENT

It is not applicable.

ETHICAL STATEMENT

All experimental procedures were carried out in accordance with the European Convention for protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. For this study we obtained permission from the Ethics Committee at Medical University of Plovdiv, protocol № 2/19.04.2018 and the Animal Health and Welfare' Directorate of the Bulgarian Food Safety Agency, permit № 4/09.12.2015.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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