Effects of Pramipexole on Learning and Memory Processes in Naïve and Haloperidol-challenged Rats in Active Avoidance Test

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Background: Parkinson’s disease (PD) is the second most common neurodegenerative disease in the world, following Alzheimer’s disease. It affects approximately 1% of the population over 65 years.1 The main feature of its pathogenesis is the loss of dopaminergic neurons in substantia nigra2–3, which results in striatal dopamine depletion and the ensuing classic motor symptoms - muscle rigidity, resting tremor, bradykinesia and postural imbalance4. They significantly affect the quality of life of PD patients and are the target of most research and clinical treatment.4

The non-motor symptoms, such as autonomic dysfunction, sleep disturbances, depression, cognitive decline, usually remain underestimated and undiagnosed although they have a major influence on quality of life as well.5 The pathology of the cognitive impairment remains unclear.6,7 The presence of Lewy bodies (alpha-synuclein deposits) in cortical structures correlates with the severity of cognitive decline.5,9 Ray et al. link the cognitive decline not only to dopamine depletion in the nigrostrial axis but also consider the implication of hippocampus, prefrontal cortex and amygdale.10 The fact that almost all PD patients develop cognitive deficit at some stage of the disease revived the interest in the role of dopamine (DA) in the cortical and hippocampal areas involved in cognition and memory.11

The naïve experimental groups significantly increased the number of conditioned responses during the tests for short- and long-term memory, compared with the saline groups (p<0.05). During the short-memory test only the animals with the lowest dose of PMX significantly increased the number of unconditioned responses whereas during the long-term memory test all experimental groups increased the number of escapes in comparison with the saline groups (p<0.05). Challenge dose of haloperidol attenuates learning and memory in pramipexol treated rats. Only the highest dose of pramipexol showed significant increase in conditioned and unconditioned responses compared with the haloperidol group (p<0.05).

Conclusion: Pramipexole improves learning and memory in naïve rats by enhancing dopaminergic neurotransmission. This is probably not the only mechanism involved. This is confirmed by the decrease in learning and memory ability in rats with haloperidol-challenge.

BACKGROUND

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the world, following Alzheimer’s disease. It affects approximately 1% of the population over 65 years.1 The main feature of its pathogenesis is the loss of dopaminergic neurons in substantia nigra2–3, which results in striatal dopamine depletion and the ensuing classic motor symptoms - muscle rigidity, resting tremor, bradykinesia and postural imbalance4. They significantly affect the quality of life of PD patients and are the target of most research and clinical treatment.4

The non-motor symptoms, such as autonomic dysfunction, sleep disturbances, depression, cognitive decline, usually remain underestimated and undiagnosed although they have a major influence on quality of life as well.5 The pathology of the cognitive impairment remains unclear.6,7 The presence of Lewy bodies (alpha-synuclein deposits) in cortical structures correlates with the severity of cognitive decline.5,9 Ray et al. link the cognitive decline not only to dopamine depletion in the nigrostrial axis but also consider the implication of hippocampus, prefrontal cortex and amygdale.10 The fact that almost all PD patients develop cognitive deficit at some stage of the disease revived the interest in the role of dopamine (DA) in the cortical and hippocampal areas involved in cognition and memory.11
Dopamine receptor agonists, such as pramipexole, are found to be beneficial in improving the dopamine-depletion related motor symptoms but their effect on cognitive functions remains disputable. Pramipexole is a second generation, non-ergot alkaloid dopamine agonist with high affinity for D₃/D₂ receptor subtypes with greater selectivity for the D₃ receptor. Dopamine agonists may be beneficial in the treatment of cognitive disorders since they enhance dopaminergic neurotransmission not only in the striatum but also in various other brain areas.

**AIM**

The aim of our study was to assess the effect of pramipexole on learning and memory processes in naïve and haloperidol-challenged rats.

**MATERIALS AND METHODS**

**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 from the Bulgarian Food Safety Agency (permit № 4/09.12.2015).

**Drugs:** Pramipexole (PMX) and haloperidol (HP) were purchased from Sigma-Aldrich.

**Animals:** Male albino rats of Wistar strain (200 ± 20 g bw) were used. They were housed in standard cages under controlled laboratory conditions (08:00-20:00 light-dark cycle, temperature 22±2°C, humidity 55±5%). Access to food and water was ad libitum. Great efforts were made to reduce the number of animals used and to minimize their suffering.

To evaluate the effect of PMX on learning and memory in naïve rats the animals were divided randomly into 4 groups (n=8) as follows: group 1: (control) saline 0.1 ml/100 g bw; group 2: pramipexole 0.5 mg/kg bw; group 3: pramipexole 1 mg/kg bw; group 4: pramipexole 3 mg/kg bw.

To evaluate the effect of PMX on learning and memory in haloperidol-challenged rats the animals were randomly divided into 5 groups (n=8) as follows: group 1: (control) saline 0.1 ml/100 g bw; group 2: (control) haloperidol 1 mg/kg bw; group 3: haloperidol + pramipexole 0.5 mg/kg bw; group 4: haloperidol + pramipexole 1 mg/kg bw; group 5: haloperidol + pramipexole 3 mg/kg bw.

PMX was administered orally (p.o.) and haloperidol intraperitoneally (i.p.). All animals were pretreated with PMX for 7 days. HP was administered only during the days of the experiments 60 minutes before PMX, which was administered 60 minutes before the tests.

**Haloperidol challenge:** haloperidol acts as an antagonist of D₂/D₄ receptors. It is administered intraperitoneally in dose of 1 mg/kg bw and the resulting dopamine striatal depletion is manifested with muscle rigidity and catalepsy within 1 hour of the injection.

**Behavioral tests**

**Two-way active (shuttle) avoidance test**

We used a fully automated shuttle-box device (UgoBasile, Comerio-Varese, Italy). The training session consisted of 30 trials daily for 4 consecutive days. Memory retention tests for short- and long-term memory were performed at days 5 and 12, respectively. The rats were conditioned by using light and buzzer (670 Hz, 70 dB, 6 sec) as conditioned stimuli (CS) and electrical foot shock (0.4 mA, 3 sec) as an unconditioned stimulus (UCS). The intermission between the CS and UCS was 12 seconds. The following parameters were registered: number of avoidances (CS response) and number of escapes (UCS response).

**Locomotor activity (activity cage) test**

An automatic apparatus (47420 multiple activity cage, UgoBasile, Italy) was used to assess horizontal and vertical spontaneous movements of the animals. The set-up comprises an electronic unit and an Infra-Red Beam cage complete with two sets of sensor arrays for horizontal and vertical activity. The animal is placed into the plastic cage for 5 minutes. The movement it makes inside the cage interrupts one or more infra-red beams. The beam interruptions are counted and recorded by the electronic device.

**Statistical analysis**

Statistical analysis was performed using IBM SPSS Statistics 19.0. Data were expressed as mean ± SEM of values for memory tests and initial latency. The Shapiro-Wilk test showed normal distribution between the groups. Comparison between groups was performed with Independent Sample t test. A value of p<0.05 was considered as a significant difference.

**RESULTS**

**Effects of pramipexole on learning and memory processes in naïve rats**

**Conditioned responses (avoidance):** the animals treated with 0.5 mg/kg and 1 mg/kg PMX significantly increased the number of conditioned responses at
days 2 (p<0.05), 3, and 4 (p<0.0001) of the learning session whereas the animals with the highest dose of PMX (3 mg/kg) increased (p<0.0001) the number of active avoidances throughout the 4 training days, compared with the respective day control group.

During the tests for short and long-term memory (days 5 and 12), the three experimental groups significantly (p<0.05) increased the number of conditioned responses, compared to the respective day control animals.

The rats treated with 3 mg/kg PMX significantly increased the conditioned responses during the two memory tests (p<0.05) in comparison with the animals given PMX in doses of 0.5 and 1 mg/kg bw (Fig. 1).

**Unconditioned responses (escapes):** the group treated with PMX in a dose of 0.5 mg/kg increased (p<0.05) the number of passive escapes at day 4 of training, compared with the saline group at the same day. The animals with PMX in a dose of 1 mg/kg significantly (p<0.05) increased the number of unconditioned stimuli response at day 2 of the learning session, compared with the respective control group. The rats given 3 mg/kg PMX increased the unconditioned escapes at day 2 (p<0.0001) and 4 (p<0.05) of training, compared with the control group for that day.

During the short-memory test only the animals with the lowest dose of PMX significantly increased (p<0.05) the number of unconditioned responses whereas during the long-term memory test all experimental groups increased the number of escapes (p<0.05), compared to the saline group.

The rats treated with 3 mg/kg PMX significantly decreased the unconditioned responses during the short and long term memory tests (p<0.05) when compared to the other groups with PMX (Fig. 2).

**Effects of pramipexole on activity-cage test in naïve rats**

The three experimental groups significantly increased the number of relative units on horizontal (p<0.0001) and vertical (p<0.0001) movements compared to the saline group. The animals treated with the highest dose of pramipexole were more active in both planes (p<0.05) than the animals treated with lower doses of pramipexole (Table 1).

**Effects of pramipexole on learning and memory processes in haloperidol-challenged rats**

**Conditioned responses (avoidance):** the HP control group showed a significant decrease in the number of conditioned responses during the training session (p<0.05) and the two memory tests at days 5 (p<0.05) and 12 (p<0.05) compared with the saline control group.

The groups treated with HP and PMX in doses of 0.5 and 1 mg/kg bw significantly decreased the number of avoidances during the learning period (p<0.05) as well as the memory retention tests (p<0.05), compared to the respective saline group. However, in comparison with the HP group they did not show significant difference in the number of conditioned responses.

The animals with HP and 3 mg/kg bw PMX significantly decreased the unconditioned responses during the short and long term memory tests (p<0.05) when compared to the other groups with PMX (Fig. 2).

**Unconditioned responses (escapes):** the group treated with PMX in a dose of 0.5 mg/kg increased (p<0.05) the number of passive escapes at day 4 of training, compared with the saline group at the same day. The animals with PMX in a dose of 1 mg/kg significantly (p<0.05) increased the number of unconditioned stimuli response at day 2 of the learning session, compared with the respective control group. The rats given 3 mg/kg PMX increased the unconditioned escapes at day 2 (p<0.0001) and 4 (p<0.05) of training, compared with the control group for that day.

During the short-memory test only the animals with the lowest dose of PMX significantly increased (p<0.05) the number of unconditioned responses whereas during the long-term memory test all experimental groups increased the number of escapes (p<0.05), compared to the saline group.

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**Effects of pramipexole on learning and memory processes in haloperidol-challenged rats**

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The groups treated with HP and PMX in doses of 0.5 and 1 mg/kg bw significantly decreased the number of avoidances during the learning period (p<0.05) as well as the memory retention tests (p<0.05), compared to the respective saline group. However, in comparison with the HP group they did not show significant difference in the number of conditioned responses.

The animals with HP and 3 mg/kg bw PMX significantly decreased the unconditioned responses during the short and long term memory tests (p<0.05) when compared to the other groups with PMX.

**Figure 1.** Effects of pramipexole on the number of conditioned responses in TWAA test in naïve rats.

* p<0.05 versus the saline control group; †p<0.0001 versus the saline control group.
did not show significant increase in the number of avoidances when compared to the saline group but significantly increased their number in comparison to the HP control at days 1, 2, and 4 of training (p<0.05), and during the short (p<0.05), and long-term memory (p<0.05) tests.

The group with haloperidol and 3 mg/kg PMX significantly increased the number of avoidances during the training session (p<0.05) and the two memory retention (p<0.05) tests, compared to the remaining two groups with HP and PMX (Fig. 3).

Unconditioned responses (escapes): the rats treated with HP significantly decreased the number of escapes throughout the whole learning session (p<0.05) and the two memory tests (p<0.05), compared with the respective day for the saline group.

The animals treated with HP and PMX in doses of 0.5 and 1 mg/kg bw significantly decreased the number of unconditioned responses during the training days (p<0.05) and the long-term memory (p<0.05) test, compared with the animals treated with saline. In comparison with the HP control group, the rats given HP and the lowest dose of PMX did not show significant difference, whereas the ones with HP and 1 mg/kg PMX significantly increased the unconditioned responses at days 1 and 4 of training (p<0.05), as well as during the long-term memory test (p<0.05).

The animals treated with HP and the highest dose of PMX significantly increased the number of escapes throughout the whole training session (p<0.05) and the two memory tests (p<0.05) compared to the animals with HP, but did not show significant increase of responses when compared with the saline group.

The comparison between the three experimental
groups did not demonstrate significant differences (Fig. 4).

Effects of pramipexole on activity-cage test in haloperidol-challenged rats: the group treated with HP significantly decreased the number of horizontal and vertical movements (p<0.05) when compared to the saline control group. The rats treated with HP and PMX in a dose of 0.5 mg/kg bw did not show significant increase in motor activity compared to both control groups. The animals treated with HP and 1 mg/kg PMX significantly increased the number of relative units on horizontal and vertical movements compared to the animals with saline (p<0.05) and those with HP (p<0.0001). The rats treated with HP and PMX in a dose of 3 mg/kg bw significantly improved their motor activity in the horizontal plane compared with both control groups (resp. p<0.05; p<0.0001), whereas increased motor activity in the vertical plane (p<0.05) was registered only in comparison with the HP group. The animals treated with HP and PMX in doses of 1 and 3 mg/kg bw significantly increased the number of relative units on horizontal and vertical movements (p<0.05), compared to the animals with HP and the lowest dose of PMX (Table 2).

DISCUSSION

Our experiments have shown that pramipexole in all studied doses improved short and long-term memory in naïve rats as well as their motor activity. Both effects are probably due to pramipexole’s effect on dopaminergic neurotransmission but in different brain areas. Haloperidol, by blocking D₂ receptors, decreases the effect of PMX on learning and memory leaving only the highest dose (3 mg/kg bw) effective.

The hippocampus is a complex structure that belongs to the limbic system and has an essential role in learning and memory consolidation, and in spatial memory that enables navigation. It is known that the hippocampus has ventral and dorsal parts. Bagot et al. suggest that the ventral part is related to stress, depression, emotion and reward while the dorsal hippocampus is associated with cognition and different types of memory. The major mechanisms involved in these processes of learning and memory are neurogenesis and long-term neuronal potentiation (LTP) which stimulate the synaptic transmission. The TWAA test is indicative for learning and memory assessment dependent on the dorsal hippocampal integrity. Based on our results that pramipexole in all studied doses significantly increased the number of conditioned responses during the memory reten-
Effects of Pramipexole on Learning and Memory

In our experiment with haloperidol challenge, significant improvement in long-term memory was demonstrated by the animals treated with haloperidol and the highest dose of pramipexole (3 mg/kg bw). Our results suggest that the dopaminergic mechanism is not the only one involved in pramipexole-related improvement of cognition.

Brain derived neurotrophic factor (BDNF) is considered to play an essential role in the hippocampal neurogenesis and synaptogenesis, which in turn are involved in learning and memory processes. BDNF ameliorates the development and differentiation of new neurons and promotes LTP. Significant BDNF expression has been demonstrated in the hippocampus. Decreased levels of BDNF lead to

Figure 4. Effects of pramipexole on the number of unconditioned responses in TWAA test in haloperidol-challenged rats.
* p<0.05 versus the saline control group; @p<0.05 versus the haloperidol group.

Table 2. Effects of pramipexole on horizontal (HM) and vertical movements (VM) in haloperidol-challenged rats

| Group                        | HM Mean ±SD        | VM Mean ±SD       |
|------------------------------|--------------------|-------------------|
| Saline                       | 369.250±291.202    | 61.125±62.494     |
| Haloperidol 1 mg/kg bw       | 204.625±90.879     | 22.750±25.689     |
| HP+PMX 0.5 mg/kg bw          | 275.000±114.629    | 23.375±19.899     |
| HP+PMX 1 mg/kg bw            | 806.625±223.119*0  | 140.375±59.379*0  |
| HP+PMX 3 mg/kg bw            | 1184.750±597.624*0 | 182.125±69.540*0  |

* p<0.05 vs saline group; @p<0.05 vs haloperidol group
impaired hippocampal-dependent memory consolidation and spatial memory which is demonstrated with poor performance in Morris water maze tests. Erickson et al. found that reduced levels of BDNF were related to a decline in hippocampal volume and memory deficits, whereas increased BDNF levels are linked to greater hippocampal volume, memory improvement and better cognition. It has been proved that PMX ameliorates the production of BDNF in cultured dopaminergic neurons. Since it is known that haloperidol acts as a D2 receptor antagonist we can speculate that an additional mechanism, related to pramipexole-induced increase in BDNF production by D3 receptor activation, is accountable for the pramipexole-enhanced learning and memory in TWAA test observed in our study.

CONCLUSIONS

Our study shows that pramipexole improves learning and memory processes in naive rats by enhancing dopaminergic neurotransmission in the dorsal hippocampal area. This is probably not the only mechanism involved in the observed effects, which is confirmed by the observed decrease in learning and memory ability in rats with haloperidol blocked D2 receptors.

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Влияние прамипексола на процессы обучения и памяти у нативных крыс и крыс с галоперидол-индукционным паркинсонизмом при тестировании на активное избегание

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Введение: Болезнь Паркинсона (БП) является вторым наиболее распространённым нейродегенеративным заболеванием и обычно диагностируется по его моторным симптомам. В последние несколько десятилетий немоторные симптомы, включая когнитивные нарушения, представляют большой интерес для учёных.

Цель: Оценить влияние прамипексола на обучение и память у нативных крыс и крыс с галоперидол-индукционным паркинсонизмом.

Материалы и методы: Самцов крыс линии Wistar разделили на 9 групп (n = 8): необработанные – физ. р-р, прамипексол в дозах 0,5; 1 и 3 мг / кг массы тела; галоперидольные группы – физ р-р, галоперидол, галоперидол + прамипексол в дозах 0,5; 1 и 3 мг / кг массы тела. Был проведен двусторонний тест активного избегания (TWAA) в челночной камере. Контролируемые параметры включали: количество условных и безусловных рефлексов, вертикальные и горизонтальные перемещения. Статистический анализ был выполнен с помощью SPSS 19.

Результаты: Необработанные экспериментальные группы значительно увеличили количество условных рефлексов во время краткосрочных и долгосрочных тестов памяти по сравнению с группами, получавшими физ. р-р (p<0.05). Во время теста кратковременной памяти только животные, получавшие самые низкие дозы прамипексола, значительно увеличивали количество условных рефлексов, тогда как во время теста долговременной памяти все экспериментальные группы увеличивали число побегов по сравнению с группами, получавшими физ. р-р. (p<0.05). Доза галоперидола ослабляет обучение и память у крыс, получавших прамипексол. Только самые высокие дозы прамипексола показали значительное увеличение условных и безусловных рефлексов по сравнению с группой галоперидола (p<0,05).

Вывод: Прамипексол улучшает обучение и память у нативных крыс за счет увеличения дофаминергической нейротрансмиссии. Это, вероятно, не единственный затронутый механизм. Это подтверждается снижением способности к обучению и запоминанию у крыс с галоперидол-индукционной блокадой дофамина.