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Original article

The effect of repeated-intermittent exposure to 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) during adolescence on learning and memory in adult rats

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ABSTRACT

Background: According to the European Drug Report, the use of novel psychoactive substances (NPS) is constantly growing. NPS are widely abused by human adolescent subjects. 5-Methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) is one of the most frequently used hallucinogenic NPS. 5-MeO-DIPT intoxication results in hallucinations, vomiting, and tachycardia. Long-term exposure to 5-MeO-DIPT was reported to lead to development of post-hallucinogenic perception disorder.
The aim of the present study was to determine whether repeated-intermittent administration of 5-MeO-DIPT during adolescence affects learning and memory in adult rats.
Methods: Rats were treated with 5-MeO-DIPT in a dose of 2.5 mg/kg from 30 to 33 and 37 to 40 Postnatal Day (PND). The experiments were conducted when the animals reached 90 PND. The effect of 5-MeO-DIPT on cognitive functions was assessed using the novel object recognition, open field, and serial pattern learning (SPL) tests.
Results: Repeated-intermittent exposure to 5-MeO-DIPT during adolescence decreased the number of crossings in the open field test at adulthood. Moreover, 5-MeO-DIPT treatment impaired adult rats' learning in the SPL test. There was no change in the novel object recognition test.
Conclusions: The present results show that the performance of adult rats treated with 5-MeO-DIPT during adolescence was impaired in the open field test, which indicates the attenuated exploratory activity. 5-MeO-DIPT treatment undermined adult rats' performance in the serial pattern learning test, suggesting impairment of long term memory and cognitive flexibility. The present study showed that the exposure to 5-MeO-DIPT during adolescence might lead to long-lasting behavioral changes which persisted long after the exposure period.

Introduction

The European Drug Report has shown that the popularity of the novel psychoactive substances (NPS) is rapidly increasing. Importantly, the NPS are widely abused by human adolescent subjects with prevalence reaching 4% in the age group of 15 to 16 years [1]. Hallucinogens are a class of NPS divided further into: indoleamines (including (+)-lysergic acid diethylamide [LSD] and tryptamines, such as 5-methoxy-*N*,*N*-dimethyltryptamine [5-MeO-DMT]) and phenylalkylamines (including 2,5-dimethoxy-4-iodoamphetamine [DOI]) [2,3].

5-Methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) is one of the best known synthetic tryptamine hallucinogenic NPS. This hallucinogen is an analogue of naturally occurring 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) and may be taken alone or jointly with other drugs, such as 3,4-dimethoxymethamphetamine (MDMA) [4,5]. 5-MeO-DIPT users experience hallucinations, euphoria, nausea, and vomiting [6]. Importantly, 'flashbacks' and a prolonged delusional state in former 5-MeO-DIPT users have been documented [7,8]. These observations suggest long-lasting changes in brain functioning after exposure to 5-MeO-DIPT.

Despite such alarming data, there have been only a few papers on the effect of 5-MeO-DIPT exposure in animals. It was shown that 5-MeO-DIPT acted as a competitive serotonin transporter (SERT) inhibitor [9,10]. Moreover, it was demonstrated that 5-MeO-DIPT displayed a high affinity for serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors. 5-MeO-DIPT induced wet dog shakes in rats [11] and

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head-twitch responses in mice [12]. The observed head-twitch response in the mice was reversed by the selective serotonin 5-HT_{2A} receptor antagonist M100907 [12]. Moreover, 5-MeO-DIPT potentiated the forepaw treading episodes induced by the selective serotonin 5-HT_{1A} receptor agonist 8-OH-DPAT [11]. Those data indicate that 5-MeO-DIPT acts as a serotonin 5-HT_{1A} and 5-HT_{2A} receptor agonist. Repeated 5-MeO-DIPT administration in adult rats elevated plasma corticosterone level suggesting propensity for anxiety [13].

Drug abuse during adolescence may be associated with alterations in brain structure and function leading to psychiatric disorders in later ages [14]. Adolescence is a period of profound developmental transformations of the brain including a massive synapse loss, a decrease in dendrite spines in the frontal cortex, an enhanced glucose metabolism, fluctuations in serotonin (5-HT) reuptake in the nucleus accumbens, a decrease in the number of serotonin synapses and an increased number of dopamine (DA) inputs to the frontal cortex [15]. For instance, cognitive deficits resulting from alcohol or marijuana use during adolescence period were potentially harmful for academic and social functioning at adulthood. Thus, NPS use in adolescence leads to abnormalities in brain functioning, and causes cognitive impairments and neuro developmental changes [16].

In the light of all the above data and the constantly increasing NPS use by human adolescent subjects, the aim of the present study was to investigate whether repeated administration of 5-MeO-DIPT during adolescence mimicking a weekend pattern of NPS use could affect learning and memory in adult rats. The dose used in the present study was selected based on a former study showing prooxidant effect of 2.5 mg/kg of 5-MeO-DIPT [11]. The data presented here are a supplementary study to our neurochemical work concerning the mechanism of 5-MeO-DIPT action in the CNS.

Materials and methods

Animals

The study was carried out on male Wistar-Han rats (Charles Rivers, Sulzfeld, Germany) weighing 75–100 g at delivery day to our facility and 280–320 g at 90 PND. The animals arrived to the vivarium on the 21st day of age (PND) and were allowed to acclimate; then they were randomly assigned to control and drug-treated groups. The animals were housed in temperature (22–23 °C)- and humidity- (50–60%) controlled rooms on a 12 h light/12 h dark cycle (light from 6 a.m.) and had free access to tap water and standard laboratory food. The total number of animal used in the study was 55. The experiments were conducted in accordance with the European Union guidelines regarding the care and use of laboratory animals (Directive 2010/63/EU revising Directive 86/609/EEC) and were approved by the II Local Bioethics Commission.

Treatment

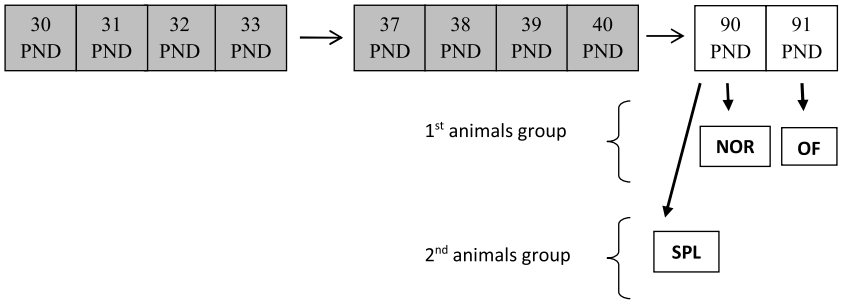
5-Methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) administration began when the rats reached 30 PND, concerned as early adolescence period. The animals received once daily 5-MeO-DIPT in a dose of 2.5 mg/kg administered subcutaneously (*sc*) for 4 days (30–33 PND), and after a 3-day break another 4-days administration (37–40 PND) started. That pattern of administration was applied to mimic weekend drug use by adolescents. All experiments were performed when the rats reached 90 PND, which is the day of beginning of adulthood [15] (see Scheme 1, below). 5-MeO-DIPT was dissolved in a 0.9% NaCl and was administered *sc* to prevent intra-abdominal irritation induced by repeated drug administration according to our previous experiments [11]. The control group received the corresponding volume of a 0.9% NaCl according to the same administration pattern as in the case of the 5-MeO-DIPT-treated animals.

Drugs and reagents

5-Methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) was purchased from Toronto Research Chemicals INC (Canada).

The novel object recognition test

The procedure was adopted from Ennaceur and Delacour [17] and Orzelska-Gorka J et al. [18]. Adult rats (90 PND) were trained in a wooden closed square arena (60 × 60 cm) with 40 cm high walls painted black. Immediately after each session, the floor and the objects were cleaned with water and dried. The rats were habituated to the experimental room and dim light for at least 1 h before the procedure began. Each animal was familiarized with the arena (without any objects) for 10 min 24 h before testing. The novel object recognition test (NOR) consisted of two 5-min sessions separated by a 1 h inter-session interval. In the introductory session, two identical objects (A1 and A2) were inserted in opposite corners, approximately 15 cm from the walls of the arena. In the recognition session, one of the objects was replaced with a novel one (A = familiar, B = novel). The objects were a green glass vase and a black metal can. Objects were filled with wet sand to prevent displacement by the rats. Half of the animals from each group were exposed to a glass vase as a novel object, and the other half a metal can. A novel object location in the recognition session was randomly assigned to each rat. Exploration of an object was defined as licking, sniffing or touching the object but not as sniffing and leaning against the object, standing or sitting on it. The exploration time was measured using a digital laboratory timer by two independent experimenters blind to the experimental design. The discrimination index (Di) was calculated for results obtained during the recognition session and considered to be an index of exploration of novel object relative to the total



Scheme 1. A scheme of repeated-intermittent 5-MeO-DIPT (2.5 mg/kg x 8, *sc*) administration during adolescence and experiment timeline. Grey bars indicate days of drug administration; PND – postnatal day, NOR – the novel object recognition test, OF – the open field test, SPL – the serial pattern learning test.

exploration of both objects. It was calculated using the equation: Di = time spent on novel object exploration x 100/(time spent on novel object exploration + time spent on familiar object exploration). The Di ratio over 50% was used to define successful discrimination.

The open field test

The open field test procedure was adopted from Hall [19] and Nikiforuk [20]. The rats were trained in a wooden circular open field (100 cm in diameter) painted black and placed 50 cm above the floor. The arena was divided into 8 equal parts with thin white lines. The centre of the arena was illuminated by focused bright white light (150 lx). The rats were trained on the following day after the NOR test. Animals were habituated to the experimental room and dim light for at least 1 h before the procedure began. Each rat was placed in the centre of the arena, and 5-min observation started. The time of walking was measured using a digital laboratory timer by two independent experimenters blind to the experimental design. Moreover, the number of sector line crossings and peeping episodes (exploration behind the edge of arena) were counted.

The serial pattern learning test

The maze consisted of a runway 185 cm long, 10 cm wide and enclosed by plywood walls 14 cm high, each section was covered with hinged Plexiglas. The start and goal boxes were 20 and 35 cm long, respectively, and were separated from the runway by two manually operated opaque guillotine doors. The start box was painted white, whereas the main runway was grey, and the goal box black. A removable opaque plastic dish was placed in the goal box approximately 5 cm from the back wall. During each trial, the food reinforcement consisting of a predetermined number of food pellets (Dustless Precision Pellets Rodent, Bio-serv, Frenchtown, NJ, USA) was introduced. The serial pattern learning test (SPL) was adapted according to Self and Gaffan [21] and Compton et al. [22]. The SPL test was performed on separate group of animals than NOR and OF tests.

Five days before the pre-training phase began the rats were weighed and their weight was reduced to 85% of the free-feeding weight. Water was freely available except for the period of trial procedure. The four-day pre-training was divided into two phases. During phase I (pre-training days 1 and 2) the rats were handled and placed on the runway for 10 min. Both guillotine doors were opened and 10 food pellets were distributed along the runway. Phase II (pre-training days 3 and 4) consisted of two preliminary runs, and the interval between the runs lasted 15–20 s. For the run each rat was placed in the start box, the doors were opened and the rat was allowed to traverse the runway. When the rat reached the goal box, the doors were closed and a rat was left therein until it ate all the 4 pellets placed in the dish. The main experiment started on the day after pre-training and lasted for 24 consecutive days. Everyday training consisted of 4 trials, each of them having 3 runs. For each run the amount of food pellets was predetermined as follows: in trial 1 there were 10, 1, 0 pellets; in trial 2 there were 0, 1, 10 pellets; in trial 3 there were 10, 1, 0 pellets; in trial 4 there were 0, 1, 10 pellets. The time of each run was measured by two independent experimenters blind to the experimental design. After completion of all the daily trials, the rats returned to the colony and received their maintenance food ration not earlier than 60 min afterwards. An inter-trial interval was approximately 15 min, while intra-trials inter-run intervals lasted 30 s. The duration of running time from the start box to the goal box was measured for each rat in every run using a digital laboratory timer. The control group reached their stable performance on the 18th day of the training. Thus, the endpoint for the SPL was the 24th day. This test is based on the knowledge that rats can anticipate forthcoming rewards within a series of stimuli and adjust their running speed [21,23]. Hence, it has been proposed that rats follow a sequence pattern when they run faster to a bigger reward. For example, when a sequence of 10, 1, 0 food pellets is presented to rats, they are expected to move faster in the first run and slower in the last one. Moreover, it has been shown that rats learn more easily when the reward is presented in a diminishing order of magnitude as in the sequence of 10, 1, 0 food pellets than when it is increased in a sequence of 0, 1, 10 food pellets [21].

Data analysis

The statistical significance was calculated using a *t*-test or, when appropriate, a repeated measures ANOVA, followed by Tukey's *post hoc* test. The results were considered statistically significant when $p < 0.05$. The data for SPL were compressed into four blocks consisting of days 1 to 6, 7 to 12, 13 to 18, 19 to 24. Statistical analyses were carried out using STATISTICA v.10 StatSoft, Inc. 1984–2011.

Results

The effect of repeated-intermittent 5-MeO-DIPT administration during adolescence on adult rats' performance in the novel object recognition test

The time of the novel object exploration compared with familiar object exploration during recognition session was observed to increase in control and 5-MeO-DIPT-treated group in comparison to the introductory session (Fig. 1b). Statistical analysis of exploration time of novel and familiar objects during introductory and recognition session (Fig. 1a, b) showed that there were no significant differences between repeatedly 5-MeO-DIPT-treated animals and the control group. There were no significant differences in the discrimination index (Fig. 1c) between repeatedly 5-MeO-DIPT-treated animals and the control group. Importantly, the discrimination index in both studied groups exceeded 50%, reaching 71.02% and 71.36% for control and 5-MeO-DIPT-treated group, respectively.

The effect of repeated-intermittent 5-MeO-DIPT administration during adolescence on adult rats' performance in the open field test

Repeated-intermittent 5-MeO-DIPT administration during adolescence decreased the number of sector crossings in the OF test ($p < 0.05$). There were no significant differences in the walking time and number of peeping episodes between repeatedly 5-MeO-DIPT-treated rats and the control group (Fig. 2).

The effect of repeated-intermittent 5-MeO-DIPT administration during adolescence on adult rats' performance in the serial pattern learning test

Statistical analysis of the running time during trial 1 (Fig. 3a) and trial 2 (Fig. 3b) in the SPL test showed that there were no significant differences between the animals repeatedly treated with 5-MeO-DIPT and the control group. However, repeated-intermittent 5-MeO-DIPT administration during adolescence decreased the running time of rats during trial 3 ($F(3,108) = 6.6$, $p < 0.05$, Fig. 3c). Significant differences between blocks of days were also observed ($F(6,108) = 2.28$, $p < 0.05$). These findings suggest that the animals improved their performance throughout the training period (Fig. 3c). Repeated-intermittent 5-MeO-DIPT administration during adolescence decreased the running time

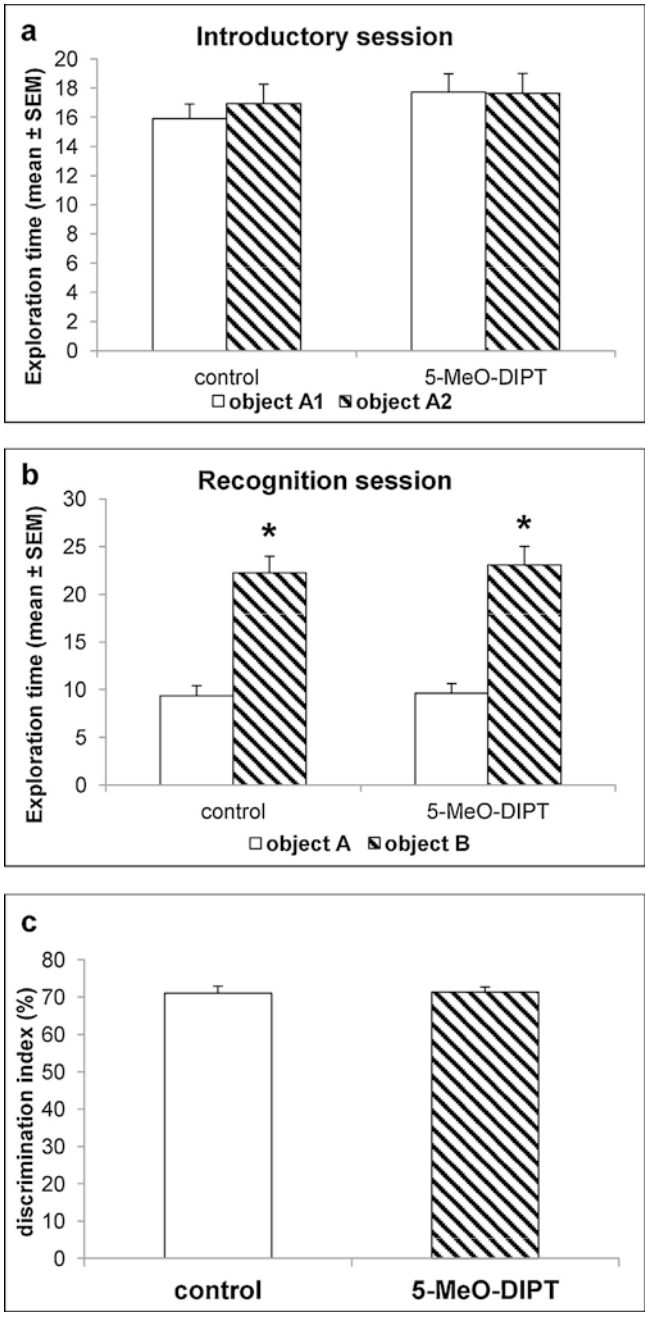


Fig. 1. The effect of chronic 5-MeO-DIPT administration (2.5 mg/kg x 8, *sc*) during adolescence on adult rats' performance in the novel object recognition test. Panel 1a shows exploration time in the introductory session for the two identical objects A1 and A2, and panel 1b in the recognition session for familiar (A) and novel object (B). Panel 1c shows discrimination index. The discrimination index expresses the time spent on novel object exploration in relation to the total time of exploration of both the novel and familiar objects. The values are the mean ± SEM (n for the control group = 14, n for the 5-MeO-DIPT animals = 27). Student's *t*-test, $^{*}p < 0.01$ novel *vs.* familiar object.

of animals during trial 4 and blocks of days 7–12 and 13–18 ($F(3,108) = 5.68$, $p < 0.05$, Fig. 3d).

Discussion

The aim of the present study was to examine the influence of repeated-intermittent 5-MeO-DIPT administration during adolescence on learning, memory, and locomotor activity in adult rats. The novel object recognition, open field and serial pattern learning tests were used. The pattern of 5-MeO-DIPT administration mimicked weekend drug use by adolescent users. However, it is impossible to strictly assess 5-MeO-DIPT abuse by humans in spite of huge efforts made by the European Monitoring Centre for Drugs and Drug Addiction. Like other NPS, 5-MeO-DIPT is frequently taken unconsciously as a random mix of designer drugs. According to the Drug Enforcement Administration, the doses used by human subjects range from 6 to 20 mg or more per session [4]. In the present study, the lowest effective multiple doses were used based on our data obtained in neurochemical study [11].

The obtained results revealed no effect of 5-MeO-DIPT given during adolescence on recognition memory in the NOR test performed during the animals' adulthood. There were no differences in the discrimination index of novel object in the control and 5-MeO-DIPT-treated group. Moreover, in both groups discrimination index was over 70%. This indicates that animals in both groups properly understood the task in the NOR test. Hence, repeated-intermittent 5-MeO-DIPT administration during adolescence did not affect short-term memory [17]. These data are consistent with the results of other authors who reported the lack of impact of repeated 5-MeO-DIPT administration (10 or 20 mg/kg x 4) in the NOR test measured during adulthood [13]. It may be speculated that cortical regions may be affected by 5-MeO-DIPT as 5-MeO-DIPT, which is an agonist of 5-HT_{2A} and 5-HT_{1A} receptors, influences dopamine, serotonin and glutamate level in this brain region as showed in our former work [11]. Furthermore, these changes may be related with hallucinogenic activity of 5-MeO-DIPT. However, the lack of impact of 5-MeO-DIPT in the NOR test shows that the observed neurochemical and behavioral changes seem not to be connected with performance in the NOR test. The divergent effects may result from differences in age of animals and 5-MeO-DIPT dosing regimen used in our former and present studies.

It has also to be noted that repeated-intermittent administration of 5-MeO-DIPT had no effect on rats' weight (see Supplementary material).

The time of walking in the OF test did not differ between the control group and the animals treated with 5-MeO-DIPT during adolescence. These data indicate the lack of locomotor impairment, which was also confirmed by other authors using the rota-rod test and the Morris water maze tests [24,25]. Moreover, repeated-intermittent exposure to 5-MeO-DIPT (10 mg/kg) during the pre-adolescence period (11–20 PND) showed no impairment of the spontaneous locomotor activity observed on 29 PND with the use of an automated activity monitor [26]. In the present study we did not observe any influence of 5-MeO-DIPT on the number of peeping episodes in the OF test, which suggests no effect of 5-MeO-DIPT on the escape behavior of adult rats [27]. Repeated-intermittent 5-MeO-DIPT administration during adolescence decreased the number of sector crossings (ambulations) performed by adult rats, which suggests attenuated exploratory activity [27]. A possible decrease in sector crossings and no effects on walking may be related with the agonist activity of 5-MeO-DIPT at 5-HT_{1A} receptors. This hypothesis may be supported by a study by Cunha and collaborators who found a decreased number of crossings after the administration of serotonin 5-HT_{1A} receptor agonist, 8-OH-DPAT but not after SERT inhibitor, fluoxetine [28]. Thus, we suggest that 5-MeO-DIPT administration during adolescence may lead to the increased sensitivity of 5-HT_{1A} receptor persisting to adulthood.

By affecting the prefrontal cortex functions, hallucinogens can change a number of cognitive functions, such as learning and memory [11,22,29,30]. Therefore, we decided to assess learning and memory functions using the serial pattern learning test after 5-MeO-DIPT administration during adolescence. The present study has shown that adult rats repeatedly treated with

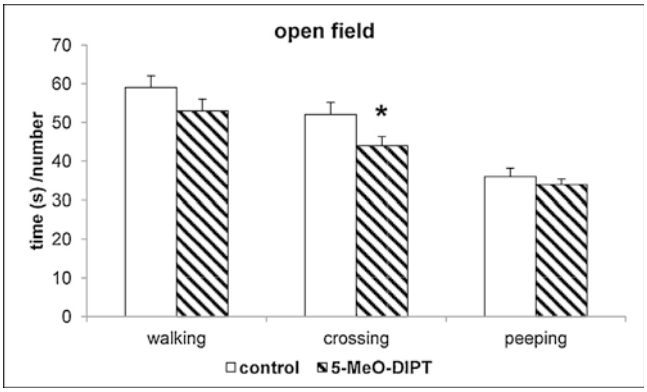


Fig. 2. The effect of chronic 5-MeO-DIPT administration (2.5 mg/kg x 8, *sc*) during adolescence on adult rats' performance in the open field test. The values are the mean ± SEM (n for control group = 14; n for the 5-MeO-DIPT animals = 27) and are shown as the time of walking, the number of crossings and peeping episodes (2); Student's *t*-test, $^{*}p < 0.05$ *vs.* the control group.

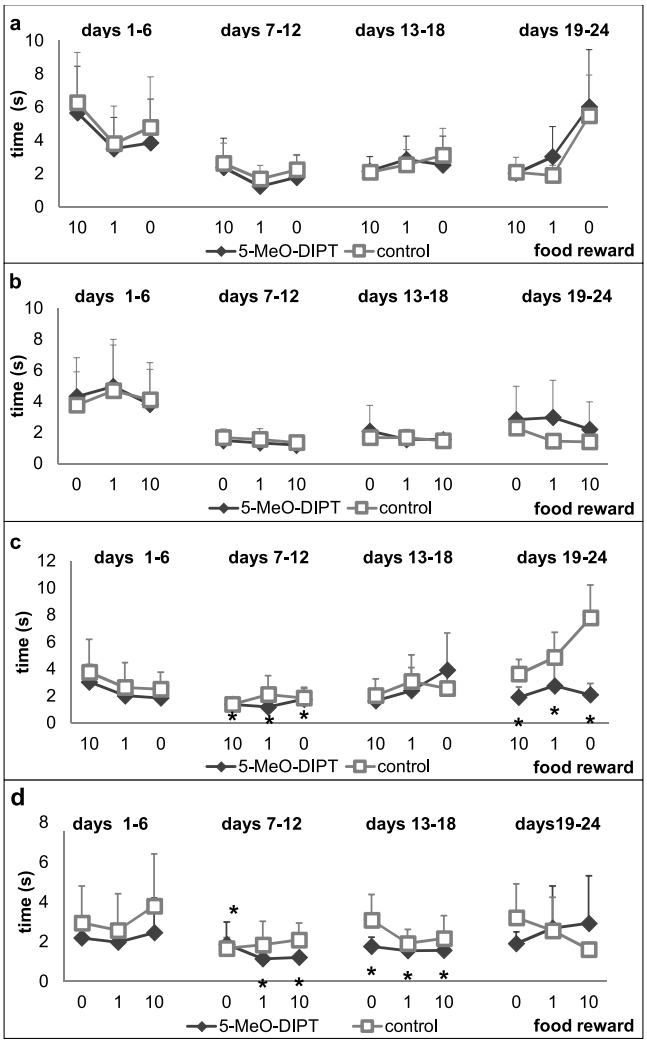


Fig. 3. The effect of chronic 5-MeO-DIPT administration (2.5 mg/kg x 8, *sc*) during adolescence on the performance of adult rats in the serial pattern learning test. The values are the mean ± SEM (n = 7 for the control and the 5-MeO-DIPT group) and are shown as a running time during each run in trial 1 (1a), trial 2 (2b), trial 3 (3c), and trial 4 (4d). The repeated measures ANOVA; $^{*}p < 0.05$ *vs.* the control group. The data are presented in four blocks referring to days: 1–6, 7–12, 13–18, 19–24.

5-MeO-DIPT during adolescence follow the sequence pattern in trial 1 (10, 1, 0) and in trial 2 (0, 1, 10) in similar way as the control group. Possibly, a longer training period, over 24 days, would bring differences between the 5-MeO-DIPT-treted and the control groups in trial 1 and 2. The control rats exhibited the expected performance only in trials 3 and trial 4. The data obtained in trials 3 and 4 show an impaired anticipation of the reward sequence pattern by the adult rats treated with 5-MeO-DIPT during adolescence compared to the control group. This finding indicates the inability of 5-MeO-DIPT-treated rats to distinguish between reward elements. Our results confirm the data obtained by Compton et al., who showed that adult rats treated with 5-MeO-DIPT (10 mg/kg) during adolescence were unable to follow the sequence pattern (21, 0, 7) [22]. In line with our results, the 5-MeO-DIPT-treated rats exhibited a shorter running time compared to the control group, which may suggest an increased impulsiveness. Since the SPL test requires several days of training, it may be regarded as a test allowing for measurement of long-term memory functions [21,23]. Hence, the obtained results indicate that repeated-intermittent 5-MeO-DIPT administration to rats during adolescence disturbs their long-term memory during adulthood. Moreover, it has been documented that genetic manipulations in the serotonin transporter (SERT) affect cognitive flexibility [31]. Therefore, it may be speculated that changes in the performance of 5-MeO-DIPT-treated rats in the SPL test may be related to the altered serotonin neurotransmission induced by 5-MeO-DIPT [9,10].

5-MeO-DIPT which acts at 5-HT_{1A} and 5-HT_{2A} serotonin receptors and blocks SERT produced an increase in DA and 5-HT release as well as induced changes in glutamatergic transmission in the rat frontal cortex [11]. The observed effects may be related to disturbances in DA, 5-HT and glutamate systems resulting in damage of cortical neuronal cells [11]. The alterations in cortical monoaminergic and glutamatergic pathways are thought to be associated with cognitive impairment [32,33]. It may be concluded that the exposure of rats to 5-MeO-DIPT during adolescence even at small doses may evoke a severe and long-lasting impairment of their cognitive functions.

Previous studies revealed that hallucinogens had no influence on memory measured in the NOR test [13]. However, Compton and collaborators demonstrated deficits in cognitive flexibility in the SPL test [22]. Importantly, in the mentioned study [22] the SPL paradigm was different and rats received 5-MeO-DIPT at a later age (35–45 PND) as well as in higher doses (6 × 10 mg/kg in every 48 h) than in our study. The present work expands our knowledge about the action of hallucinogens given at the earlier time of development (30–40 PND) and in smaller doses. We showed that this small doses of 5-MeO-DIPT affect learning of animals, measured in adulthood. Thus, differences in the time of exposure and the dose used were important factors in cognitive flexibility and long-term memory development.

In conclusion, our results show that rats pretreated with 5-MeO-DIPT in low repeated-intermitted doses (2.5 mg/kg) during adolescence exhibited the decreased exploratory activity, impaired long-term memory and cognitive flexibility in the SPL test. The obtained results may be a consequence of changes in serotonin system activity induced by 5-MeO-DIPT, which is a 5-HT_{2A} receptor agonist. It may be suggested that other NPS displaying activity at 5-HT2A receptors, like MDMA, DOI, similarly to 5-MeO-DIPT, may affect cognitive functions.

Conflict of interest

None.

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