International Journal of Comparative Psychology, 2001, **14**, 151-160.

Normal Spatial Learning and Improved Spatial Working Memory in Mice (*Mus musculus*) Lacking Dopamine D4 Receptors

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Dopamine terminals in the hippocampus and prefrontal cortex modulate cognitive processes such as spatial learning and working memory. Because dopamine D4 receptors are expressed in these brain areas we have analyzed mutant mice lacking this receptor subtype (*Drd4*-/-). Wild-type and *Drd4*-/- mice were challenged in two spatial learning paradigms: the Morris water maze and an alternation T-maze. *Drd4*-/- mice showed normal place learning ability to find a hidden platform based on spatial extra-maze cues. In addition, *Drd4*-/- mice were able to find a new platform location with the same learning plasticity as wild type-mice. Spatial working memory assessed on a T maze showed that *Drd4*-/- mice were more efficient than wild-type mice in acquiring the maximum plateau of correct alternation scores. These results provide further evidence that the functional consequence of lacking D4 receptors is more evident in behaviors dependent on the integrity of the prefrontal cortex.

Spatial learning and spatial working memory are two distinct complex cognitive processes that involve the participation of different brain circuits. In spatial learning, environmental information is processed into a long-lasting neuronal representational map that depends on the integrity of the hippocampal formation. Lesions in this brain area are known to dramatically impair the ability of rodents to, for example, locate a submerged hidden platform based on the integration of contextual cues. In spatial working memory a short-term spatiotemporal neuronal code is formed that depends on the functional integrity of the brain prefrontal cortex (PFC). Experimental evidence has shown that dopamine (DA) neurotransmission into the hippocampus and the PFC is critically involved in the modulation of these two cognitive functions. Selective lesions of hippocampal DAergic terminals with 6-hydroxydopamine cause deficits in spatial performance (Gasbarri et al., 1996). When DA neurotransmission decreases in this brain region as a consequence of aging, a similar cognitive dysfunction is observed (Winocur, 1992; Lee et al., 1994). DA also modulates working memory processing via a pathway that projects from the ventral tegmental area to the PFC. Lesions in mesocortical DAer-

Our thanks to M. Garibaldi and N. Malarini for their excellent technical assistance. This work has been supported in part by an International Research Scholar Grant of the Howard Hughes Medical Institute, Agencia Nacional de Promoción Científica y Tecnológica, Universidad de Buenos Aires, and Ministerio de Salud de la Nación Argentina. Tomás Falzone, María Elena Avale, and Diego Gelman are recipients of doctoral fellowships from Consejo Nacional de Investigaciones Científicas y Tecnológicas, Argentina. Correspondence concerning this article may be addressed to Marcelo Rubinstein, Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (CONICET), Vuelta de Obligado 2490, 1428 Buenos Aires, Argentina (mrubins@dna.uba.ar).

gic neurons impair cognitive functions (Simon et al., 1980). Moreover, a normal balance of PFC DA receptor stimulation appears to be necessary for optimal working memory performance in rodents and primates. Deficits in behavioral tasks that depend on this cognitive ability are observed when cortical DA transmission is either elevated or deficient (Arnstenet al., 1994; Murphy et al., 1996; Verma, & Moghaddam, 1996; Williams, & Goldman-Rakic, 1995; Zahrt et al., 1997). In addition, patients diagnosed with neuropsychiatric disorders associated with DA malfunction in the PFC, such as schizophrenia (Berman & Weinberger, 1990; Okubo et al., 1997), attention deficit and hyperactivity disorder (Russell et al., 1995), and Parkinson's disease (Bradley et al., 1990) often manifest working-memory disabilities.

Among the five DA receptor subtypes, the D4 receptor exhibits a particularly enriched distribution in the PFC and the hippocampus (Ariano et al., 1997; Defagot et al., 1997). This unique pattern suggests that the D4 receptor may play an important role in the modulation of brain circuits that participate in spatial learning and working memory. This possibility has been strengthened by our recent demonstration that the genetic disruption of D4 receptors increases the excitability of cortical pyramidal neurons suggesting that, normally, D4 receptor stimulation exerts a hyperpolarizing control on brain circuits that express this receptor subtype (Rubinstein et al., 2001). To test the hypothesis that the absence of D4 receptor stimulation may induce a significant imbalance in cognitive processing, we evaluated the behavioral performance of mutant mice lacking D4 receptors in experimental paradigms used to study spatial learning and working memory in rodents.

Method

Subjects

Mice lacking the dopamine D4 receptor were generated by homologous recombination as described previously (Rubinstein et al., 1997). Heterozygous *Drd4*+/- mice were backcrossed for seven generations with the C57BL/6J strain. Molecular, immunohistochemical, neurochemical, and pharmacological studies indicate that *Drd4*-/- mice are completely devoid of D4 receptor functional activity (Defagot et al., 2000; Rubinstein et al., 1997, 2001). Eight to twelve week-old C57BL/6J congenic (n = 7) male *Drd4*+/+ or *Drd4*-/- mice derived from the mating of heterozygous mice were used in the behavioral experiments. Genotyping was carried out with PCR amplification of tail DNA samples. Mice were housed in standard animal cages in same-sex groups of 4-6 per cage, in a temperature-controlled room (21-23 ºC) and maintained in a 12-h light:dark cycle (lights on at 07:00 h). Standard pellet diet and tap water were offered ad libitum. One week prior to the behavioral tests animals were moved to a separate experimental room where they lived throughout the experiment. Sessions were conducted during the light phase from 14:00 to 19:00 h by an observer that was blind to the animal's genotype.

Apparatus

Spatial learning was assessed using a Morris water maze adapted for the mouse (Morris, 1984; reviewed by Brandeis et al., 1989). Mice were trained and tested to find a hidden platform in a 122-cm diameter swimming pool with a wall 25 cm in height. The pool was filled to a depth of 10 cm with nontoxic white dyed water (white vegetables resins, Alba, Buenos Aires, Argentina) to hide a white escape platform (13 cm X 10 cm) located 1.5 cm below the water surface in the middle of an arbitrary quadrant. The water surface was 15 cm from the rim of the pool and the inner wall of the pool presented no cues. A number of obvious distal cues were present in the experimental room during training sessions, including a door, a desk, a chair, shelves on a wall, and the experimenter

using a white lab coat. Ceiling lamps illuminated the room and also a camera for video recording was fixed to the ceiling.

Spatial working memory was assessed using the alternation T-maze task (Sarter et al., 1988). The apparatus made of black acrylic consists of three arms arranged in a T shape. Each arm of the maze is 5-cm wide with black acrylic 15-cm tall walls and the arms have closed ends. The central arm is 25-cm long and the other two arms, perpendicular to the central arm, are 30-cm long.

Procedure

Training sessions in the Morris water maze began with the mouse placed on the platform for 15 s. The animal was then placed in the water and allowed to swim. The acquisition training (Days 1-4) consisted of nine trials divided in three blocks per day during four days with an intertrial interval of 5 min. Each subject was given nine training trials per day that started by placing the mouse on the water surface, near and facing the wall of the pool. The starting points for each subject were chosen randomly from any of the three quadrants other than the platform quadrant. The animals were allowed to swim for 60 s to find the platform and, if they failed to reach it within that time, they were manually guided to the platform. Mice were allowed up to a 10-s rest on the platform before they were removed to their cage. During the intertrial interval, the animals were individually placed in resting cages with dry paper towels. The latency to reach the platform was recorded and every mouse that did not reach the platform within 1 min was assigned a latency score of 60 s. Two separate tests without platform were conducted after trials 27 and 36, on Days 3 and 4, respectively, and the swimming trajectory was video-recorded for posterior analysis. The reversal version of the test was performed two days after the last training session. On Day 7 the mice received the first block (3 trials) with the platform in the same place and in the consecutive blocks the platform was relocated in the opposite quadrant with respect to its original location. The latency to reach the new location of the platform was recorded.

The night before each training or testing session in the T maze, mice were water deprived. Experiments consisted of ten trials per day during four days (Days 1-4). Mice were placed at the beginning of the central arm and forced to alternate to obtain 0.1 ml of water. One of the horizontal arms was alternatively blocked with a black acrylic wall part. The experiment continued for six additional days (Days 5-10) during which the animals had to alternate to find 0.1 ml of water at the end of the arms; both arms were now open. Once the animal chose an arm, a mobile door closed and the mouse spent a few seconds drinking before it was carefully removed and placed again in the central arm. Each of these laps took 15 s. On Day 11, the animals received similar training except that they were placed in a small cup between trials to increase the time interval to 1 min. After each daily session the animals were allowed ad libitum to access water for one hour and then deprived until the next T-maze trial on the following day. The percentage of correct alternation for each mouse was registered in blocks of two days. Reentry into the already visited arm during the last trial was recorded as an error. Analysis of variance (ANOVA) was used to interpret the results. The value of alpha was set at 0.05 in all the statistical tests.

Results

Spatial Learning

The Morris water maze was used to study the spatial learning abilities of *Drd4*$^{-/-}$ mice. In this test, mice learn to find a submerged platform based on spatial extra-maze cues. During the initial habituation trials, no impairment in swimming capability was observed in *Drd4*$^{-/-}$ mice (n = 14) compared to wild type controls (n = 13). In the four days of training both wild type and *Drd4*$^{-/-}$ mice demonstrated a clear improvement in the time needed to find the hidden platform [Figure 1; repeated-measure one-way ANOVA: $F(11, 467) = 66.91$ for wild type mice; $F(11, 503) = 35.29$ for *Drd4*$^{-/-}$ mice). Latency to find the hidden platform was significantly reduced as a function of the number of training blocks. Comparisons between genotypes did not show any difference when they were analyzed trial by trial (two-way ANOVA: $F < 1$). Because time to reach the platform is only one the

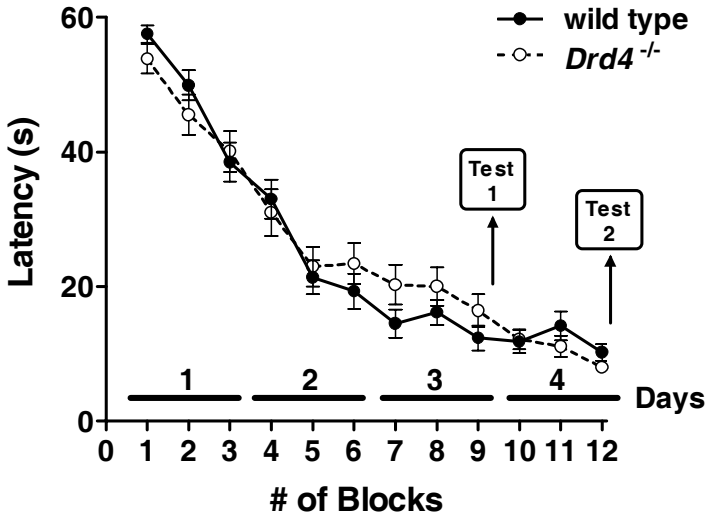

Figure 1. Latency to locate a hidden platform in a Morris water maze. WT (n = 13, black circles) and *Drd4-/-* (n = 14, white circles) mice display similar learning performance to find a hidden platform during the consecutive daily training. Block latencies are expressed in seconds (mean +/- SEM). Mice were tested during four consecutive days with three blocks per day. At the end of Days 3 and 4, Tests 1 and 2 were conducted with no platform in the pool.

different measures of spatial learning in a water maze, mice were also tested for 60 s in a probe trial in which the platform was removed from the pool (Brandeis et al., 1989). Figure 2 shows the average of Tests 1 and 2 performed without the platform at the end of training Days 3 and 4, respectively. Both wild type and *Drd4-/-* mice spent more than 50% of the time swimming in the quadrant where the platform had been located during the training [two-way ANOVA: quadrant effect $F(3, 75) = 128.6$; Tukey's multiple comparison posttest]. This result demonstrates that the *Drd4-/-* mutation does not impair performance in this spatial learning task. We then investigated long-term spatial memory performance of *Drd4-/-* mice and also their ability to locate the platform in a new position. On Day 7, seventy two hours after the previous test, the platform was placed in the training location for one block and then placed in the opposite quadrant for the subsequent trials. *Drd4-/-* mice displayed normal retention of the location of the platform three days after the last training session evidenced by a short latency to reach the platform (Figure 3 left; repeated-measure one-way ANOVA: $F(5, 233) = 28.91$ for wild type mice; $F(5, 251) = 25.58$ for *Drd4-/-* mice). Once the platform was relocated, wild type and mutant mice were equally efficient in relearning to find the new location of the hidden platform as evidenced by the decreasing latencies along the five blocks of trials (Figure 3, right). These results demonstrate that *Drd4-/-* mice have normal long-term memory and learning plasticity to adapt to a novel spatial context.

Spatial Working Memory

Dopamine neurotransmission in the prefrontal cortex participates in spatial working memory processing. Because this brain area is particularly enriched in D4

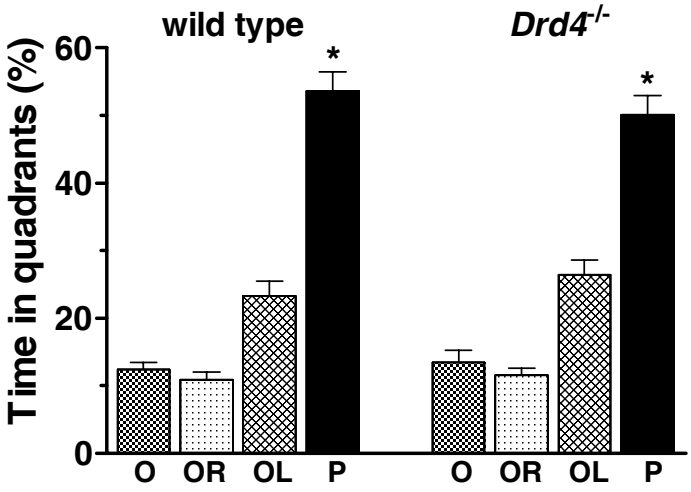

Figure 2. Test trials without the platform show that mice of both genotypes spend more time in the quadrant where the platform was located during training sessions. Bars represent the average of Tests 1 and 2 as percentage of time swimming in each quadrant. Wild type and *Drd4-/-* mice show significant preference for the quadrant where the platform had been located. P: quadrant where the platform was located during training, O: quadrant opposite to P, OR: quadrant next to the right of P, OL: quadrant next to the left of P. * : significantly higher (Tukey's multiple comparison post-tests).

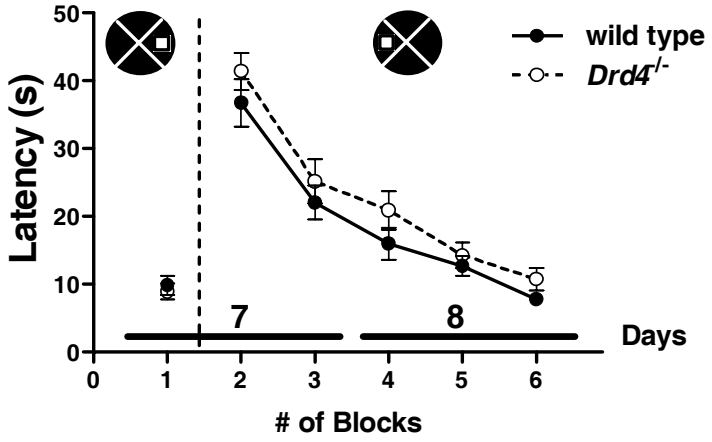

Figure 3. Normal long-term memory and learning plasticity in *Drd4-/-* mice. Seventy two hours after the last training trial mice were tested maintaining the location of the platform for long-term memory evaluation (left of dotted line). In the following trials, the platform was placed in the opposite quadrant to assess adaptive learning capabilities (right of dotted line).

receptors we decided to evaluate the performance of *Drd4*-/- mice on an alternation T-maze task. Sixteen wild type and 15 *Drd4*-/- water-deprived mice were trained to alternate between the horizontal arms of a T-maze to receive water reinforcement. Alternation training consisted in four one-day sessions where water was located alternatively at the end of each arm and mice were forced to alternate on successive trials by blocking the entrance to the previously visited arm. Alternation testing continued with free arm choice for six days, during which only correct arm alternations were reinforced with 0.1 ml of water. To succeed, mice had to remember which arm was reinforced on the previous trial to make the correct alternation choice on the next trial. Both wild type and *Drd4*-/- mice started with low levels of correct alternation scores during the first testing block that lasted two days (Figure 4). A two-way ANOVA evidenced a significant Genotype x Test block interaction effect, $F(3, 38) = 4.03$. Interestingly, in the second test block *Drd4*-/- mice outperformed their wild type siblings displaying a significantly higher percentage of correct alternations (Bonferroni's posttest). No changes in the response time were observed between genotypes. During the third testing block the percentages of correct alternation for both genotypes were maximal and similar (Figure 4). This result shows that *Drd4*-/- mice were more efficient than wild type mice in learning this spatial discrimination paradigm because they were able to reach their alternation score plateau sooner. This analysis also shows that the introduction of a longer delay (1 min) between successive trials produced a drop in the percentage of correct alternation to the level of no arm preference (50%) in mice of both genotypes (Figure 4, right bars). The higher alternation scores showed by the *Drd4*-/- mice during earlier phases of training suggests that the D4 receptor participates in brain circuits involved in spatial working memory.

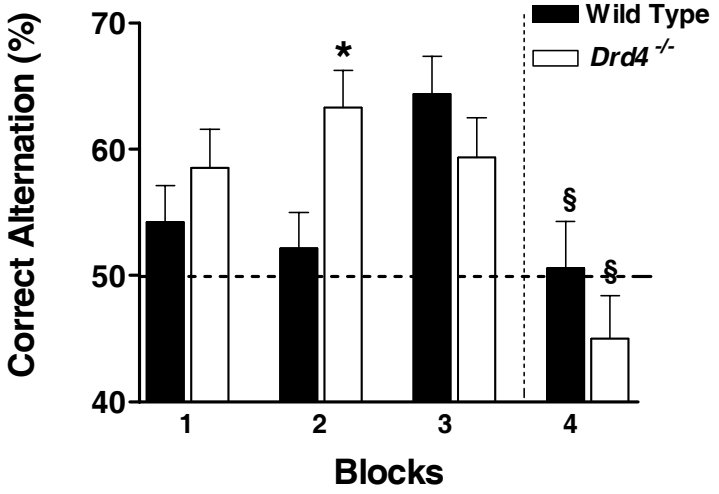

Figure 4. Wild type ($n = 16$, black bars) and *Drd4*-/- ($n = 15$, white bars) mice were water restricted and trained daily in a T maze to learn how to alternate for a water reward. Bars represent the mean +/- SEM of 20 trials determined along two consecutive days. The horizontal dashed line denotes chance level. To the right of the vertical dotted line is shown the percentage of correct alternations when the interval delay between trials was increased to 1 min.

Discussion

Brain circuits involved in spatial learning and working memory have increased in complexity throughout evolution to provide animals with a more accurate and reliable spatiotemporal representation of their surrounding environment. A more efficient orientation in time and space confers adaptive survival advantages in searching for food and water supplies, escaping from predators, and interacting with other individuals of the same species. Mouse inbred strains are a very useful source to identify genetic polymorphisms or mutations involved in learning and memory (Crawley et al., 1997). For example, the good performance of C57BL/6J mice in the Morris water maze (Owen et al., 1997) and in a conditional spatial alternation task (Paylor et al., 1993), contrary to the poor performance of DBA/2 mice in these tests, provides a solid basis to perform quantitative trait locus studies (Valentinuzzi et al., 1998). Reverse genetics is also a powerful tool in determining the potential contribution of a gene to a cognitive trait. We used this approach to study the involvement of the D4 receptor in the overall modulation that dopamine neurotransmission exerts on spatial learning and working memory by introducing a null allele mutation of the mouse D4 receptor gene for the D4-receptor protein in an congenic (n = 7) C57BL/6J genetic background. We have found that mice lacking D4 receptors show normal place learning ability to find a hidden platform in the Morris water maze based on spatial extra-maze cues, and display normal retention and retrieval of the platform location during consecutive daily training sessions. *Drd4*$^{-/-}$ mice did not show any impairments of perception, motivation, or information processing and retrieval during place recall because they spent a longer time swimming in the platform quadrant during the tests performed without platform. Swimming abilities strategies and speed were similar in mutant mice compared to wild type controls. In addition, after positioning the platform in a different quadrant, *Drd4*$^{-/-}$ mice were able to find its new location with the same learning plasticity as their wild type siblings. Therefore, the absence of D4-receptor stimulation did not impair spatial learning, retention, or readaptation of a learned task that depends strongly in the integrity of hippocampal circuits. These results are in agreement with our recent study on hippocampus-dependent associative learning where we showed that *Drd4*$^{-/-}$ mice displayed normal fear responses in both, a contextual fear conditioning paradigm and a step-through passive avoidance test (Falzone et al., 2002). Normal spatial learning ability has also been observed in mice engineered to lack D3 receptors (Karasinska et al., 2000) and D5 receptors (Holmes et al., 2001). Conversely, *Drd1*$^{-/-}$ mice did exhibit impairments in spatial learning and memory (El-Ghundi et al., 1999; Smith et al., 1998). The lack of impairment in spatial learning in *Drd4*$^{-/-}$ mice does not have to be interpreted as if D4 receptors expressed in the hippocampus do not participate in circuits related to this complex cognitive process. Because *Drd4* null allele mutant mice lack functional D4 receptors since ontogenesis, it is possible that an alternative developmental program emerged to overcome the genetic deficit.

In the study reported here, we have also observed an improvement of *Drd4*$^{-/-}$ mice in spatial working memory as evidenced by fewer number of training sessions to acquire the maximum plateau of correct alternation scores. However, a longer delay between trials produced the same deleterious effect on alternation

performance in wild type as in mutant mice indicating that mice of both genotypes were successfully trained in this test. These results are in agreement with recent findings showing that the D4 receptor antagonist PNU-101387G prevented stress-induced working memory deficits in monkeys (Arnsten et al., 2000) and with the hypothesis that excessive DA stimulation impairs working memory (Murphy et al., 1996). Thus, D1-like and D2-like receptors appear to play a key role in the cortical integration of temporal information. The ability to hold information transiently until a goal is achieved is critical because learning typically involves associations between events separated in time. The reason why lack of D4-receptor stimulation improves working memory performance may be due to the fact that an enhancement in cortical excitability strengthens synaptic connections that normally need a longer stimulation to be substantiated. An alternative explanation that cannot be ruled out involves the key role that DA neurotransmission plays in motivation. Because mice tested in the T maze were water deprived, a difference in their motivational states could account for a better alternation performance in this test. Experiments that directly measure the motivational aspect of reward-seeking behavior in *Drd4-/-* mice remain to be performed. One of the key roles of the PFC is to filter out irrelevant environmental information and D4-receptor function in this brain area is supposed to be essential in this control. We have reported that in the absence of D4 receptors mice display increased anxiety and a hypervigilant state when placed in novel environments (Falzone et al., 2002). However, in the study presented here, the T-maze does not constitute any more a novel environment due to the long-lasting procedure necessary to train mice to alternate. This methodological aspect may account for the manifestation of a more efficient performance of *Drd4-/-* mice in a spatial discrimination task. These findings may be relevant in assigning a pivotal role of D4 receptors in stress-sensitive disorders such as schizophrenia, memory impairments produced in Parkinson's disease, and age-related memory decline. Analysis of working memory performance of *Drd4-/-* mice using other tasks such as operant behavior will be necessary to make more definitive assessments of the role of D4 receptors in the mediation of this cognitive process.

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Received January 28, 2002.
Revision received March 29, 2002.
Accepted April 30, 2002.