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Increasing the number of 5-HT$_{1A}$-receptors in cortex and hippocampus does not induce mnemonic deficits in mice

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ABSTRACT

Even though the role of the serotonin1A (5-HT$_{1A}$)-receptor for cognitive processes is undisputed, the exact involvement of pre- and postsynaptic sites remains unexplained. Recently, we introduced a mouse line overexpressing the 5-HT$_{1A}$-receptor in the hippocampus and cortex. In this study we investigated in comparison to wild-type mice their cognitive abilities using the Morris water-maze task and inhibitory avoidance test. Acute effects of pre- and posttraining administered 8-OH-DPAT (0.03–0.3 mg/kg i.p.) were examined in the inhibitory avoidance test. Additionally, habituation learning was studied in the hole-board test.

Transgenic mice showed no overall learning deficit. Spatial learning and memory revealed in the Morris water-maze task was comparable to wild-type mice, and both genotypes habituated to the hole-board arena in a similar manner. Comparing the performance of both genotypes in the inhibitory avoidance test, cognitive functions of transgenic mice seemed to be slightly impaired. When 8-OH-DPAT was administered pretraining an amnesic effect was produced only in transgenic mice and only at the highest dose (0.3 mg/kg). Posttraining administered 0.3 mg/kg 8-OH-DPAT did not affect the performance of both genotypes.

Overall, the cortical and hippocampal overexpression of the 5-HT$_{1A}$-receptor had no major effect on cognitive functions in mice, suggesting that changes in the 5-HT$_{1A}$-receptor density are not necessarily accompanied with alterations of learning and memory processes.

1. Introduction

The modulatory function of serotonergic pathways for learning and memory is well established (Buhot et al., 2000; Meneses and Hong, 1999; Sirvio et al., 1994). However, the significance of each of the at least 14 5-HT-receptor subtypes for cognitive processes requires further research. The 5-HT$_{1A}$-receptor is one of the best described receptor subtypes of the serotonergic neurotransmitter system. High densities are found in the median and dorsal raphe nuclei, where the 5-HT$_{1A}$-receptor functions as a somatodendritic autoreceptor on 5-HT containing neurons (Albert et al., 1990). Activation of 5-HT$_{1A}$-autoreceptors leads to decreased neuronal firing rate and therefore reduces 5-HT release in various brain areas (Ago et al., 2003; Blier and de Montigny, 1990). The 5-HT$_{1A}$-receptor is also expressed postsynaptically as a heteroreceptor, particularly in the hippocampus, septum, amygdala, enthorinal and frontal cortex (Pompeiano et al., 1992). In vitro, stimulation of postsynaptic 5-HT$_{1A}$-receptors induced hyperpolarisation of non-serotonergic neurons (e.g. Blier and de Montigny, 1990; Sprouse and Aghajanian, 1988; Van den Hooff and Galvan, 1992).

The recently published review by Meneses and Perez-Garcia (2007) summarizes in vivo studies that have investigated effects of 5-HT$_{1A}$-receptor agonists and antagonists in various behavioral tasks for learning and memory. Cognitive functions have been described to be either improved or declined by drugs acting at the 5-HT$_{1A}$-receptor. Solely different experimental designs cannot be the reason for these contradictory findings, although the studies are difficult to compare. At higher doses, the full 5-HT$_{1A}$-receptor agonist 8-OH-DPAT was found to cause learning impairment, most likely due to activation of postsynaptic sites (Carli and Samanin, 1992; Egashira et al., 2006; Misane et al., 1998). However, it was also observed that 8-OH-DPAT positively influenced cognition when mainly presynaptic sites were stimulated by low doses (Carli et al., 2001; Micheau and Van Marrewijk, 1999).

When reviewing latest published data it is apparent that one hypothesis has been favored: Substances acting at postsynaptic 5-HT$_{1A}$-receptor sites as antagonists and at presynaptic sites as agonists may ameliorate learning and memory deficits associated to cholinergic or glutamatergic dysfunctions. The selective partial 5-

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HT_{1A}-receptor agonist/antagonist S15535, for example, was found to prevent scopolamine-induced learning deficits in rodents and had precognitive effects in old rats (Carli et al., 1999; Millan et al., 2004; Millan et al., 1993). Recently, a 5-HT_{1A}-receptor antagonist (lecozotan) that was found to increase the extracellular glutamate concentration in the dentate gyrus and the acetylcholine concentration in the CA1 region in rats, was presented for auxiliary therapy of patients with Alzheimer's disease (Childers et al., 2005; Raje et al., 2007; Schechter et al., 2005). Even though the role of the 5-HT_{1A}-receptor for cognitive processes is undisputed, the exact involvement of pre- and post-synaptic sites remains unexplained.

5-HT_{1A}-receptor knockout mice, that showed consistently elevated anxiety levels and antidepressant-like responses (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998), were found to be inconsistent concerning their learning and memory abilities: Improvement (Pattij et al., 2003), impairment (Sarnyai et al., 2000) or no effect at all (Dirks et al., 2001; Dulawa et al., 2000; Parsey et al., 2002) were observed in 5-HT_{1A}-receptor knockout mice. As a complementary approach overexpressing the 5-HT_{1A}-receptor might have the advantage that an up-regulation of the gene does not interfere with physiological functions to the same extent as deletion of the receptor and probably triggers less compensatory mechanisms.

Recently, we have presented a mouse line with an overexpression of the 5-HT_{1A}-receptor in the outer cortical layers and dorsal and ventral hippocampus. Since they are located in projection areas of the serotonergic neurons, we assume that the overexpressed 5-HT_{1A}-receptors are located on postsynaptic sites. Results of the previously published receptor-autoradiography (Bert et al., 2006) have been confirmed by [^{3}H]8-OH-DPAT binding study using whole brain tissues. Binding capacity (B_{max}) of transgenic mice was increased in comparison to wild-type mice, at the same time dissociation constant values (K_d) did not differ between the genotypes (Bert et al., 2008). Transgenic animals showed no altered anxiety-related behavior in the elevated plus-maze test (Bert et al., 2006) and in a free exploratory paradigm (unpublished data). Furthermore, transgenic mice reacted highly sensitive to the systemic administration of 8-OH-DPAT in relation to body temperature and motor activity (Bert et al., 2006). Additionally, some signs of the serotonin syndrome, which can be induced by high doses of 8-OH-DPAT in mice and is thought to be mediated by postsynaptic 5-HT_{1A}-receptors (Blanchard et al., 1997; Yamada et al., 1988), were provoked in transgenic mice at a third of the dosage used for wild-type mice. This indicates that the overexpressed 5-HT_{1A}-receptors are pharmacologically active.

In this study we investigated the learning and memory abilities of mice overexpressing the 5-HT_{1A}-receptor using the inhibitory avoidance test and Morris water-maze task. Additionally, habituation to a new environment using the hole-board was tested. Furthermore, the pre- and posttraining effects of 8-OH-DPAT on learning performance in the inhibitory avoidance test were studied.

2. Materials and methods

2.1. Animals

Male transgenic NMRI mice with an overexpression of the 5-HT_{1A}-receptor in the hippocampus and outer cortical layers and male NMRI wild-type mice bred separately (generation of mice described in detail in Bert et al., 2006) at an age of 12 to 14 weeks were used. Mice were group-housed by sex and genotype with 4–7 animals per cage (Makrolon type IV) under standard laboratory conditions (22±2 °C room temperature, 55±10% humidity) with an artificial 12 h light–dark cycle (lights on 06.00–18.00). They had free access to food (Altromin 1326, Lage, Germany) and tap water. All behavioral tests were conducted in a sound attenuated chamber. Animals were transferred into an anteroom at least 1 h before the beginning of the experiments. Experiments were performed according to the guidelines of the German Animal Protection Law and were approved by the Berlin State Authority ("Landesamt für Gesundheit und Soziales").

2.2. Inhibitory avoidance test

The inhibitory avoidance test was conducted according to the protocol by Voigt et al. (1996). The apparatus consisted of an illuminated start compartment (16×16×20 cm) joined by a 3×3 cm opening to a smaller dark compartment (11×9×7 cm). The dark compartment contained a grid floor, which was connected to an isolated programmable stimulator (Coulbourn Instruments, Allentown, PA, USA).

2.2.1. Procedure

On day 1 (training), a mouse was placed into the start compartment. The sliding door was closed when the animal entered the dark compartment with all four paws, and the mouse received an unavoidable foot-shock (0.2 mA) for 1 s. 24 h later, the animals were tested in the same manner as in the training trial, except for receiving the foot-shock when entering the dark compartment. Testing was terminated either when the mouse reentered the dark compartment or after 180 s without entry. Between each trial the compartments were cleaned with a solution containing 2-propanol 30 vol.-%.

2.2.2. Experiment 1

Naïve, i.e. untreated, male wild-type and transgenic mice (10 per group) were tested.

2.2.3. Experiment 2

(±)-8-OH-DPAT (8-hydroxy-N-(di-*n*-propyl)-aminotetralin; by Sigma-Aldrich, Steinheim, Germany) was freshly dissolved in 0.9% saline and intraperitoneally (i.p.) administered 15 min before training (pretraining). In order to study posttraining effects of 8-OH-DPAT the effective doses of pretraining administration were tested in a new batch of animals. Therefore, the animals received the injections immediately after removing them from the apparatus on day 1. Control animals were treated with 0.9% saline in equivalent volumes (10 ml/kg body weight). The group size varied from 9–10 animals per genotype and treatment.

2.3. Morris water-maze task

15 transgenic and 24 wild-type mice were used for the Morris water-maze task. The test was performed according to the protocol previously described by Bert et al. (2005). Briefly, a circular pool (120 cm in diameter, 36 cm height) was filled with water (20±1 °C) to a height of 24 cm. The maze was indirectly illuminated and placed in an experimental chamber containing several visual cues.

2.3.1. Procedure

On the day prior to the first place learning session, the mice were subjected to a free swim trial (adaptation trial) for 90 s without a platform present. On the following 8 days (*place version*) a transparent platform (10×10 cm) was submerged 1 cm below water level in the center of one of four virtual maze quadrants. During the adaptation trial, the time a mouse spent in the four maze quadrants was recorded. Platform positions for the place version were allocated for each animal by choosing one of the two quadrants which were not avoided or preferred by the animal during the adaptation trial. It was ensured that each of the four platform locations was well represented in the two groups. The animals were placed into the maze from three equidistant starting points (situated left, opposite, and right relative to the platform quadrant). Mice, which did not find the platform within 90 s, were placed manually onto it. After reaching the platform the animals were allowed to stay on it for 30 s for orientation. During intertrial interval, the mice were

placed in a heated cage for 60 s to recover. The search times (escape latencies) to find the platform were measured by a computerized tracking system (TSE VideoMot, Version 1.43, Bad Homburg, Germany). For each mouse an average was taken for the three daily trials. One day after the last place learning session the platform was removed (*spatial probe*) and the time spent in the platform quadrant and the averaged time of the other three quadrants during a single 60 s trial was registered. On the following day the platform was elevated 1 cm above water level, signaled by a white cylinder (3 cm in diameter and 4 cm high), and moved to the sector opposite to the former platform quadrant. This test was performed to assess the motivation to escape from the water and sensor-motor integrity (*cued version*). The testing procedure was consistent with the hidden platform version of the task.

2.4. Hole-board test

Non-associative spatial habituation to a novel environment was evaluated using a hole-board paradigm as previously described for rats (Voits et al., 1995) and mice (Bert et al., 2005). The apparatus consisted of a box measuring 28×28×28 cm, with 16 equidistant holes (2.2 cm in diameter, 2 cm in depth) drilled into an aluminum floor (TruScan 99, Coulbourn Instruments, Allentown, PA, USA). The hole-board was illuminated by a neon lamp embedded into the ceiling. Three infrared beam sensors detected the number of nose-pokes and the distance traveled.

2.4.1. Procedure

The test was conducted on two consecutive days. On both days the animal (7 wild-types and 8 transgenic mice) was placed in the centre of the apparatus and the behavior was observed for 10 min. A significant reduction of exploratory behavior, i.e. a decrease in nose-poking, on the second day is indicating habituation to the hole-board arena. After each trial the box was cleaned with a solution containing 2-propanol 30 vol.-%.

2.5. Statistical analysis

2.5.1. Inhibitory avoidance test

Step-through latencies of day 1 and day 2 were scored and differences between both days (day 2 − day 1) were calculated for each animal. Data was analyzed by Mann–Whitney–*U*-tests in order to detect differences between wild-type and transgenic mice as well as to identify treatment effects.

2.5.2. Morris water-maze task

2.5.2.1. Place version. Escape latencies for the three daily trials were averaged for each animal. *Genotype* and *genotype×day* interactions were analyzed by two-way ANOVA on repeated measures. The day effect within a group was calculated by one-way ANOVA on repeated measures followed by Dunett's method versus day 1.

2.5.2.2. Spatial probe. The times spent in the quadrants to the left, opposite and right of the platform quadrant were averaged and compared to the time spent in the platform quadrant. Data were analyzed by paired *t*-tests.

2.5.2.3. Cued version. Escape latencies for the three trials were scored for each animal. *Genotype* and *genotype×trial* interaction were analyzed by two-way ANOVAs on repeated measures.

2.5.3. Hole-board test

For each animal and day the total number of nose-pokes was recorded. Day-dependent differences were analyzed by two-way ANOVAs on repeated measures followed by Bonferroni *t*-test versus day 1.

For all behavioral tests the effects were considered significant when *p* values which were lower than 0.05 were found.

3. Results

3.1. Inhibitory avoidance test

3.1.1. Experiment 1

Untreated wild-type and transgenic mice showed a comparable performance of the inhibitory avoidance test ($p=0.162$, Fig. 1).

3.1.2. Experiment 2

Pretraining administration of 8-OH-DPAT at a lower dose (0.03 and 0.1 mg/kg) did not affect the performance of both genotypes, whereas at a higher dose of 0.3 mg/kg a significant amnesic effect was apparent, yet only in transgenic mice ($p=0.001$, Fig. 2). In wild-type mice learning and memory impairment could only be achieved by the administration of 1.0 mg/kg 8-OH-DPAT (data not displayed in Fig. 2; saline: 160.0+/−4.5 s and 1.0 mg/kg 8-OH-DPAT: 62.0+/−25.4 s, $p<0.001$, Mann–Whitney–*U*-test vs. saline).

There was a significant *genotype* effect when the animals were treated with 0.1 ($p=0.037$) and 0.3 mg/kg ($p<0,001$) 8-OH-DPAT: transgenic mice reentered the dark compartment within a shorter time than wild-type mice (Fig. 2).

The effective dose of 8-OH-DPAT (0.3 mg/kg) achieved in the pretraining experiment did not affect consolidation of the inhibitory avoidance task in both genotypes when administered posttraining (Fig. 3). We additionally tested the posttraining effect of 1.0 mg/kg 8-OH-DPAT in wild-type mice and 0.1 mg/kg 8-OH-DPAT in transgenic mice, both doses were ineffective (WT: $p=0.622$ and TG: $p=0.755$, Mann–Whitney–*U*-test vs. saline; data not displayed in Fig. 3). However, wild-type and transgenic mice differed in their performance when treated with saline: transgenic mice displayed a decreased step-through latency compared to wild-type mice ($p=0.008$; Fig. 3).

3.2. Morris water-maze task

The mean latencies of wild-type and transgenic mice to locate the platform are shown in Fig. 4. Both groups mastered the task in a similar manner (*genotype*: $F_{1,37}=0.632$; $p=0.432$); *genotype×day*: $F_{7,259}=0.477$; $p=0.851$): From the second day onwards the mean latencies were significantly lower than on the first day (*day*: $F_{7,259}=14.455$; $p<0.001$). The good performance in the place version was reflected in the spatial probe (see Fig. 5): Both groups spent significantly more time in the former platform quadrant in comparison to the averaged time of the other three quadrants (*wild-type:* $p=0.020$; *transgenic:* $p=0.026$). During

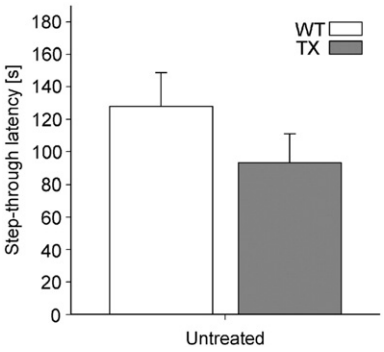

Fig. 1. Shown are the differences of step-through latencies between day 2 and day 1 as means+SEM of untreated wild-type (WT) and transgenic (TX) mice in the inhibitory avoidance-test.

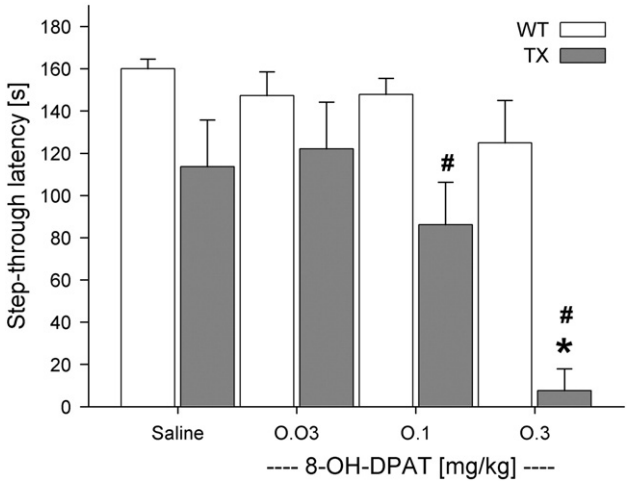

Fig. 2. Effect of 0.03–0.3 mg/kg 8-OH-DPAT administered pretraining on the inhibitory avoidance performance of wild-type (WT) and transgenic (TX) mice. Shown are the differences of step-through latencies between day 2 and day 1 as means+SEM. *$p<0.05$ vs. saline; #$p<0.05$ vs. WT.

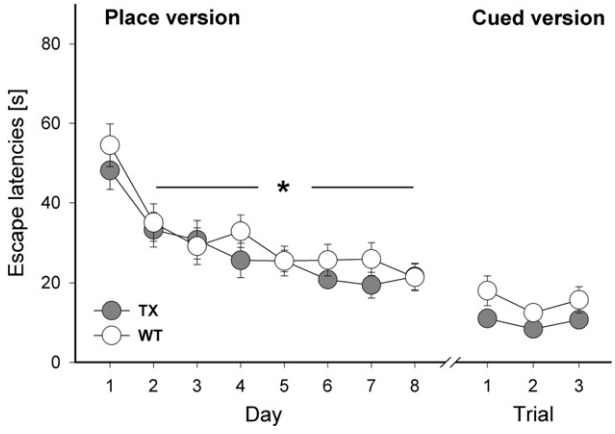

Fig. 4. Shown are the averaged escape latencies±SEM [s] during the place version and cued version of the Morris water-maze test. *$p<0.05$ vs. day 1 for both wild-type (WT) and transgenic (TX) mice.

the cued version, which tests motor-visual integrity, there were also no differences among the genotypes (*genotype*×*trial*: $F_{2,74}=0.242$; $p=0.786$, see Fig. 4).

3.3. Hole-board test

Both genotypes habituated to the hole-board in a similar manner (see Fig. 6). The reduction of nose-pokes on the second day (*day*: $F_{1,13}=57.736$; $p<0.001$) was irrespective of genotype (*genotype*×*day*: $F_{1,13}<0.005$; $p=0.944$).

4. Discussion

Pharmacological studies investigate the role of the postsynaptic 5-HT_{1A}-receptor by either injecting agonists or antagonists locally in specific projection areas of the serotonergic system or by depletion or lesion of serotonergic neurons. However, even with these specific techniques it was still not possible to fully clarify the exact role of the postsynaptic 5-HT_{1A}-receptor for various physiological and pathological functions. One possible reason is that locally administered substances can diffuse to other brain areas and therefore might lead to different outcomes. Additionally, the consequences of serotonergic lesion or reduction of 5-HT contents in the synaptic cleft are not only restricted to the 5-HT_{1A}-receptor they can also affect other postsynaptic 5-HT-receptor subtypes. As a complementary approach to pharmacological studies we generated a mouse line with an overexpression of 5-HT_{1A}-receptors in the dorsal and ventral hippocampus and outer cortical layers. The overexpression in mice led to no obvious behavioral phenotype concerning anxiety-related behavior and motor activity (Bert et al., 2006). However, receptor activation with the 5-HT_{1A}-receptor agonist 8-OH-DPAT produced a distinct hypothermic effect and an exaggerated serotonin syndrome in transgenic mice. This effect appeared in a third of the dosage that was used for wild-type mice (Bert et al., 2006). The behavioral and physiological outcome that was observed after the administration of 8-OH-DPAT indicates the functioning of the overexpressed receptors. This, together with the distribution pattern of the overexpressed 5-HT_{1A}-receptors speaks for a postsynaptic localization of the surplus 5-HT_{1A}-receptors.

Changes in the density of the 5-HT_{1A}-receptor were identified in aged humans and patients suffering from Alzheimer's disease (AD). The majority of studies have revealed decreased 5-HT_{1A}-receptor levels especially in cortical areas, but also in the hippocampus (Kepe et al., 2006; Lai et al., 2003; Lanctot et al., 2007; Moller et al., 2007; Tauscher et al., 2001). In animal experiments aging was also

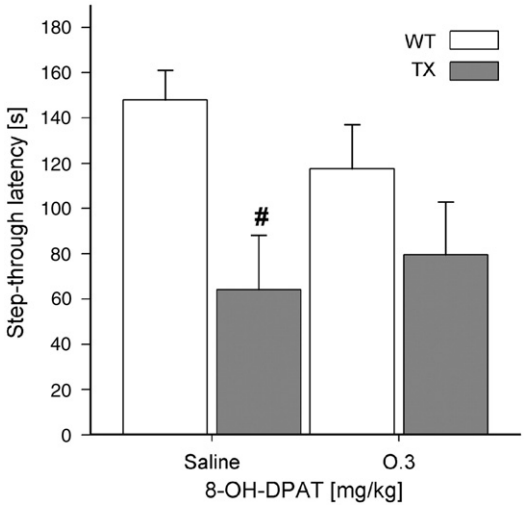

Fig. 3. Effect of 0.3 mg/kg 8-OH-DPAT administered posttraining on the inhibitory avoidance performance of wild-type (WT) and transgenic (TX) mice. Shown are the differences of step-through latencies between day 2 and day 1 as means+SEM. #$p<0.05$ vs. WT.

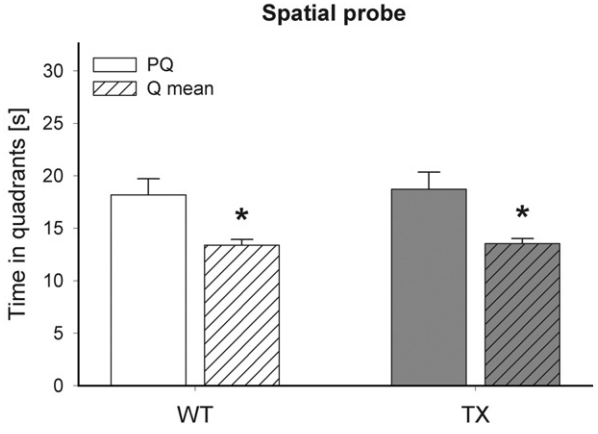

Fig. 5. Shown are the swimming durations in each sector as means+SEM [s] during the spatial probe of the Morris water-maze test of wild-type (WT) and transgenic (TX) mice. PQ=platform quadrant, Q mean=mean value of the other three quadrants. *$p<0.05$ vs. PQ.

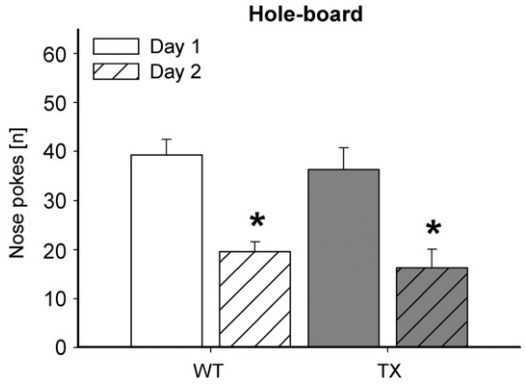

Fig. 6. Shown are the averaged number of nose-pokes + SEM on days 1 and 2 of the hole-board test of wild-type (WT) and transgenic (TX) mice. *$p < 0.05$ vs. day 1.

found to be linked with decreased 5-HT_{1A}-receptor binding in the forebrain and cortex of rats (Huguet et al., 1994; Nyakas et al., 1997). All these findings support the assumption that the 5-HT_{1A}-receptor is involved in the pathomechanism of dementia and that it can serve as a possible target for cognitive enhancers. If the 5-HT_{1A}-receptor density is crucial for normal learning and memory abilities our transgenic mice overexpressing the 5-HT_{1A}-receptor in the hippocampus and cortex should show altered cognitive functions. However, transgenic mice did not differ in their performance from wild-type mice in three different learning tasks. In the Morris water-maze task both genotypes learned to locate the hidden platform in a comparable manner and remembered the original platform position. There was also no significant difference in learning and memory of wild-type and transgenic mice in the inhibitory avoidance test. Additionally, habituation to a new environment, i.e. to the hole-board, was similar for both genotypes. Specifically the result gained in the Morris water-maze task seems contradictory to the finding by Topic et al. (2007). They have shown that hippocampal density of 5-HT_{1A}-receptors is increased in aged rats which additionally were inferior learners in the Morris water-maze task. However, since different protocols, species and especially ages were used our results are difficult to compare with the work by Topic et al. (2007).

Although many of the clinical studies revealed a decreased number of 5-HT_{1A}-receptors in projection areas of serotonergic neurons in humans who show cognitive deficits, there is also evidence that cognitive impairment is linked to an increased 5-HT_{1A}-receptor binding. This was seen in humans with mild mnemonic deficits (Truchot et al., 2007) and was also described for schizophrenic patients (Joyce et al., 1993; Kasper et al., 2002; Simpson et al., 1996; Tauscher et al., 2002). Hence, it seems questionable that changes in the number of 5-HT_{1A}-receptors are the cause of cognitive dysfunctions. Our results point in the same direction that the sole increase in 5-HT_{1A}-receptor density in the hippocampus and cortex is not necessarily associated with alterations in learning and memory in mice. Especially, since we could show that the surplus expression is not accompanied by an increase in 5-HT turnover (Bert et al., 2006). Finding by Borg et al. (2006) underline this hypothesis, because they could not reveal a significant correlation between 5-HT_{1A}-receptor binding and cognitive functioning in healthy volunteers.

However, it remains undisputed that 5-HT_{1A}-receptor activation has an effect on cognitive functions. Low doses of the full 5-HT_{1A}-receptor agonist 8-OH-DPAT are assumed to mainly stimulate 5-HT_{1A}-autoreceptors (Dourish et al., 1985) and were found to facilitate retention in a passive avoidance test in mice and rats when administered pretraining (Luttgen et al., 2005; Madjid et al., 2006). In our study pretraining administration of low doses of 8-OH-DPAT (0.03 and 0.1 mg/kg) did not affect learning and memory either in wild-type or transgenic mice. Anameliorative effect of 8-OH-DPAT could not be achieved in wild-type mice, since the control group already showed the maximum learning performance. In transgenic mice amelioration would have been possible. However, low doses of 8-OH-DPAT (0.03 and 0.1 mg/kg) were ineffective. Hence, we assume that pretraining activation of presynaptic 5-HT_{1A}-receptors does not interfere with learning and memory in the inhibitory avoidance test.

High doses of 8-OH-DPAT were found to cause cognitive impairment in the passive avoidance task, most likely due to activation of postsynaptic sites (Carli and Samanin, 1992; Mendelson et al., 1993; Misane et al., 1998; Sanger and Joly, 1989). In our study 0.3 mg/kg 8-OH-DPAT administered before the training session of the inhibitory avoidance test produced only in transgenic mice impaired acquisition. A threefold higher dose (1.0 mg/kg) of 8-OH-DPAT had to be used to induce a similar effect in wild-type mice. This indicates a higher sensitivity of mice overexpressing the 5-HT_{1A}-receptor. Since the transgenic mice have an increased number of 5-HT_{1A}-receptors in projection areas of serotonergic neurons it is most likely that the pronounced amnesic effect of 8-OH-DPAT is mediated by the surplus postsynaptic receptors. This underlines the previous findings that anterograde amnesia induced by 8-OH-DPAT is mediated by post-synaptic 5-HT_{1A}-receptors in the inhibitory avoidance test.

It can be excluded that in our study the amnesic effect of high doses of 8-OH-DPAT is caused by increased anxiety levels in both genotypes, since this dose range was ineffective on the anxiety-related behavior in the elevated plus-maze test (Bert et al., 2006). However, it cannot be denied, that, in our study, the effect on anterograde memory is partly based on low attention of the transgenic mice. In the earlier published study, 0.25 mg/kg 8-OH-DPAT reduced motor activity in the open field as well as in the elevated plus-maze test (Bert et al., 2006), indicating a sedative effect. But nevertheless for all animals, jump and vocalization responses were recorded when they were exposed to the foot-shock. Therefore, we assume that the sedative effect of 8-OH-DPAT did not interfere with the amnesic effect.

Posttraining administration of 0.3 mg/kg 8-OH-DPAT did not influence the performances of either genotypes, which confirms findings of Madjid et al. (2006). They observed that posttraining administration of 0.01 and 0.3 mg/kg 8-OH-DPAT failed to alter learning and memory in the passive avoidance task in mice. In our study also 1.0 mg/kg in wild-type mice and 0.1 mg/kg in transgenic mice did not affect the behavior.

Summarizing all findings, the overexpression of 5-HT_{1A}-receptors in the dorsal and ventral hippocampus and outer cortical layers did not produce changes in cognitive functions in the inhibitory avoidance test, the Morris water maze task, and hole-board test. Therefore, it appears that the 5-HT_{1A}-receptor density is not crucial for learning and memory functions and the results implicate that the postsynaptic 5-HT_{1A}-receptors in the hippocampus and cortex play a modulatory role in cognitive processes. However, activation of postsynaptic 5-HT_{1A}-receptors when overexpressed seems to cause cognitive impairment in specific tasks and therefore, drugs acting at postsynaptic sites could have an augmentative effect for learning and memory.

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