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Serotonin 1A receptors and sexual behavior in a genetic model of depression

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ABSTRACT

The Flinder Sensitive Line (FSL) is a rat strain that displays distinct behavioral and neurochemical features of major depression. Chronic selective serotonin reuptake inhibitors (SSRIs) are able to reverse these symptoms in FSL rats. It is well known that several abnormalities in the serotonergic system have been found in FSL rats, including increased 5-HT brain tissue levels and reduced 5-HT synthesis. SSRIs are known to exert (part of) their effects by desensitization of the 5-HT_{1A} receptor and FSL rats appear to have lower 5-HT_{1A} receptor densities compared with Flinder Resistant Line (FRL) rats. We therefore studied the sensitivity of this receptor on the sexual behavior performance in both FRL and FSL rats. First, basal sexual performance was studied after saline treatment followed by treatment of two different doses of the 5-HT_{1A} receptor agonist ±8-OH-DPAT. Finally we measured the effect of a 5-HT_{1A} receptor antagonist to check for specificity of the 5-HT_{1A} receptor activation. Our results show that FSL rats have higher ejaculation frequencies compared with FRL rats which do not fit with a more depressive-like phenotype. Moreover FRL rats are more sensitive to effects of ±8-OH-DPAT upon EL and IF than FSL rats. The blunted response of FSL rats to the effects of ±8-OH-DPAT may be due to lower densities of 5-HT_{1A} receptors.

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1. Introduction

The Flinder Sensitive Line (FSL) is a rat strain that displays distinct behavioral and neurochemical features of major depression that includes face, construct and predictive validity (Neumann et al., 2011; Overstreet and Wegener, 2013). Comparable to symptoms in major depressed patients, FSL rats exhibit psychomotor retardation such as reduced mobility in the forced swim test (behavioral despair) and lower activity in novel open-field tests (El Khoury et al., 2006; Overstreet and Russell, 1982; Schiller et al., 1992). Moreover, FSL rats show decreased appetite and weigh less compared to controls (Overstreet, 1993, 2002). Also, FSL rats have memory impairments (Eriksson et al., 2012) and display increased rapid eye movement sleep, as found in depressed patients (Benca et al., 1996; Shiromani et al., 1988). Decreased activity of the brain serotonergic system has been described in both humans with depression as well as in animal models for depression (Lesch and Heils, 2000). FSL rats also display several abnormalities in the serotonergic system. Although extracellular serotonin (5-HT) levels and 5-hydroxyindoleacetic acid (5-HIAA, metabolite of 5-HT) are comparable between FSL and control rats (Dremencov et al., 2005; Zangen et al., 2001), it was found that FSL rats have 6–7 times higher tissue levels of 5-HT and 5-HIAA in several brain areas (Zangen et al., 1997), suggesting a reduced 5-HT turnover. Moreover, 5-HT synthesis has been found reduced in FSL rats (Hasegawa et al., 2006). Thus, FSL rats have increased intraneuronal 5-HT levels, but because there are no alterations in extracellular levels it is possible that 5-HT is not packed into vesicles (Hasegawa et al., 2006). Some of the behaviors seen in FSL rats can be reversed by chronic but not acute antidepressants such as selective serotonin reuptake inhibitors (SSRIs; El Khoury et al., 2006; Eriksson et al., 2012). Anatomically, FSL rats have reduced hippocampal volume and dendritic spines, which can be reversed by antidepressants as well (Chen et al., 2010). SSRIs are known to exert (part of) their effects by desensitization of 5-HT_{1A} receptors (Kinney et al., 2000). Although 5-HT_{1A} receptor densities are lower in several brain areas of FSL rats compared to FRL rats (Eriksson et al., 2012; Nishi et al., 2009), FSL rats are more sensitive to the 5-HT_{1A} receptor agonist 8-OH-DPATin the hypothermia paradigm (Overstreet et al., 1994). However, Eriksson et al. (2012) found a blunted response to 8-OH-DPAT in FSL rats compared to FRL rats in a cognitive task. Limited

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid (5-HIAA metabolite of 5-HT); 5-HT, serotonin; CE, copulatory efficiency; E, ejaculation; EF, ejaculation frequency; EL, latency to the ejaculation; FRL, Flinders Resistant Line; FSL, Flinders Sensitive Line; I, intromission; IF, intromission frequency; IL, latency to first intromission; M, mount; MF, mount frequency; ML, latency to first mount; PEL, post-ejaculatory latency; SSRI, selective serotonin reuptake inhibitors.

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research has been performed on the sensitivity of the 5-HT_{1A} receptor in the social behavior of FSL rats. Because depressed patients often display symptoms of sexual dysfunction (Gregorian et al., 2002; Mathew and Weinman, 1982; Williams and Reynolds, 2006), we aimed to investigate the role of the 5-HT_{1A} receptor in sexual behavior of FSL rats. Sexual behavior has never been assessed before in FRL and FSL rats and therefore we first investigated the basal sexual behavior after a saline injection followed by treatment of two different doses of the 5-HT_{1A}receptor agonist ±8-OH-DPAT. We finally measured the effect of a 5-HT_{1A} receptor antagonist (WAY100635) on ±8-OH-DPAT-induced effects to check for specificity of 5-HT_{1A} receptor activation.

2. Material & methods

2.1. Animals

Adult male FSL and FRL rats were bred at the Karolinska University Huddinge. All animals were housed 4 per cage (FRL separated from FSL) in a reversed 12/12 h day/night cycle (lights off at 7:00 AM) and food and water were available *ad libitum*. Training of sexual behavior started when FRL ($N = 12$) and FSL ($N = 8$) rats were approximately 5 months old. Animals were weighed before each drug experiment. FRL female rats (at least 3 months old) were used as stimulus rats and estrus was induced by a single injection of 50 μg of estradiol benzoate in sesame oil 36–42 h prior to testing. Experimental procedures were approved by the local Animal Ethics Committee (Stockholms Södra Djurförsöksetiska Nämnd).

2.2. Drugs

±8-Hydroxy-2-(di-n-propylamino)tetraline (±8-OH-DPAT) and N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl]-N-(2-pyridyl) cyclohexanecarboxamide (WAY100635) were obtained from Sigma–Aldrich, St Louis, MO, USA. Doses of ±8-OH-DPAT (0.01 and 0.03 mg/kg) were based on previous studies that showed these doses were active in sexual behavior (Chan et al., 2011). The 0.1 mg/kg WAY100635 dose was chosen as an effective dose in blocking the effects of ±8-OH-DPAT, without having an effect on its own (de Jong et al., 2005). ±8-OH-DPAT (s.c.) was injected right before the introduction of the female stimulus rat, while WAY100635 (i.p.) was injected 30 min before the introduction of the female stimulus rat. Both drugs were dissolved in 0.9% NaCl and injected in a volume of 1 mL/kg.

2.3. Sexual behavior

2.3.1. Experimental design and testing

The sexual behavior experiment lasted 11 weeks in total with a 1-week washout period between each experiment. Sexual behavior was performed in an observation cage (50 × 50 × 50 cm) with plexiglass surroundings. The floor of the test cage was covered with sawdust which was not refreshed between sessions. Males were trained for 30 min once weekly for seven consecutive weeks against an estrus female (Chan et al., 2011). In the 7th week rats received a saline injection right before the sexual behavior session. From week 7 (saline injection) and on, all sexual behavior was scored during a 30-min test (see behavioral parameters). In week 8 rats received 0.01 mg/kg ±8-OH-DPAT, in week 9 rats received 0.03 mg/kg ±8-OH-DPAT, and in week 10 rats received 0.1 mg/kg WAY100635 + 0.03 mg/kg ±8-OH-DPAT. After all pharmacological experiments rats were tested again for their sexual behavior after a saline injection in week 11 in order to test whether the drug treatment had influenced basal sexual behavior performance. Testing was performed between 8:00 AM and 5:00 PM in the dark phase of the light/dark cycle under red light. Rats were placed in the test cage 10 min prior to the test to habituate to the cage. WAY100635 was injected in the home cage, while ±8-OH-DPAT was injected right before placing an estrus female into the test cage.

2.3.2. Behavioral parameters

The following parameters were scored for each ejaculation series within the 30-min test using Keys® (Nijmegen, The Netherlands): number of mounts (M) and intromissions (I), time of first mount and intromission, and time of ejaculation (E). From these data the following parameters were deduced: number of ejaculations/test (EF), latency to first mount(s) (ML), latency to first intromission(s) (IL), total number of mounts (MF), total number of intromissions (IF), and latency to the ejaculation(s) (EL; calculated as time of ejaculation minus the time of the very first behavior (M or I) of that ejaculation series) per ejaculation series. After ejaculation, the post-ejaculatory latency (PEL) was calculated, using the time from the first ejaculation and the time of the first M/I (whichever occurred first). Copulatory efficiency (CE) was calculated as: CE = (#I/[#I + #M]) × 100% per ejaculation series. All data are represented as mean ± standard error of the mean.

2.4. Statistical analysis

An outlier test was performed using the stem-and-leaf box-plotting of the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) to exclude extremes for statistical comparisons. Statistics analyses were performed using a 2 × 5 (strain × treatment) linear mixed model ANOVA because of missing values (see result section). Where appropriate, LSD post hoc testing was used. Differences within FRL rats or FSL rats (strain effects), or differences within treatment (drug effect) were analyzed using an independent *T*-test or one-way ANOVA respectively. Data were analyzed separately for the first and second ejaculatory series. Level of significance was set at $p < 0.05$ (n.s. = non-significant). All statistical analyses were performed using SPSS version 20.0 for windows.

3. Results

3.1. Missing values

Some animals had no ejaculation during the fixed test duration of 30 min. In the FRL rats, 2 out of 12 animals and in the FSL rats 2 out of 8 animals never showed sexual activity during training. Because it is impossible to calculate the sexual parameters for these rats, it was decided to exclude them for statistical comparison. Also when rats didn't reach a second ejaculation, these rats were excluded for the statistical comparisons for the secondary ejaculation series. Initially two FRL rats were treated with 0.1 mg/kg ±8-OH-DPAT but because they showed a heavy serotonin syndrome, it was decided that all remaining animals will receive 0.03 mg/kg ±8-OH-DPAT. Therefore two FRL rats are missing in the 0.03 mg/kg ±8-OH-DPAT analysis.

3.2. Sexual behavior

3.2.1. Strain effects of all tested weeks in the first ejaculatory series

An overall strain effect was found for the EF (Fig. 1A; $F_{(1,27)} = 8.15$; $p < 0.01$). Although the EF was higher after all treatments in FSL compared to FRL rats, a significant difference was only found after week 7 saline treatment ($T_{(1,12)} = 2.14$, $p = 0.05$). An overall strain effect was also found for the EL (Fig. 1B; $F_{(1,28)} = 4.82$; $p < 0.05$). Post hoc analyses revealed a strong tendency for reduced EL in FSL rats compared with FRL rats in the week 7 saline treatment ($T_{(1,11)} = 2.16$; $p = 0.06$), but not with other treatments. Moreover, a tendency for an overall strain effect for the IF was also found (Fig. 1C; $F_{(1,24)} = 3.30$; $p = 0.08$) but post hoc analyses did not reveal further differences at different treatments. No overall strain effects were found for the IL ($F_{(1,18)} = 1.71$; n.s.). For the MF, an overall strain effect was found (Fig. 1D; $F_{(1,26)} = 5.40$; $p < 0.05$), but post hoc analyses did not reveal any further differences at the different treatments. No further strain effects were found for ML ($F_{(1,20)} = 1.46$; n.s.), PEL ($F_{(1,22)} = 0.78$; n.s.) and CE ($F_{(1,24)} = 2.11$; n.s.).

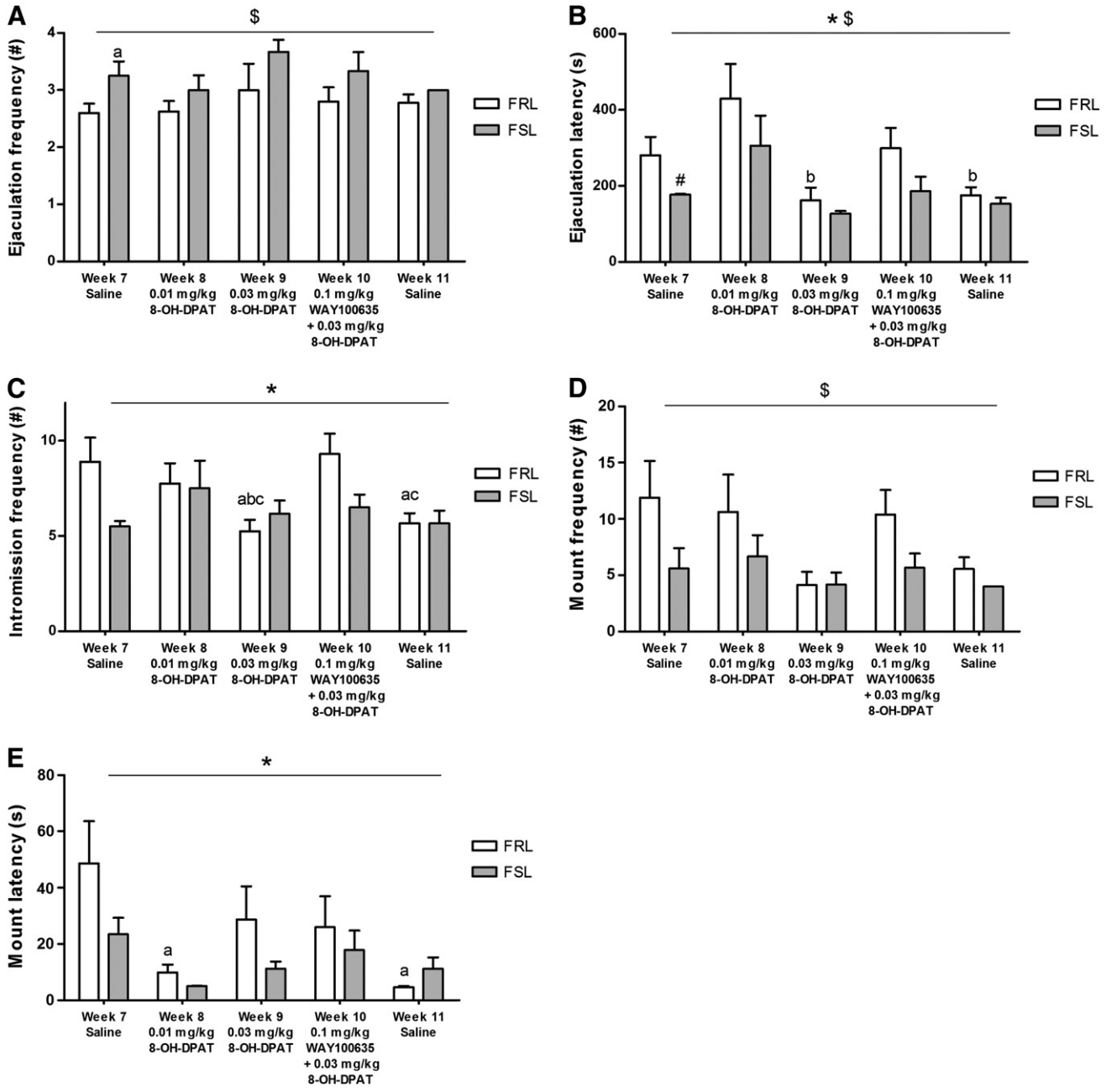

Fig. 1. Effects of saline (week 7 and 11), ±8-OH-DPAT (week 8 and 9) and WAY100635 combined with ±8-OH-DPAT (week 10) on ejaculation frequency (A), ejaculation latency (B) intromission frequency (C), mount frequency (D) and mount latency (E) during the first ejaculation series. $ = overall strain difference; * = overall treatment effect; a = significantly different from week 7 saline treated FRL rat; b = significantly different from 0.01 mg/kg ± 8-OH-DPAT treated FRL rats, c = significantly different from 0.1 mg/kg WAY100635 + 0.03 mg/kg 8-OH. DPAT treated FRL rats, d = tendency to be different from week 7 saline treated FRL rats.

3.2.2. Treatment effects of all tested weeks in the first ejaculatory series

No overall treatment effects were found for the EF (Fig. 1A; $F_{(4,56)} = 1.20$; n.s.). However, an overall treatment effect was found for the EL (Fig. 1B; $F_{(4,53)} = 6.38$; $p < 0.001$). The EL at 0.01 mg/kg ±8-OH-DPAT is higher compared to the EL after week 7 saline treatment ($p < 0.01$), 0.03 mg/kg ±8-OH-DPAT ($p < 0.001$), 0.1 mg/kg WAY100635 combined with 0.03 mg/kg ±8-OH-DPAT ($p < 0.05$) and compared to week 11 saline ($p < 0.001$). Moreover the EL is higher after the combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT treatment compared with 0.03 mg/kg ±8-OH-DPAT ($p < 0.05$) treatment. When the data was split into strains a significant treatment effect for the EL was found in FRL rats $F_{(4,42)} = 3.72$; $p < 0.05$), post hoc analyses revealed that the EL in FRL rats treated with 0.03 mg/kg ±8-OH-DPAT ($p < 0.01$) or with week 11 saline ($p < 0.01$) was lower compared to the EL in FRL rats treated with 0.01 mg/kg ±8-OH-DPAT (see Fig. 1B). No treatment effects were found for the EL in FSL rats. An overall treatment effect was found for the IF (Fig. 1C; $F_{(4,49)} = 3.01$; $p < 0.05$). The IF was lower in week 11 saline treated rats compared with week 7 saline, 0.01 mg/kg ±8-OH-DPAT, and combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT treated rats (for all $p < 0.05$). Moreover, the IF in 0.03 mg/kg ±8-OH-DPAT treated rats was lower compared with 0.01 mg/kg ±8-OH-DPAT, and combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT treated rats (both $p < 0.05$). This effect was caused mainly by the FRL rats as they showed a significant treatment effect for the IF ($F_{(4,44)} = 3.37$; $p = 0.05$), while no treatment effects were found for the IF in FSL rats. Post hoc analyses revealed further that the IF in FRL rats treated with 0.03 mg/kg ±8-OH-DPAT was lower compared with the IF in

week 7 saline ($p < 0.05$), 0.01 mg/kg ±8-OH-DPAT ($p < 0.05$) and combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT treated FRL rats ($p < 0.01$). Moreover, the IF in week 11 saline treated FRL rats was lower compared with week 7 saline and combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT treated FRL rats (both $p < 0.05$).No treatment effects were found for the IL (Fig. 1C; $F_{(4,55)} = 0.93$; n.s.) and MF (Fig. 1D; $F_{(4,49)} = 2.28$; n.s.). But, an overall treatment effect was found for the ML (Fig. 1E; $F_{(4,45)} = 4.56$; $p < 0.01$). The ML in week 7 treated saline rats was higher compared with 0.01 mg/kg ±8-OH-DPAT ($p < 0.01$), 0.03 mg/kg ±8-OH-DPAT ($p < 0.05$) and week 11 saline treated rats ($p < 0.01$). Again this effect is mainly due to the FRL rats as they showed a treatment effect for the ML ($F_{(4,43)} = 2.73$; $p = 0.05$), while no treatment effects were found for the ML in FSL rats. Post hoc analyses revealed that week 7 saline treated FRL rats had a higher ML compared with 0.01 mg/kg ±8-OH-DPAT ($p < 0.05$) and week 11 saline treated rats ($p < 0.01$). Finally, no treatment effects were found for PEL ($F_{(4,49)} = 0.14$; n.s.) and CE ($F_{(4,48)} = 0.11$; n.s.).

3.2.3. Strain effects of all tested weeks in the second ejaculatory series

In the second ejaculation series no strain effects were found for EL ($F_{(1,23)} = 0.88$; n.s.), IF ($F_{(1,27)} = 0.86$; n.s.), IL ($F_{(1,31)} = 0.07$; n.s.), ML ($F_{(1,26)} = 3.66$; n.s.), MF ($F_{(1,24)} = 1.68$; n.s.), PEL ($F_{(1,35)} = 0.70$; n.s.) and CE ($F_{(1,29)} = 1.61$; n.s.).

3.2.4. Treatment effects of all tested weeks in the second ejaculatory series

An overall treatment effect was found for the EL (Fig. 2A; $F_{(4,50)} = 3.21$; $p < 0.05$), with a lower latency after treatment with 0.03 mg/kg ±8-OH-DPAT compared with week 7 saline treatment ($p < 0.01$) and 0.01 mg/kg ±8-OH-DPAT treatment ($p < 0.01$). This effect was mainly caused by FRL rats as they showed a high tendency for a treatment effect ($F_{(4,42)} = 2.22$; $p = 0.08$), while FSL rats did not show a treatment effect. The EL in FRL rats was lower after treatment with 0.03 mg/kg ±8-OH-DPAT compared with week 7 saline treatment ($p < 0.05$) and 0.01 mg/kg ±8-OH-DPAT treatment ($p < 0.05$). Another overall treatment was found for the IF ($F_{(4,49)} = 3.61$; $p < 0.05$). Fig. 2B shows that treatment with 0.03 mg/kg ±8-OH-DPAT decreased the IF compared with week 7 and week 11 saline treatment (both $p < 0.01$). FRL rats had a tendency for a treatment effect ($F_{(4,42)} = 2.17$; $p = 0.09$, with the IF being lower after 0.03 mg/kg ±8-OH-DPAT treatment compared with week 7 saline treatment ($p < 0.01$). Moreover, a treatment effect was found for FSL rats ($F_{(4,25)} = 2.96$; $p < 0.05$). In FSL rats, treatment with 0.03 mg/kg ±8-OH-DPAT decreased the IF compared with week 7 saline treatment ($p < 0.05$). In addition, the IF in FSL rats after week 11 saline was higher compared with 0.01 mg/kg ±8-OH-DPAT ($p < 0.05$) and 0.03 mg/kg ±8-OH-DPAT treatment ($p < 0.01$) in FSL rats. No further treatment effects were found in the secondary ejaculation series in IL ($F_{(4,57)} = 1.49$; n.s.), ML ($F_{(4,56)} = 1.92$; n.s.), MF ($F_{(4,51)} = 1.74$; n.s.), PEL ($F_{(4,50)} = 1.43$; n.s.) and CE ($F_{(4,53)} = 4.53$; n.s.).

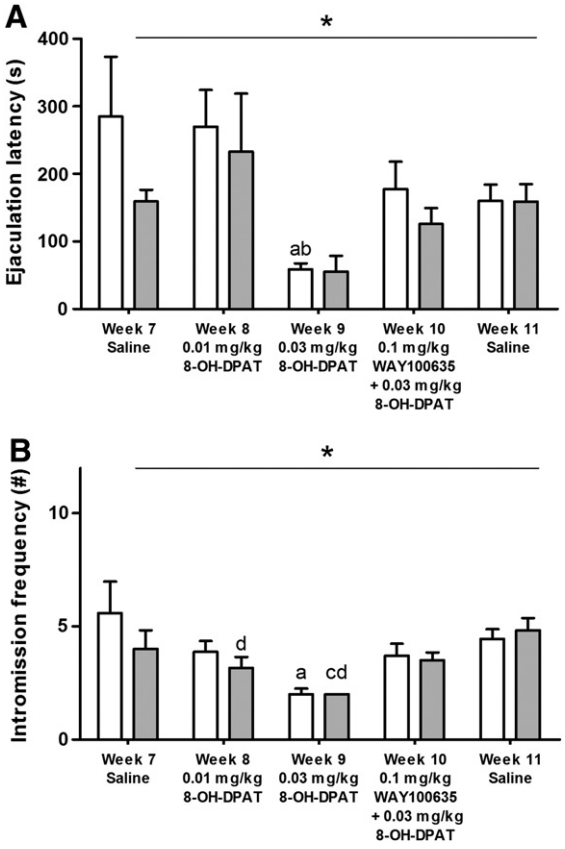

Fig. 2. Effects of saline (week 7 and 11), ±8-OH-DPAT (week 8 and 9) and WAY100635 combined with ±8-OH-DPAT (week 10) on ejaculation latency (A) and intromission frequency (B) during the second ejaculation series.* = overall treatment effect; a = significantly different from week 7 saline treated FRL rats; b = significantly different from 0.01 mg/kg ±8-OH-DPAT treated FRL rats, c = significantly different from week 7 saline treated FSL rats, d = significantly different from week 11 saline treated FSL rats.

4. Discussion

The aim of the present study was to investigate the sensitivity of the 5-HT_{1A} receptor agonist ± 8-OH-DPAT on sexual behavior in FRL and FSL rats. With regard to basal behavior we observed that both FRL and FSL rats show normal sexual behavior, including mounts, intromissions and ejaculations. The EF of FRL and FSL rats in week 7 saline treatment is statistically not different from the EF in the training of week 5 and 6 (data not shown). At week 7 saline treatment FSL rats have more ejaculations and tend to have a lower EL in a 30 min test compared to FRL rats, indicating that FSL rats are more efficient in their sexual behavior. This finding was surprising as it is well-known that depression results in sexual dysfunction (Gregorian et al., 2002; Mathew and Weinman, 1982; Williams and Reynolds, 2006) a finding that is also apparent in animal models for depression (Chan et al., 2011). It has been reported that FSL rats have alterations in their serotonergic system such as increased 5-HT brain levels (Zangen et al., 1997). It is well known that SSRIs increase the extracellular 5-HT levels by blocking the 5-HT reuptake transporter (5-HTT). However, chronic treatment with SSRIs in both humans and rats is known to delay the EL or even prevent having ejaculations at all (Clayton et al., 2002; Montejo-Gonzalez et al., 1997; Rosen et al., 1999; Rowland et al., 2010; Waldinger et al., 1998). It should be mentioned that this effect is only seen after chronic SSRI treatment and only during adulthood. Perhaps alterations in sexual behavior arise when 5-HT tissue levels are already high during development. The 5-HTT knockout rat (5-$HTT^{-/-}$) might be helpful in this aspect as in these rats the 5-HTT has been abolished from conception on. Although these rats have increased extracellular 5-HT levels, the 5-HT tissue levels are reduced in several brain areas (Homberg et al., 2007). In contrast to FSL rats, the 5-$HTT^{-/-}$rats display reduced EF and delayed latencies to ejaculate (Chan et al., 2011). This could be explained by the fact that FSL rats have life-long increased 5-HT tissue levels, already during development, which might have an influence on the sexual performance of the FSL rats later in life. Probably the increased EF and tendency for reduced EL found in the present study are the result of increased 5-HT levels during development. However, other neurotransmitter systems and neuropeptides are altered as well in the FSL rats (Overstreet and Wegener, 2013), making it hard to conclude from these data whether the increased number of ejaculations found in FSL rats are directly linked to the serotonergic system.

4.1. 5-HT_{1A} receptor agonism

The most interesting findings after treatment with ±8-OH-DPAT were the reduced EL in both the first and the second ejaculation series

(mainly caused by effects in FRL rats), reduced IF in the first (mainly caused by effects in FRL rat) and second ejaculation series (caused by effects in FRL and FSL rats), and finally the reduced MF (overall effect) in the first ejaculation series. These data indicate that activation of the 5-HT_{1A} receptor with ±8-OH-DPAT stimulates sexual behavior in FRL and FSL rats. The effects found in FSL and FRL rats are similar to the effects found in rats before. ±8-OH-DPAT has been shown to reduce the number of intromissions, mounts and the ejaculation latency (Ahlenius et al., 1981; Coolen et al., 1997; Mos et al., 1991). Since mostly the FRL rats responded to ±8-OH-DPAT administration it may indicate that the responses to ±8-OH-DPAT are blunted in FSL rats. Eriksson et al. (2012) also showed that FSL rats have a blunted response to 8-OH-DPATin a passive avoidance task. Although brain areas involved in emotional memory function (passive avoidance task) are different from those involved in sexual behavior, it is tempting to think that FSL rats are generally blunted in their response to ±8-OH-DPAT. Overall the results show that 5-HT_{1A} receptor activation enhances sexual behavior in both FRL and FSL rats, yet with FRL rats showing a higher sensitivity to ±8-OH-DPAT compared to FSL rats.

4.2. 5-HT_{1A} receptor antagonism

To test whether the behavioral effects of ±8-OH-DPAT were due to specific activation of the 5-HT_{1A} receptor, rats were acutely treated with the 5-HT_{1A} receptor antagonist WAY100635. The 0.1 mg/kg dose used in this study has previously shown to block $5HT_{1A}$ receptor with no alterations upon sexual behavior when given alone (Chan et al., 2011; de Jong et al., 2005). The treatment of 0.1 mg/kg WAY100625 combined with 0.03 mg/kg ±8-OH-DPAT in FRL and FSL rats gave similar results to the week 7 saline treatment. In addition, pretreatment with WAY100635 effectively blocked all behavioral effects of 0.03 mg/kg ±8-OH-DPAT. The reduced EL and IF caused by 0.03 mg/kg ±8-OH-DPAT treatment, mainly found for FRL rats, were blocked by 0.1 mg/kg WAY100635 treatment, indicating that the effects found with ±8-OH-DPAT were 5-HT_{1A} receptor dependent.

4.3. Changes in baseline sexual behavior after pharmacological treatment

In the final set of observations of week 11, under acute saline injection, rats displayed decreased IF, MF and ML compared to week 7. These results suggest that both FRL and FSL rats have enhanced their sexual behavior during the course of pharmacological treatments. Because no saline groups have been included for weeks 8, 9 and 10, this might also reflect a learning or conditioned response effect upon sexual performance, perhaps triggered by some experimental cues (e.g. handling, injection). Pattij et al. (2005)found that ±8-OH-DPAT was able to stimulate sexual behavior in rats that were selected on sexual performance and found that testing after these stimulations had no effect on the basal sexual performance, indicating that pharmacological priming did not happen. It has however been shown that manual stimulation such as a tail pinch can stimulate male sexual behavior (Leyton and Stewart, 1996; Wang and Hull, 1980). Moreover, no differences were observed between the week 7 saline group and combined 0.1 mg/kg WAY100635 and 0.03 mg/kg ±8-OH-DPAT which was performed in week 10. Regardless of the cause of the improved sexual activity, we believe that it did not confound our results, as these changes could not influence the treatment outcome seen after ±8-OH-DPAT administration.

5. Conclusions

Overall we showed that FSL rats have a higher EF compared with FRL rats, but that FRL rats are more sensitive to stimulating effects of ±8-OH-DPAT upon EL and IF. Responses to 8-OH-DPAT are reduced in both cognitive behavior (Eriksson et al., 2012) and sexual behavior (this study), therefore these data indicate that FSL rats have blunted responses to 5-HT_{1A} receptor activation in general, which may be due to the reduced number of 5-HT_{1A} receptors as demonstrated in previous research (Eriksson et al., 2012; Nishi et al., 2009).

Conflict of interest

All authors disclose no actual or potential conflict of interest.

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