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Original Scientific Article

SEX-SPECIFIC BEHAVIORAL EFFECTS OF FLUOXETINE TREATMENT IN ANIMAL MODELS OF DEPRESSION AND ANXIETY

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Summary: There are strong sex differences in clinical characteristics and in responses to treatment of several psychiatric diseases. Depressive and anxiety disorders are 2 to almost 3 times more common in women, but the majority of experiments examining the biological basis of these disorders and pharmacological agents for treatments are conducted in male animals. Several studies suggest that females respond better than males to the action of selective serotonin reuptake inhibitors (SSRIs), suggesting that gonadal hormones modulate mood and the response to these drugs. The beginning of clinical use of SSRI fluoxetine (Prozac) in late 80-ies was the frst major breakthrough in the treatment of depression since the introduction of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) nearly 30 years earlier. Fluoxetine is today widely prescribed for the treatment not only of depression but also of some anxiety related disorders. Animal models of depression and anxiety represents a useful tool for the investigation of sex differences of pharmacokinetics and pharmacodynamics of antidepressants. In this review the animal models of depression/anxiety using three most common performed acute stressor behavior tests (forced swim test – FST, elevated plus maze – EPM and open field – OF) will be introduced, followed by presenting behavior alterations after fluoxetine treatment in male and female rodents. In addition, data from our lab in C57BL/6J mice of both sexes on the behavioral effects of chronic fluoxetine treatment in comparison to other studies will be presented. Given the overlap between human and rodent findings, rodents provide a good model for further research on the sex-dependent effects of SSRIs and other antidepressants.

Key words: depression and anxiety; SSRI antidepressants; fluoxetine; sex differences; animal models

Introduction

Decreased serotonergic activity has been implicated in depressive and anxiety disorders, and antidepressants directly increase the long-term activity of the serotonin system (1). Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressants in the treatment of depressive and some anxiety disorders (2). This predominance is due in part to their limited side-effects and high selectiveness to serotonin transporter inhibitor, in comparison to tricyclic antidepressants (3). Fluoxetine was the first of SSRIs and is the most studied antidepressant (4), mostly in men and male animal models. Results obtained in men have been often uncritically generalized to women, therefore exact response to SSRIs in women is still not well known. A growing amount of data shows that differences in pharmacokinetics, pharmacodynamics, and physiology exist between women and men and that they contribute to the occurrence of sex-gender differences in drugs response (reviewed in 5).

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Depressive disorders

Depression is a heterogeneous, multifaceted disorder with symptoms manifested at the psychological, behavioral and physiological levels (6). There are three frequent types of depressive disorders that vary in severity of symptoms and persistence: *major depression* (also called *unipolar depression*) where symptoms interfere with the ability to eat, sleep, work and enjoy life and last chronically for at least 2 weeks; *dysthymia* which is a long-term or chronic disease lasting for at least 2 years and is characterized by less severe, non-disabling symptoms; and *bipolar disorder*, which is characterized by wide mood swings ranging from deep lows to manic highs (1, 7, 8). Both major depression and dysthymia occur in the absence (*primary depression*) or presence (*secondary depression*) of the other psychological or physical problems beside the reduced mood, low self-esteem, feelings of worthlessness, general fatigue, feelings of guilt, disturbances in sleep, sex drive and food intake, anger, absence of pleasure and agitated or retarded motor symptoms (6). Depressive disorders are the fourth leading cause of disease burden worldwide (9, 10). Epidemiological and clinical studies have consistently observed significant sex-specific differences among patients with depression, with women outnumbering men at least 2:1 (11, 12) and this sex difference becomes evident after the onset of puberty (13). While in recent years a number of hormonal systems have been demonstrated to be associated with depression (i.e., appetite-regulatory, thyroid and growth hormones; reviewed in (7), evidence overwhelmingly supports the involvement of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes in the development of mood dysregulation (7, 14). Co-morbidity with HPA-HPG-axis dysregulation is not surprising, as depression is a disorder that involves hypothalamic nuclei (paraventricular and ventromedial), central amygdala, hippocampus, subgenual anterior cingulate cortex, and medial and orbitofrontal cortex, regions that have dense expression of glucocorticoid and sex steroid hormone receptors (reviewed in (1, 14).

Anxiety disorders

Anxiety disorders can be described in terms of the situation, object or thoughts which provoke anxiety, the specific expression of anxiety in terms of autonomic, and cognitive or motoric features, as well as the specific behaviors used to cope with the provoked anxiety (6). Anxiety reactions can vary in intensity, frequency, persistence, trigger situations, severity and consequences and other qualifying features (15). DMS-5® specifies over 12 different anxiety disorders (6), classified in five types: phobias, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder. Anxiety is reported to be the most prevalent disorder among all psychiatric diseases (16). Data from epidemiological studies have consistently shown that anxiety disorders are at least twice as common in women as in men (11, 12). Anxiety is also a common symptom of depression. Many individuals with major depression disorder experience severe anxiety and many individuals with anxiety disorders develop major depression disorder (3), what is not surprising as it is known that neural circuits thought to regulate both conditions do overlap (17). Corticotropin-releasing hormone (CRH), a strong anxiogenic neuropeptide, and its receptors are localized within the serotonergic raphe nuclei suggesting that interactions between the CRH system and serotonin may play a role in fear and anxiety (reviewed in 18).

SSRI antidepressants

In the treatment of depression, different antidepressant such as selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and monoamine oxidase inhibitors (MAOIs) are used. Today, the most widely prescribed antidepressants with a minimum of side effects are SSRIs (3). SSRI antidepressants are also effective in treating some anxiety disorders (2).

Serotonin (5-HT) is produced by serotonergic cell bodies in the raphe nuclei, which form a cluster of nuclei in the brain stem (3) and send their axons to many brain regions throughout the brain and affect multiple central processes, including emotion, learning and memory, feeding, sleep, sexual and other social behaviors and sensory perception (19). Serotonin at the synapses may undergo several different molecular processes after release into synaptic cleft, one of them is reuptake by a presynaptic serotonin transporter channel (5-HTT or SERT). The targets

of SSRIs are 5-HTTs, which are located at the plasma membrane of serotonergic neurons, and are responsible for 5-HT reuptake (3). SSRIs inhibit the 5-HTT, resulting in increased extracellular 5-HT levels, and thereby sustained activation of pre- and postsynaptic 5-HT receptors (3, 19). However, the therapeutic action of SSRI antidepressants is dependent on long-term administration, suggesting that adaptations to the upregulation of 5-HT are required for therapeutic responses (mood improvement) (1).

The mostly prescribed SSRIs are fluoxetine, sertraline, paroxetine, citalopram and escitalopram (3, 19, 20). Fluoxetine was first synthesized in 1971 (21) and the United States Food and Drug Administration (FDA) approved fluoxetine in 1987. In 1988 it was launched on the market under the trade name Prozac as a first SSRI to be marketed in the United States (reviewed in 22).

Sex differences in treatment of depression and anxiety disorders

Women are clearly different from men in clinical appearance and characteristics of many psychiatric illnesses (12, 23), and also in therapy responses. An increasing number of studies have reported differences in the pharmacokinetics and/ or pharmacodynamics of antidepressants between women and men, although the clinical treatment at present is still identical in both sexes (reviewed in 24). Physiological differences in women and men that may affect pharmacokinetics include average body weight, body composition, and the affinity and/or capacity of metabolizing enzymes for the administered drug. Many studies have shown that sex hormones could influence absorption, distribution, metabolism, pharmacodynamics, and adverse effects of many different drugs (reviewed in 5).

Several studies have identified sex differences in fluoxetine treatment with women of reproductive age responding to fluoxetine better than men (25, 26). Estrogens may boost the effects of SSRIs, as postmenopausal women taking estrogens and treated with fluoxetine responded significantly better than women treated with fluoxetine only (27). Some laboratory studies in rodents also suggest that gonadal hormones modulate mood and the response to SSRIs (e.g., 28, 29) with inducing changes in the serotonin systems (30). Antidepressant effects in female rats are reported to be weaker during phases with lower levels of gonadal hormones (metestrus/diestrus) in comparison to females in higher gonadal hormone phases (proestrus/estrus) or to males (31). Gonadal hormone responsible for these differences seems to be estradiol, as orchidectomized male rats treated simultaneously with 17β-estradiol (10 μg/rat) and fluoxetine had much better behavioral response in comparison to males treated with fluoxetine only (29).

Animal models

The ideal animal model for any human clinical condition must fulfill three criteria (16): [1] pharmacological treatments effective in patients should induce comparable effects in the animal model (predictive validity); [2] the responses/ symptoms in patients should be the same in the animal model (face validity); [3] the underlying rationale should be the same in both humans and animal models (construct validity). Meeting all three validity criteria is difficult for an animal model of depressive/ anxiety disorders. Namely, many of the human symptoms of depression/ anxiety like recurring thoughts of death or suicide or excessive thoughts of guilt are impossible to be modeled in laboratory rodents (6). However, the physiological and behavioral responses to aversive stimuli, similar in both humans and animals, are allowing animal models to be used for at least two distinct purposes: as behavioral tests to screen for potential antidepressant/ anxiolytic properties of drugs and as tools to investigate specific pathogenetic aspects of cardinal symptoms of disease (reviewed in 16).

Behavioral data from our laboratory (32) in C57BL/6J mice of both sexes as a potential animal model to study depression/anxiety in comparison to behavioral data of other studies in mice and rats is presented. C57BL/6J male and female mice were originally obtained from Harlan Italy and bred at the University of Ljubljana, Veterinary Faculty, in standard conditions with 12-12 LD cycle (lights on at 3 am and off at 3 pm) and food (phytoestrogen free diet; Harlan Teklad Diet 2016, Harlan, Milan, Italy) and water *ad libitum*. Mice were weaned at 21 days of age and group-housed (3 mice of same sex per cage) in 15 cm high cages with floor area of 37.5 x 22

cm. At 55 days of age mice were divided into four groups with 9 mice per group: Control males and females, Fluoxetine males and females. Fluoxetine (Sigma-Aldrich®) was delivered in drinking water (10 mg/kg/day) as described elsewhere (33). At approximately 70 days of age (or at least 14 days of fluoxetine treatment) the behavior assessment using "stopwatch" software (Center for Behavioral Neuroscience, Atlanta, GA, USA) began with at least 2 days break between each behavioral test in the following order: elevated plus maze (EPM), open field (OF) and forced swim test (FST). Females were tested in the diestrus phase what was checked before each behavior assessment by vaginal smears as described previously (34). All animal experiments were approved by Veterinary Administration of the Republic of Slovenia and were done according to ethical principles, EU directive 2010/63/EU, and NIH guidelines. Statistical analyses were done using NCSS software (NCSS statistical software, Kaysville, UT, USA). To test differences between groups, repeated measures ANOVA was performed with sex and treatment as independent variables, followed by post hoc Fisher LSD test. Differences were considered statistically significant with $p < 0.05$ (32).

Depression-related behavioral assessments

Forced swim stress is one example of acute stressors that was developed as a tool to test the efficacy of antidepressant compounds (35) and is probably the most used tool among all animal models for screening antidepressants in mice and rats (36, 37). The critical response measured is immobility in an inescapable situation, which is believed to measure despair-like behavior (38).

Forced swim test (FST)

The first forced swim test (FST), also termed as behavioral despair test, was developed by Porsolt and coworkers in the rat (35) and subsequently in the mouse (39). In this animal model of depression animals are forced to swim in a tall cylinder and the time spent swimming or climbing (active behavior) versus the time spent floating (passive behavior) is measured. Session durations between 4 and 20 minutes have been used in mice, with 2 to 5 minutes of pre-exposure period (36, 40). If the animals cease all movements (active swimming motions), except those necessary for survival (keeping the head above the water), the behavior is considered to be immobile (floating). This immobile behavior is considered as an index of despair in response to the stressor or as an index of coping with the stressful procedure (41) and is diminished by antidepressant administration (38).

In our lab the FST was performed as described elsewhere (33), with 5 minutes session duration and 2 minutes of pre-exposure period (32).

Sex differences in FST

Studies of sex differences in the FST in rats and mice have shown highly controversial results likely due to several causes such as strain, different behaviors analyzed, exposure to various conditions prior to testing, estrous cycle phase and others (42). Some studies have shown that female Wistar rats in estrus phase are showing lower immobility and higher active behaviors in comparison to males (28, 43) what could be the result of high estrogens levels in females. However, some other studies that did not control for the phase of the estrus cycle showed higher levels of despair (longer immobility periods) during the FST in female rats (Wistar, Sprague-Dawley) in comparison to males (44, 45, 46). The second important difference between these contradictory results is that in the latter studies rats were exposed to at least two other stressors/ behavior tests (open field, light and dark transitions) prior to the exposure to the FST, suggesting that expositions to other stressors might increases the vulnerability of female rats to develop depressive-like behaviors (45).

In another study, chronic fluoxetine treatment (10 mg/kg) reduced immobility and increased active behaviors in male rats (Sabra strain derived from Wistar) only, and had no effects in females (estrous cycle phase was not reported; 47). However, some newer studies have shown that acute or chronic fluoxetine treatment (10 or 20 mg/kg) produced an antidepressant-like effect (reduced immobility) in both male and female rats (Wistar; females tested in estrus phase; 28, 48) and in females this effect was observed at lower doses (5 mg/kg) in comparison to males (10 mg/kg) (28), suggesting that estrus females are more sensitive to the antidepressant-like effects of fluoxetine.

In our laboratory, similar studies were performed with socially housed adult C57BL/6J mice, chronically treated with fluoxetine in drinking water (10 mg/kg for at least 14 days). All females were tested in the diestrus phase what was checked by vaginal smears, taken before each behavior assessment. Although we did observe fluoxetine effect in both male and female mice, no sex difference in immobility/ swimming time in the FST was observed (Figure 1), even after exposure to three other behavioral tests (elevated plus maze, open field, social recognition test) prior to FST (32), suggesting that female rats might be more vulnerable to the acute stress caused by FST than female mice.

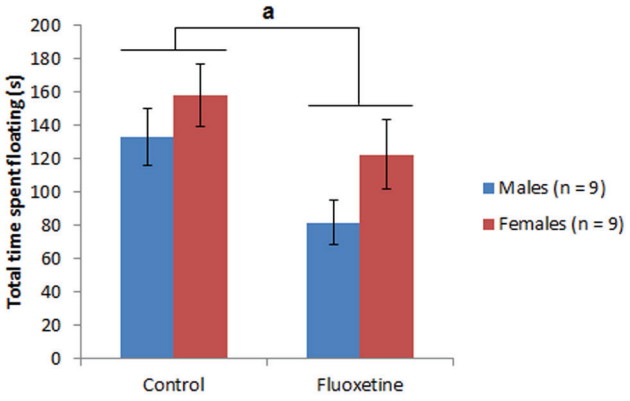

Figure 1: FST in male and female mice did not reveal any significant sex difference in response to fluoxetine or in behavior in FST, although fluoxetine treatment significantly reduced immobile time in both sexes. Data are reported as mean ± SEM; [a] Significant effect of treatment, $p < 0.05$

Anxiety-related behavioral assessments

Anxiety in rodents is defined as a high level of avoidance of novel and unfamiliar environment and increased fear reaction (16). Probably the most widely used test to assess the anxiety is the elevated plus maze (EPM), and less often the open field test (OF). OF test is mostly used to check whether changes in immobility observed in FST are associated with alterations in the motor activity (e.g., 48).

Elevated plus maze (EPM)

Probably the most frequently used test for unconditioned anxiety assessment, widely used in pharmaceutical companies, is the elevated plus maze (EPM), which was first introduced by File and coworkers in rats (49) and later in mice (50). The plus maze, elevated above the ground, consists of four arms arranged in a cross formation: two opposing non-anxiogenic closed arms with walls and other two anxiogenic open arms without walls (40). Rodents tend to avoid elevated, brightly lit areas, and avoidance of the open arms is interpreted as anxiety like behavior (49, 50). The animal is placed in the junction of the open and closed arms, and entries into the each arm and time spent in each arm over a 5-minute test session is scored (40).

In our lab the EPM was performed as described elsewhere (50), with 5 minutes session duration (32).

Sex differences in EPM

Previous reports in male mice are inconsistent, with some studies reporting higher levels of anxiety in C57BL/6J compared to BALB/c mice (51), other reported opposite results (52, 53). A newer study in both sexes showed that C57BL/6J female mice are more anxious, spending less time in open arms, than males, but no sex difference was observed in BALB/c mice when females were tested in the diestrus phase (53). This is in agreement with our study (32) showing that females of C57BL/6J strain are more anxious than males (Figure 2), suggesting that C57BL/6J strain could be a good animal model for studying sex differences in anxiety disorders. In contrast, female rats tested in proestrus phase appear to be less anxious than male rats (54, 55).

Many previous studies of fluoxetine effects were performed only in males and are showing controversial results in behavior responses. Some studies in male rats (mostly used Wistar strain; ~10 mg/kg) of acute fluoxetine administration have shown an anxiolytic (56, 57), anxiogenic (58, 59, 60), or no effect (49, 61). In several studies (55, 57, 59) the chronic treatment (5, 10 or 20 mg/kg) did not affect behavior in EPM of male rats (Wistar-Kyoto, Sprague-Dawley or Wistar). Interestingly, one study reported that chronic fluoxetine treatment (5 mg/kg) decreased the time spent in the open arms (anxiogenic effect) in female rats during proestrous phase (Sprague-Dawley), and the stress exposure even potentiated

this effect (55). Our study with C57BL/6J male and female mice showed no treatment difference, neither in the number of entries nor in the total time spent in the open arms (32), what is in agreement with the study by Kobayashi and coworkers in males (62), suggesting that chronic fluoxetine has neither anxiolytic nor anxiogenic effects in EPM in either sex in C57BL/6J mice (Figure 2) and that fluoxetine treatment does not contribute to the major improvement of anxiety behavior like in humans (63).

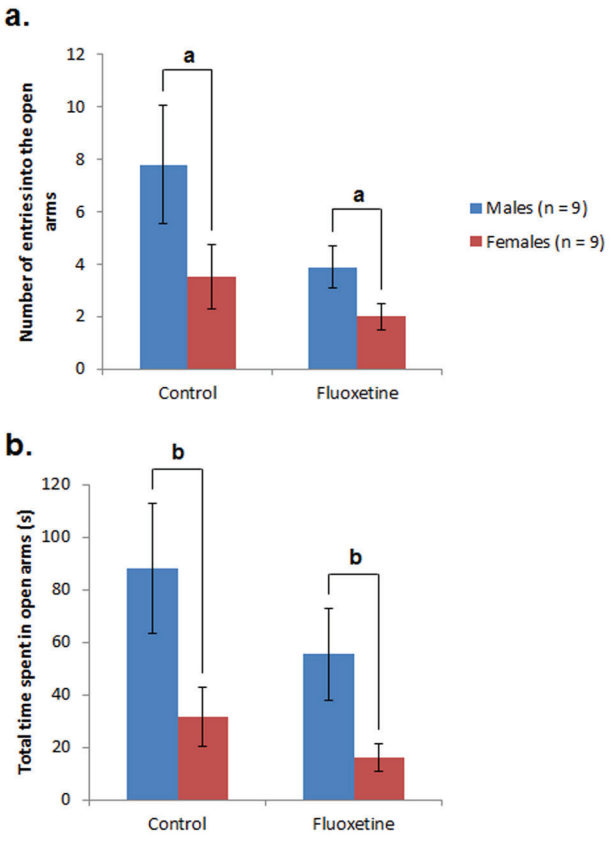

Figure 2: Sex differences are present in C57BL/6J mice (females were tested in the diestrus phase): **(a.)** number of entries into the open arms, **(b.)** total time spent in open arms. No significant effect of fluoxetine treatment in either sex was found ([a] $p < 0.05$, [b] $p < 0.01$). Data are reported as mean ± SEM; [a,b] Significant difference between males and females

Open field (OF)

In 1934 Calvin Hall designed the first open field test to assess "emotionality" in rats (64) and since then different types of open fields have been used. The modern standard open field is a Plexiglas box with square floor area, surrounded by high walls to prevent animals from escaping, and usually equipped with either photocells or videotracking and computer software to assess locomotor parameters. The animal is placed in the center or in the periphery of the area and the behavior assessment can last from 2 min to several hours. Like in EPM the avoidance of exploratory behavior towards the anxiogenic unprotected area (center zone) is the indicator for anxiety or fear-related behavior (16, 40). OF is mostly used for assessing spontaneous motor activity (distance traveled, average speed, duration of (im)mobility and others), which is the most standardized general measure of locomotor function (40), or to exclude the increased immobility in FST due to reduced locomotor ability (48).

In our lab the OF was performed as described elsewhere (62), with 30 minutes session duration (32).

Sex differences in OF

Previous studies in C57BL/6J and BALB/cJ mice have shown that males and females in diestrus phase did not differ in their locomotor or exploratory activity having similar duration of locomotion and spent similar time in the center area of OF (53), what is in agreement with our study (unpublished results) performed in C57BL/6J strain (Figure 3 and 4b).

There are numerous studies of fluoxetine effects on OF activity in mice but far less in rats. Neither acute (2 and 10 mg/kg) nor chronic (10 and 20 mg/kg) treatment in male rats (Wistar) have shown any effect on locomotor and exploratory activity of center area in comparison to controls (48, 61), and study in both sexes by Ghorpade et al. does not mention any sex differences between treated or control rats (48).

In regard to spontaneous motor activity, previous studies in male mice after chronic fluoxetine treatment (mostly 10 mg/kg) have shown differences between strains, with C57BL/6J mice having reduced, and BALB/cJ mice unchanged distance traveled in comparison to untreated males (62, 33). Indeed, C57BL/6J treated males in our study (unpublished results) also traveled shorter distance (Figure 3a), moved slower (Figure 3b) and had longer immobile periods (Figure 3c) in comparison to controls, and there was no sex difference observed (Figure 3).

Our results in females (unpublished results) are in agreement with the study of Marlatt et al. where chronically treated (18 mg/kg) C57BL/6J females also traveled shorter distance than control mice (65). Similar decrease in traveled distance with no sex difference was reported also after acute fluoxetine administration (15 mg/kg) (66).

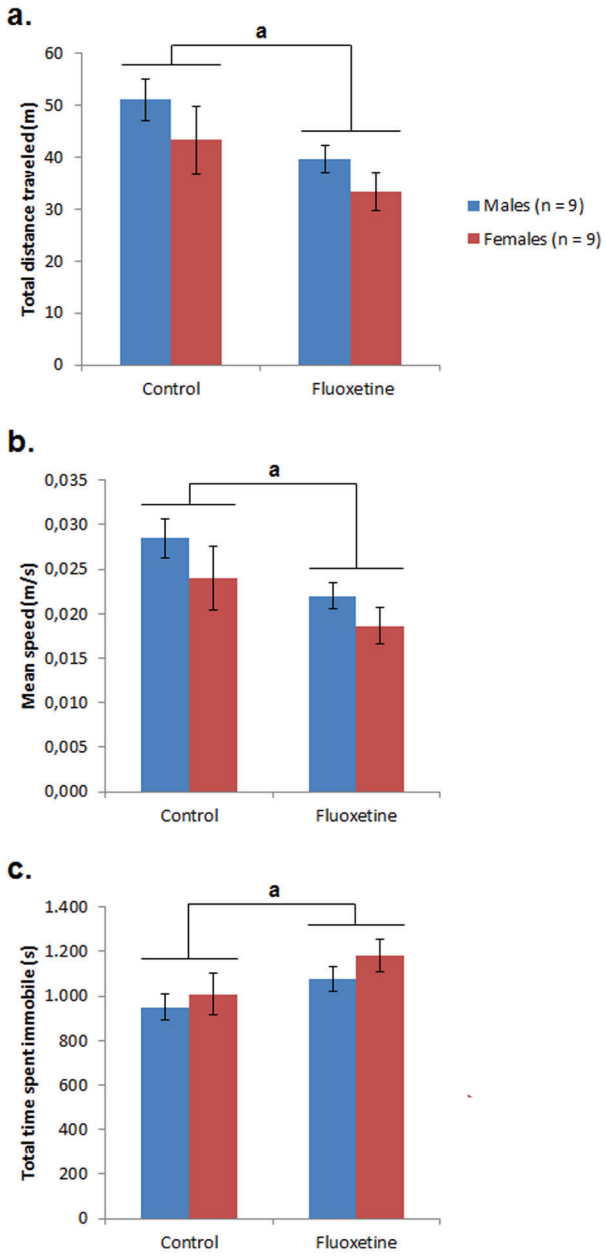

Figure 3: Spontaneous motor activity in OF did not differ between male and female C57BL/6J mice in response to fluoxetine or in behavior in OF, although fluoxetine treatment significantly affected locomotor activity in both sexes: **(a.)** reduced distance traveled, **(b.)** reduced average speed and **(c.)** prolonged time of immobility. Data are reported as mean ± SEM; [a] Significant effect of treatment, $p < 0.05$

In regard to the anxiety like behavior, chronic fluoxetine exposure in previous studies reduced the number of entries or time spent in the center of the OF in C57BL/6J, but not in BALB/cJ males relative to controls (62, 33), and such reduction in time spent in the center zone was revealed also in C57BL/6J females in comparison to controls (65), but there are no previous reports about sex differences in such effects of fluoxetine. However, in contrast to these studies, in our study (unpublished results) there was no effect of fluoxetine treatment on these two parameters in C57BL/6J males and females (Figure 4a and b), although there was a small, but significant sex difference in the number of entries into the central zone that was reduced in females but not in males (Figure 4a).

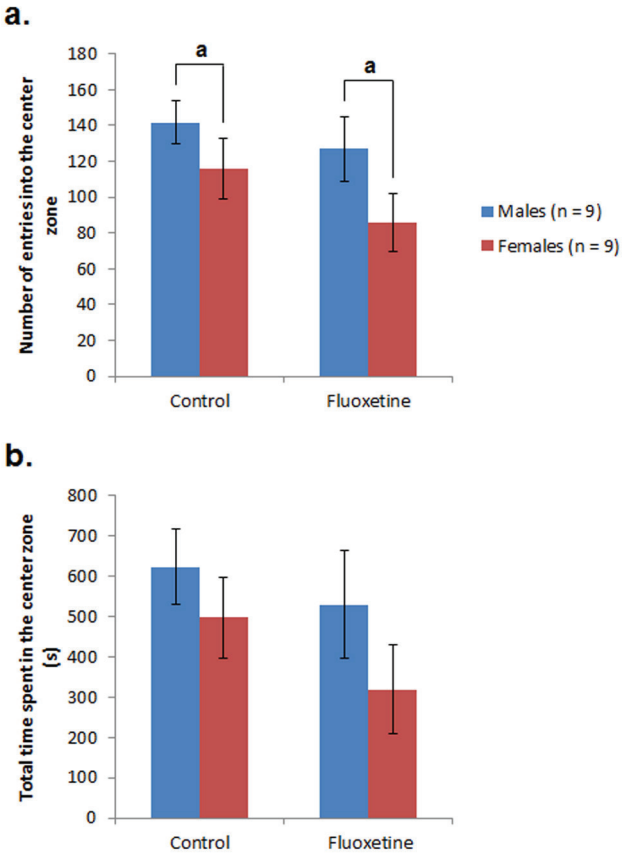

Figure 4: Sex differences in C57BL/6J mice (females were tested in the diestrus phase) were observed in the number of entries into the center zone of OF **(a.)**, but not in the total time spent in the anxiogenic area **(b.)**. No significant effect of fluoxetine treatment in either sex was found. Data are reported as mean ± SEM; [a] Significant difference between males and females, $p < 0.05$

Conclusions

Studies of sex differences in the FST, EPM and OF behavioral tests in mice and rats have yielded controversial results, most likely caused by several factors which are known to influence animal behavior such as species, strain, age, body weight, handling, social isolation or enriched environment, food, various kinds of stress, endocrine manipulations and surgery, schedule and routes of treatment, dosage of the drugs as well as experimental design and others. Consideration of these factors in planning experiments could result in more consistent results. However some common conclusions connected the main findings in the different rodent studies of FST, EPM and OF can be made:

- Proestrus/estrus females are usually less despaired and anxious than males or females in metestrus/diestrus.
- No consistent sex difference in the locomotor or exploratory activity in mice and rats are found.
- Chronic fluoxetine treatment provided more consistent effects than acute treatment.
- Proestrus/estrus females are usually more sensitive to the antidepressant like effects of fluoxetine than males.
- No effect of anxiogenic/anxiolytic treatment is usually found in males and metestrus/diestrus females, but anxiogenic effects of fluoxetine have been described in estrus/proestrus females.
- No sex/treatment difference in locomotor or exploratory activity in rats, but reduced locomotion in treated mice regardless of sex, was found.

Our data (32) with chronic fluoxetine administration in C57BL/6J mice of both sexes revealed that fluoxetine has an antidepressant like effect in FST with decreased immobility time but no effect on latency to float. Males and females did not significantly differ in their despair like performance. In regard to the anxiety like behavior, a chronic fluoxetine treatment had no anxiolytic or anxiogenic effect in the EPM or in the OF, but females behaved more anxiously than males in EPM and OF tests. However, fluoxetine did impair locomotor activity in comparison to control mice of both sexes as tested in OF. Taking together, C57BL/6J mice could be a good animal model for anxiety assessment studies as females were significantly more anxious than males, but not for despair behavior studies as females were equally depressed than males. Chronic fluoxetine treatment might not be a good model to study its effects in anxiety related disorders studies in C57BL/6J mice.

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We would like to thank Ana Strgar and Ariadna Štorman for performing EPM and OF behavioral assessments.

Ethical statement

Animal experiments from our lab were approved by Veterinary Administration of the Republic of Slovenia and were done according to ethical principles, EU directive, and NIH guidelines.

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RAZLIKE MED SPOLOMA V DELOVANJU ZDRAVILA FLUOKSETIN PRI ŽIVALSKIH MODELIH ZDRAVLJENJA DEPRESIVNIH IN ANKSIOZNIH MOTENJ

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Povzetek: Bolezenski znaki in uspešnost zdravljenja z različnimi zdravili se pri številnih duševnih boleznih med spoloma močno razlikujejo. Depresivne in anskiozne motnje se 2- do 3-krat pogosteje pojavljajo pri ženskah kot pri moških, vseeno pa se večina predkliničnih raziskav in preizkušanj novih zdravil opravi samo pri samcih poskusnih živali. Več raziskav je nakazalo, da je odziv žensk in ženskih živali na selektivne zaviralce prevzema serotonina (SSRI) boljši kot pri moških, kar kaže, da spolni hormoni vplivajo na odzivnost organizma na tovrstna zdravila. Uvedba prvega zdravila iz skupine SSRI, in sicer prozaca v osemdesetih letih prejšnjega stoletja, je bil pomemben napredek pri zdravljenju motenj depresivnosti od odkritja zaviralcev monoaminskih oksidaz in tricikličnih zdravil proti depresiji trideset let prej. Fluoksetin je danes v široki uporabi za zdravljenje depresivnih motenj, pa tudi za zdravljenje motenj anksioznosti. Živalski modeli predstavljajo dober model za proučevanje vpliva zdravil proti depresivnim in anksioznim motnjam in tudi za proučevanje spolnih razlik v delovanju tovrstnih zdravil. V preglednem članku smo predstavili različne živalske modele za proučevanje motenj depresivnosti in anksioznosti, in sicer test prisilnega plavanja, test dvignjenega labirinta in test odprtega polja. Poleg tega je predstavljen vpliv fluoksetina na obnašanje živali v teh testih s poudarkom na razlikah med spoloma. Številne raziskave v preteklosti so pokazale, da so laboratorijski glodavci primeren model za proučevanje tovrstnih motenj , v prihodnosti pa bo treba večji poudarek dati raziskavam razlik med spoloma pri nastanku tovrstnih obolenj in pri njihovem zdravljenju.

Ključne besede: depresivne in anksiozne motnje; zdravila iz skupine SSRI; fluoksetin; spolne razlike; živalski modeli