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Brief Report

BRIEF REPORT

Distinct Antidepressant-Like and Cognitive Effects of Antidepressants with Different Mechanisms of Action in Middle-Aged Female Mice

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Abstract

Background: Cognitive dysfunction is among the key symptoms of major depressive disorder and can be affected by antidepressants. Cognitive decline also occurs in normal aging. The effects of different antidepressants on affective and cognitive domains in older subjects are seldom assessed simultaneously.
Methods: Healthy middle-aged female mice received vehicle or antidepressant (vortioxetine, vilazodone, duloxetine, or fluoxetine) at therapeutic doses. After 1 month treatment, mice were accessed for visuospatial memory and depression-like behavior. A separate cohort of mice received 3 months of treatment and was test for recognition memory and depression-like behavior.
Results: After 1 month treatment, vortioxetine improved visuospatial memory and reduced depression-like behavior. Vilazodone reduced depression-like behavior. Duloxetine and fluoxetine were ineffective in both tests. After 3 months treatment, vortioxetine reduced depression-like behavior without affecting recognition memory, while fluoxetine impaired recognition memory. Duloxetine and vilazodone had no effect in both tests.
Conclusion: Different antidepressants have distinct effects in middle-aged female mice.

Keywords: multi-modal antidepressant, SNRI, SSRI, memory tests, forced swim test

Introduction

Cognitive dysfunction is frequently reported among major depressive disorder patients, and improvement of cognitive symptoms is important for functional recovery (McIntyre et al., 2014). However, currently available antidepressants are not always effective in treating cognitive dysfunction, and cognitive deficits can remain even when antidepressants effectively improve mood (Reppermund et al., 2007; Conradi et al., 2011). Furthermore, cognitive impairment is a reported side effect of antidepressant treatment (Popovic et al., 2015). In addition, older subjects respond differently to antidepressants than young patients (Alamo et al., 2014). Finally, antidepressants with different mechanisms of actions may have distinct effects on cognitive function (Herrera-Guzman et al., 2009; Soczynska et al., 2014; McIntyre and Lee, 2016). This is substantiated by preclinical studies demonstrating specific cognitive effects of different antidepressants in rodents (Carlini et al., 2012; Gray and Hughes, 2015), though little is known regarding the influence of age.

Cognitive decline is evident during normal aging. For example, visuospatial ability is a domain affected early in the aging process (Salthouse, 2010; Hoogendam et al., 2014), and spatial memory deficits have also been detected in middle-aged

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(Li et al., 2015b; Scheinert et al., 2015) as well as in old rodents (Yau et al., 2002). Considering that many patients undergoing antidepressant treatment are middle-aged, it is of interest to investigate drug effects on both depression and cognition in this age group, which may be more sensitive to agents potentially compromising cognitive functions.

The current study focused on measuring the long-term effects of several classes of antidepressants in middle-aged but otherwise healthy female mice. Two multimodal antidepressants were included. Vortioxetine is a serotonin (5-HT) transporter (SERT) inhibitor, an agonist for 5-HT_{1A}, a partial agonist for 5-HT_{1B}, and an antagonist for 5-HT_{1B} 5-HT_3 and 5-HT_7 receptors (Bang-Andersen et al., 2011). Vilazodone is a SERT inhibitor and a partial agonist for 5-HT_{1A} receptors. Also included were the serotonin and norepinephrine reuptake inhibitor (SNRI), duloxetine, and the selective serotonin reuptake inhibitor (SSRI), fluoxetine. After 1 month of treatment, a cohort of middle-aged female mice was assessed for visuospatial memory (object placement test), which is negatively affected in early aging and responsive to 1 month of vortioxetine treatment in our previous study (Li et al., 2015b). These mice also underwent a forced swim test to measure their depression-like behavior. In addition, the long-term effects of these drugs were examined after 3 months of treatment in a separate cohort of middle-aged mice. This treatment length was chosen as 1 month of fluoxetine had partially affected the recognition memory (in novel object recognition test), even though it did not reach statistical significance (Li et al., 2015b). Longer treatment period should allow a full assessment of antidepressant effects. Antidepressant-like efficacies were also measured in forced swim test in this second cohort of mice. Only one memory test was conducted in each cohort of mice to minimize potential effect of behavioral testing on forced swim test results.

Methods

Animals

Retired female breeder C57BL/6 mice (11 months old) were acquired from Charles River (Wilmington, MA) and group housed (3/cage). Animals were kept under a 12:12 light:dark cycle (lights on 6 AM, lights off 6 PM) with ad libitum access to water and food. All animal experiments were conducted in accordance to the Guide for the Care and Use of Laboratory Animals and the U.S. National Institutes of Health, and approved by the Institutional Animal Care and Use Committee of Lundbeck Research USA.

Experimental Design

Two cohorts of 11-month-old mice were randomly divided into 5 groups and received 1 month or 3 months of following treatments: vehicle, vortioxetine, duloxetine, vilazodone, or fluoxetine. Drugs were mixed into Purina 5001 chow (Research Diets Inc, New Brunswick, NJ) at doses previously determined to reach roughly 90% SERT occupancy levels in rodents (Li et al., 2015a, 2015b), comparable to the clinical therapeutic range. Base concentrations per kilogram of chow were: 600 mg vortioxetine, 143 mg fluoxetine, 200 mg duloxetine, or 100 mg vilazodone (synthesized by H. Lundbeck A/S, Valby, Denmark). The middle-aged mice in the vehicle group were fed with Purina 5001 rodent chow. In a pilot study and prior studies, administration of drugs according to this protocol did not induce gross change in the subjects' feeding behavior or body weights (Li et al., 2015b).

For cohort 1 (1 month treatment,17–30/group), visuospatial memory was assessed in the object placement test. They were then accessed in the forced swim test for depression-like behavior. For cohort 2 (3 month treatment, 16–24/group), recognition memory was assessed in novel object recognition test. They were then accessed in the forced swim test. Locomotor activity was measured using total track length from Trial 1 in object placement test (cohort 1) or in novel object recognition test (cohort 2).

Behavioral Tests

Animals were brought into the laboratory for acclimatization at least 30 minutes prior to behavioral testing. All tests were conducted under low levels of incandescent lighting between 9 AM and 5 PM.

Novel Object Placement Test

Visuospatial memory was examined using a novel object placement test (a.k.a. novel object location test, place recognition test, spatial novelty test) (Ennaceur and Meliani, 1992; Yassine et al., 2013). Briefly, mice were first allowed to explore an open field (50 cm × 50cm × 45 cm) containing 2 identical objects (with high contrast intra-arena visual cues) for 3 minutes (Trial 1: training trial). The amount of exploration for each object (defined as rearing on, whisking, sniffing, or touching the objects with nose and/or forepaws) was scored manually using stopwatches. After spending 45 minutes in their home cages (retention interval), mice were returned to the same testing arena for another 3 minutes (Trial 2: testing trial), with one object moved to a different location. Exploration of each object was again manually scored. Animals with intact visuospatial memory preferentially explore the relocated (novel) object and thus spend more than 50% of total object exploration time on the relocated object in Trial 2. The results of the object placement test were reported as the proportion of animals passing (preference score >55%) or failing (preference score ≤55%). Criteria for establishing this cutoff are detailed and justified elsewhere (Li et al., 2010). Total exploration of both objects during Trial 1 was recorded as an internal control for exploratory behavior. Track length was measured using Viewer tracking software (Biobserve, Bonn, Germany).

Novel Object Recognition Test

Recognition memory was assessed in the novel object recognition test (Ennaceur and Delacour, 1988). Similar to the novel object placement test, mice were allowed to explore 2 identical objects in an open field (50 cm × 50 cm × 45 cm) for 3 minutes (training trial, Trial 1). After spending 2 hours in their home cages (retention interval), mice were returned to the same testing arena for 3 minutes (testing trial, Trial 2), now containing one familiar object, and one novel object. Exploration of the objects was manually scored and results presented as pass/fail, similar to object placement test described above.

Forced Swim Test

Depression-like behavior was assessed by a modified forced swim test (Porsolt et al., 1977). Briefly, mice were put in plexiglass cylinders (20 cm in diameter) filled with 25°C water (30 cm deep) for 7 minutes. Immobility was manually scored using stopwatches, excluding the first minute of the trial. Immobility was defined as no movement other than that necessary to keep the animal's head above water, and presented as percent immobility: 100% x immobile period (s)/360. Immobility in the

forced swim test has been extensively validated as a measure of depression-like behavior.

Statistical Analysis

JMP12 (SAS, Cary, NC) was used for all statistical analysis. A chi-square contingency test was used to analyze results in memory tests (numbers of animals had clear preference in object placement test or novel object recognition test). Results of immobility, locomotor activity, and total object exploration in the memory tests were expressed as mean ± standard error. Distributions of some of these datasets were not normal; therefore, these results were analyzed using Wilcoxon/Kruskal-Wallis 1-way test (non-parametric equivalent for 1-way ANOVA) followed by a protected Dunn method for joint ranking test (comparing drug treatment groups to vehicle group). Significance level was defined as $p < .05$.

Results

After 1 month of treatment, middle-aged female mice were assessed in the object placement test for visuospatial memory, and in the forced swim test for depression-like behavior (Figure 1).

Results from the object placement test are illustrated as the proportion of animals having a clear preference for the relocated object. Compared with vehicle, only vortioxetine significantly increased the number of middle-aged mice demonstrating a clear preference for the relocated object, indicating improved visuospatial memory (contingency test $\chi^2 = 4.4$, likelihood ratio $p < .05$) (Figure 1A). Interestingly, this is accompanied by a decrease in initial object exploration in the training trial (Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 16.52$, $p < .01$; post-hoc vehicle vs vortioxetine, $p < .05$). The apparent difference between vehicle vs fluoxetine was not statistically significant. This is consistent with a body of data demonstrating that levels of initial object exploration are not related to cognitive performance, as we have previously published (Li et al., 2015b). Neither fluoxetine, duloxetine, nor vilazodone altered the performance of mice in the object placement test compared with vehicle-treated subjects in terms of either visuospatial memory or object exploration.

Depression-like behavior was assessed in the forced swim test as the amount of time each animal was immobile, shown as a percentage of total test duration (% immobility, Figure 1C). Drug treatment induced a significant overall effect (Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 12.89$, $p < .05$) on this measure. Post-hoc analysis indicates both vortioxetine and vilazodone significantly reduced immobility compared with vehicle, whereas duloxetine and fluoxetine were ineffective. There was no drug-induced effect on locomotor activity (Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 4.74$, $p < .05$) (Figure 1D).

In a separate cohort of mice, the effects of antidepressants were measured after 3 months of treatment (Figure 2).

Memory was assessed in the novel object recognition test. Middle-aged mice receiving fluoxetine for 3 months demonstrated a deficit compared with those that received vehicle ($\chi^2 = 5.4$, likelihood ratio $p < .05$; Figure 2A), while other drugs did not affect memory in this test. There was no drug-induced change in initial object exploration in the training trial (Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 7.17$, $p > .05$) (Figure 2B).

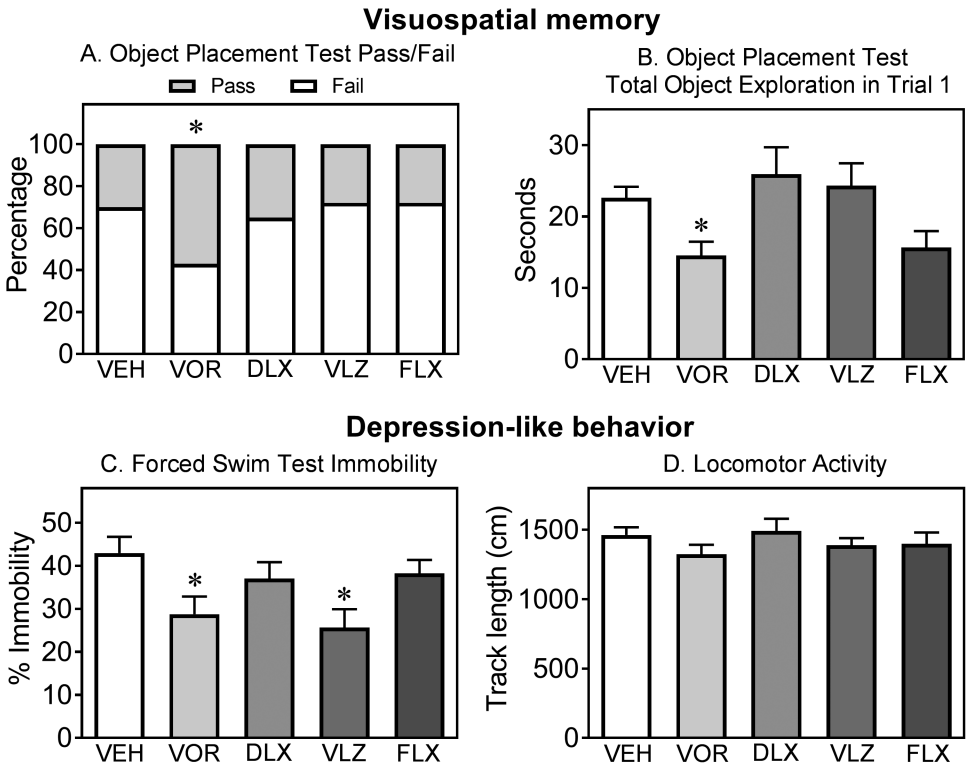

Figure 1. Effects of antidepressants after 1 month of treatment. After receiving 1 month of different treatments, middle-aged female mice were assessed for visuospatial memory in the object placement test. (A) The proportion of mice with or without a clear preference for the relocated object (pass or fail, respectively). (B) The overall object exploration levels during Trial 1 (training trial). (C) Animals then underwent forced swim test for depression-like behavior (% immobility). (D) The total track length from Trial 1 of the object placement test was used as a measure for the locomotor activity. (B-D) Mean ± SE in n = 17 to 30/group. *$p < .05$ compared with vehicle-treated middle-aged mice.

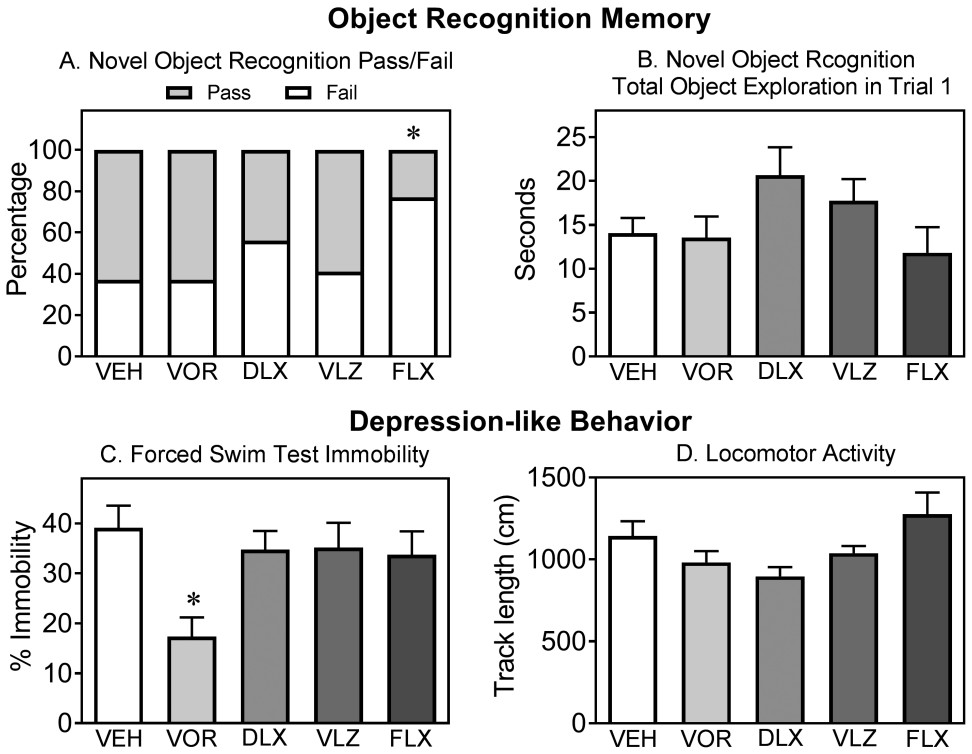

Figure 2. Effects of antidepressant after 3 months of treatment. A separate cohort of middle-aged female mice received 3 months of different treatments and was assessed for recognition memory in novel object recognition test. (A) The proportion of mice with or without clear preference for the novel object (pass or fail, respectively). (B) The overall object exploration levels during Trial 1 (training trial). (C) Animals then underwent forced swim test for depression-like behavior (% immobility). (D) The total track length from Trial 1 in novel object recognition test was used as a measure for the locomotor activity. (B-D) Mean ± SE in n = 13 to 24/group. *$p < .05$ compared with vehicle-treated middle-aged mice.

There was an overall significant difference in the immobility in the forced swim test (% immobility, Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 14.81$, $p < .01$) (Figure 2C). Posthoc analysis indicated that vortioxetine significantly reduced immobility compared with vehicle in middle-aged mice, but there was no significant effect of duloxetine, vilazodone, or fluoxetine. This was not due to a general change in locomotor activity (Wilcoxon/Kruskal-Wallis 1-way test $\chi^2 = 8.46$, $p > .05$) (Figure 2D).

Discussion

The current study demonstrates differential effects of antidepressants with different mechanisms of action in middle-aged mice. After 1 month of treatment, the multimodal antidepressant vortioxetine reduced depression-like behavior and improved visuospatial memory. Another multimodal antidepressant, vilazodone, reduced depression-like behavior without altering visuospatial memory. The SNRI, duloxetine, and the SSRI, fluoxetine, did not alter cognition or depression-like behavior. After 3 months of treatment, vortioxetine reduced immobility in middle-aged mice in the forced swim test without affecting their object recognition memory. Fluoxetine induced a deficit in the novel object recognition test without affecting depression-like behavior, a detrimental effect also reported by other researchers (summarized in a recent review, Pehrson et al., 2015). Neither vilazodone nor duloxetine altered cognition or depression-like behavior after 3 months administration. Given that the majority of patients take antidepressants for longer than 1 month, these data highlight the importance of establishing the long-term effects of these drugs. As impaired cognitive function is often comorbid with major depressive disorder, can be a side effect of antidepressant treatment, and may be evident as early as middle age, it is relevant to assess the effects of antidepressants in cognitive domains in addition to in assays for emotion. The current study supports the assertion that, in a preclinical setting, antidepressant effects are not always accompanied by improvements in cognitive function, at least in nondepressed subjects. It will be interesting to examine this notion in animal models of cognitive impairment comorbid with depression-like behavior.

The present study was conducted using retired breeder females for several reasons. Firstly, subjects engaging in mating and parturition are more reflective of the human population. Secondly, retired breeders have been used in behavioral studies previously and behave similarly in these assays to virgin animals (De Butte-Smith et al., 2009; Li et al., 2015b). However, it should be noted that a previous study demonstrated multiparous rats perform better in object placement test than nulliparous rats (Paris and Frye, 2008). Furthermore, animals were tested at ages when most or all are no longer cycling regularly (Felicio et al., 1984). This is similar to the situation in human-spatial memory deterioration becoming noticeable at the age of menopause (Salthouse, 2010; Hoogendam et al., 2014). Finally, a previous study demonstrated that estrus stages do not affect object placement test performance in cycling young adult female C57BL/6 mice (Spencer et al., 2008); however, see also Paris and Frye (2008). Therefore, female retired breeder middle-aged mice were used in the present study.

The lack of antidepressant-like efficacy of duloxetine and fluoxetine is not likely due to insufficient doses. We have previously demonstrated that these doses result in full occupancy of SERT in young adult female rats (Li et al., 2015a) and in middle-aged female mice (Li et al., 2015b). It is more

likely that age differences in the response to antidepressant are the cause, as has been reported in both preclinical and clinical studies. For example, SSRIs (fluoxetine, paroxetine, or citalopram) failed to reduce forced swim immobility in a wide range of doses in older mice but were effective in young animals (Bourin et al., 1998; Li et al., 2015b). In one clinical trial in older major depression patients (65 years and older), fluoxetine was not different from placebo (Schatzberg and Roose, 2006). Furthermore, >60% of major depressive disorder patients older than 65 years of age did not respond to duloxetine (Raskin et al., 2007). The results from the current study support the age difference in drug response for some antidepressants.

The multimodal antidepressants vortioxetine and vilazodone were more effective than duloxetine or fluoxetine in the current study in reducing the depression-like behavior. This suggests that adding modulation of 5-HT receptors to a general increase of 5-HT levels is more effective and may cause fewer side effects than a global increase of this neurotransmitter. The 5-HT_{1A} receptor agonists buspirone and flesinoxan have antidepressant effects, and 5-HT_{3} receptor antagonism also modulates both cognitive and affective functions in rodent studies (Li et al., 2013; Leiser et al., 2015). In addition, 5-HT_{7} receptor antagonists have antidepressant-like effect in preclinical studies (Mnie-Filali et al., 2011). Based on the different effects of vortioxetine and vilazodone, it is possible that modulating additional 5-HT receptors contribute to the effects of vortioxetine in middle-aged mice.

In future studies, it will be interesting to compare effects of different antidepressants on the underlying mechanisms at molecular, cellular, and circuitry levels. Furthermore, the contribution of modulating individual 5-HT receptor in middle-aged mice warrant further clarification.

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Statement of Interest

Drs Yan Li and Connie Sanchez were full-time employees of Lundbeck Research USA. Dr. Maria Gulinello was a consultant for Lundbeck Research USA.

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