Prenatal Bupropion Exposure Enhances the Cocaine Reward and Stress *SuscEptibility* in Adult Mice

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Abstract

Although a growing body of evidence supports the notion that certain antidepressant treatments in pregnancy produce earlier delivery and minor behavioral teratogenesis in infants, the long-term effects of such treatments in adulthood remain ill-defined. Recently, postnatal exposure to psychotropic drugs was found to affect the emotional development and susceptibility to abused drugs. Thus, this study aimed to examine whether prenatal exposure of four frequently-used antidepressants, bupropion, fluvoxamine, citalopram, and trazodone, altered the responsiveness to stress and cocaine in the adulthood. Dams received daily injection of bupropion (25 or 12.5 mg/kg), citalopram (5 mg/kg), fluvoxamine (10 mg/kg), trazodone (20 mg/kg) or saline throughout their third trimester of gestation, and several birth outcome indices were then examined. Locomotor activity, naive anxiety levels, and the sensitivity to the cocaine reinforcing effects were observed in pups at their day 56-60 post partum. We found that trazodone treatment produced a high mortality rate in pups after weaning. Mice, prenatally treated with bupropion at 25 mg/kg, exhibited lower rearing numbers and ambulatory activity as compared to the saline-treated mice. More importantly, such treatment enhanced the mouse sensitivity to the reinforcing effects of cocaine. Taken together, these results suggest that use of bupropion in the late pregnancy may run a risk of enhancing the offspring's susceptibility to stress and cocaine reward in adulthood.

Key Words: SSRI, NDRI, SARI, psychomotor stimulant, CPP, anxiety

Introduction

Depressive symptoms afflicted approximately 25% of the pregnant women and a total of 10% pregnant women met diagnostic criteria for depression (14, 19). A proportion of pregnant women with depression and depressive symptoms were recommended to use antidepressants to relieve their symptoms (21). Antidepressant and their metabolite concentrations were detectable in 86.8% of umbilical cord blood as the medications were taken in the late pregnancy (17, 29). Many women started the antidepressant medications at the time of conception and even extended through the nursing episode due to the concern of relapse (24). To date, most of the human and animal studies suggested that prenatal exposure to antidepressants did not affect global IQ, language and behavioral development, susceptibility to neurotoxicity or cognitive functions in the offspring (5, 8, 28, 36). Nevertheless, sporadic reports posited the correlations of antidepressant exposure and birth outcome indices and behavioral teratogenesis, such as an

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increased incidence in earlier delivery, minor anomalies and admission to special care nurseries, respiratory problems, jitteriness and enhanced aggression (4, 6, 7, 8, 13, 15, 32).

An increase in cyclic adenosine monophosphate response element binding protein (CREB) expression within the nucleus accumbens was closely associated with the decreased function of the mesolimbic dopaminergic system, decreased responsiveness to the reinforcing efficacy of cocaine and aversive status (1, 3, 9). Selective serotonin reuptake inhibitors (SSRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs) (12, 33), and serotonin antagonists and reuptake inhibitors (SARIs) (16, 20, 23, 25, 30) are current drugs of choice for treating depression. Treatment with these antidepressants can enhance the dopaminergic, serotonergic and noradrenergic tones. Since almost all serotonergic, dopaminergic and adrenergic receptor subtypes were found in the nucleus accumbens (10, 11, 18, 26, 27, 34, 35, 36), acute administration of these antidepressants may enhance accumbal CREB phosphorylation *via* activation of 5-HT2, 3, 4, D1, 5, adrenergic α1, β1, and β2 receptors, while decrease accumbal CREB phosphorylation *via* activation of 5-HT1, D2, 3, 4 or α2 receptors. However, long-term modifications in the mesolimbic dopaminergic function, indexed as animals' responsiveness to the reinforcing efficacy of cocaine, following prenatal treatment of these antidepressants remain elusive. Thus, this study was undertaken to study whether prenatal exposure of antidepressants alter the responsiveness to cocaine's reinforcing efficacy in adults. Lately, early-life blockade of serotonin transporter by fluoxetine, an SSRI used as the first-line treatment for depression, was reported to enhance the anxiety susceptibility in adults (2). Such increased susceptibility to anxiety was evident especially in novelty-induced stress conditions. Thus, antidepressants at varied neurochemical targets, including bupropion (NDRI), citalopram, fluvoxamine (SSRIs), and trazodone (SARI), were used to treat the dams during their third trimester of gestation. We then examined a few birth outcome indices, the locomotor activity in a novel and stress environment, naive anxiety level in the elevated plus maze, and the sensitivity to the cocaine reinforcing effects in pups at their days 56-60 post partum.

Materials and Methods

Animals

C57BL/6J mice were obtained from National Cheng Kung University College of Medicine Laboratory Animal Center. Mice were housed in a temperature- and humidity-controlled colony room maintained on a 12-h light/dark schedule (lights on at 0700) with mouse chow and tap water ad libitum. Male retired breeders were used for their mating experiences. Female mice with no history of pregnancy, approximately 8-9 wks of age, received daily, subcutaneous (s. c.) bupropion (25 mg/kg or 12.5 mg/kg), citalopram (5 mg/kg), fluvoxamine (10 mg/kg), trazodone (20 mg/kg) or saline treatment throughout their third trimester of gestation. Pups were nursed by their dams and housed separately by sex on weaning. On days 56-60 postpartum, mice underwent locomotor activity test, followed by the elevated plus maze test and cocaine-induced conditioned place preference trainings and tests. This study was performed in accordance with the Taiwanese Psychological Association Guide for the Care and Use of Laboratory Animals. All procedures were approved by the local Animal Care Committee at the National Cheng Kung University College of Medicine.

Drugs

Bupropion hydrochloride, fluvoxamine hydrochloride, trazodone hydrochloride, and cocaine hydrochloride were obtained from Sigma (St. Louis, MO, USA), while citalopram hydrobromide was purchased from Tocris (Northpoint, Britol, UK). Doses of bupropion (25 or 12.5 mg/kg), citalopram (5 mg/kg), fluvoxamine (10 mg/kg), and trazodone (20 mg/kg) were selected from the effective dose ranges in clinical use. A dose of 2.5 mg/kg cocaine has been proven the minimal dose for establishing the cocaine-induced conditioned place preference with the current protocol in our preliminary study. Considering high doses of cocaine may overshadow the modulating effects of the antidepressants on the conditioned place preference performance, 5 mg/kg cocaine was used in this study.

Locomotor Activity Test

Mouse locomotor activity (including ambulatory activity and vertical rearing) was assessed in a custom-made transparent Plexiglas box ($41 \times 41 \times 30$ cm) inside the Optovarimex (Columbus, Columbus, OH, USA). Two sets of infrared lamps and photocells were mounted on the horizontal and the vertical edges of the Optovarimex. Under a strong light illumination, mice were individually placed in the center of the box and allowed for a free navigation over a 3-min period. The vertical beam breaks were used as an index for the rearing numbers and the horizontal distance traveled were recorded as the ambulatory activity.

Elevated Plus Maze Test

Performance in the elevated plus maze was used

Table 1. Effects of prenatal antidepressant treatment on birth rate, mortality rate, and male/female ratio

Treatment	No. of pups per delivery	Male/Female ratio in delivery	No. of survivors after weaning	Mortality rate (%)
Saline	6.8 ± 0.2	26/23	4.9 ± 0.7	27
Fluvoxamine (10)	4.8 ± 0.5	6/13	3.8 ± 1.1	20
Citalopram (5)	6.7 ± 0.6	12/14	4.3 ± 1.1	32
Trazodone (20)	6.3 ± 0.5	10/12	2.8 ± 1.1	54*
Bupropion (25)	6.8 ± 0.6	12/13	5.0 ± 0.6	26
Bupropion (12.5)	7.7 ± 0.9	10/6	5.5 ± 1.0	30

Numbers in the bracket depict the dose (mg/kg) used for the antidepressants. No. is short for number. Numbers of pups per delivery and survivors after weaning are represented in mean ± SEM. *Significantly higher than the saline-treated group.

as an index for revealing the naive anxiety level. The test consisted of an elevated (50 cm off the floor), plus-shaped, black Plexiglas runway with two opposing arms (32 × 6 cm) being closed by 15-cm side walls and the other two arms being open. Mice were placed, facing a close arm, at the center platform (6 × 6 cm) of the maze and allowed to explore the maze for 5 minutes. The entries made onto the open arms with two front paws and the time spent in these open arms were individually recorded and analyzed.

Cocaine-Induced Conditioned Place Preference Trainings and Tests

Following the locomotor activity and elevated plus maze tests, mice underwent three days of trainings for cocaine-induced conditioned place preference (CPP). The CPP units and the experimental protocols were described in our previous study (22). Briefly, the commercial unit consisted of three compartments with a center chamber and two cue-distinct side chambers. The side chambers differed in three sets of distinctive cues: medium *vs*. dim light illumination, opaque black *vs*. white wall and ceiling, wire mesh *vs*. steel bar grid floor. The center chamber was bright-lit with gray color of Plexiglas wall, ceiling, and floor. Automatic guillotine door controlled passages between the center and the side chambers. Mouse location in each unit was monitored by photocell detectors and the time spent in each compartment was recorded by the MED-PC for Windows. On day 1 of CPP training, mice were treated with cocaine hydrochloride (5 mg/kg, i. p.) and confined to one side compartment (drug side) for 30 min in the morning. Eight hours later mice were treated with an equivalent volume of saline and confined to the other side (saline side) for 30 min. These procedures were repeated for the next two days. On day 4, mice were placed in the central compartment and allowed to explore the entire unit for 15 min. Cocaine-induced CPP for each mouse was expressed as subtraction of the time spent in the saline side from the time spent in the drug side.

Statistical Analysis

All data were analyzed by employing Statistical Package for Social Science (SPSS, Chicago, IL, USA) to evaluate the main effects and followed by Scheffe post-hoc analyses if appropriate unless otherwise mentioned. Mann-Whitney U tests were used to examine the differences in numbers of pups per delivery and survivors after weaning. A Chi-square test was utilized to evaluate the male and female pup ratio and mortality rate after weaning. A P-value of 0.05 was considered statistically significant.

Results

Birth Outcome Indices

Regardless of the antidepressants used, prenatal treatment in pregnant dams did not affect the number of pups or male/female ratio in delivery (Table 1). Trazodone (20 mg/kg) treatment produced a higher mortality rate in pups compared to the saline treatment ($X^2 = 5.22$, $P < 0.05$), while the other antidepressant treatments did not seem to alter the mortality rate after weaning.

Locomotor Activity in a Novel Open Field

Mouse locomotor activity was delineated by the rearing and ambulatory activity, respectively. Since no sex difference was observed, data from male and female mice were combined together for analysis. Numbers in rearing and the ambulatory activity in a 3-min test are plotted as shown in Fig. 1. Mice, prenatally treated with bupropion at a dose of 25 mg/kg, exhibited lower rearing numbers and ambulatory activity as compared to the saline-treated mice. The

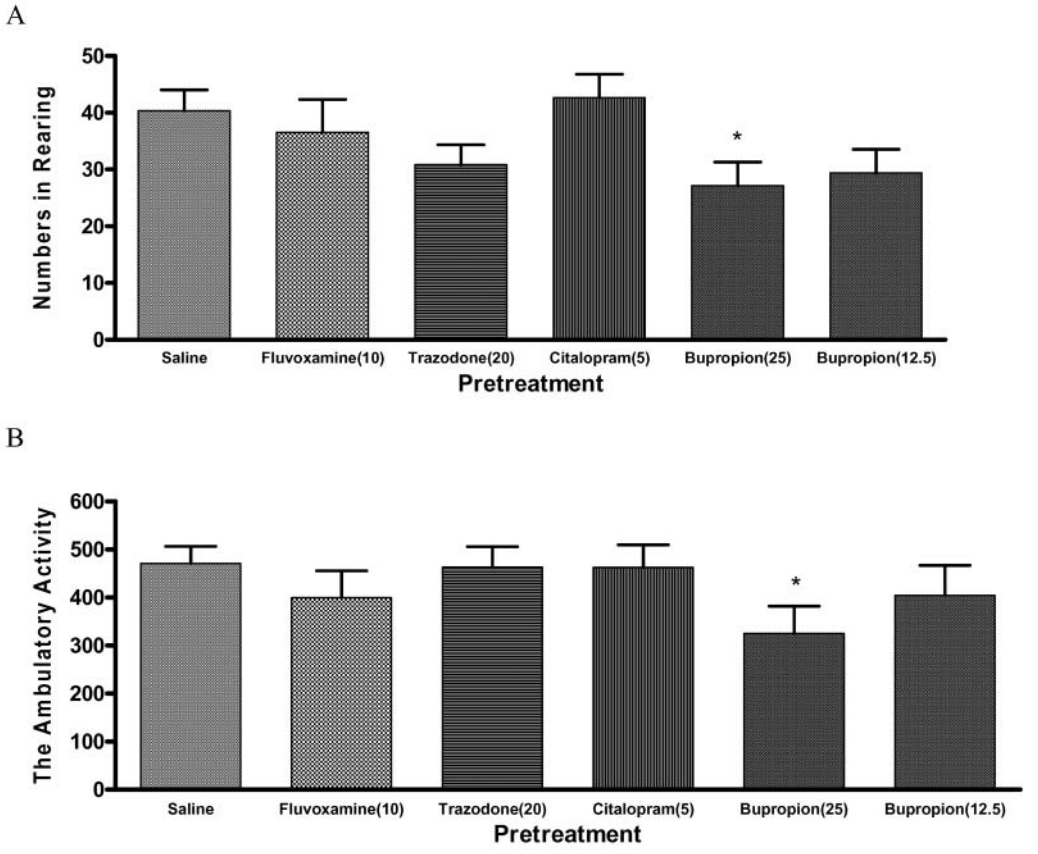

Fig. 1. Effects of prenatal antidepressant treatment on (A) numbers in rearing and (B) the ambulatory activity in adult mice. *Significantly lower than the saline-treated group. Numbers in the bracket depict the dose (mg/kg) used for the antidepressants. Data are represented as mean ± SEM.

other antidepressant-treated mice all demonstrated indistinctive rearing numbers and ambulatory activity as them in saline-treated mice.

Naive Anxiety Levels in Elevated Plus Maze

In an attempt to examine the naive anxiety levels produced by the prenatal antidepressant treatments, the elevated plus maze was used. The open arm entries and the time spent in open arms in a 5-min test were analyzed. Antidepressant- and saline-treated mice all displayed similar numbers in open arm entry and time spent in the open arms (Fig. 2).

Cocaine-Induced Conditioned Place Preference

To investigate the effects of prenatal antidepressant exposure on the rewarding properties of cocaine, cocaine-induced CPP was studied. Regardless of prenatal treatments, male mice performed the similar cocaine-induced CPP as the female mice. Thus, data from two sexes were combined for comparison of prenatal treatment effects. Mice, prenatally-exposed to citalopram, fluvoxamine, and trazodone revealed comparable cocaine-induced CPP to the saline-treated mice. In contrast, mice with prenatal exposure to bupropion at a dose of 25 mg/kg demonstrated higher levels of the cocaine-induced CPP (Fig. 3). Nonetheless, mice prenatally-treated with bupropion at 12.5 mg/kg did not reveal such elevation in cocaine-induced CPP.

Discussion

Although prenatal trazodone, an SNRI, treatment did not affect pup numbers in delivery or male/female ratio, an association between trazodone exposure and the pup mortality rate after weaning was found. Since the quality of maternal behavior was not excluded in our experimental design, dams who delivered the pups were responsible for nursing and caring of the pups before weaning. Thus, trazodone effects on dams and pups both could contribute to such high mortality rate in pups. We observed that trazodone-treated dams were prone to stop the nursing bout immediately in response to close observations by the experimenters. Moreover, these trazodone-

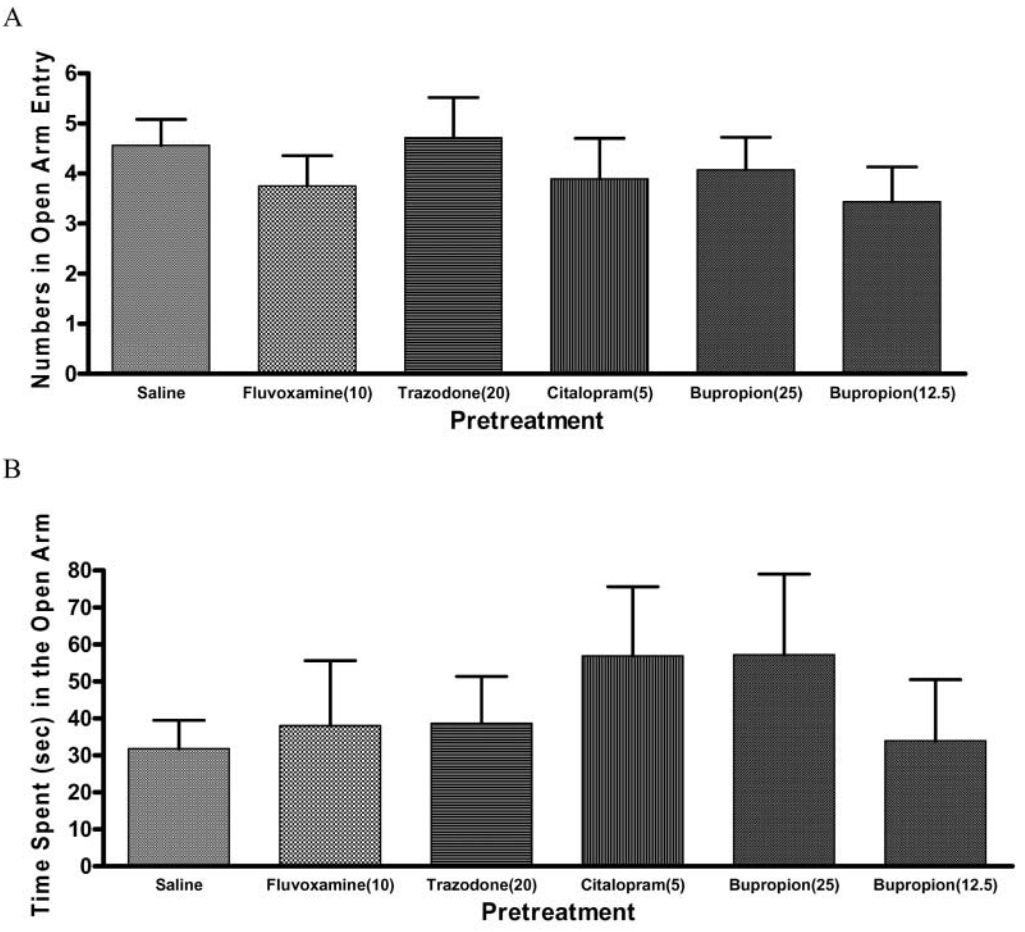

Fig. 2. Effects of prenatal antidepressant treatment on (A) numbers in open arm entry and (B) the time spent (sec) in the open arm in adult mice. Numbers in the bracket depict the dose (mg/kg) used for the antidepressants. All data are plotted as mean ± SEM.

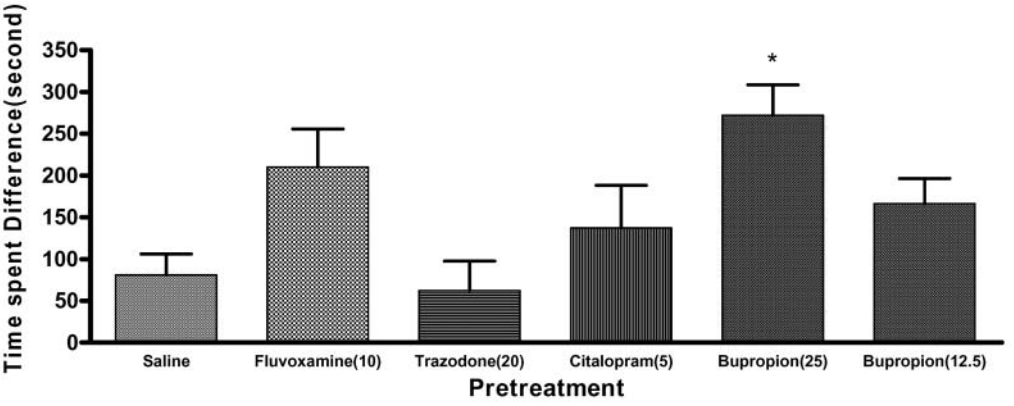

Fig. 3. Effects of prenatal antidepressant treatment on the cocaine-induced conditioned place preference in adult mice. *Significantly higher than the saline-treated group. Cocaine-induced CPP (in second) is obtained from subtracting the time spent in saline-pairing side from the time spent in cocaine-pairing side. Numbers in the bracket depict the dose (mg/kg) used for the antidepressants. Data are shown in mean ± SEM.

treated dams exhibited sluggish retrieval for the scattered pups between the nursing bouts. Ongoing studies are proceeded to validate our observations and to further investigate the cause for such trazodone-related mortality rate in pups.

We did not employ the habituation procedure before the locomotor activity test. Thus, the test box and the surrounding Optovarimex in combination

was a novel place to these mice. Moreover, a strong light illumination was used at the top of the test box. Low locomotor activity in the test is most likely attributed to the high anxiety levels in response to a stress source. Mice, prenatally treated with bupropion (25 mg/kg), an NDRI, exhibited lower rearing numbers and ambulatory activity as compared to the saline-treated mice in the test. Obviously, prenatal bupropion treatments enhance the mouse anxiety levels in a stress condition. Nonetheless, mice under the same treatment did not show higher anxiety levels compared to the saline-treated mice in another novelty-induced stress test, elevated plus maze. Three possibilities are provided to amalgamate these paradoxical findings. First, a floor effect is achieved in the elevated plus maze performance due to the stringently high level of stress raised in the test. It was of interest to note that even the saline-treated mice did not navigate any open arm to the end. Such observation seems to support the likelihood of the floor effect with our elevated plus maze test. Second, the anxiety level is directly linked to the performance in locomotor activity test, whereas a naive fear response is revealed in the elevated plus maze test. Given the hypothetical contrast between anxiety level and fear in these two models, prenatal bupropion treatment seems to enhance the anxiety levels but spare the naive fear response. Third, a rapid behavioral cross-tolerance is involved because these two tests were conducted in order in two consecutive days, with the locomotor activity test on the first, the elevated plus maze test on the next day. The order of such tandem anxiety tests should be reversely arranged to examine the interaction effects between these tests. Surprisingly, two SSRIs used in this study, citalopram and fluvoxamine, did not alter the stress responses in either test. In contrast, another SSRI, fluoxetine, was found to enhance the anxiety levels in mice (2). These discrepancies may arise from the use of mice with different genetic background, various treatment protocol, and specificity of the SSRIs.

More importantly, prenatal bupropion treatment (25 mg/kg) enhanced the adult mouse sensitivity to the reinforcing effects of cocaine, indicating the bupropion-induced elevated susceptibility to cocaine reward. In contrast, prenatal treatment of bupropion at a dose of 12.5 mg/kg did not exert such effect in the same cocaine-induced CPP paradigm. Likewise, a previous study reported that long-term daily bupropion administration (15 mg/kg/day) did not alter conditioned reinforcement responding or cocaine-enhanced conditioned responding in rats (31). Combined the latter findings and our results, multiple doses of bupropion at a dose of 15 mg/kg did not seem to engender behavioral changes. We conjecture that prenatal exposure to bupropion (25 mg/kg) may enhance the mouse anxiety level in a stress condition and consequently lead to an increased sensitivity to the reinforcing and/or hedonic effects of cocaine. Dose-dependent behavior in cocaine self-administration should be contrasted in mice treated with prenatal bupropion at 25 and 12.5 mg/kg to validate our hypothesis. Taken together, these results suggest that use of bupropion (25 mg/kg) in late pregnancy may run a risk of enhancing the offspring's susceptibility to stress and cocaine reward in adulthood.

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