Prenatal Exposure of Bupropion May Enhance Agitation, Anxiety Responses, and Sensitivity to Cocaine Effects in Adult Mice

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Abstract

Major depression and dysthymia afflict a proportion of gravid and breast-feeding women. These women are frequently recommended on antidepressants to relieve their symptoms even if the drug effects on fetal growth and postnatal development are not completely known. In a previous study, we reported that prenatal bupropion exposure seemed to enhance the hedonic value of cocaine in adult mice. This study was undertaken to examine the dose-related effects for prenatal bupropion exposure on the stress susceptibility, cocaine-associated reinforcing property, and cocaine-induced behavioral sensitization in adult mice. Our results showed that various doses (ranging 12.5-50 mg/kg) of prenatal bupropion administration at the third trimester of pregnancy did not affect body weight of the adult mice. Bupropion administration at 50 mg/kg enhanced both ambulatory and rearing responses in the open field test. Moreover, bupropion administration (at 25 and 50 mg/kg) significantly decreased the numbers in open arm entry in the elevated plus maze test. Furthermore, prenatal bupropion treatment appeared to facilitate the cocaine-induced place preference in a sex-dependent manner. Finally, prenatal bupropion exposure (at 25 and 50 mg/kg) accelerated and elevated the development of cocaine-induced sensitization in locomotor activity. While the antidepressant and smoking-curbing effects of bupropion have been addressed in literature, we suggest that prenatal bupropion exposure could run a risk of enhancing individual's agitation, stress susceptibility and cocaine stimulating propensity in adulthood.

Key Words: prenatal, stress, excitability, sex, mice, cocaine, reward, sensitization

Introduction

A proportion of gravid women afflicted with depression, dysthymia and depressive symptoms were recommended on antidepressants to relieve their symptoms throughout their gestation (17, 20). Such antidepressant regimen was even extended through the nursing episode due to the concern of relapse (17, 20). These antidepressant and metabolite concentrations were mostly detectable in umbilical cord blood samples as the medications were taken in late pregnancy (11, 22). Psychotropic drug use during pregnancy inexorably render fetus running a risk of the drug-associated teratogenic effects, neonatal toxicity, and late-onset neurobehavioral sequelae (6). Although no major congenital anomalies have been related to prenatal antidepressant exposure, cumulated data indicated the association of antidepressant use during pregnancy and behavioral teratogenesis, including admission to special care nurseries, respiratory problems, jitteriness and enhanced aggression (6).

Lately, early-life exposure to the antidepressant,

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fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been reported to enhance the anxiety susceptibility in adult mice (1). Such increased anxiety susceptibility was evident in a novelty-induced stress condition. Nonetheless, repeated doses of fluvoxamine, also an SSRI, during the third trimester of pregnancy failed to alter adult mice's susceptibility to novelty-induced stress (12). Interestingly, we observed that prenatal treatment of bupropion, an antidepressant known as a mixed norepinephrine and dopamine reuptake inhibitor (10, 31), at a daily dose of 25 mg/kg for 6-7 days, seemed to enhance the hedonic value of cocaine in adult mice (12).

Bupropion is as effective as the other frequently prescribed antidepressants. It does not cause weight gain and sexual dysfunction, which are the most common causes of long-term noncompliance (35). Moreover, bupropion has been demonstrated to be effective in smoking cessation treatment whereas no obvious effect in relapse prevention with its extended therapy is found (13, 25, 27). Due to sporadic data about its use in anxiety disorders and conflicting results in animal studies, psychiatrists are inclined to avoid prescribing bupropion for depressed patients with high anxiety (8, 29, 30, 32, 35). In animal studies, both anxiolytic and anxiogenic effects have been reported to be associated with bupropion treatment. For example, repeated doses of bupropion pretreatment effectively reversed triazolam withdrawal-induced hyperlocomotor activity in mice (15). Acute bupropion treatment increased open arm entries in elevated plus maze tests, suggesting its anxiolytic-like effects (4). In contrast, acute bupropion enhanced spontaneous locomotion in mice (4, 24). Bupropion, similar to certain anxiogenic drugs, decreased head-dip numbers and increased head-dip latency in the hole-board test (24).

In this study, we decided to examine the dose-related effects of prenatal bupropion exposure on locomotor activity, stress susceptibility, and cocaine-associated effects in adult mice. Since elevated plus maze (EPM) has been widely adopted in studying antidepressant effects and the neurochemical mechanisms for anxiety-like behavior (3, 21), this paradigm was employed to evaluate prenatal bupropion effects on adult animals' stress susceptibility. Locomotor activity in a novel environment, potentially confound the observation in EPM, was also monitored. Finally, cocaine-induced conditioned place preference (CPP) and locomotor activity sensitization were used to assess the effects of prenatal bupropion exposure on the stimulating effects of cocaine.

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 chosen for their mating experiences, while female mice with no history of pregnancy, approximately 8-9 wks of age, were used. Significant body weight gain was used to index pregnancy. Pregnant female mice received daily, subcutaneously (sc), bupropion (0, 12.5, 25, and 50 mg/kg) treatment beginning at their third trimester of gestation. To control the nursing factor, newborns were culled to 6-8 pups and nursed by surrogate dams. Pups were then raised separately by sex after weaning with 3 to 4 animals per plastic cage. On their days 56 to 60 postpartum, mice underwent locomotor activity test, followed by the elevated plus maze (EPM) test and cocaine-induced conditioned place preference (CPP) trainings and tests. Another batch of animals was examined only for their cocaine-elicited sensitization in locomotor activity during their days 56 to 63 postpartum.

Drugs

Bupropion hydrochloride was purchased from Sigma Chem. (St. Louis, MO, USA). Bupropion hydrochloride was dissolved in saline, and various doses (50, 25, or 12.5 mg/kg) were prepared. These doses were determined by the effective dose ranges in clinical use. Cocaine hydrochloride was obtained from Sigma Chem. Our previous studies have demonstrated that 5 mg/kg of cocaine was the minimal dose required to establish reliable CPP performance with the current protocol (5, 12). Considering that high doses of cocaine may overshadow the modulating effects of prenatal bupropion treatment, 5 mg/kg cocaine was used in all CPP trainings accordingly. Daily doses (10 and 20 mg/kg) of cocaine were used to examine the development of cocaine-induced sensitization of locomotor activity.

Locomotor Activity Test

Mouse locomotor activity, including ambulatory activity (horizontal movement) and vertical rearing, was monitored in a custom-made transparent Plexiglass box (41 × 41 × 30 cm) inside the Optovarimex (Columbus instrument, Columbus, OH, USA) under a light illumination (200 Lux). Two sets of infrared lamps and photocells were mounted on the horizontal and the vertical edges of the Optovarimex. Mice were individually placed in the center of the box and allowed for a free navigation in the Plexiglass box over a 10-min period. The vertical beam break was used as an index for the vertical rearing numbers and the horizontal distance traveled was recorded as the ambulatory activity.

Elevated Plus Maze (EPM) and Naive Anxiety Levels

Performance in EPM was used for revealing the naïve 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 10 min. The number of entries made onto the open arms with four paws and time spent in these open arms were individually recorded.

Cocaine-induced Conditional Place Preference (CPP)

One day following the locomotor activity and EPM tests, mice underwent three consecutive days of trainings for cocaine-induced CPP. The CPP units and the experimental protocols were described in our previous study (19). In brief, the commercial unit consisted of three compartments with a center and two side compartments (Med Associates, St. Albans, VT, USA). The side compartments differed in three sets of distinctive cues, including light illumination (40 *vs*. 160 Lux), wall, ceiling color (black *vs*. white), and floor texture (mesh wire *vs*. grid bar). The center was bright-lit (200 Lux) with gray Plexiglas walls and a platform floor. Automatic guillotine door controlled passages between the center and side compartments. The location of the mouse in each compartment was monitored by photocell detectors and the time spent in each compartment was recorded by the MED-PC for Windows. On training day 1, 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 compartment (saline side) for 30 min. These procedures were repeated for the next two days. At noon of the day 4, mice were placed in the center and allowed to freely explore the entire apparatus for 15 min. In each mouse, the time spent in the cocaine side minus the time spent in the saline side was expressed as place preference induced by cocaine.

Cocaine-elicited Sensitization in Locomotor Activity

An 8-day protocol was used for evaluating cocaine-induced behavioral sensitization. A daily dose of cocaine (10 and 20 mg/kg, i.p., respectively) was given and animals' locomotor activity in the Optovarimex box was recorded for five consecutive days. Following two days of withdrawal, cocaine administration and locomotor activity monitoring procedure were repeated on the last day. Since mice exhibited comparable locomotor activity on the first day following cocaine treatment, their first day data was used as baseline for each group. Percents of increase for the following days of each group were obtained accordingly.

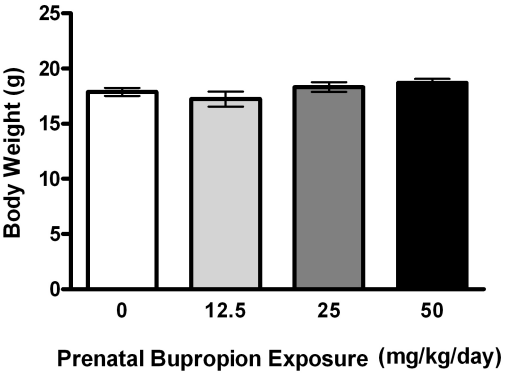

Fig. 1. Prenatal bupropion exposure and adult body weight. Regardless of the doses used at late pregnancy, bupropion did not affect adult mice' body weight at their two months of age. n ≥ 23 for each group.

Data Analysis

All data were analyzed by employing Statistical Package for Social Science (SPSS 10.1 version, Chicago, IL, USA) to evaluate the main effects and followed by post-hoc Tukey analyses if appropriate. A *P*-value of 0.05 was considered statistically significant.

Results

Prenatal Bupropion Did Not Affect the Observed Birth Outcome Indices

Regardless of the doses used, prenatal bupropion treatment did not affect pup numbers or male/female ratio in delivery. Likewise, prenatal bupropion treatment did not affect body weight of pups at their two months of post partum (Fig. 1).

Prenatal Bupropion Treatment at the Highest Dose Used (50 mg/kg) Enhanced Spontaneous Locomotor Activity in Adult Mice

Spontaneous locomotor activity (including ambulatory activity and vertical rearing) of prenatally bupropion-exposed mice were examined at their 56 days of post partum. Since male and female mice in each treatment condition exhibited indistinctive ambulatory activity or rearing number, their data were combined for dose-dependent analysis. We found that mice prenatally exposed with the highest dose (at 50 mg/kg) of bupropion exhibited significantly higher ambulatory activities ($F(3,88) = 2.77$, $P = 0.0463$) (Fig. 2a), vertical rearing numbers ($F(3,88) =$

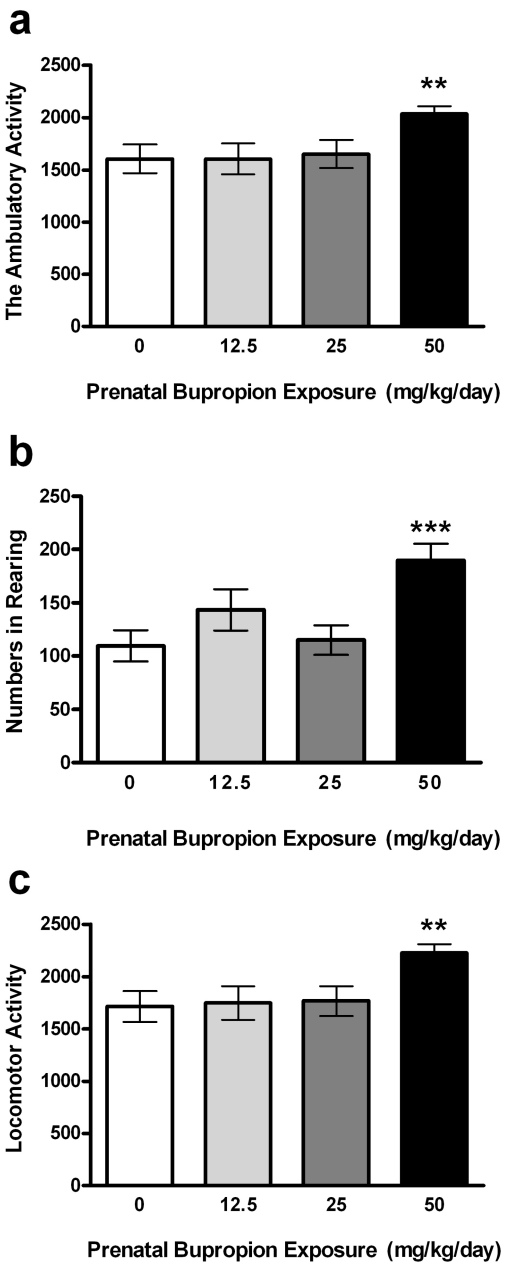

Fig. 2. Prenatal bupropion exposure and spontaneous locomotor activity in an open field test. Mice, prenatally exposed to daily bupropion treatment at 50 mg/kg for 6-7 consecutive days, exhibited higher a) ambulatory activity, b) vertical rearing numbers, and c) total locomotor activity as compared to those in prenatally saline-exposed control mice. n ≥ 23 for each group. ** $P < 0.01$. *** $P < 0.001$.

5.132, $P = 0.0026$) (Fig. 2b), and total locomotor activities ($F(3,88) = 3.149$, $P = 0.0290$) (Fig. 2c) as compared to those of the saline-exposed mice. Prenatal bupropion treatment at 12.5 and 25 mg/kg/day for 6-7 consecutive days did not seem to alter mice' spontaneous locomotor activity (Fig. 2a-c).

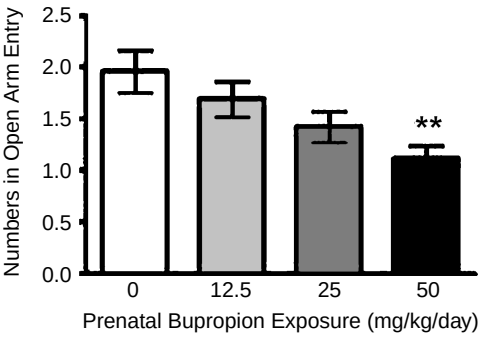

Fig. 3. Prenatal bupropion exposure and open arm entry numbers in elevated plus maze test. Prenatal bupropion treatment at 50 mg/kg/day for 6-7 days significantly decreased the number of open arm entry in elevated plus maze test. n ≥ 23 for each group. ** $P < 0.01$.

Prenatal Bupropion Treatment at 25 and 50 mg/kg Elevated Mice' Naïve Anxiety Levels in EPM Test

Both indices, open arm entry number and time spent in open arm, were used to examine mice' naïve anxiety levels in EPM test. Since there were no sex differences for each treatment condition, data from male and female mice were pooled for further analysis. Mice prenatally exposed to bupropion at doses of 25 and 50 mg/kg demonstrated lower numbers in open arm entry (Fig. 3) as compared with those in mice exposed to saline. Mice prenatally exposed to bupropion at 12.5 mg/kg displayed similar numbers in open arm entry as saline-exposed mice. Nonetheless, all groups of mice spent similar time durations in open arms (data not shown).

Prenatal Bupropion Exposure Distinctively Altered Cocaine Reward in a Sex-dependent Manner

Cocaine rewarding effects were examined using the cocaine-induced CPP paradigm. Male mice, prenatally exposed to daily bupropion treatment at 25 mg/kg/day for 6-7 consecutive days, showed higher level of cocaine-associated CPP when compared with the saline-exposed male mice (Fig. 4a). Female mice under the same dosing regimen exhibited comparable levels of cocaine-induced CPP (Fig. 4b). However, female mice prenatally exposed to daily bupropion treatment at 12.5 mg/kg/day for 6-7 days did not show significant cocaine-associated CPP (Fig. 4b). Prenatal treatment of 50 mg/kg bupropion did not alter cocaine reward in either sex.

Prenatal Bupropion Treatment at 25 and 50 mg/kg Were Prone to Facilitate the Development of Cocaine-induced Locomotor Sensitization

An 8-day protocol with drug withdrawal on day

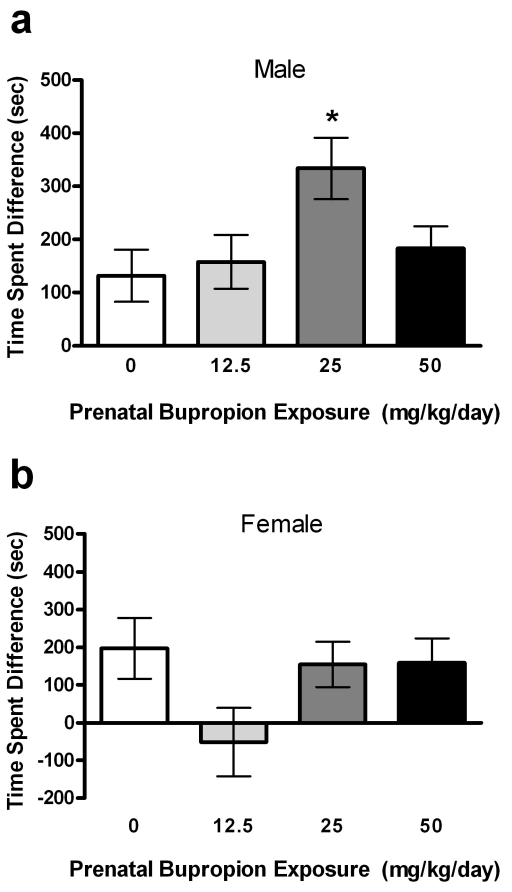

Fig. 4. Prenatal bupropion exposure and cocaine-induced conditioned place preference (CPP) in adult mice. a) Male mice prenatally exposed to bupropion at 25 mg/kg/day for 6-7 days exhibited significantly higher levels of cocaine (5 mg/kg, i.p.)-induced conditioned place preference than it in sex-matched saline-exposed mice. n ≥ 12 for each group. b) Female mice under various bupropion dosing conditions demonstrated comparable cocaine-induced conditioned place preference. n ≥ 12 for each group. *$P < 0.05$.

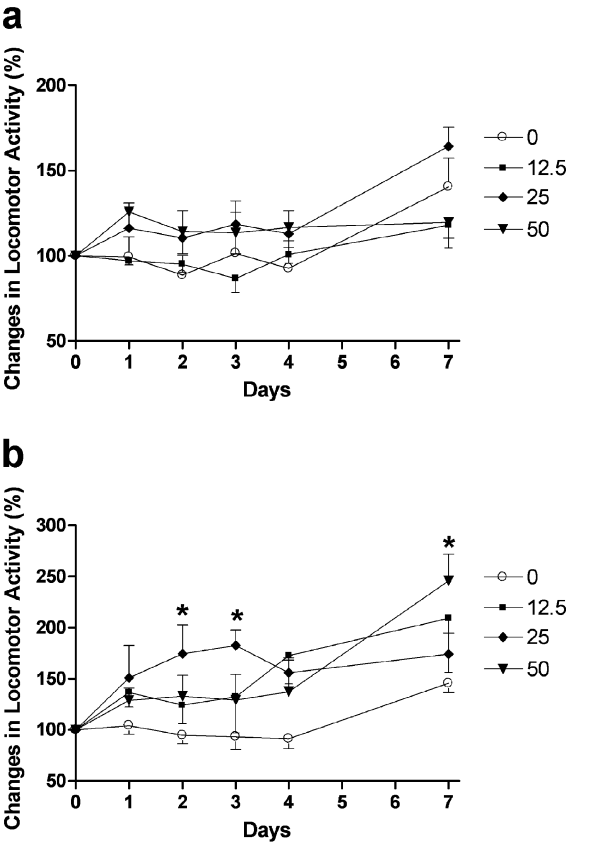

Fig. 5. Prenatal bupropion exposure and cocaine-induced sensitization in locomotor activity. a) Mice prenatally exposed to bupropion at 25 mg/kg/day for 7 days exhibited the highest cocaine-stimulated sensitization in locomotor activity on day 7 among all groups under a 8-day cocaine dosing protocol with days 5 and 6 withdrawal of drug treatment and locomotor activity observation. n ≥ 9 for each group. b) Mice prenatally exposed to bupropion at 50 mg/kg/day for 7 days displayed higher cocaine-stimulated locomotion sensitization on day 7 as compared to the saline-exposed mice. Mice prenatally exposed to bupropion at 25 mg/kg/day performed higher cocaine-stimulated locomotion sensitization on days 2 and 3 than those in saline-exposed control mice under the same 8-day protocol. n ≥ 10 for each group. *$P < 0.05$.

5 and 6 was used to evaluate the development of cocaine (10 and 20 mg/kg/day, ip)-induced locomotor sensitization. There were no obvious differences between two sexes, therefore, their data were combined for analysis. On the last day of our protocol, mice prenatally exposed to daily bupropion treatment at 50 mg/kg/day for 6-7 days demonstrated the highest percentage of increase in cocaine (10 mg/kg)-induced locomotor sensitization (Fig. 5a). Under similar protocol, mice prenatally exposed to bupropion treatment at 50 mg/kg exhibited the highest percentage of increase in cocaine (20 mg/kg)-induced locomotor sensitization on the last day (Fig. 5b). Moreover, mice prenatally exposed to bupropion treatment at 25 mg/kg exhibited the highest percentage of increase in cocaine (20 mg/kg)-induced locomotor sensitization on days 2 and 3 (Fig. 5b).

Discussion

Accrued evidence has demonstrated that acute bupropion treatment enhanced spontaneous locomotion in mice (4, 7, 24, 34). In this study, we found that prenatal bupropion exposure at the highest dose used (50 mg/kg) increased spontaneous locomotion (both ambulation and vertical rearing) in adult mice. Since our mice underwent the locomotor activity test approximately at their two months of age under a drug-free regimen, bupropion-modulated long-

term neuronal plasticity is suspected to play a primary role in these elevated locomotor activities. Although mice' locomotor activity was observed in a novel test box, prenatal bupropion exposure appeared to reverse the stress-associated behavioral suppression in locomotion test (26). Prenatal bupropion treatment may produce this effect by diminishing mice' stress responses or raising their agitation. However, the former possibility is less likely due to the findings that comparable doses (at 25 and 50 mg/kg) of prenatal bupropion treatment increased animals' stress responses as indicated by decreased numbers of open arm entry in EPM test. It is of importance to notice that bupropion-produced increase of spontaneous locomotor activity did not compensate for the stress-elicited locomotor suppression in EPM test. These observations, taken together, prompt us to suggest that prenatal bupropion exposure at high doses (50 mg/kg) could run a risk of raising both agitation and anxiety levels in adult mice.

Although mice were allowed to freely explore in EPM and locomotor activity chamber, evaluation and interpretation of such exploratory behavior for each test could be unique. In our design, limited exploratory behavior in EPM could reveal the strength of animals' naive aversion for stress in open arms, whereas exploration in locomotion test may signify the combined results of animals' aversion to stress and novelty-seeking propensity (33). Given certain treatment induces decreases in both open arm entry and locomotor activity, a conclusive anxiogenic treatment can not be determined because treatment-decreased novelty-seeking inclination may contaminate this conclusion. Likewise, treatment-increased exploratory behavior in both EPM and locomotor activity tests can not be used to draw any solid conclusion due to the possible confounds such as treatment-increased novelty seeking and/or agitation (4). Nonetheless, we found that adult mice' exploratory behavior in EPM and locomotion tests were altered by prenatal bupropion treatment (at 50 mg/kg) in an opposite direction, suggesting that prenatal bupropion treatment distinctively modulates the stress aversion and novelty seeking (agitation) components. Since the EPM paradigm has been frequently used in rodents as an anxiety model, we hereby suggest that combined use of EPM with stress-related spontaneous locomotor activity test as employed in this study is required to decide the treatment effects on anxiety.

Prenatal bupropion treatment at 25 mg/kg, not 12.5 or 50 mg/kg, seemed to enhance cocaine rewarding efficacy in male mice as revealed in their prominent CPP performance. These results, in part, repeat and extend our observation that prenatal bupropion (at 25 mg/kg) exposure primed adult mice susceptible to cocaine reward in the same paradigm (12). A previous study reported that repeated bupropion administrations at 15 mg/kg did not affect conditioned reinforcement responding in adult male rats (28). Thus, repeated low doses of bupropion do not appear to affect the hedonic motivation system in male animals regardless of the developmental stages. Neither bupropion treatment at high doses (50 mg/kg), in this regard, affected cocaine reward in adult mice. Taken together, we conclude that prenatal bupropion exposure enhances the hedonic value and/or reinforcing efficacy of cocaine in adult male mice at a limited dose-sensitive range, which includes clinical frequently-prescribed doses. Interestingly, prenatal exposure to daily bupropion at 25 mg/kg/day for 6-7 days did not alter cocaine reward in female mice. Bupropion (12.5 mg/kg)-exposed female mice barely showed cocaine-induced CPP. Jackson *et al.* (14) reported that female gonadal hormones modulated cocaine self administration behavior, therefore acute modulating effects of cyclic gonadal hormones on the hedonic value of cocaine should be left out before any neuroplastic effect of prenatal bupropion exposure can be concluded in female mice.

Mice prenatally exposed to daily bupropion treatment at 25 mg/kg/day demonstrated the highest percent of increase in cocaine (10 mg/kg)-induced locomotor sensitization on the last day of our protocol although such increase did not reach significance level. Moreover, mice prenatally exposed to bupropion at 50 mg/kg exhibited the highest percent of increase in cocaine (20 mg/kg)-induced locomotor sensitization on the last day of our protocol. Nevertheless, mice prenatally exposed to bupropion at 25 mg/kg exhibited significant locomotor increase on days 2 and 3 in 20 mg/kg cocaine experiment. In parallel with the results of an increased cocaine reinforcing efficacy specifically observed with the prenatal bupropion treatment at 25 mg/kg/day, these findings all together indicate that the rewarding and psychomotor-stimulating effects of cocaine can be modulated by a limited dose-sensitive range of prenatal bupropion administration. It has been known for a while that repeated exposure to cocaine may result in sensitization to both the rewarding and psychomotor-stimulating effects of the drug (16). Although the relationship of psychostimulant rewarding efficacy and their sensitization development remains elucidated, our findings indicate that prenatal bupropion exposure at high doses (above 25 mg/kg) may enhance adult animals' susceptibility to cocaine-associated reward and locomotion-sensitizing effects.

Bupropion is a weak inhibitor for norepinephrine and dopamine reuptake and has a greater effect on dopamine reuptake than any other biogenic amines (2, 23). However, bupropion produced attenuated or increased firing rate in noradrenergic neurons, serotonergic neurons, respectively, while sparing the

firing rate of dopaminergic neurons in mesolim bic/cortical regions (9). Li *et al*. (18) claimed that acute bupropion treatment increased extracellular dopamine and norepinephrine concentrations in mesocorticolimbic areas. A recent study has also indicated that bupropion increased dopamine and norepinephrine levels in mouse frontal cortex (36). Based on our findings in this study, noradrenergic and dopaminergic systems following repeated bupropion treatment during prenatal development deserves further investigation. Since prenatal bupropion-exposed mice may be sensitive to the reinforcing and psychomotor-stimulating effects of cocaine in adults, we suspect that mesencephalic dopaminergic pathways are involved in such prenatal bupropion-induced neuroplasticity.

Acknowledgments

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