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ORIGINAL INVESTIGATION

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Bupropion effects on aggressiveness and anxiety in OF1 male mice

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Abstract *Rationale:* Bupropion is an antidepressant drug that is being used to help in giving up smoking. Its behavioral effects have been evaluated in different animal models, although limited information is available regarding its effects on aggressiveness, anxiety and exploratory behavior. *Objectives:* Evaluate acute effects of bupropion on locomotor activity, isolation-induced aggression, hole-board and elevated plus-maze tests in OF1 male mice. *Methods:* In the first experiment, effects of bupropion (2.5, 5, 10, 20 and 40 mg/kg) on locomotion were evaluated. In the second experiment, isolation-induced aggression was assessed in isolated male mice previously classified as short attack latency (SL) and long attack latency (LL). Mice were treated with bupropion or vehicle and confronted with standard opponents for 10 min. In experiments 3 and 4, mice were treated with bupropion or vehicle and 30 min later examined in the plus-maze or in the hole-board apparatus. *Results:* In the actimeter, bupropion induced a dose-dependent increase in locomotion. During agonistic encounters, bupropion (10 mg/kg and 40 mg/kg) increased time devoted to attack in LL mice. In the plus-maze, no significant differences were found between bupropion-treated and vehicle-treated mice in the percentage of entries or time spent in open arms. In the hole-board, the highest dose of bupropion (40 mg/kg) significantly decreased number of head-dips and increased latency to the first head-dip. *Conclusions:* During agonistic encounters the two sub-groups of mice (SL and LL) may display differential sensitivity in drug-induced changes on aggressiveness, since bupropion increased attack only in mice with "long attack latency" in the pre-screening test. In the plus-maze, this drug does not seem to have specific actions on anxiety and in the hole-board a high dose had similar effects to those induced by anxiogenic drugs.

Keywords Mice · Bupropion · Locomotor activity · Isolation-induced aggression · Plus-maze · Hole-board

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Introduction

Bupropion is an atypical antidepressant that is currently being used in smoking cessation (Hughes et al. 2003; Richmond and Zwar 2003), although its mechanism of action is not completely understood (Miller et al. 2002; Cryan et al. 2003; Shoaib et al. 2003). Beneficial effects on mood and some withdrawal symptoms, such as depression, irritability, difficulty in concentrating or decrease in positive affect have been described after its administration in patients who were not trying to quit tobacco (Shiffman et al. 2000). Changes in negative affect could be a mediating mechanism of bupropion action on smoking cessation (Lerman et al. 2002), although its effectiveness in the treatment of tobacco dependence seems to be independent of its antidepressant effects (Hays and Ebbert 2003).

Bupropion is a re-uptake inhibitor of dopamine and noradrenaline and enhances dopaminergic activity in the mesolimbic system and nucleus accumbens (Ascher et al. 1995). After sustained administration in rats, it was observed that bupropion induced a dose-dependent attenuation of spontaneous firing rate of norepinephrine, an increase in 5-HT firing neurons, without altering the firing rate of dopaminergic neurons of mesolimbic/cortical regions (Dong and Blier 2001). In rats, bupropion can increase extracellular dopamine and norepinephrine concentrations in mesocorticolimbic areas without affecting serotonin concentrations (Li et al. 2002). Recent experi-

ments in mice have also indicated that bupropion increased levels of dopamine and norepinephrine in the frontal cortex (Zocchi et al. 2003). Bupropion can act as a nicotine receptor antagonist, blocking the effects of nicotine in several behavioral tests (Fryer and Lukas 1999; Slemmer et al. 2000), although there are some discordant results (Young and Glennon 2002; Shoaib et al. 2003). The efficacy of this drug in smoking cessation has been related to its ability to alter brain reward circuits influenced by nicotine (Cryan et al. 2003). In rats, bupropion reduces affective and somatic signs of nicotine withdrawal (Lake et al. 2001; Cryan et al. 2003).

Behavioral effects of this drug have been evaluated in different animal models, although limited information is available regarding its effects on anxiety, exploratory behavior and aggressiveness. Studies in rodents have demonstrated that bupropion produced a dose-dependent increase in motor activity (Cooper et al. 1980; Zarrindast and Hosseini-Nia 1988), sniffing (stereotyped behavior) (Zarrindast et al. 1996), hypothermia and anorexia (Zarrindast and Hosseini-Nia 1988). In the forced swimming task, a pre-clinical test for antidepressant drug effects, bupropion decreased immobility (Baizman et al. 1987; David et al. 2003; Zocchi et al. 2003). In learning tasks, bupropion inhibited reserpine-induced impairment in conditioned avoidance response (Nakawaga et al. 1997) and enhanced retrieval of step-down inhibitory avoidance (Barros et al. 2002). The effects of bupropion on anxiety were evaluated in an animal model based on conflict behavior. It has been observed that acute treatment with a high dose induced anxiogenic-like effects, whereas chronic administration had no clear effects (Comissaris et al. 1990). There also appear to be no published data concerning bupropion's effects on isolation-induced aggression in mice. In muricide tests in rats, bupropion administered 30 min before testing antagonized muricidal behavior and significantly increased the latency to mouse-killing (Strickland and Da Vanzo 1986). In clonidine-induced aggression in mice, chronic administration of bupropion had no significant effects (Klimek et al. 1985).

Understanding the behavioral profile of bupropion using a wide range of experimental procedures may be an important key to determine its pharmacological properties. We considered, as suggested by other authors (File 1992; Van Gaalen and Steckler 2000), that the use of several tests in the same study could aid in clarifying the effects of a given drug on different emotional states. Effects of bupropion on anxiety were evaluated using the elevated plus-maze, since this test is extensively used in neurobiological research on anxiety (Pellow and File 1986) and is also one of the most widely applied models to study the effects of antidepressants in anxiety-like behavior (Borsini et al. 2002). Behavioral changes induced by this drug were also examined in the hole-board, which is used to assess drug effects on exploration and activity, although it has also been applied to evaluate emotionality and anxiety in mice (Tsuji et al. 2000). Since behavior displayed by mice in these anxiety models can be influenced by changes in locomotor activity, direct effects of bupropion on spontaneous locomotion in the actimeter were registered. Its effects on aggression were examined in isolated mice, since social isolation is the method most frequently used in the laboratory to induce mice to fight (Miczek et al. 2001). Social interaction shown by mice during these agonistic encounters have also been applied to detect anxiolytic and anxiogenic-like effects of drugs (Navarro et al. 2004).

Materials and methods

Animals

OF1 male mice obtained commercially from Charles River (Barcelona, Spain), weighing between 30 g and 32 g, were used for all experiments. The laboratory was maintained in standardized conditions, with a reversed 12 h light/dark cycle (lights on: 1930 hours). Mice had free access to food and water. All procedures complied with "Principles of laboratory animal care" as well as international guidelines (European Communities Council Directive of November 24, 1986 (86/609/EEC)) for care and treatment of animals.

For experiments 1, 3 and 4, mice housed in groups of five per cage (25×25×15 cm) were used as experimental subjects. For experiment 2, half of the subjects were isolated for 4 weeks in cages measuring 24×13×14 cm^3 and the other half were housed in groups of five to be used as "standard opponents".

Drugs

Bupropion hydrocloride, obtained commercially from Sigma (Sigma-Aldrich, Madrid, Spain) was administered intraperitoneally (IP) in doses of 2.5, 5, 10, 20 and 40 mg/kg in experiments 1 and 2, and doses of 1.25, 2.5, 5, 10, 20 and 40 mg/kg in experiments 3 and 4. Control groups received physiological saline. All injections were administered in a volume of 10 ml/kg.

For the measure of motor activity in experiment 1, the drug was administered immediately before putting each mouse in the activity cages. In the other behavioral measures (isolation-induced aggression, plus-maze and hole-board) mice received the injection of bupropion or physiological saline and 30 min later their behavior was observed.

Apparatus and procedure

Experiment 1: effects of bupropion on locomotor activity
Spontaneous locomotor activity of the animals was measured using an actimeter (ACTISYSTEM II, Panlab SL, Barcelona, Spain), consisting of four sensory plates (35×35 cm) (pb 46603) which registered the activity of the animals through an electromagnetic system. The acquisition and storage of data was performed using a computerized program (DAS 16 version 1.0), a computer

and an interface (pb 40035). Mice were allowed a 30 min habituation period to the plexiglas test cages (25×25×15 cm). Spontaneous locomotor activity was measured beginning immediately after administering IP bupropion injection to each mouse. Activity counts were registered for 90 min in periods of 10 min.

Experiment 2: effects of bupropion on isolation-induced aggression After the completion of the isolation period (30 days), all isolated mice underwent a pretest of aggression in order to select those with different levels of aggressiveness. In this pretest, isolated mice were confronted with an anosmic opponent in a transparent neutral cage (60×33×30 cm) for 5 min and the latency to the first attack was measured, as previously reported (Moragrega et al. 2003). For the present study, mice were classified according to their attack latency as mice with "long attack latency" (LL; latency to the first attack longer than 3 min) and mice with "short attack latency" (SL; latency to the first attack shorter than 2 min). This selection criteria has been previously validated for the OF1 strain (Felip et al. 2001).

Aggressive encounters took place in the neutral cage, in which isolated mice (treated with bupropion or vehicle) were confronted with a standard opponent (marked with fur dye) for 10 min. Before the agonistic encounter, mice were allowed 1 min of adaptation to the neutral cage while remaining separated by a plastic barrier. Standard opponents were rendered anosmic with intranasal lavage with zinc sulfate. These opponents were employed because they elicit attack but never initiate it (Brain et al. 1981) and, therefore, effects of drugs administered to the experimental animal can be more easily observed (Redolat et al. 1991). The frequencies and duration of the following behaviors of the experimental animal were recorded during the 10 min of test duration: body care, digging, non-social exploration, explore from a distance, social investigation, threat, attack, avoidance/flee, defense/submission and immobility (a more detailed description of these categories can be found in Redolat et al. 2000). Encounters were videotaped with a video camera (Sony Handycam CCD, TR401E, Japan). Behavioral scores were analyzed by a trained observer blind to the different treatment conditions, using the "mouse-time program", which allows the estimation of the time allocated to the 11 behavioral categories. Analysis of the videotapes involved assessment of only the behavior of the experimental animals (isolated mice).

Experiment 3: effects of bupropion on the plus-maze In order to facilitate the adaptation of the animals, mice were taken to the test enclosure, illuminated with a dim red light, 1 h before the trials. The plus-maze consisted of two open arms (30×5 cm) and two closed arms (30×5×15 cm), elevated 45 cm from the floor. The base of the arms and central platform were made of black Plexiglas and the walls of the closed arms of clear Plexiglas. All animals were tested during the first half of the light/dark cycle. The test was initiated by placing the mouse on the central platform facing one of the open arms. Each test lasted 5 min and was videotaped with a digital camera (Sony Handycam, CCD-TR401E, Japan). Videotapes were scored by a trained observer blind to the treatment conditions, using a computerized method. The measures recorded were frequency of entries and percentage of time spent in each section of the apparatus (open arms, closed arms, central platform). An arm entry was considered when the animal entered it with all four paws. The number of open arm entries, time spent in open arms, and percentage of open arm entries are usually used to characterize anxiolytic effects of drugs (Pellow and File 1986; Rodgers et al. 1997). Total arm entries are considered an indicator of the locomotor activity of the animals (Rodgers and Cole 1993; Espejo 1997; Zarrindast et al. 2001), although closed arm entries could be even a better measure (Zarrindast et al. 2000). Additionally, the following ethological parameters, described according to operational definitions offered by Rodgers and colleagues (Rodgers and Cole 1994) were assessed: *rearing*, vertical movement against the side and/or end walls; *stretched attend posture (SAP)*, an exploratory posture in which the mouse stretches forward and then retracts to original position without moving the feet; *head dipping (HD)*, an exploratory movement of head and shoulders over the sides of the maze. SAP and HD were differentiated as "protected" (pSAP and pHD, occurring in the closed arms or central platform) or "unprotected" (occurring from the open arms). These parameters were selected from those which the ethological factor analysis suggests are the most representative to evaluate anxiety-like behavior of mice (Wall and Messier 2000). In Table 2, data are expressed as totals (total SAP and HD) and percent protected (% pSAP and % pHD). A decrease in total SAP and in the percentage of protected SAP and HD has usually been interpreted as anxiolytic (Rodgers et al. 1997).

Experiment 4: effects of bupropion on the hole-board This apparatus consisted of a box (32×32×29 cm) which had 16 equidistant holes in the floor and walls of clear Plexiglas. Photocells below the surface of the holes detected the number of times mice displayed head dipping. The hole-board was introduced by Boissier and Simon (1962) and is considered a measure of exploration, although it has also been used to assess emotionality and anxiety in mice (Tsuji et al. 2000). At the beginning of each test, mice were placed in the central area of the hole-board and allowed to explore it freely for 5 min. Frequency of head-dips was recorded automatically by the apparatus for each animal. Rearing and grooming episodes were evaluated from videotapes by an observer blind as to the treatment. In this apparatus, it has been described that the number of head-dips and the latency to the first head-dipping displayed by mice could be useful for evaluation of drug effects on anxiety (Takeda et al. 1998).

Statistical analysis

Data of the actimeter, plus-maze and hole-board were analyzed with analysis of variance (ANOVA) followed by Newman–Keuls or Duncan test for multiple comparisons. *P*-values of 0.05 or less were considered statistically significant.

In experiment 2 (isolation-induced aggression), and due to the non-continuous nature of the data of the behavioral parameters, analyses were performed using Kruskal–Wallis one-way ANOVA followed by two-tailed Mann–Whitney *U*-test when appropriate. A general ANOVA was performed considering data from all the sample, and two separate ANOVAs to evaluate effects of bupropion on the two subgroups of mice differing in attack latency.

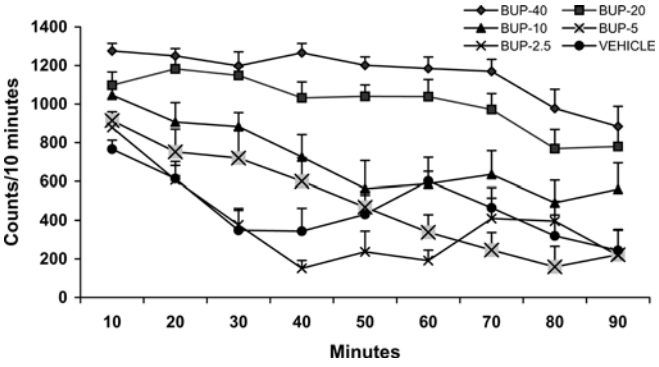

Fig. 1 Mean (±SEM) of locomotor activity shown for six groups of mice treated with vehicle (*VEH*) (*n*=12) or different doses of bupropion: 40 mg/kg (*BUP-40*) (*n*=11), 20 mg/kg (*BUP-20*) (*n*=10), 10 mg/kg (*BUP-10*) (*n*=12), 5 mg/kg (*BUP-5*) (*n*=12) and 2.5 mg/kg (*BUP-2.5*) (*n*=10). Activity counts per time period (10 min) for 90 min

Results

Effects of bupropion on locomotor activity

Locomotor activity during the overall period Bupropion induced a significant increase in the activity of animals throughout the testing period, having a significant stimulatory effect on motor activity counts [$F(5,61)=28.13$, $P<0.0001$]. Follow-up comparisons indicated that this increase was significant in mice treated with 40, 20 ($P<0.0001$) and 10 mg/kg ($P<0.005$) of bupropion in comparison with vehicle-treated animals. It was also found that those receiving 40 mg/kg displayed higher activity than those treated with 20 ($P<0.05$), 10, 5 and 2.5 mg/kg of bupropion ($P<0.0001$). In addition, mice treated with 20 mg/kg showed higher activity counts than those receiving 10, 5 and 2.5 mg/kg ($P<0.002$). Finally, mice treated with 10 mg/kg displayed higher locomotion than those to which 5 mg/kg and 2.5 mg/kg ($P<0.005$) were administered.

Temporal course of changes in motor activity The main factor time [$F(8,488)=43.39$, $P<0.0001$], and the interaction drug×time [$F(40, 488)=3.26$, $P<0.0001$], reached statistical significance (see Fig. 1). Post-hoc Newman–Keuls tests indicated that in groups treated with 40 mg/kg and 20 mg/kg, locomotor activity counts were significantly higher than in the control group in the nine time periods evaluated ($P<0.05$). Mice treated with 10 mg/kg were significantly more active than vehicle-treated animals from the second (11–20 min) to the fourth time period (31–40 min), and during the last time period (81–90 min) ($P<0.05$). In contrast, mice treated with 5 mg/kg showed reduced motor activity in comparison with controls from the sixth (51–60 min) to the eighth time period (71–80 min), whereas those treated with the lowest dose (2.5 mg/kg) also displayed less motor activity than control group from the fourth (31–40 min) to the sixth time period (51–60 min) ($P<0.05$).

Effects of bupropion on isolation-induced aggression

Analysis of the effects of bupropion on the whole group of mice When data from all mice were taken into account, there were no significant differences between control and bupropion-treated mice in any of the following categories: “explore from a distance”, “social investigation”, “threat”, “avoidance-flee”, “defense/submission” and “immobility”. An increase in time devoted to “attack” was observed in mice receiving 10 mg/kg and 40 mg/kg of bupropion, although it did not reach statistical significance. Kruskal–Wallis analysis showed that there was significant variance in the category of “body care” [$H(5)=16.79$, $P<0.005$]. Paired comparisons by Mann–Whitney *U*-tests revealed that time allocated to this behavioral category was reduced by the highest dose of bupropion (40 mg/kg) in comparison with vehicle group ($U=11$, $P<0.02$). Time spent in “digging” also presented a significant variance [$H(5)=37.78$, $P<0.0001$], being significantly reduced in mice treated with 40 mg/kg ($U=0$, $P<0.02$), 20 mg/kg ($U=1$, $P<0.02$), 10 mg/kg ($U=3.5$, $P<0.02$) and 5 mg/kg bupropion ($U=16$, $P<0.02$), with respect to vehicle-treated animals. Finally, Kruskal–Wallis tests revealed that bupropion significantly influenced time allocated to the category of “non-social exploration” [$H(5)=12.02$, $P<0.035$]. Further post-hoc tests indicated that 20 mg/kg bupropion increased the time dedicated to this behavior, in comparison with vehicle ($U=16$, $P<0.02$).

Analysis of the effects of bupropion in groups differing in their attack latency Tables 1 and 2 illustrates medians (with ranges) of accumulated times allocated to each behavioral category in mice with “short attack latency” (SL) and “long attack latency” (LL), respectively. When effects of bupropion were analyzed separately in SL and LL mice, statistical comparisons indicated that in SL mice there were no significant differences between groups treated with bupropion and the control group, either in any of the behavioral categories or in “latency to the first attack” displayed during the behavioral test. However, in

LL mice some interesting differences emerged. For instance, the drug significantly decreased time allocated to "digging" [$H(5)=18.16$, $P<0.003$] in mice treated with 40 mg/kg ($U=0$, $P<0.02$) and 20 mg/kg of bupropion ($U=0$, $P<0.02$) in comparison with vehicle-treated mice (see Fig. 2). Kruskal–Wallis tests also indicated that there were significant differences in time spent in "non-social exploration" [$H(5)=11.6$, $P<0.04$]. Mann–Whitney U-test confirmed that in LL mice treated with the dose of 20 mg/kg the time dedicated to this behavior was increased ($U=0$, $P<0.02$). Finally, Kruskal–Wallis tests also revealed that bupropion had no significant effects on "latency to the first attack" displayed during the behavioral test but significantly influenced time allocated to "attack" [$H(5)=13.57$, $P<0.01$]. Further comparisons confirmed that in mice treated with 40 mg/kg ($U=1$, $P<0.05$) and 10 mg/kg bupropion ($U=0$, $P<0.02$) the increase in time devoted to attack reached statistical significance. In Fig. 2, the differences in time allocated to these behavioral categories in which statistical differences between vehicle and bupropion-treated LL mice emerged are displayed. No significant differences were obtained in the categories of "avoidance-flee", "defense-submission" and "immobility". In fact, median values for these categories in all groups were "zero" and, for that reason, have not been included in Tables 1, 2.

Effects of bupropion on the plus-maze

Table 3 illustrates the effects of bupropion on the behavior exhibited by mice in the elevated plus-maze test. ANOVA indicated that there were significant differences between groups in the percentage of time spent in open arms [$F(6,62)=2.349$, $P<0.04$]. Post-hoc Newman–Keuls tests did not identify the source of any of these differences whereas Duncan tests revealed that mice treated with the two highest doses (40 mg/kg and 20 mg/kg) spent significantly more time in open arms than those treated with 2.5 mg/kg and 1.25 mg/kg bupropion ($P<0.05$).

With regard to the ethological measures, there was a significant effect of bupropion on the frequency of rearing behavior [$F(6,62)=2.23$, $P<0.04$]. Duncan tests showed that mice treated with the highest doses (40 mg/kg and 20 mg/kg) displayed a lower frequency of rearing than vehicle-treated mice or those treated with 5 mg/kg. There were no significant differences in the total and percentage of protected HD or SAP.

Effects of bupropion on the hole-board

The effects of acute administration of bupropion on the behavioral responses of mice in the hole-board are shown in Fig. 3. The number of head-dips was decreased with bupropion [$F(6,65)=3.25$, $P<0.01$], being statistically significant at 40 mg/kg in comparison with vehicle ($P<0.01$) and in comparison with the groups treated with 1.25 and 2.5 mg/kg ($P<0.01$). Moreover, the latency to the first head-dip dose-dependently increased after bupropion administration [$F(6,65)=3.29$, $P<0.01$], reaching statistical significance at the dose of 40 mg/kg in comparison with vehicle ($P<0.05$) and with the doses of 1.25 and 5 mg/kg ($P<0.05$). Bupropion did not significantly alter the incidence of rearing or grooming during the test.

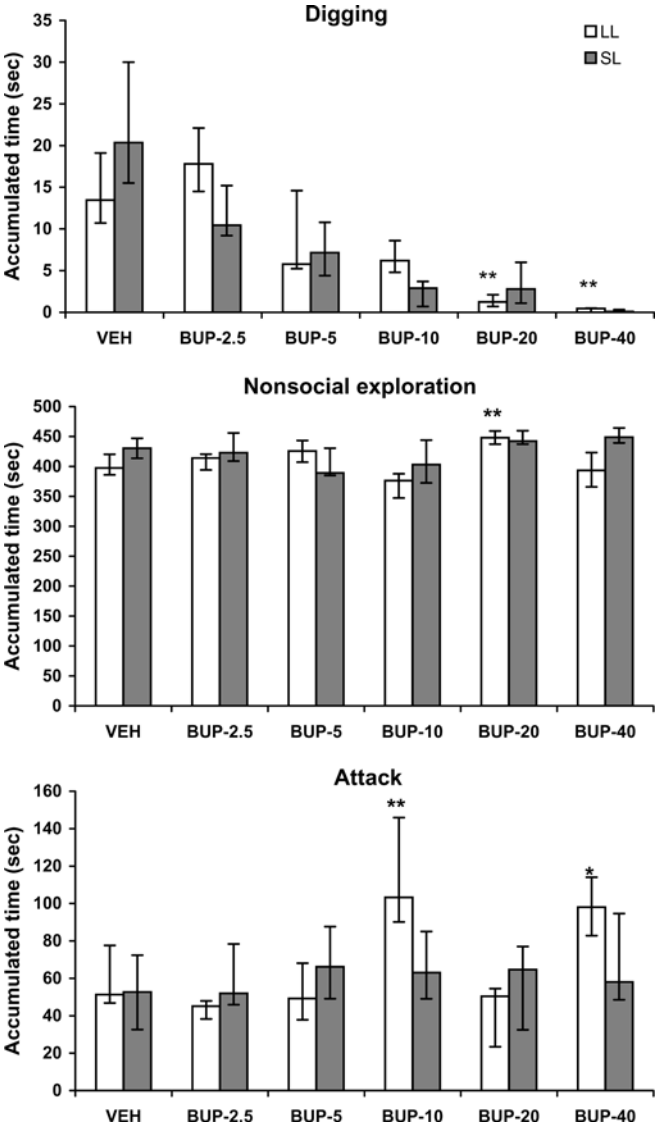

Fig. 2 Median time (±interquartile range) allocated by SL (mice with short attack latency) and LL (mice with long attack latency) groups to the behavioral categories of digging, attack and non-social exploration. Mice were injected (IP) with vehicle (*VEH*) or different doses of bupropion: 40 mg/kg (*BUP-40*) ($n=10$), 20 mg/kg (*BUP-20*) ($n=10$), 10 mg/kg (*BUP-10*) ($n=10$), 5 mg/kg (*BUP-5*) ($n=10$), 2.5 mg/kg (*BUP-2.5*) ($n=10$) and 1.25 mg/kg (*BUP-1.25*) ($n=10$). Thirty minutes later mice were confronted to an anosmic opponent for 10 min. $^{**}P<0.02$ vs LL vehicle-treated mice, $^{*}P<0.05$ vs LL vehicle-treated mice

Discussion

Effects of bupropion on locomotor activity The highest doses of bupropion increased spontaneous locomotion

Table 1 Effects of acute bupropion treatment with 2.5 (*BUP-2.5*), 5 (*BUP-5*), 10 (*BUP-10*), 20 (*BUP-20*) and 40 mg/kg (*BUP-40*) or vehicle (*VEH*) on median (with ranges) time (in seconds) allocated to broad categories of behavior during agonistic encounters by male mice with "short attack latency" (*SL*) when confronted with "standard opponents"

Behavioral categories	VEH	BUP-2.5	BUP-5	BUP-10	BUP-20	BUP-40
Body care	15.20 (11.80–37.30)	15.05 (8.80–33.30)	14.50 (5.70–21.30)	9.95 (4.30–32)	6.95 (1.80–31.40)	6.25 (0.3–18.5)
Digging	20.35 (10.3–36.80)	10.45 (0–28.40)	7.15 (0–13.6)	2.9 (0–4.2)	2.8 (0–9.7)	0 (0–0.90)
Non social exploration	430.5 (409–452)	423 (263–472)	398 (359–472)	403 (325–465)	442 (418–482)	448.8 (422–472)
Explore from a distance	5 (0–11.50)	3.40 (1.90–9.90)	5.85 (0–45.40)	8.35 (0–23.20)	8.15 (0–16.60)	7.65 (4–10.85)
Social investigation	11.65 (1.2–36.40)	15.25 (9.20–25.20)	35.65 (4–71.60)	35.65 (4–71.6)	11.50 (0–31.60)	24.95 (13.30–48.1)
Threat	59.10 (27.8–66)	55.85 (30.40–102)	48.15 (7.5–135.8)	61.85 (29.30–141.1)	50.45 (7.40–90)	37.35 (24.2–85.8)
Attack	52.7 (13.10–98.6)	51.9 (27.9–138.9)	66.15 (34.8–101.9)	63.5 (29.7–103)	64.65 (6.2–94.7)	58 (26.6–124.9)

Table 2 Effects of acute bupropion treatment with 2.5 (*BUP-2.5*), 5 (*BUP-5*), 10 (*BUP-10*), 20 (*BUP-20*) and 40 mg/kg (*BUP-40*) or vehicle (*VEH*) on median (with ranges) time (in seconds) allocated to broad categories of behavior during agonistic encounters by male mice with "long attack latency" (*LL*) when confronted with "standard opponents"

Behavioral categories	VEH	BUP-2.5	BUP-5	BUP-10	BUP-20	BUP-40
Body care	10.25 (7.10–16.9)	16.1 (9.2–32.7)	11.2 (5.70–18.2)	7.35 (3.10–15.20)	11.45 (4.30–18.50)	5.75 (0.4–6.4)
Digging[a]	13.45 (7.30–26.2)	17.8 (14.3–25.2)	5.77 (5.70–21.30)	7.35 (2.3–14.10)	1.25** (0–3.6)	0.45** (0–1.6)
Non social exploration[b]	397.25 (298–430)	414.10 (374–426.8)	425.9 (380–465)	376.1 (269–413.8)	448** (431–465)	393.3 (365–430)
Explore from a distance	3.35 (0.30–5.80)	5.45 (2–11.20)	5.8 (1–10.70)	3.95 (0–6.80)	9.05 (4–10.90)	7.40 (3.4–16.60)
Social investigation	53.70 (40–70.10)	41.70 (12.20–134.9)	62.15 (5.30–67.8)	26.45 (6–39)	26.50 (15.80–74.10)	22.10 (3.20–65.45)
Threat	29.60 (17.30–123.6)	48.85 (30–70.70)	41.20 (38.60–42)	67 (52.20–78.40)	43.50 (31.60–58.80)	43.50 (31.60–58.8)
Attack[c]	51.3 (25.3–69.7)	45.1 (24.6–49.7)	49.2 (37.5–91)	103.3** (75.9–247.7)	50.4 (47–59)	98.05* (63.1–136.4)

*Differs from controls $P<0.05$ on two-tailed Mann–Whitney *U*-test
**Differs from controls $P<0.02$ on two-tailed Mann–Whitney *U*-test
[a]Shows significant variance $P<0.003$ on Kruskal–Wallis test
[b] Shows significant variance $P<0.04$ on Kruskal–Wallis test
[c] Shows significant variance $P<0.01$ on Kruskal–Wallis test

Table 3 Effects of acute bupropion treatment with 1.25 (*BUP-1.25*), 2.5 (*BUP-2.5*), 5 (*BUP-5*), 10 (*BUP-10*), 20 (*BUP-20*) and 40 mg/kg (*BUP-40*) or vehicle (VEH) on elevated plus-maze behavior in OF1 male mice

Behavioral categories	VEH	BUP-1.25	BUP-2.5	BUP-5	BUP-10	BUP-20	BUP-40
Total entries	26.1±3.8	21.0±2.4	24.3±2.8	26.5±2.6	28.2±3.3	25.0±2.8	36.9±6.3
Open entries	13.5±4.9	6.10±1.4	6.90±1.6	11.3±2.1	10.0±1.7	11.1±1.6	21.1±6.7
Closed entries	12.7±1.7	14.9±1.7	17.4±1.7	15.2±1.0	18.2±2.7	13.9±2.7	15.8±2.1
% Open entries	42.5±8.9	29.2±5.3	26.6±4.1	39.7±4.2	37.0±4.9	48.8±7.0	50.9±8.7
% Open time	22.9±5.8	18.3±4.3	18.1±3.2	31.9±3.8	27.2±5.3	36.6±6.3	39.7±8.5
% Center time	39.0±4.2	43.2±3.4	42.7±4.2	35.9±5.0	33.0±3.3	35.1±4.0	27.7±4.0
Total HD	19.3±2.4	17.9±1.6	12.7±2.6	21.6±3.0	13.8±1.7	17.0±3.3	18.6±3.9
% p HD	52.8±8.8	64.2±6.0	67.1±7.7	54.2±7.0	52.0±8,1	42.7±9.3	36.4±9.3
Total SAP	8.50±1.2	8.20±0.4	8,20±0,5	8.90±0.3	10.3±0.4	10.9±0.5	9.40±1.6
% p SAP	40.7±9.7	59.0±9.0	46.4±8.8	23.0±8.0	24.4±9.8	29.7±65	36.8±3.2
Total rears	18.8±3.7	10.6±0.5	15.9±1.1	19.6±1.3	13.6±0.9	9.20±0.7^{+}	9.00±2.1^{+}

Data are presented as mean values±SEM. HD head dipping, SAP stretched attend posture, % p, percent protected
$^{+}P< 0.05$ vs VEH

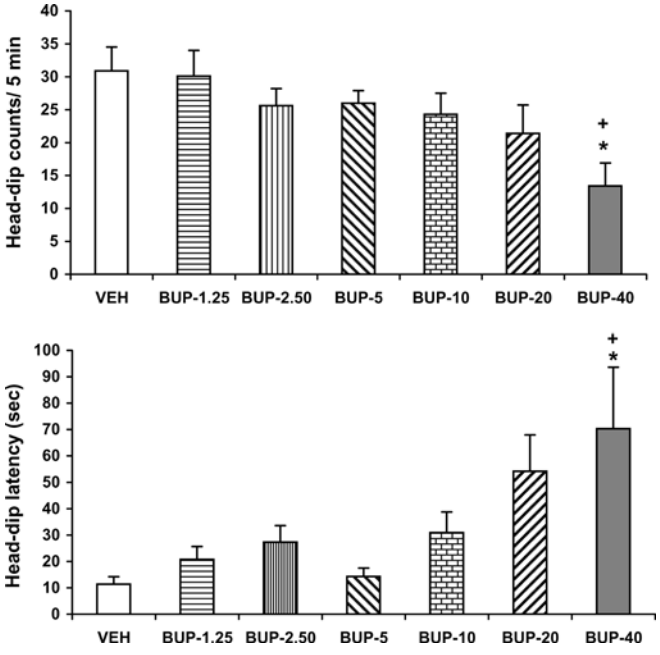

Fig. 3 Effects of bupropion on head-dipping behaviour (number of total counts in upper panel and latency to the first head-dip in lower panel) in mice tested on the hole-board apparatus (5 min). Mice were injected (IP) with vehicle (*VEH*) (n=11) or different doses of bupropion: 40 mg/kg (*BUP-40*) (n=12), 20 mg/kg (*BUP-20*) (n=10), 10 mg/kg (*BUP-10*) (n=10), 5 mg/kg (*BUP-5*) (n=10), 2.5 mg/kg (*BUP-2.5*) (n=10) and 1.25 mg/kg (*BUP-1.25*) (n=10). Thirty minutes later, exploratory behavior was assessed. Each column represents the mean±SEM. *P<0.05 vs VEH; + P< 0.05 vs BUP-1.25 and BUP-5

group-housed mice, in accord with previous reports indicating that it causes dose-dependent locomotor stimulation in rodents (Cooper et al. 1980; Zarrindast and Hosseini-Nia 1988), decreases immobility in the forced-swimming test (David et al. 2003; Zocchi et al. 2003) and in the tail-suspension test in some mouse strains (Ripoll et al. 2003).

Mice treated with the lower doses of bupropion (5 and 2.5 mg/kg) decreased locomotion in some temporal intervals. In previous studies, low doses of bupropion also induced no significant change or even a lower percentage of activity levels than controls in the forced swimming test in mice (Baizman et al. 1987). As these results underscore the importance of the dose of bupropion employed in behavioral studies, we are in agreement with Young and Glennon (2002), who have recently emphasized that research about effects produced by low doses of bupropion could aid in providing a more complete understanding of the pharmacology of this drug.

Effects of bupropion on isolation-induced aggression

During agonistic encounters, a decrease in body care was obtained with 40 mg/kg bupropion and in digging with 5, 10, 20 and 40 mg/kg. Changes in digging have been interpreted as reflecting anxiolytic or anxiogenic activity depending on the experimental situation. In some tests, such as "marble burying" or "defensive burying", in which mice are confronted with an aversive stimulus, an increase in digging seems to denote anxiety (Njung'e and Handley 1991; De Boer and Koolhaas 2003). Conversely, during social encounters increased digging and reactivity to unfamiliar environmental stimuli have been reported with some anxiolytic drugs (Cutler 1994).

In rodents, social interactions have been applied as a dependent measure for evaluating anxiolytic effects of drugs and an increase in this behavior has been considered to reflect less anxiety (File and Seth 2003). In our ethological analysis, bupropion did not influence social investigation, so there was no evidence of anxiolytic effect on this behavior. It was also observed that bupropion did not have significant effects on immobility. In fact, the median time allocated to this category was zero in all groups.

In regard to aggressive behavior, when all mice were considered jointly no significant differences were observed from control group. The most interesting results were obtained in the analysis of sub-groups of mice with long or short attack latencies. Longer attack latencies displayed in the pre-screening test may indicate a lower baseline level of irritability and a higher threshold to attack in this group of mice, as previously observed in other studies using similar classification to that employed in the present study (Martínez-Sanchis et al. 2003). As Fig. 2 shows, mice with "long attack latency" treated with bupropion (10 mg/kg and 40 mg/kg) attacked longer than vehicle-treated animals, suggesting that behavior exhibited in the pre-test could influence the effect of this drug on

aggression. A similar result has been previously reported with dopaminergic drugs (Rodriguez-Arias et al. 1998; Felip et al. 2001). Changes induced by bupropion in attack were not clearly dose-dependent, since no significant effects were obtained with 20 mg/kg. This dose increased non-social exploration in mice with long attack latency, which could be correlated with less time devoted to attack. It is worth mentioning that although some actions of bupropion (on locomotion, sniffing or body temperature) are dose-dependent (Zarrindast and Hosseini-Nia 1988), in other measures such as nicotine self-administration, more complex effects related to the dose have been described (Rauhut et al. 2004).

The need to consider individual differences in pharmacological studies on aggression has been previously underlined (Miczek et al. 2002). In the current study, mice have been classified in terms of their "attack latency", one of the most frequent measures used to assess aggressive behavior (Miczek et al. 2001; Moragrega et al. 2003) during a pre-screening test. In previous studies using mice with short and long attack latencies (SL and LL) obtained after selective breeding, differential expression of several genes, which may imply a different organization of the hippocampus in LL and SL mice, has been demonstrated (Feldker et al. 2003). It has also been reported that they differ in stress responsiveness of the hypothalamic–pituitary–adrenal system (Veenema et al. 2003). Differences in attack latency correlate with behavioral strategy toward environmental challenges, with LAL mice displaying a more passive coping style (Sluyter et al. 1996) and higher stress reactivity (Veenema et al. 2003). Although in the present study mice were not genetically selected and sub-groups of mice do not represent such extreme differences, it can be postulated that different coping styles in each group may be associated with differential sensitivity in drug-induced changes in the threshold to attack the opponent.

Effects of bupropion on the elevated plus-maze and the hole-board test In the plus-maze, the increases in entries and percentage of time spent in open arms is interpreted as an indicator of reduced anxiety (Rodgers et al. 1997). In our experiment, mice treated with bupropion did not display a significant increase in these parameters when compared with vehicle-treated mice. Some ethological measures of risk assessment may be useful to dissociate drug effects of anxiety from effects on locomotion (Weiss et al. 1998) and may also provide more consistent results than classic spatio-temporal measures obtained in the plus-maze (Belzung and Griebel 2001). Ethological measures indicated that there was no significant decrease in total SAP or in the percentage of protected SAP and HD, effects interpreted as indicators of anxiolytic activity (Rodgers et al. 1997). These results would suggest that bupropion did not display a clear anxiolytic-like profile in OF1 male mice. These data agree with other reports which have found no anxiolytic effects of other antidepressants in different animal models of anxiety (Borsini et al. 2002; Holmes and Rodgers 2003).

The number of head-dips in the hole-board is considered a useful parameter for the evaluation of anxiety, anxiolytic drugs being reported to increase the number of head-dips and anxiogenic drugs to decrease them (Takeda et al. 1998). Effects of a high dose of bupropion on head dipping found here were very similar to those induced by some anxiogenic drugs. Some authors have described a dissociation between locomotor activity and number of hole visits in the hole board (Van Gaalen and Steckler 2000). Our findings indicate that lower doses of bupropion (10 mg/kg and 20 mg/kg) which induced hyperactivity in the actimeter (10 mg/kg and 20 mg/kg) had no significant effects on head-dipping, supporting the claim of Boissier and Simon (1962) that head-dipping provides an exploration measure distinct from ambulatory behavior. In fact, this apparatus is more complex than cages used in the actimeter and reduced exploratory activity would indicate anxiety and poor adaptation to a more provocative environment (Vaglenova et al. 2004).

It can be concluded that there were some differences in effects of bupropion under different experimental paradigms, namely social interaction, plus-maze, and hole-board tests. This would support the suggestion that the modeling of anxiety depends on the tests used (Ohl 2003). Responses observed in different paradigms could be influenced by genetic and environmental factors. Thus, housing conditions (isolation in the social interaction test and group-housing in the plus-maze and hole-board) may influence behavioral changes induced by bupropion. Additionally, in the plus-maze, mice are alone in a novel environment, in comparison with the situation encountered in a social interaction test (Elliott et al. 2004). In the present study, bupropion had no clear actions on anxiety-like behavior in any of these tests. In contrast, in the hole-board a high dose had similar effects to those induced by anxiogenic drugs. Although both the plus-maze and hole-board depend on the free exploration of novel environments, the plus-maze is based on the natural aversion of rodents for the open arms, whereas in the hole-board novelty seeking and exploratory drive intervene (Van Gaalen and Steckler 2000). Thus, specific procedures employed may explain some of the differences in the sensitivity for the actions of bupropion on anxiety.

The present findings underline the fact that effects of bupropion on isolation-induced aggression are related to baseline behavior exhibited by mice in a pre-screening aggressive encounter. The division of mice into two subgroups, which can be displaying different thresholds of attack, increased the sensitivity of the measures used to detect the effects of bupropion on aggressive behavior, confirming that the basal level of aggressiveness in mice may be a factor which influences drug effects on isolation-induced aggression (Lumley et al. 2004). In the current study, the behavioral profile observed during agonistic encounters indicates that acute bupropion may have a pro-aggressive effect on mice with a higher threshold to attack. Considering our results, it might be interesting in future studies to determine whether there could be differences in other animal models between mice displaying different

thresholds to attack, which could aid in obtaining a more consistent profile of behavioral actions of bupropion. As previously pointed out (Miczek et al. 2001), these studies on the behavioral biology of aggression can aid us to better understand the neurobiological and molecular mechanisms which mediate social conflict.

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