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Original article

Bupropion induces social anxiety in adolescent mice: Influence of housing conditions

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ABSTRACT

Background: The antidepressant bupropion has received increasing attention as a pharmacological tool to treat addiction although little is known about its effects on social behaviour in adolescents. The present study aimed to evaluate if environmental housing conditions influence bupropion's actions on social behaviour of adolescent mice.

Methods: Mice were either group- or individually housed for 2-weeks and then randomly divided into 2 cohorts: half of the mice remained in the initial housing condition and the other half were changed to isolated conditions for further 2-weeks. The following groups were compared: isolated/isolated (ISO/ISO), isolated/group-housed (ISO/GR), group-housed/isolated (GR/ISO), and group-housed/group-housed (GR/GR). The effects of bupropion (40, 20, 10 mg/kg) or saline on social interaction were assessed for each housing condition. Social encounters were evaluated using ethological analysis.

Results: Data showed significant effects of bupropion on grooming and digging. This drug diminished time mice allocated to these behavioural categories in all housing conditions. In ISO/GR and GR/ISO conditions, bupropion increased environmental exploration (non-social exploration and exploration from a distance), reduced social investigation and increased avoidance/flee and defence/submission behaviours. An augment of avoidance/flee during social interactions was observed in bupropion-treated mice in GR/GR housing condition.

Conclusion: These results suggest that this drug exhibits anxiogenic-like properties in social encounters between adolescent mice, especially when a transition in housing conditions has been experienced during this period. Changes in housing conditions may be a useful model for evaluating the effects of bupropion on social behaviour and the role of environmental housing conditions.

Introduction

It is known that a lack of appropriate stimulation during development can have important consequences on neural maturation. Increasing experimental evidence suggests that environmental conditions have a clear influence on emotionality [1]. Adolescence is a time of brain maturation during which there are critical neurobiological changes in the regulation of social behaviour [2]. This period is sensitive to affective-related disorders and the risk of problems of maladaptation augments, including alterations in social behaviour, stress control and drug addiction [3,4]. Isolation rearing is a paradigm commonly applied for studying the influence of environmental conditions on social behaviour in rodents [5]. Deprivation of social contacts in mice induces changes in neuroplasticity although its effects depend on the timing of housing conditions [6]. The age at which the social isolation is initiated seems to be a critical factor and early isolation elicits neurobiological and behavioural changes that continue into adulthood [7]. Social isolation during adolescence has been proposed as an animal model for identifying vulnerability to anxiety disorders [8] and for researching developmental psychopathology [9]. One pharmacological treatment that has received increasing attention in the area of addiction is the antidepressant bupropion, a monoamine (dopamine and norepinephrine) reuptake inhibitor transporter [10,11] and non-competitive antagonist of nicotinic acetylcholine receptors [12]. Bupropion is used for the

Abbreviations: BUP, Bupropion; BUP-10, 10 mg/kg of bupropion; BUP-20, 20 mg/kg of bupropion; BUP-40, 40 mg/kg of bupropion; GR/GR, group-housed/group-housed; GR/ISO, group-housed/isolated-housed; *ip*, : intraperitoneal injection; ISO/ISO, isolated-housed/isolated-housed; ISO/GR, isolated-housed/group-housed; PND, post-natal day; SAL, physiological saline.

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treatment of dependence on tobacco and of different drugs of abuse [13–15].

Earlier evidence indicates that acute administration of bupropion antagonizes muricidal behaviour and augments latency to mouse-killing in rats [16]. In mice, chronic treatment with this drug did not to induce effects in the clonidine-induced aggression model [17]. Bupropion increases attack during social interactions in mice with lower aggression levels [18] although it didn't have significant influence on aggression in group-housed adults [19] or on the time devoted to social investigation [18], but following a 2-weeks of social isolation adolescents were more sensitive to bupropion than individually-housed adults [20]. Previous findings support investigating bupropion's effects on social behaviour and the modulatory influence of housing conditions in adolescent rodents since no prior study has evaluated the effects of this drug when housing conditions change. Indeed, little it is known concerning the consequences of early exposure to bupropion on social behaviour and no studies have evaluated the influence of the re-socialization of adolescents on the effects of bupropion.

The main aim in this work was to evaluate if environmental housing conditions influence bupropion's effects on social behaviour of adolescent mice. We also intend to investigate the impact of transition between different housing conditions since this factor may be relevant for future investigations including the isolation of experimental animals. The evaluation of this animal model during adolescence may be particularly useful since it is a developmental period characterized by vulnerability to psychiatric disorders and drug addiction and, consequently, of the initiation to pharmacological treatments.

Materials and methods

Subjects

OF1 male mice (Charles-River, Spain) aged 24 days (post-natal day, PND-24) on arrival at the laboratory were used. Animals were randomly assigned to isolated or group-housed conditions: i.e. 72 subjects were individually-housed in cages (24 × 13.5 × 13 cm) and 78 group-housed in 5 per cage (25 × 25 × 15 cm). After 2-weeks, half the subjects were maintained in the same housing condition (isolated-housed *vs.* group-housed) and the remainder were challenged by the other housing condition (group-housed *vs.* isolated-housed), in both cases for a period of 2-weeks before test. 200 grouped mice were rendered anosmic (intranasal lavage with 4% zinc-sulphate solution) 1-day before test and used as "standard opponents".

Drugs

Bupropion hydrochloride (Sigma–Aldrich, Spain) was dissolved in physiological saline (SAL). Mice received 30-min before testing 40, 20, 10 mg/kg (BUP-40, BUP-20, BUP-10, respectively) or SAL by intraperitoneal injection (*ip*) in a volume of 10 ml/kg. Doses employed are habitually used to assess the effects of burpopion in rodents [18,21,22].

Procedure

Mice (PND-24) were distributed into two groups on arrival at the laboratory: half the mice were housed during 2-weeks in groups of five and the rest were housed individually. In a second phase initiated on PND-38, subjects were allocated to different groups. Group-housed/group-housed (GR/GR): mice remained group-housed for 4-weeks (PND 24-52); group-housed/isolated-housed (GR/ISO): mice remained group-housed for 2-weeks (PND 24-37) and then individually-housed for 2-weeks (PND 38-52); isolated-housed/isolated-housed (ISO/ISO): mice were individually-housed for 4-weeks (PND 24-52); isolated-housed/group-housed (ISO/GR): mice individually-housed for 2-weeks (PND 24-37) and then group-housed for 2-weeks (PND 38-52). At the end of the housing periods, mice received acute treatment with BUP40, BUP20, BUP10 and SAL, and the 16 groups were evaluated in the social interaction test (Fig. 1).

Social interaction test

Social encounters took place in a neutral cage (60 × 33 × 30 cm) in which mice were confronted during 10-min with a "standard opponent" after 1-min of adaptation to the apparatus. Responses were video-recorded during the social interaction test: grooming, digging, non-social exploration, exploration from a distance, social investigation, threat, attack, avoidance/flee, defence/submission and immobility (more detailed explanation of categories in [23,24]). After each encounter, the apparatus was cleaned (ethanol and water) and the sawdust bedding was changed. The responses during social encounters were examined by a trained observer blind to the treatment using a custom-developed "Raton-time" software [25,26], a program that allows ethological analysis of behavioural categories [18,20,23].

Statistical analyses

The time allocated to each behavioural category is indicated as a median with ranges. Due to great variability in the expression of each behavioural category, data were not normally distributed and only drug effects were analyzed and housing conditions were not compared directly. Data were analyzed using Kruskal-Wallis test and two-tailed Mann-Whitney *U*-test at a significance of $p < 0.05$.

Results

Analysis revealed a main effect of Treatment in the following categories: grooming [$\chi^2 = 65.674$ df = 15 $p < 0.001$], digging [$\chi^2 = 60.902$ df = 15 $p < 0.001$], non-social exploration [$\chi^2 = 62.471$ df = 15 $p < 0.001$], exploration from a distance [$\chi^2 = 35.425$ df = 15 $p < 0.002$], social investigation [$\chi^2 = 38.057$ df = 15 $p < 0.001$], threat [$\chi^2 = 67.320$ df = 15 $p < 0.001$], attack [$\chi^2 = 53.886$ df = 15 $p < 0.001$], avoidance/flee [$\chi^2 = 45.630$ df = 15 $p < 0.001$], defence/submission [$\chi^2 = 45.564$ df = 15 $p < 0.001$].

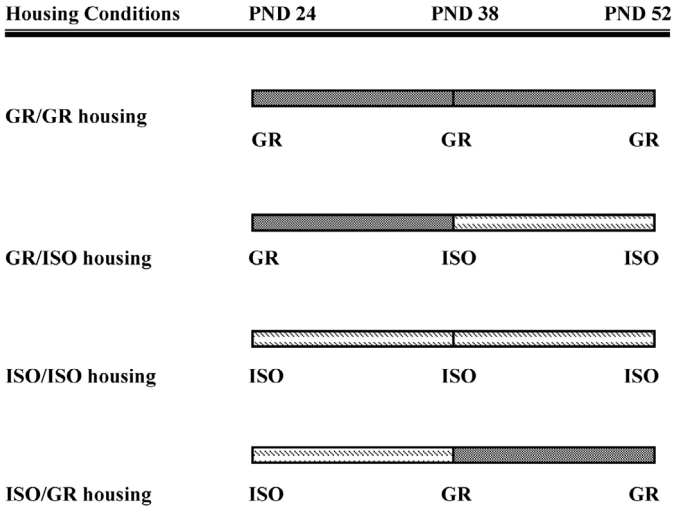

Fig. 1. Experimental design of the experimental procedure. At the end of the housing periods (PND 52) mice received acute treatment with BUP-40, BUP-20, BUP-10 and SAL and were assessed in a social interaction test.