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Original article

Adolescent and adult mice display differential sensitivity to the effects of bupropion on the acquisition of a water maze task

Carmen Gómez, Carmen Carrasco*, Rosa Redolat

Departamento de Psicobiología, Facultad de Psicología, Universitat de València, Blasco Ibañez, 21, Valencia 46010, Spain

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ABSTRACT

Background: Adolescence is characterized by major neurobiological changes, and the effects of some psychoactive drugs seem to differ between adolescents and adults. Bupropion, an antidepressant that is also used to treat nicotine addiction, induces behavioral actions in both adolescent and adult rodents. However, the effects of this drug on spatial ability have not been compared in animals at different stages of their development. The present study was conducted to assess the effects of bupropion on spatial learning and memory in adolescent and adult mice.

Methods: Adolescent (post-natal day: PND35-36) and adult (PND >65) NMRI mice received bupropion (10, 20 and 40 mg/kg) or saline during the acquisition (4 trials/day on 5 consecutive days) of a Morris water maze (MWM) task. Retention was evaluated with a probe trial performed after the acquisition phase.

Results: Data showed that age did not affect performance of the task. However, the factor Drug treatment reached statistical significance, with high doses of bupropion (40 and 20 mg/kg) impairing acquisition of the MWM test in adolescents. The drug did not induce detrimental effects on the acquisition or retention of the task in adults.

Conclusion: Bupropion impairs acquisition of the spatial task in adolescent but not in adult mice. It does not seem to alter retrieval of previously acquired spatial information in either adolescents or adults. Our findings suggest that, during the adolescent period, mice are more vulnerable to the actions of bupropion on spatial learning.

Introduction

Adolescence is a developmental period in which important neurobiological changes take place. At this age individuals are particularly sensitive to the development of comorbid patterns of psychiatric problems and substance abuse disorders [1]. Recently, different studies have reported a frequent comorbidity between mood disorders and tobacco dependence in adults [2] and adolescents [3]. The antidepressant bupropion is used as an aid for nicotine cessation in both adult and adolescent smokers [4,5] and there are suggestions that it could also be applied as a pharmacological treatment for disorders associated with cognitive deficits such as major depression [6] or attention deficit hyperactivity disorder in children and adolescents [7].

Bupropion is characterized by norepinephrine-dopamine reuptake inhibition, but it also acts as a nicotinic acetylcholine receptor (nAChR) antagonist and indirectly on serotonin metabolism [8–10]. Preclinical studies indicate that bupropion improves memory in nicotine-abstinent mice [11], although it can also impair learning in a dose-dependent manner [12]. Some studies using both classical conditioning and discrimination operant tasks have demonstrated that bupropion induces actions similar to nicotine [13,14] and replaces the interoceptive effects induced by nicotine in operant and paulovian tests [15,16]. Recently, Kruk-Słomka et al. [17] used the novel object recognition test to demonstrate that bupropion attenuated nicotine-induced memory improvement and scopolamine-induced memory deficit in mice. Bupropion also improved performance of an inhibitory avoidance task [18] and learning processes during an active avoidance test, but this

Abbreviations: BUP, bupropion; BUP10, 10 mg/kg of bupropion; BUP20, 20 mg/kg of bupropion; BUP40, 40 mg/kg of bupropion; HSD, honestly significant-difference; MWM, Morris water maze test; nAChR, nicotinic acetylcholine receptor; NE, north east; NW, north west; PND, post-natal day; SAL, physiological saline; SE, south east; SW, south west.

* Corresponding author.
E-mail addresses: m.carmen.gomez@uv.es (C. Gómez), carmen.carrasco@uv.es (C. Carrasco), rosa.redolat@uv.es (R. Redolat).

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antidepressant did not enhance retention of the task in "expert" mice, indicating that its effects on emotional memory are mediated by the mnemonic performance basal level of each animal [19].

Data regarding the effects of bupropion on spatial learning and memory are limited. In the APP23 transgenic mouse model of Alzheimer's disease, bupropion (20 mg/kg) did not improve spatial learning in a complex dry-land maze [20]. In the Morris water maze task (MWM), a paradigm commonly used to assess hippocampal-dependent spatial learning in rodents [21], bupropion (20 mg/kg) reduced escape latencies during the training period in nicotine-dependent rats [22]. However, applying the same animal model, no differences between the control group and mice treated with bupropion alone (10 mg/kg) or with a combination of caffeine and bupropion (5 mg/kg) were observed [23]. The developmental effects of bupropion have also been the subject of little research, and no studies have compared the effects of this drug on spatial learning in adolescents and adults. It has been shown that the age at which bupropion is administered can influence the behavioral effects induced by this drug. For instance, a previous work concluded that the influence of bupropion on anxiety-like behavior in mice depends on age, showing adolescents to have an anxiogenic-like profile in the elevated plus-maze, unlike adults [24]. In contrast, it was reported that this drug exerted comparable locomotor actions in both age groups [25].

Taking into account that the influence of bupropion on spatial learning is still unclear and no prior research has evaluated the age-related differences of this drug on spatial learning, the main aim of the present study was to evaluate age-related differences in the behavioral effects of bupropion on spatial learning comparing the acquisition and retention of the MWM test in adolescent and adult mice treated with bupropion. Data obtained could be of interest for better understanding neurobiological effects of this drug at different ages, Moreover, findings obtained may have clinical implications related to the use of bupropion on neuropsychiatric disorders and tobacco cessation in adolescents.

Material and methods

Animals

Eighty-four male NMRI mice were used as experimental subjects. On their arrival at the laboratory, young mice were 23 days of age (post-natal day or PND 23) and adults PND 52. Animals were kept under standard laboratory conditions with a reversed 12 h light/dark cycle (lights on: 19:30 h), a constant temperature (21 ± 2 °C) and relative air humidity (55–60%). They were housed in groups of five with water and standardized food available *ad libitum*. NMRI mice were selected because this strain performs well in learning and memory tasks [19,26,27]. All procedures complied with the "principles of laboratory animal care" and with international guidelines (EU Directive 2010/63/EU) for the care and treatment of animals.

Drugs

Mice received bupropion hydrochloride (Sigma-Aldrich) dissolved in physiological saline to obtain the concentration for each dose (10, 20 and 40 mg/kg). Injections were administered intraperitoneally at volumes of 10 ml/kg. Adolescent (n = 44; 11 mice per group) and (n = 40; 10 mice per group) adult mice were divided into four groups according to the doses of bupropion received: 10 mg/kg (BUP10); 20 mg/kg (BUP20); 40 mg/kg (BUP40) or physiological saline (SAL) employed as vehicle. A total of 8 groups were evaluated in the current study. The doses were selected based on prior research about the behavioral effects of bupropion in mice [24,25,28,29] and are in the range of doses normally employed to examine behavioral effects in rodents [11,30].

Apparatus and procedure

Spatial learning was tested in a MWM task [21] adapted for mice. The maze was made of black Plexiglas (1 m diameter and 30 cm high) and was filled with water to a depth of 15 cm and maintained at 24 ± 1 °C. A small transparent platform (6 × 6 cm) submerged 1 cm below the surface of the water was located in the centre of an arbitrarily determined quadrant of the maze (NW: target quadrant). The position of the hidden platform remained constant throughout the experiment. The correct acquisition of the task requires animals to swim from the starting position to the hidden platform, so that they remember the location of the platform using extra-maze cues.

All experimental procedures were carried out during the dark phase of the light/dark cycle, and were similar to those described in previous studies [31,32]. Animals were used for experiment at the end of an adaptation period (13–14 days) to laboratory conditions. Adolescent (PND35-36) and adult (PND > 65) mice performed 4 trials per day on 5 consecutive days, as reflected in Table 1.The mouse was placed on the platform for 30 s before the first test and was then introduced into the pool for 60 s. If the animal reached the escape platform, it was left on it for 30 s. If unable to do so, the mouse was put on the platform by the experimenter and allowed to remain on it for 30 s. The inter-trial interval lasted 30 s, during which the mice were housed in an individual cage. The escape latency or time to reach the submerged platform was assessed during the training sessions. At the end of the fourth trial of the fifth daily session, retention of the task was tested with a probe trial, during which the platform was removed and mice were allowed to swim freely for 60 s. The total time spent in each quadrant was registered with the purpose of comparing the time spent searching in the North West (NW) target quadrant, where the hidden platform was located, with the time spent in the other quadrants (NE, SE, SW). During training sessions and the probe trial test, the animals' performance was recorded using a video camera and analyzed using "Raton Time" software.

Statistical analysis

Differences in task acquisition between groups were assessed by two-way analysis of variance (ANOVA) with Age (adolescents and adults) and Drug treatment (BUP10, BUP20, BUP40, SAL) as between-subject factors and Day (1–5 days) and Trial (1–4 trials) as within-subject factors. ANOVAs were also performed to evaluate the data of the probe trial, with Age and Drug treatment as between-subject factors and Quadrant (NW, NE, SE, SW) as within-subject factor. *Post-hoc* Tukey's HSD (honestly significant-difference) test comparisons were conducted when appropriate. In all cases, a $p < 0.05$ was considered as significant.

Table 1
Start positions in the Morris water maze during acquisition sessions (1–5 days) and probe trial.

Acquisition				
Day	Trial 1	Trial 2	Trial 3	Trial 4
1	NE	SW	SE	NW
2	SE	NE	NW	SW
3	NW	SE	SW	NE
4	SW	NW	NE	SE
5	NW	SE	NW	NE
Probe trial	SE			