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Differential effects of bupropion on acquisition and performance of an active avoidance task in male mice

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ABSTRACT

Bupropion is an antidepressant drug that is known to aid smoking cessation, although little experimental evidence exists about its actions on active avoidance learning tasks. Our aim was to evaluate the effects of this drug on two-way active avoidance conditioning. In this study, NMRI mice received bupropion (10, 20 and 40 mg/kg) or saline before a daily training session (learning phase, days 1–4) in the active avoidance task. Performance was evaluated on the fifth day (retention phase): in each bupropion-treated group half of the mice continued with the same dose of bupropion, and the other half received saline. Among the vehicle-treated mice, different sub-groups were challenged with different doses of bupropion. Results indicated that mice treated with 10 and 20 mg/kg bupropion exhibited more number of avoidances during acquisition. The response latency confirmed this learning improvement, since this parameter decreased after bupropion administration. No differences between groups were observed in the retention phase. In conclusion, our data show that bupropion influences the learning process during active avoidance conditioning, suggesting that this drug can improve the control of emotional responses.

1. Introduction

Bupropion is an antidepressant that has shown to be effective in the treatment of tobacco dependence (Hughes et al., 2014) and it is included in the seven first-line pharmacological agents for smoking cessation (Hudmon et al., 2010). In addition, bupropion is a candidate for treatment of psychostimulant drug abuse (Castells et al., 2010; Schindler et al., 2011), cannabis addiction (Penetar et al., 2012), pathological gambling (Dannon et al., 2005), or excessive online game playing (Han and Renshaw, 2012). The treatment with naltrexone plus bupropion may also be useful for overweight and obesity (Greenway et al., 2010; Yanovski and Yanovski, 2015).

Cognitive effects of bupropion have been reported in children and adults with attention deficit hyperactivity disorder (ADHD) (Clay et al., 1988; Wilens et al., 2005) and in patients with major depression (Herrera-Guzmán et al., 2008; Gorlyn et al., 2015), suggesting that bupropion treatment could improve neuropsychological functioning in these patients. However, some inconsistencies regarding cognitive effects of this drug have been reported. For example, acute treatment with the antidepressants bupropion and sertraline had no detectable effects on the retrieval of emotionally arousing material learned one week prior to testing in healthy adult subjects (Carvalho et al., 2006). In contrast, bupropion improves cognitive performance after overnight smoking abstinence in healthy adult smokers (Perkins et al., 2013a).

The neuropharmacological actions of bupropion indicate that this agent has an atypical antidepressant profile sharing some similarities with traditional psychostimulants (Dwoskin et al., 2006). The drug is a relatively weak dopamine-uptake inhibitor which also inhibits firing of locus coeruleus norepinephrine (NE) neurons at high concentrations (Cooper et al., 1994). Bupropion also inhibits the function of the dopamine and NE transporters (Dwoskin et al., 2009). The effectiveness of bupropion (and/or its hydroxy metabolites) in the treatment of nicotine dependence has been related to its effects on mood, which are mediated by enhancement of noradrenergic and dopaminergic signals, as well as to its effects on NE transporters and on members of the diverse family of nicotinic cholinergic receptors (nAChRs) (Damaj et al., 2004). It has been reported that bupropion acts as a non-competitive nicotinic receptor antagonist (Arias, 2009; Slemmer et al., 2000), which could contribute to their efficacy as an antidepressant and as a smoking cessation agent (Dowskin et al., 2006). However, the mechanisms

Abbreviations: ADHD, attention deficit hyperactivity disorder; BUP, bupropion; IP, intraperitoneally; ITI, intertrial interval; nAChRs, nicotinic cholinergic receptors; NE, norepinephrine; US, unconditioned stimulus; VEH, vehicle.

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by which it increases abstinence rates in smokers are not clear (Perkins et al., 2013b; Wright and Rodgers, 2013).

Monoamine neurotransmitter systems are involved in the regulation of mood and cognition (Booij et al., 2003; Hamon and Blier, 2013), suggesting that monoamine-elevating medications may be useful for emotional and cognitive improvement. There is, for example, evidence of the positive effects of antidepressant treatment on synaptic plasticity in cortical and subcortical brain circuits related with mood disorders and memory (Castrén and Hen, 2013; Sairanen et al., 2007). In animal models, bupropion has been found to induce place preference (Ortmann, 1985; Rauhut et al., 2008), to improve performance in a novel object recognition task (Kruk-Słomka et al., 2014), to disrupt latent inhibition measured in a conditioned emotional response (Lipina and Roder, 2010), to facilitate extinction of avoidance responses in a lever-press avoidance task in animals with innate vulnerability to anxiety (Jiao et al., 2014). Bupropion also improves the retrieval of an inhibitory avoidance response (Barros et al., 2002) and reverses the reserpine-induced impairment in conditioned avoidance response when administered at 40 mg/kg (Nakagawa et al., 1997), although this drug failed to alter the conditioned place preference induced by nicotine (Rauhut et al., 2008). However, the administration of a low dose of bupropion (5 mg/kg) reverses nicotine withdrawal-associated deficits in contextual fear conditioning, whereas high doses (20 or 40 mg/kg) induce deficits in contextual and cued fear conditioning (Portugal and Gould, 2007). In a Pavlovian fear learning task, Carmack et al., (2014) have recently reported that bupropion induced long-term memory-enhancing effects. This cognitive improvement was similar to that observed for animals treated with the psychostimulant methylphenidate, an agent used as a cognitive enhancer for a diversity of disorders, in particular as treatment for ADHD (Carmack et al., 2014).

Despite of these findings obtained in animal models, limited work has evaluated effects of bupropion on learning and memory tasks. Specifically, its direct actions on an active avoidance conditioning using a two-way shuttle box model have not been previously studied. Therefore, our aim was to evaluate the effects of varying doses of bupropion on acquisition and performance in a two-way active avoidance task. Preclinical previous research has been reported memory-enhancing effects of bupropion using different animal models, however, no study has yet examined whether the two-way active avoidance conditioning can be improved with bupropion treatment in mice. This animal model is based on the acquisition of a relatively complex learning task that requires the control of emotional responses.

Recent evidence indicates that during the active avoidance response both emotional and motivational circuitries contribute to the acquisition of the task: the amygdala plays a central role in the emotional circuitry whereas different midbrain dopaminergic structures integrate the motivational circuitry (Ilango et al., 2014). The two-way active avoidance conditioning task can be useful for gathering information about the behavioral responses displayed by the animal both during the acquisition and the retention phases. These data could provide information regarding differential effects of the drug on learning and emotional memory.

2. Material and methods

2.1. Animals

Sixty male NMRI mice (Charles River, Barcelona, Spain) weighing 26–28 g were used for the experiment. The animals were housed five per cage under standard laboratory conditions, with food and water ad libitum, and exposed to a reversed 12:12 h light/dark cycle (lights off at 8:00 h). NMRI mice were selected since this strain performs well in different learning paradigms (Ghaderi et al., 2015; Moragrega et al., 2005). All procedures complied with the "principles of laboratory animal care" and international guidelines (EU Directive 2010/63/EU) for the care and treatment of animals.

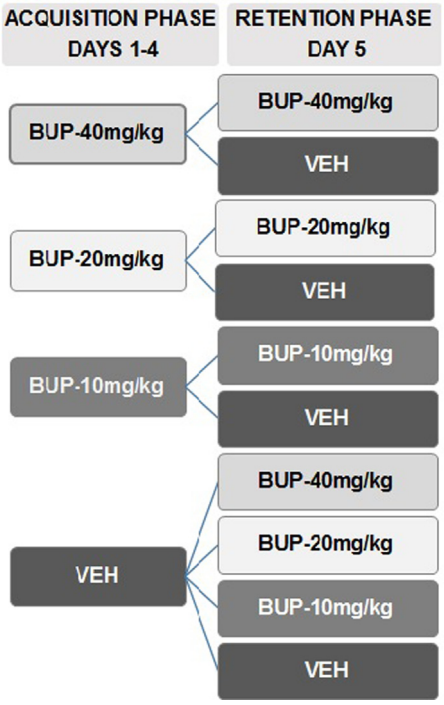

Fig. 1. Experimental design, including the acquisition and retention phases of the study. In the retention phase, half of the mice in each bupropion-treated group continued with their dose of bupropion and the other half began to receive saline.

2.2. Drugs

Bupropion hydrochloride (Sigma–Aldrich, Madrid, Spain) was dissolved in physiological saline. During acquisition phase (1–4 days), bupropion (40, 20, 10 mg/kg) or the vehicle was administered intraperitoneally 30 min before each daily shuttle box training session. In the performance session or retention phase (5 day), half of the mice in each bupropion-treated group ($n = 12$) continued with their dose of bupropion and the other half began to receive saline. This treatment challenge was performed in order to differentiate effects of drug on performance and acquisition. In this session, the control group ($n = 24$) was subdivided into four groups which received 10, 20, 40 mg/kg of bupropion or vehicle (see experimental design in Fig. 1).

The doses employed in the current research were selected on the basis of previous studies about the effects of bupropion in NMRI mice (Carrasco et al., 2004, 2013; Gomez et al., 2009a,b; Redolat et al., 2005a,b) and are in the range of doses habitually used to assess behavioral effects of bupropion in rodents (Biała and Kruk, 2009; Lipina and Roder, 2010; Randall et al., 2014).

2.3. Apparatus and procedure

Mice were trained in an automated two-way shuttle-box (45 × 24.5 × 19 cm) (Shuttle Scan, Model SC-II, OMNITECH, Columbus, OH) which was placed in a sound-attenuating box in order to avoid disturbances. A light (6 w) was used as conditioned stimulus, preceding by 10 s the onset of the unconditioned stimulus (US) and overlapping it for 10 s. The US consisted of an electric shock (0.3 mA) applied to the grid floor, which was formed by stainless steel bars. The box was divided into two compartments with a white