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Dose related effects of buspirone on pain, learning / memory and food intake

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ABSTRACT

The present study concerned extending the therapeutic use of buspirone for treating pain and improving cognition. Effects of single and repeated administration of buspirone were therefore monitored on pain threshold in the hot plate test and on spatial memory in the water maze test in rats. Effects on cumulative food intake were also monitored. The drug was administered intraperitoneally in doses of 0.1, 0.3, 1.0 and 2.0 mg/kg. We found that single and repeated administration of buspirone in doses of 0.1 mg/kg decreased pain threshold in the hot plate test, while doses of 1.0 and 2.0 mg/kg increased it. Effects of single and repeated administration were not different. A dose of 0.3 mg/kg had no effect. Food intake increased following single as well as repeated administration of 0.1 mg/kg buspirone; higher doses had no effect. Low doses (0.1 and 0.3 mg/kg) improved acquisition and retention of memory in the water maze test, while memory extinction was reduced. Higher doses had either no effect (1.0 mg/kg) or impaired (2.0 mg/kg) performance in this test. The results suggest potential therapeutic use of selected doses of buspirone as an analgesic and nootropic drug.

1. Introduction

The importance of drug repurposing, a process of identifying new therapeutic uses of previously approved drugs, is becoming increasingly recognized by researchers in academia and the pharmaceutical industry. These studies reduce the time and cost involved in drug discovery because data on pharmacology and toxicology of an approved drug are already available (Lee and Kim, 2016). Drug repurposing studies targeting buspirone, an azapirone derivative, support a role of buspirone in preventing and treating drug abuse and addiction (Haleem, 2013; Leggio et al., 2016). Co-used with typical antipsychotics, it can prevent extrapyramidal symptoms and ameliorate negative symptoms of schizophrenia (Haleem et al., 2004, 2007a; b; Haleem, 2015). Clinical studies show that co-use of buspirone with typical or atypical antipsychotics is effective in reducing negative symptoms in patients with chronic schizophrenia (Ghaleiha et al., 2010; Sheikhmoonesi et al., 2015). In a recent study, we have shown that co-use of buspirone can reduce morphine abuse and hyperalgesia (Haleem and Nawaz, 2017) suggesting that it can also modulate pain transmission.

Buspirone, synthesized in 1968, became commercially available for the treatment of generalized anxiety disorder in 1986 (Apter and Allen, 1999). It is also effective in the treatment of depression either alone or in combination with an antidepressant drug (Howland, 2015). Buspirone has affinity for 5-hydroxytryptamine (5-HT)-1A as well as dopamine receptors. It is a full agonist at 5-HT-1A autoreceptors present on soma and dendrites of serotonergic neurons and partial agonist at post synaptic 5-HT1A receptors (Loane and Politis, 2012). It also exhibits antagonist activity for dopamine D2 and D3 receptors (Bergman et al., 2013), but is more selective for dopamine D3 than D2 receptors (Di Ciano et al., 2017). Low doses of buspirone preferentially activate 5-HT1A autoreceptors in the raphe region, resulting in a decrease in 5-HT synthesis and release (Hiner et al., 1988; Mauk et al., 1988; Shireen and Haleem, 2005; Loane and Politis, 2012). A mixed 5-HT1A agonist and dopamine receptor blockade activity of buspirone makes it a useful tool for preventing antipsychotic drug-induced extrapyramidal symptoms and for treating negative symptoms of schizophrenia (Haleem, 2015).

The 5-HT1A receptors are G protein coupled receptor, activation of these receptors inhibits adenylyl cyclase resulting in a decrease in the intracellular concentration of cAMP (Rojas and Fiedler, 2016). Subsequent opening of potassium channels and closing of calcium channels produces an inhibitory influence on neuronal firing. The 5-HT1A receptors are present as autoreceptors on the cell body and dendrites of serotonergic neurons and, as heteroreceptors at the postsynaptic sites

Abbreviations: 5-HT, 5-hydroxytryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino) tetralin

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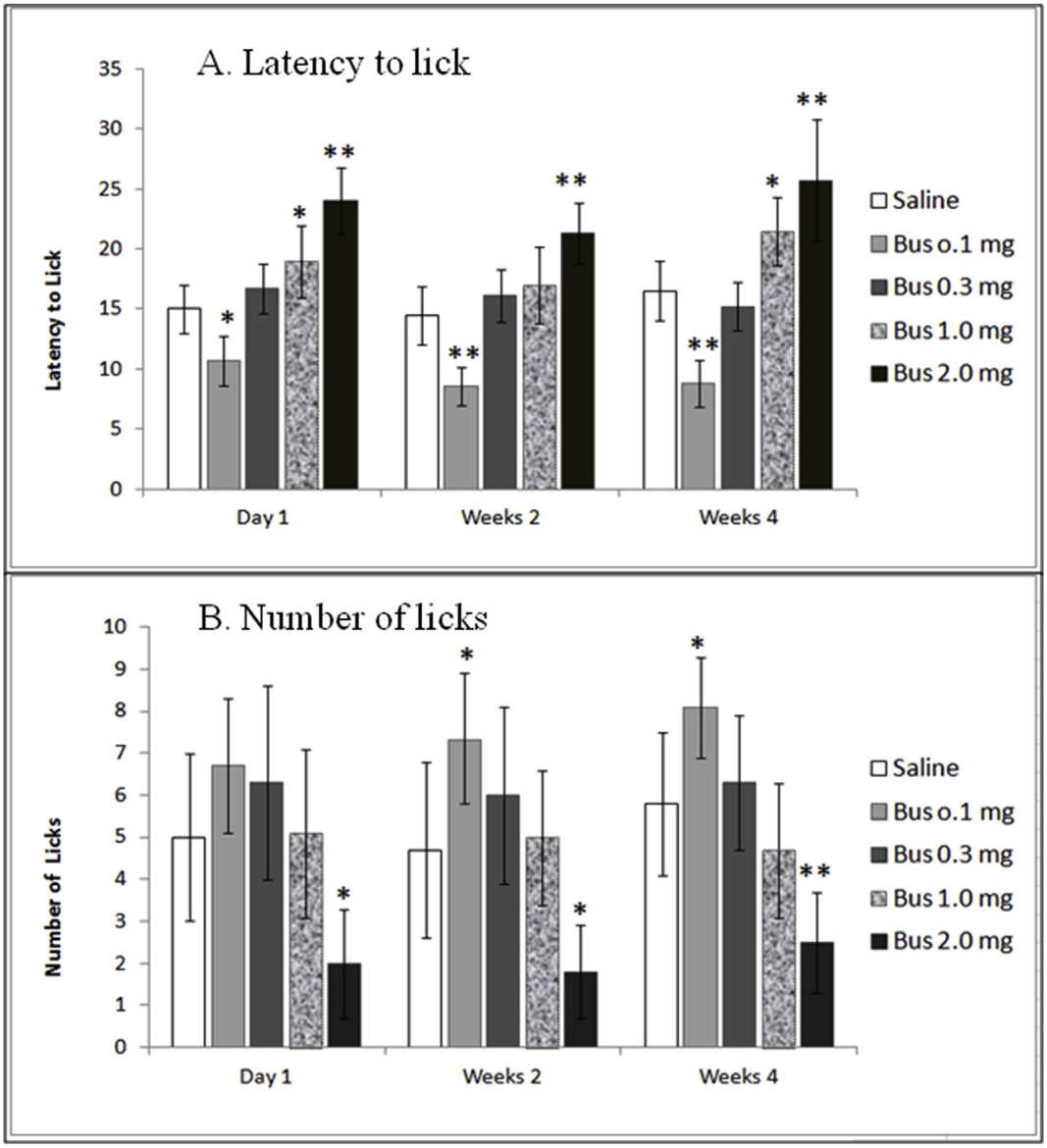

Fig. 1. Dose related effects of single and repeated administration of buspirone on pain perception. Values reported as latency to lick (A) and numbers of licks (B) are means ± SD 30 min after the injection. Significant differences by Tukey's test: *p < 0.05, **p < 0.01 from saline injected controls following two way ANOVA repeated measure design.

(García et al., 2014; Haleem, 2016). As autoreceptors, they provide feedback control over the synthesis and release of 5-HT. The activation of autoreceptors therefore decreases the availability of 5-HT at post-synaptic receptors. Activation of postsynaptic 5-HT1A receptors reduces the GABA mediated inhibitory influence on the activity of ventral tegmental area dopaminergic neurons (Haleem, 2013) to facilitate dopamine neurotransmission.

Evidence suggests that 5-HT1A receptors have a role in pain (Mico et al., 2006; Jeong et al., 2012), feeding behavior (Dill et al., 2013; Brosda et al., 2015) and learning and memory (Glikmann-Johnston et al., 2015; López Hill et al., 2017). To extend the potential therapeutic use of buspirone, the present study concerns dose related effects of single and repeated administration of buspirone on pain perception, food intake and learning and memory. The drug is administered in doses (0.1–2 mg/kg) that have been shown previously to preferentially activate pre and post synaptic 5-HT1A receptors (Shireen and Haleem, 2005; Loane and Politis, 2012).

2. Methods and materials

2.1. Animals and drugs

Animals used in the present study were male albino Wistar rats of weight ranging from 180 to 200 g. The animals were housed individually in a 12 h light-dark cycle, with lights turned on at 6: 00 a.m. and switched off at 6:00 p.m., 5 days before starting the experiment. The temperature of the housing room was kept 24 ± 2 °C. All animals had free access to standard rodent food and tap water. The experiments were conducted according to a protocol approved by the institutional Ethics and Animal Care Committee. All behavioral tests were monitored by a blind observer. Buspirone (Research Biochemicals Incorporated, USA) dissolved in saline was injected i.p. in doses of 0.1, 0.3, 1.0 and 2.0 mg/kg.