

ORIGINAL ARTICLE

DOSE RELATED EFFECTS OF BUSPIRONE ON SERUM ELECTROLYTE BALANCE, PLASMA OSMOLALITY AND SYSTOLIC BLOOD PRESSURE (SBP) IN RATS

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ABSTRACT

Buspirone is a potent anxiolytic that decreases serotonin transmission. Changes in electrolyte balance, plasma osmolality and systolic blood pressure are often associated with stress-induced anxiety in rats as well as in human but effects of buspirone on changes in serum electrolytes balance, plasma osmolality and SBP of rats has not been reported. Present study concerns the effects of different doses of buspirone (0.25, 0.5, and 1mg/kg) on serum electrolyte, plasma osmolality and systolic blood pressure (SBP) of rats. Anxiolysis related variable are also monitored. Results show that the administration of buspirone (0.25mg/kg and 0.5mg/kg) significantly increased the serum concentration of electrolytes and plasma osmolality but decreased the serum level of magnesium. These doses also reduced the systolic blood pressure (SBP). A dose of 1mg/kg buspirone produced no effect on the concentration of serum electrolytes, and plasma osmolality. Anxiolytic effects of the drug were dose dependent but 1mg/kg dose decreased the effect. The results are discussed in the context of serotonin receptors (5-HT_{1A}) to be involved in buspirone-induced changes of electrolytes, SBP and plasma osmolality.

Keywords: Stress-induced anxiety, buspirone, electrolytes changes, systolic blood pressure and plasma osmolality.

INTRODUCTION

Buspirone a partial agonist of (5-hydroxy tryptamine) 5-HT_{1A} reduced anxiety in human and as well as in rats (Viadya *et al.*, 2005; Griebel *et al.*, 1998; Pokk and Zharkosky, 1998). Previous research reported that buspirone binds with somatodentric receptors to modulate 5-HT release from the presynaptic neuron in various regions of brain including the hippocampus (Haleem, 1999; Sakaue *et al.*, 2000; Haleem and Parveen, 1994). A decrease in serotonin transmission reduces the anxiety (Johnson, 2004; Malt *et al.*, 2003). Buspirone also acts via other hormones such as the noradrenaline and adrenaline and adrenal corticoid hormones (Liu *et al.*, 2004; Pshennikove *et al.*, 1990) to decrease sympathetic activity (Owusu and Serogin, 2004). Decreased activity of these hormones by buspirone in stressed rats may alter serum electrolyte balance, plasma osmolality and SBP of rats. If changes of electrolytes are involved in stress-induced hypertension it would be expected buspirone and other 5-HT_{1A} agonists elicit this effect by changing the electrolyte balance. The present study concerns with dose related effects of buspirone on serum electrolytes, plasma osmolality and systolic blood pressure (SBP) in rats. Anxiolytic effects of drug are also monitored in light and dark activity box.

MATERIAL AND METHODS

Animals

Male albino Wistar rats (n=24) weighing 175-250g purchased locally were caged individually in a quiet temperature controlled room (25±4C°) for 3 days. Rats had free access to water and standard rodent diet.

Drug

Buspirone purchased from Research Biochemical U.S.A was dissolved in deionized water and injected at doses of 0.25mg/kg, 0.5mg/kg and 1mg/kg intraperitoneally. Control animals were injected with deionized water (1ml/kg).

Experimental protocol

Male albino Wistar rats (n=24) were injected buspirone i.p at doses of 0.25mg/kg, 0.5mg/kg and 1mg/kg. Control animals were injected with deionized water (1ml/kg). The animals injected with water or buspirone were kept back in their home cages. Light- dark box activity was monitored for 5 minutes starting 45 minutes post injections. SBP of rats were also noted 45minutes post injection. Animals were decapitated 1hr post injection to collect serum and plasma respectively in non-heparinized and heparinized tubes for the analysis of serum

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electrolytes and plasma osmolality.

Light-dark box activity

Light-dark activity box was conducted in a locally made two-compartment box. The compartments of equal size (26x26x26), with an access (12x12cm) between the compartments, differed in their sensory properties. Walls of one compartment were light (transparent) and other dark (Black) are connected with a door to observe the behavioral locomotor habit. A rat was placed in the light box and the number of entries and time spent in light box was noted for five minutes starting 45 minutes post injection.

Systolic blood pressure (SBP) measurements

SBP was measured by using NIBP (non-invasive blood pressure) controller (ML0126) attached to the recorder. Rats were restrained in a clear, plastic tube at 39°C, and the cuff was placed on the tail and inflated to 200 mm Hg. The reappearance of a pulse during deflation of the cuff was used to determine SBP. To minimize stress, no animal was restrained for more than 10 min at a time, and a minimum of three clear SBP recordings were taken per animal.

Analytical methods

Serum sodium, calcium and potassium were estimated by a flame photometer (Corning 410c). Concentration of magnesium in serum was estimated by the method describe earlier by Hallry and Sky peck (1964). Plasma osmolality of drugs treated and untreated animals were determined by direct Cryoscopic osmometer (Osmomat-030).

Results are represented as means \pm S.D. Data were analyzed by one-way ANOVA. Significant results were further compared by Newman-Keuls test. Level of Significance was $p < 0.05$ or $p < 0.01$.

RESULTS

1-Dose related effects of buspirone on number of events and time spent in the light compartment of light-dark activity box

Fig-1(a and b) shows the effects of different doses (0.25, 0.5 and 1 mg/kg) of buspirone on the number of events and time spent in the light box. Results show significant effects of buspirone on the number of events ($F=36.05$ df3, 20 $p < 0.01$) and time spent ($F=15$ df3,20 $p < 0.01$) in the light compartment of light-dark activity box. Post-hoc analysis revealed that doses of 0.25-0.5mg/kg increased number of events and time spent in the light box. But a dose of 1mg/kg decreased the number of events and time spent in light box.

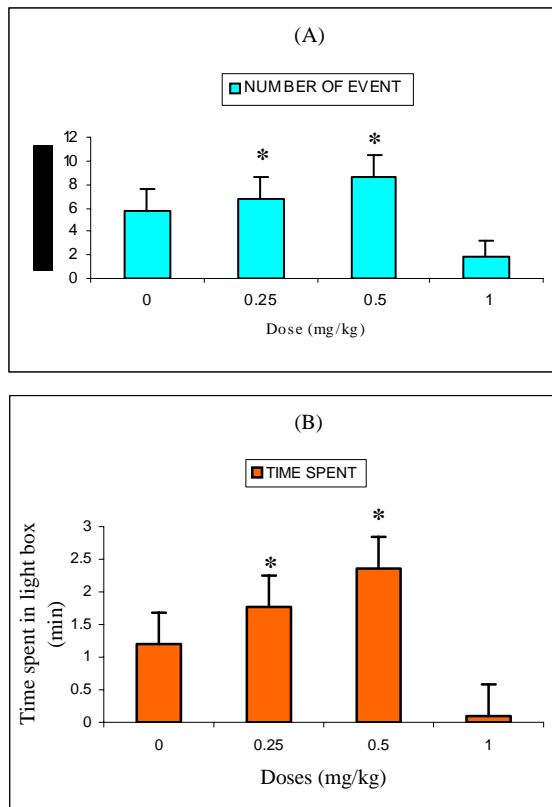


Fig. 1. Dose related effects of buspirone on number of events (A) and time spent (B) in light compartment of light-dark activity box of rats.

Values are means \pm S.D (n=6). Significant differences by Newman Keuls test, * $p < 0.01$ from respective water treated rats following one way ANOVA.

2-Dose related effects of buspirone on serum sodium, plasma osmolality and SBP of rats

Effects of administration of 0.25, 0.5 and 1mg/kg doses of buspirone on serum sodium, plasma osmolality and SBP are shown in fig.2 (a, b and c). One-way ANOVA showed significant effects of buspirone on concentration of sodium ($F=10.86$ df3, 20 $p > 0.01$), plasma osmolality ($F=6.8$ df3, 20 $p < 0.01$), and SBP ($F=5.7$ df3, 20 $p < 0.01$). Post hoc analysis showed that at doses of 0.25-0.5mg/kg significant ($p < 0.01$) increase in sodium, plasma osmolality and decrease in SBP of rats occurred. The increases of sodium and plasma osmolality and decrease of SBP were dose dependent. No significant effect was found when 1mg/kg dose of buspirone was injected.

3-Dose related effects of buspirone on serum calcium, magnesium and potassium of rats

Fig-3 (A, B and C) shows the effects of different doses of buspirone on serum calcium, magnesium and potassium levels. One way ANOVA revealed significant effects of buspirone on calcium ($F=4.9$ df3, 20 $p < 0.01$), magnesium ($F=6.08$ df3, 20 $p < 0.01$) and potassium ($F= 5.2$ df3,20

$p < 0.01$). Newman-Keuls test showed that administration of buspirone increased serum calcium, potassium and decreased magnesium concentration in a dose dependent manner at doses of 0.25mg/kg and 0.5mg/kg. Dose of 1mg/kg did not produce any effect on potassium calcium and magnesium.

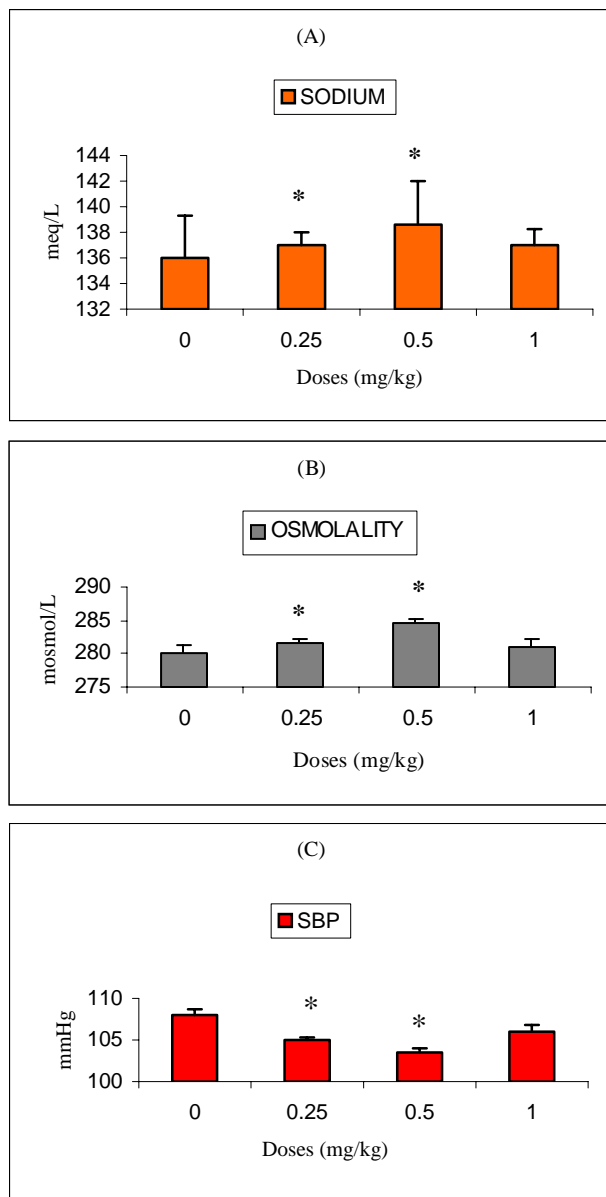


Fig. 2: Dose related effects of buspirone on serum sodium (A), Osmolality (B) and SBP (C) in rats. Values are means \pm S.D (n=6). Significant differences by Newman-Keuls test, $*p < 0.01$ from respective water treated rats following one way ANOVA.

DISCUSSION

The present study shows that administration of buspirone (0.25mg, 0.5mg/kg i.p) elicited anxiolytic effects in light-dark box but a dose of 1mg/kg did not produce anxiolytic effects. A previous study has also reported that buspirone

produced anxiolytic effects at a narrow dose range (0.03-0.3mg/kg) with maximum efficacy at 0.3mg/kg (Sakaue *et al.*, 2000; Haller *et al.*, 2000, 2001; Viadya *et al.*, 2005), while at doses of 2-4mg/kg buspirone produced a decrease in motor activity that is reflected by a decrease in number of entries in the lit area (fig.1a and b). Other authors have reported that behavioral and neurochemical effects of 5-HT_{1A} agonists such as buspirone depend on the dose and duration of treatment (Griebel *et al.*, 1998; Pokk and Zharkovsky, 1998).

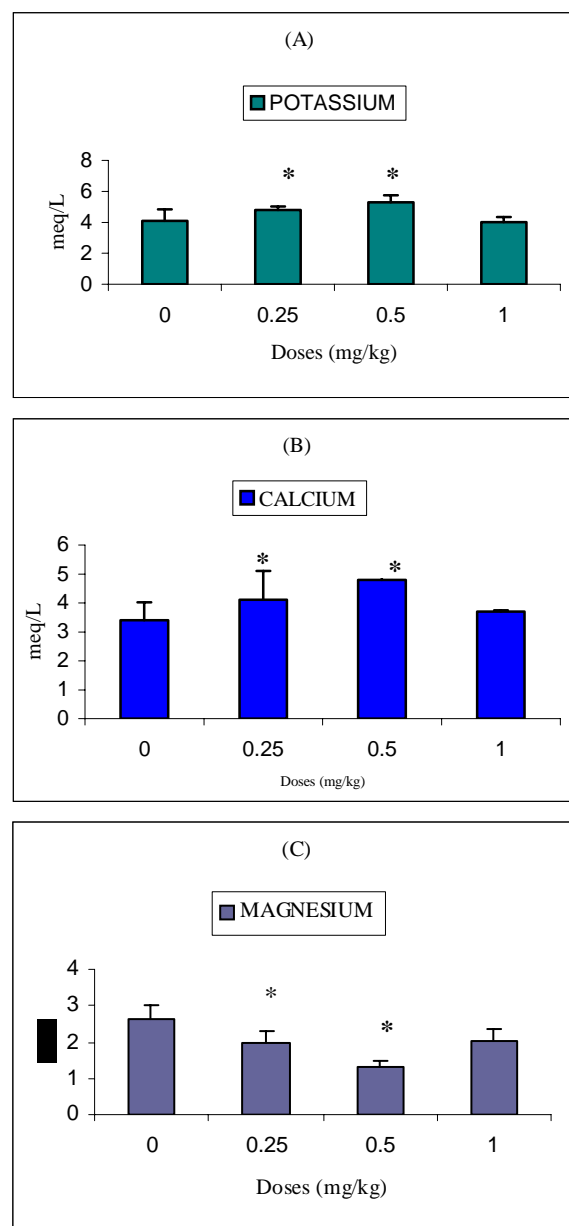


Fig. 3: Dose related effects of buspirone on serum potassium (A), calcium (B), and magnesium (C) of rats. Values are means \pm S.D (n=6). Significant differences by Newman-Keuls test, $*p < 0.01$ from their respective water treated rats following one way ANOVA.

The present study shows that buspirone at doses of 0.25 and 0.5mg/kg eliciting an anxiolytic effect changes the concentration of serum sodium, potassium, calcium, magnesium, plasma osmolality and SBP (fig. 2 and 3 a, b and c). The changes are explainable in terms of decreased secretion and activity of adrenal hormones in buspirone treated rats. It was reported that administration of buspirone decreased the activity of adrenal glands and secretion of aldosterone and catecholamines through serotonergic mechanisms (Liu *et al.*, 2004; File and Andrews 1994; Jeffrey and Clothier, 2001). It was believed that buspirone elicits an antianxiety effect by decreasing serotonin function (Malt, 2003; Liu *et al.*, 2004). It acts on the noradrenergic system by blocking of serotonin receptors, (Lechin *et al.*, 1998; Lechin and van der Dijs, 2006; Davis *et al.*, 1988). Lechin and Co-workers (1998) reported that buspirone stimulates central sympathetic activity. Acute effects of buspirone are reflected in an increase in peripheral neural sympathetic activity, but not adrenal sympathetic activity in healthy individuals. In addition, buspirone increases free serotonin plasma concentrations and decreases systolic blood pressure plus heart rate through mechanisms associated with parasympathetic activation. Decreased activity of adrenal hormones (catecholamines and adrenal corticoid hormone) may reduce the retention of sodium from renal tubules (Chobanian *et al.*, 2003) and decrease intracellular sodium. It results in increased efflux of sodium and calcium and influx of magnesium (Blaustein, 1977) that may lead to an elevation of serum sodium, potassium and calcium and decreased magnesium as observed in present study (fig. 1, 2 and 3). The decrease of intracellular calcium may cause vasodilatation to decrease blood pressure in rats. Another reason of increased serum electrolytes and reduced blood pressure in the present study may be due to the inhibition of Na-K-ATPase activity. Administration of buspirone to inhibit the activity of catecholamines and aldosterone (Hegart and Vogel, 1995) that may effect the activity of Na-K-ATPase and decrease the intracellular sodium, potassium and calcium but increase intracellular magnesium via the same mechanism as described above that ultimately decreases the systolic blood pressure of rats.

The present study shows that buspirone induced changes in electrolytes, plasma osmolality and SBP are involved in the anxiolytic effects of drug.

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