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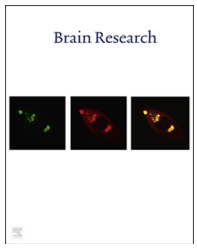

Research Report

Inhibition of apomorphine-induced conditioned place preference in rats co-injected with buspirone: Relationship with serotonin and dopamine in the striatum

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ABSTRACT

Apomorphine is a non-narcotic derivative of morphine, which acts as a dopamine agonist to produce psychostimulant like effects. Currently, apomorphine is used in patients with advanced Parkinson's disease, for the treatment of persistent and disabling motor fluctuations, but a constellation of addictive syndromes such as excessive over use of medication, compulsive behaviors, and disturbances of impulse control are noticed in certain patients. Research on rodent models using conditioned place preference (CPP) paradigm also shows that the drug is rewarding. Previously we have shown that repeated administration of apomorphine produces behavioral sensitization which is prevented in rats co-injected with a low (1.0 mg/kg) but not higher (2.0 mg/kg) dose of buspirone. The present study shows that rewarding effects of apomorphine (1.0 mg/kg) in a CPP paradigm are also blocked in rats co-injected with a low (1.0 mg/kg) but not higher (2.0 mg/kg) dose of buspirone. The levels of serotonin and its metabolite are decreased in the caudate as well as nucleus accumbens of rats exhibiting CPP and the decreases do not occur in animals co-injected with low or higher dose of buspirone. The levels of dopamine and its metabolites are not affected in animals exhibiting CPP; administration as well as co-administration of higher dose of buspirone decreased dopamine metabolism in the caudate as well as nucleus accumbens. The findings suggest a critical role of serotonin in the rewarding effects of apomorphine and imply that co-use of buspirone at low doses can help to control addictive syndromes in Parkinson's disease patients on apomorphine therapy.

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1. Introduction

Apomorphine is a non-narcotic derivative of morphine, which acts as a dopamine agonist to produce psychostimulant like effects. Currently, apomorphine is used in patients with advanced Parkinson's disease, for the treatment of persistent and disabling motor fluctuations which do not respond to levodopa or other dopamine agonists (Antonini et al., 2011; Carron et al., 2011; Ribarič, 2012). A potential role of apomorphine in the treatment of Alzheimer's disease is also suggested (Himeno et al., 2011; Ma et al., 2011).

While apomorphine and other dopamine receptor agonists act positively in partially restoring the motor deficits elicited by Parkinson's disease, a constellation of addictive syndromes has been also noticed in certain patients. It includes addiction to medications, compulsive behaviors, and disturbances of impulse control (Struhal et al., 2012; Pontone et al., 2006, Voon et al., 2006; Weintraub et al., 2010)

Preclinical research also shows that dopamine agonists including apomorphine are rewarding when tested in conditioned place preference (CPP) paradigm (Papp, 1988; Khroyan et al., 1995; Hoffman et al., 1988, Graham et al., 2007; Zengin-Toktas et al., 2013). Development of novel pharmacological agents for the suppression of rewarding effects of apomorphine and other dopamine agonists is therefore important for improving therapeutics in Parkinson's disease (Haleem, 2013).

In this regard, one potential target system is the 5-hydroxytryptamine (5-HT; serotonin) neurotransmitter system. At least 14 different types and subtypes of serotonin receptors have been identified (Hoyer et al., 2002). The 5-HT-1A receptor subtype, which occurs on the soma and dendrites of serotonin neurons and also postsynaptically has been shown to have an important role in the rewarding effects of drugs of abuse (Filip et al., 2010; Fletcher et al., 2008; Haleem et al., 2002; Haleem, 2013; Lanteri et al., 2009; Müller et al., 2007; Nic Dhonnchadha and Cunningham, 2008).

Buspirone, an azaspirodecanedione derivative is clinically recommended for the treatment of patients with generalized anxiety disorder (Rickels, 1990; Gorman, 2003; Loane and Politis, 2012). It has partial affinity for 5-HT-1A receptors as agonist and dopamine D2 receptors as an antagonist (Peroutka, 1985; Gobert et al., 1999), although its affinity as an antagonist of dopamine D2 receptors is 15-fold weaker than for the 5-HT-1A receptors (Peroutka, 1985). Systemic administration of buspirone at a dose of 1.0 mg/kg results in a decrease of 5-HT turnover in many brain regions without producing a significant decrease of motor activity (Mitchell and Thomas, 1988; Haleem et al., 2004; Shireen and Haleem, 2005). It is therefore suggested that at this dose the drug could preferentially stimulate somatodendritic 5-HT-1A receptors resulting in a decrease in 5-HT availability in terminal regions.

Our previous work shows that co-administration of buspirone at a dose of 1 mg/kg but not at higher dose (2 mg/kg) inhibits apomorphine-induced behavioral sensitization (Ikram et al., 2011). In view of a potential role of 5-HT-1A receptors in behavioral sensitization induced by amphetamine and apomorphine (Haleem, 2013), the present study is designed to determine the effects of buspirone at these doses on apomorphine-induced CPP.

We hypothesized that co-administration of buspirone can inhibit apomorphine-induced CPP. Apomorphine was injected at doses that were previously found to produce behavioral sensitization (Ikram and Haleem, 2011; Haleem et al., 2013) and CPP (Ikram et al., 2012). To understand a role of serotonin and dopamine neurotransmission in apomorphine-induced CPP; effects of apomorphine, buspirone and their co-administration are also determined on the metabolism of 5-HT and dopamine in the caudate and nucleus accumbens.

2. Results

2.1. *Effects of buspirone on apomorphine CPP*

Fig. 1 shows rewarding effects of apomorphine with or without buspirone in a CPP paradigm. Three way ANOVA (repeated measure design) showed significant effect of apomorphine ($F=21.9$ df1,42 $p<0.01$), buspirone ($F=9.1$ df2,42 $p<0.01$) and a significant interaction between apomorphine and buspirone ($F=12.88$ df2,42 $p<0.01$). Repeated measure (day) effects ($F=42.7$ df1,42 $p<0.01$), day × apomorphine ($F=11.4$ df1,42 $p<0.01$), day × buspirone ($F=9.5$ df2,42 $p<0.01$) and day × buspirone × apomorphine ($F=7.9$ df2,42 $p<0.01$) interactions were also significant.

Post-hoc test showed that pre-conditioning values of time spent in the drug paired compartment were comparable in the six groups. Post-conditioning values of time spent in the drug paired compartment were much higher in Bus0mg+Apo than Bus0mg+Sal ($p<0.01$) injected animals. The values in Bus1mg+Apo and Bus2mg+Apo injected animals were no greater ($p>0.05$) than the values in respective saline injected controls. The values were smaller in Bus1mg+Apo ($p<0.01$) and Bus2mg+Apo ($p<0.05$) injected than Bus0mg+Apo injected animals. These were greater ($p<0.05$) in Bus2mg+Sal than Bus0mg+Sal injected animals.

Post-hoc comparison of post-conditioning values with pre-conditioning values showed an increase in post-conditioning than pre-conditioning values of time spent in drug paired compartment in Bus0mg+Apo ($p<0.01$), Bus2mg+Sal ($p<0.05$) and Bus2mg+Apo ($p<0.01$) injected animals. The results show an induction of CPP by apomorphine and 2 mg/kg buspirone. The results also show that apomorphine (1 mg/kg)-induced CPP is attenuated and blocked respectively in rats co-injected with 2 mg/kg and 1 mg/kg buspirone.

2.2. *Effects of buspirone on apomorphine-induced motor behavior*

Fig. 2 shows effects of apomorphine, buspirone and their co-administration on motor behavior. Three way ANOVA (repeated measure design) showed significant effect of apomorphine ($F=298$ df1,42 $p<0.01$), buspirone ($F=169$ df2,42 $p<0.01$) and a significant interaction between apomorphine and buspirone ($F=119$ df2,42 $p<0.01$). Repeated measure (day) effects ($F=20.3$ df5,42 $p<0.01$), day × buspirone ($F=22.9$ df10,42 $p<0.01$) and day × buspirone × apomorphine ($F=16.1$ df10,42 $p<0.01$) interactions were also significant. Day × apomorphine interaction ($F=1.7$ df5,42 $p>0.05$) was not significant.