THE EFFECTS OF QUINPIROLE AND SULPIRIDE ON CONFLICT RESPONSES IN RAT

H. Alaei., A. Komaki and A. Nasimi

Department of physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract - In this investigation we studied the effect of dopaminergic system on the conflict behavior in rat, using Vogel's test. The related drugs were injected intraperitonealy (IP), and produced the following results:

Diazepam at doses of 0.5 and 1 mg/kg increased the lick-shock responses in the Vogel's test. Quinpirole (D_2-Agonist), at doses of 0.1 and 10 mg/kg, increased the conflict responses, whereas sulpiride (D_2 Antagonist) did not affect them. Apomorphine (D_1 and D_2 agonist) had a biphasic effect on the conflict responses. This drug decreased the number of shocks at low dose (0.01 mg/kg) while increased them at high dose (1 mg/kg). Haloperidol at dose of 1 mg/kg reduced the conflict responses significantly. Administration of both sulpiride (30 mg/kg) and quinpirole (10 mg/kg) together, increase the conflict responses.

These results suggest that D_2-receptor agonist drugs may exert anxiolytic and D_2-receptor antagonists may produce anxiogenic effects in rat.

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Key Words: Anxiety, Vogel's test, dopaminergic drugs,

INTRODUCTION

Anxiety is a psychological and physiological complex response, which is manifested by tachycardia, increase in blood pressure and respiratory rate. Many reports have shown that anxiety also increase the secretion of catecholamins and cortisol (1-3). In animals, behavior tests are usually used to validated the anxiety rather than physiological concomitants (5).

The roles of GABAergic, serotonergic, and noradrenergic are the key points of most neurobiological investigation on anxiety (6,7). However, several reports suggest that dopaminergic (DA) system might have a modulatory role in emotional behavior. For instance, in vivo studies have shown that acute exposure to stress (such as foot-shock, restraint and social deficit) activates mesolimbic/cortical DA systems and these effects can be attenuated by antianxiety drugs (1,2,3,8,9,10). Although at least five dopamine receptor subtypes have been recognized (11), but the most functionally important are the D_1 and D_2 receptors(7).

One of the predictive model for study of anti-anxiety agents in rats and mice is the Vogel lick-shock conflict task (3,7). The effect of drugs on increasing the number of punished responses in a conflict situation in rat is corresponding to an anxiolytic action in human (12).

In this study the effects of agonist and antagonists of D_1 and D_2 receptors on the conflict behavior in rat using Vogel's test has been examined. Therefore, the effects of diazepam, apomorphine, haloperidol, sulpiride and quinpirole on the conflict behavior in rat have been evaluated.

MATERIALS AND METHODS

The modified Vogel lick-shock conflict test (1,3) was conducted in operant conditioning chambers consisting of a plexiglas cubicle (30 × 20 × 15 cm) with an aluminum grid floor and aluminum front panel equipped with an optical licometer. In the test chamber a water spout was connected to a shocker and during 10 minute sessions, rats were administered a shock (40 V, 1 second, PALMER instrument shocker: CVP model) for every lick. If an animals pretreated with a drug make more licks than the control group, it demonstrates the anxiolytic effect of the drug and vice versa. The chamber was enclosed in sound and light attenuating cubicle equipped with a ventilating fan.

Animal model : practical protocol and design

Male Wistar rats weighing 190-210 grams were housed in groups of five in a climate and controlled room with a 12-hour light-dark cycle (lights on 0700-1900h) and allowed free access to food and water for two weeks. Rats were then deprived from water for 48 hours prior to testing.

For the first session water-restricted (48h deprived) rats were placed in the experimental chamber and allowed to consume water freely without any shock. After one week of non-shock sessions, drugs were administered intraperionealy (IP) (number of animals : 8-10 per dose) 20 minutes prior to testing and then placed in the lick-shock chamber. The mean number of conflict responses for each dose group was compared to the vehicle treated group by a one-way analysis of

variance (ANOVA). In all experiments, subjects were tested individually at the same time of the day.

RESULTS

Data from lick-shock conflict study are summarized in figures 1,2 and table 1. The IP injection of diazepam (0.5 mg/kg) significantly ($P<0.01$) increased the conflict responses compared to that of the vehicle group. The high dose (1 mg/kg) of diazepam had a similar effect, but the effect of low dose was stronger (Fig. 1). Compared to the vehicle group, quinpirole at doses of 0.1 and 10 mg/kg significantly increased the conflict responses (Fig. 1). Apomorphine had a biphasic effect on the conflict responses (Fig. 2). This drug at low dose (0.01 mg/kg) decreased the number of shocks, whereas increased them ($P<0.01$) at high dose (1 mg/kg).

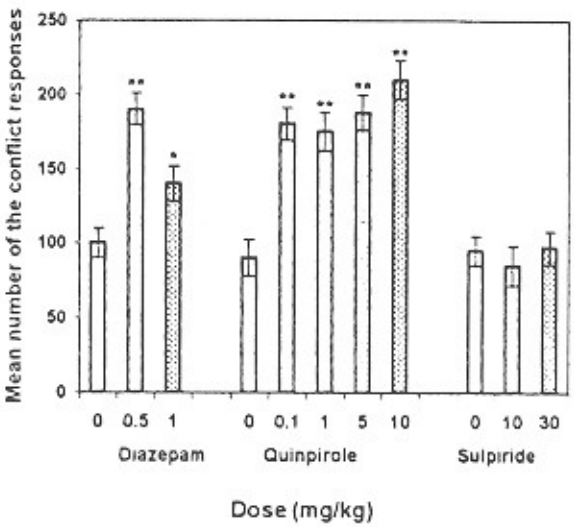
The D_2 selective antagonist sulpiride (at 10 and 30 mg/kg) didn't have any effect on this anxiety-related behavior (Fig. 1).

Figure 2 shows that haloperidol at high dose (1 mg/kg) significantly reduced the conflict responses ($P<0.05$).

Simultaneouse injection of sulpiride (30 mg/kg) and quiniprole (10 mg/kg) increased the conflict responses (Tab. 1). The effect was similar to that of diazepam and quinpirole.

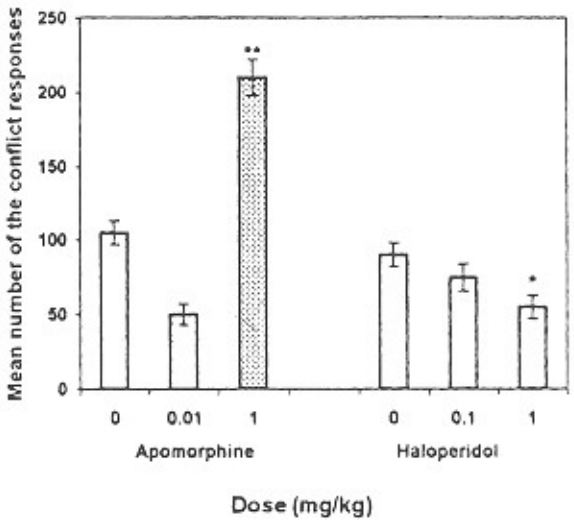
Table 1. Effects of Sulpiride, Quinpirole and Sulptide + Quinpirole (Sul. + Quin.) administration on the conflict behavior. Valuse represent the mean SEM of shock received; n = 8-12*: $P< 0.05$; **: $P< 0.01$

Drug group	Vehicle	Sulpiride		Quinpirole		Sul. + Quin.
Dose		10 mg/kg	30 mg/kg	0.1 mg/kg	10 mg/kg	30,10 mg/kg
No. of shocks received	102.45±13.56	91.77±11.2	99.07±10.42	*180.9±27.5	**205±21.5	239±34.46



Dose (mg/kg)

Fig. 1. Effects of diazepam, quinpirole and sulpiride on the conflict behavior in water deprived rats (n: 8-12). Each column shows the mean number of the conflict responses during the first 10 minutes after the drug administration. The error bars represent the SEM. Dose of zero denotes the data of the control group. * $P < 0.05$, ** $P < 0.01$



Dose (mg/kg)

Fig. 2. Effects of apomorphine and haloperidol on the the conflict behavior in water deprived rats (n: 8-12). Each column shows the mean number of the conflict responses during the first 10 minutes after the drug administration. The error bars represent the SEM. Dose of zero denotes the data of the control group. * $P < 0.05$, ** $P < 0.01$

DISCUSSION

This study showed that, diazepam at doses of 0.5 and 1 mg/kg increased the lick-shock responses. Similary, in other conflict behavior studies, it was shown that diazepam produced an anxiolytic-like effect in various models of anxious states (13-15). In this investigation, low dose of diazepam induced more anxiety effect than high dose of it, which might be due to sedative effect of this drug appeared in this stage. Diazepam as the same as other benzodiazepins, exerts this effect via the GABA receptor (15). The ability of this drug to increase the number of punished responses in animals in the conflict situations could be predictive of an anxiolytic action in human (16).

It was found that, haloperidol (D_1 and D_2 antagonist) at a dose of 1 mg/kg reduce the conflict responses (7) (Fig. 2), which is a reflection of its anxiogenic-like effect. Confirming this findings, it has been already found that haloperidol can reduce overall exploratory activity at all tested doses and induced catalepsy (17). Halopridole also remove the antianxiety effect of picrotoxin in the avoidance test (18). A similar effect has been also found in diazepam-elicited plus-maze activity as well (19). The anxiogenic effect of this drug is mediated through interaction with D_2-receptors (7).

Using apomorphine (D_1 and D_2 agonist) in this study produced a biphasic effect, showing anxiolytic-like effect at high dose (1 mg/kg). Whereas anxiogenic effect at low dose (0.01 mg/kg) (Fig. 2). Presen data supports the earlier reports of anxiolytic-like effects following apomorphine treatment (at high dose) in punished-drinking and light-dark tests in rats (7). Apomorphine also reversed anxipgenic activity of yohimbine in elevated plus-maze test (20). This antianxiety effect of apomorphine is also related to the involvement of D_2 receptors in various models of anxiety (7). Quinpirole (D_2 selective agonist) produced an anxiolytic-like effect (Fig. 1). It may produce this effect by activation of D_2 receptors, especially in post-synaptic site (21). A research on DA receptor agonists provides further support to the involvement of D_2 receptor subtypes in anxiety (22). Although these results agree with the reports suggesting that, D_2 receptor agonists enhance the anxiety-related behaviours in mice (7), but it has consistently been shown that quinpirole induces hyperdefensiveness towards non-aggressive partners in the previously defects male rats (23). It might then be argued that the paradoxical results might be related to the specific test situations, where increased defensiveness has been observed in a social context, while the lick-shock conflict is a solitary test.

In contrast to the above findings with quinpirole, our results in this study showed that sulpiride (D_2 antagonist), do not alter any of the recorded variables. The only nonsignificant effect, observed at the low dose (10 mg/kg) was a reduction in the conflict responses. In other studies, an anxiogenic behavior has been observed when the open field-test had been employed (17). The anxiogenic effects were also found in the plus-maze (7) and murine defensive reactivity (4). The non-significant effect in our study might be due to diversity of employed methods.

In conclusion, the dopamine receptor agonists and antagonists provides further support to the involvement of the D_2 receptor subtypes in anxiety.

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