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Involvement of Central Presynaptic Noradrenergic Neuron Activity in Head Twitches Induced by Bromocriptine in Rats

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Abstract The study was carried out in an attempt to understand the contribution of endogenous catecholamine on head twitches induced by bromocriptine (BRC), a dopamine D-2 receptor agonist, in rats. Intraperitoneal (i.p.) injection of BRC (1-10 mg/kg) induced head twitches which are prominent at 2.5 mg/kg. The pretreatment with α-methyl-p-tyrosine (α-MPT ; 200 and 400 mg/kg) inhibited in dose-dependent manner, whereas reserpine (2 mg/kg) did not affet but reserpine plus α-MPT (200 mg/kg) markedly decreased. Apomorphine (0.1 and 1 mg/kg) tended to increase the behavior but no significant. Thyrotropin releasing hormone (TRH ; 5 mg/kg) potentiated the behavior, whereas clonidine (0.05 and 1 mg/kg) completely blocked, but phentolamine (10 mg/kg), a α-1 and α-2 receptor blocker, and yohimbine (1 mg/kg), a direct α-2 receptor blocker, did not affect. Yohimbine, however, reversed inhibitory effect of low dose of clonidine (0.05 mg/kg). These results suggest that endogenous catecholamine especially noradrenaline synthesis and release mediated in presynaptic sites may be involved in head twitches induced by BRC.

Key Words : Bromocriptine, Dopamine D-2 agonist, Head twitches, Noradrenaline synthesis and release

Introduction

Selective dopamine D-2 agonist BRC is of value in the treatment of Parkinson's disease[1] to its dopamine receptor stimulating properties[2]. A large number of studies with the drug have described psychiatric side effects and hallucinations in human patients[3]. Hallucinogens such as mescaline and lysergic acid diethylamide (LSD-25) in mice and rats, produce abnormal behavior including characteristic head-twitches and backward locomotion which are blocked by serotonin antagonists[4]. Corne and Pickering (1967)[5] indicated that head twitches in animals can serve as a useful indicator of hallucinogenesis in man. Our previous report[6], however, suggested that since the BRC-induced head twitch responses are potentiated by serotonin antagonists such as methysergide and cyproheptadine, the behavior may differ from hallucinogen-induced head twitches. The present studies were designed to understand whether synthesis and release of endogenous catecholamines contribute to head twitch responses induced by BRC.

Materials and Methods

Animals. Healthy male Wistar rats (200-250 g) were obtained from Kyudo Animal Laboratory (Kumamoto, Japan). Commercial food (MF,

Oriental Yeast Ltd.) and tap water were available ad libitum except during trials. All trials and breeding were carried out at an environmental temperature of 23 ± 1℃, with a 12 h light-dark cycle (7 : 00 am - 7 : 00 p.m.)

Measurement of Head Twitches. "Head twitch" in the rat is a paroxysmal shudder of the head, neck and trunk. Pairs of rats were placed in transparent plastic boxes (35×30×17cm) containing wood shavings. Head twitches were counted every 10 min for 120 min after injection of BRC or 3 % Tween 80 solution.

Administration of Drugs. To induce head twitches, rats received intraperitoneal injections of BRC (2.5 mg/kg). The time interval between pretreatment with the following drugs and BRC was 24 h for reserpine (2 mg/kg), for 6 h for α-MPT (200 and 400 mg/kg), and 10 min for apomorphine (0.1 and 1 mg/kg), clonidine (0.05 and 1 mg/kg), TRH (5 mg/kg), phentolamine (10 mg/kg) or yohimbine (1 mg/kg). To examine the effects of reserpine plus α-MPT, BRC (2.5 mg/kg) was administered after 24 h of reserpine (2 mg/kg) and 6 h of α-MPT (200 mg/kg). Furthermore, to examine the antagonism of yohimbine on effect of clonidine, BRC (2.5 mg/kg) was administered after 15 min yohimbine (1 mg/kg) and after 10 min clonidine (0.05 mg/kg). In the control experiments, 3 % Tween 80 solution instead of BRC was injected at the same time interval.

Drugs. The following drugs were used. BRC (Bromocriptine mesylate ; Sandoz A. G.), reserpine (Sigma, St. Louis), α-methyl-p-tyrosine methylester (α-MPT ; Sigma, St. Louis) and apomorphine hydrochloride (Sigma, St. Louis), clonidine hydrochloride (Sigma, St. Louis), TRH (L-pyroglutamyl-L-histidyl-L-prolineamide L-tartrate monohydrate ; Takeda, Osaka), phentolamine mesylate (Regitine, Ciba-Geigy, Basel, Switzerland) and yohimbine hydrochloride (Sigma, St. Louis). BRC, reserpine and α-MPT were suspended in 3 % Tween 80. The other drugs were dissolved in saline. These drugs were injected intraperitoneally (IP) using 1 ml/kg. Doses are expressed in term of the salt.

Statistical Analysis. Head twitch was expressed as mean values, and statistical analysis was calculated using ANOVA and subsequently two-tailed Mann-Whitney U-test. The level of significance chosen was $p<0.05$.

Results

Head Twitch Responses Induced by BRC. Intraperitoneal injection of BRC (1-10 mg/kg) elicited not only head twitches but also yawning behavior. The most effective dose was 2.5 mg/kg in this study. Head twitches began within 5 min and were marked 10-20 min after injection, whereas yawning response 20-30 min later, accompanied by grooming. chewing or penile erections. Head twitch responses reached a maximum 40-60 min after drug administration. These results are summarized in Fig. 1 and Fig. 2.

Effects of Various Drugs on BRC-Induced Head Twitches. As shown in Table 1, head

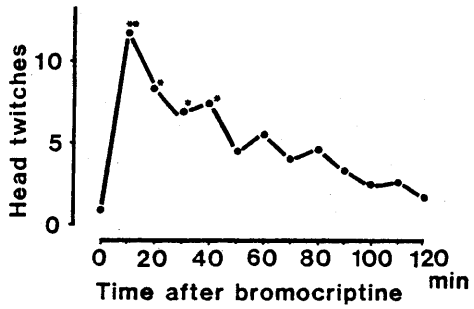

Fig. 1 Dose-response of head twitch responses to bromocriptine (BRC). Each point represents mean number of head twitches during 120 min. *$p<0.05$, **$p<0.002$; significant difference from the vehicle group (0 point), determined by ANOVA and subsequent the Mann-Whitney U-test (n=6 - n=8)

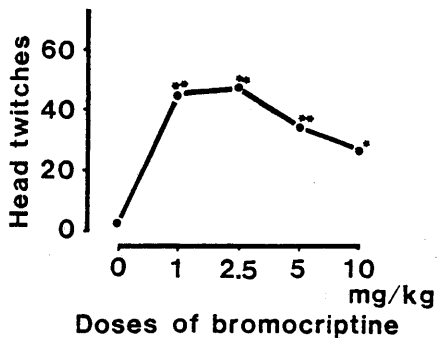

Fig. 2 Time course of head twitch responses induced by bromocriptine (2.5 mg/kg i.p.). Each point indicates mean value of head twitches observed every 10 min after drug injection for 120 min in 6-8 rats. Further explanation as in Fig. 1.

Table 1 Effects of Various Drugs on Head Twitches induced by BRC.

Pretreatments	(mg/kg)	Head twitches in 120 min Vehicle	BRC
Control		2.5	45.4 † †
Reserpine	2	3.0	43.0 † †
α-MPT	200	0.0	26.7* † †
α-MPT	400	0.0	15.3** † †
Reserpine + α-MPT	2 200	0.0	7.7** †
TRH	5	5.5	99.0** † †
Clonidine	0.05	0.0	3.0** †
Clonidine	1	0.0	0.0**
Phentolamine	10	3.2	50.0 † †
Yohimbine	1	3.3	48.2 † †
Apomorphine	0.1	8.3*	59.0 † †
Apomorphine	1	0.0	56.1 † †

The respective drugs were injected as described in the text. *, † ; $p<0.05$, **, † † ; $p<0.002$; significant difference from control group (*, **) and from vehicle group (†, † †), determined by analysis of variance and subsequent Mann-Whitney U-test (n=6 - n=8)

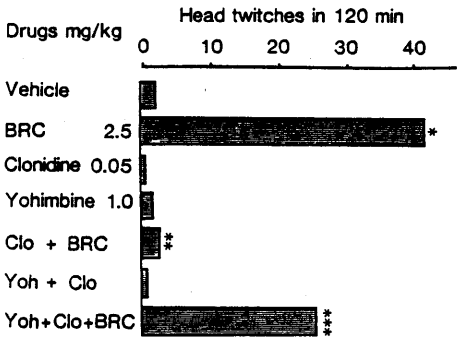

Fig. 3 Yohimbine-reversibility to inhibitory effect of clonidine on the head twitches. *, * *, * * *, $P<0.05$; significant difference from the vehicle (*), BRC (* *) and Clo + BRC (* * *) group, determined by ANOVA and subsequent the Mann-Whitney U-test (n=6 - n=8). Clo : Clonidine, Yoh : Yohimbine

twitches induced by BRC (2.5 mg/kg) were not affected by reserpine (2 mg/kg) or apomorphine (0.1 and 1.0 mg/kg) but were increased by TRH (5 mg/kg). The behavior was decreased by α-MPT (200 and 400 mg/kg) in dose-dependent manner and the decrement was potentiated by combined treatment with reserpine (2 mg/kg) and α-MPT (200 mg/kg). Moreover, clonidine (0.05 and 1.0 mg/kg) markedly inhibited head twitches. Phentolamine (10 mg/kg) and yohimbine (1 mg/kg) did not affect the behaviors. The inhibitory effect of clonidine (0.05 mg/kg) was reversed by yohimbine (1.0 mg/kg) (Fig. 3).

Discussion

In the present study, rats given BRC initially exhibited head twitches and subsequently showed yawning behavior, accompanied by hypomotility, grooming, chewing and penile election, as previously reported[6]. Since BRC-induced head twitches are potentiated by serotonin antagonists, methysergide and cyproheptadine, the behaviors may involve serotonergic inhibition and differ from hallucinogen-induced head twitches[6]. On the other hand, there is growing evidence suggesting the existence of distinct types of shaking behaviors, not exclusively related to serotonergic functions[7,8]. It is noteworthy that carbachol[9,10], enkephalin[11], kainic acid[12] and TRH[13] elicited shaking behaviors which are not mediated

through the function of serotonergic neurons. Shaking behavior appears in response to the abrupt termination of morphine treatment and after the precipitation of abstinence in dependent animals with narcotic antagonists[14-16]. Dopamine receptor antagonists such as haloperidol and fluphenazine, which block both pre- and postsynaptic dopamine receptors[17-19], have already been shown to inhibit body shaking following morphine withdrawal[20], 5-hydroxytryptophan[21], kainic acid[12], carbachol[9], α-melanocyte stimulating hormone[19], TRH[13] or BRC[6]. These inhibitory effects of dopamine antagonists on body shaking suggest that dopaminergic function may be involved in a common mechanism of shaking behavior[13].

In this study, BRC-induced head twitches were not affected by reserpine (2 mg/kg), but were inhibited by α-MPT, a tyrosine hydroxylase inhibitor, in dose dependent manner, and markedly inhibited by combined treatment with reserpine and α-MPT. TRH potentiated BRC-induced head twitches at dose which did not produce[13]. Furthermore, Both low and high doses of clonidine completely inhibited the behaviors, but α-1 and α-2 adrenoceptor antagonist phentolamine and selective α-2 receptor antagonist yohimbine did not affect. Low and high doses of apomorphine did not affect. Clonidine, at lower doses, preferentially activate presynaptic α-2-adrenoceptors which result in an inhibition of noradrenaline release[22], while at higher doses, stimulate both pre- and postsynaptic α-2- and α-1-adrenoceptors[23-25]. TRH enhances the synthesis and release of central catecholamine[26-28]. From the result that inhibitory effect of clonidine on BRC-induced head twitches was reversed by yohimbine, the inhibitory effect of clonidine may be due to blockade of noradrenaline release from presynaptic sites rather than to direct stimulation of postsynaptic noradrenergic receptors. These results suggests that catecholamine, especially noradrenaline synthesis and release in presynaptic sites may be involved in BRC-induced head twitch responses.

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