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α-Noradrenergic Receptor Modulation of the Phencyclidine- and Δ^9-Tetrahydrocannabinol-Induced Increases in Dopamine Utilization in Rat Prefrontal Cortex

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ABSTRACT The noncompetitive NMDA receptor antagonist phencyclidine (PCP) and the neuronal cannabinoid receptor agonist Δ^9-tetrahydrocannabinol (THC) are two agents shown to have psychotomimetic properties in humans. Both drugs increase dopamine release and utilization in the prefrontal cortex, a brain region thought to be dysfunctional in schizophrenia. In the present series of studies, the effects of drugs acting at α-noradrenergic receptors on PCP- and THC-induced increases in prefrontal cortical and nucleus accumbens dopamine utilization in the rat were examined. Clonidine, an α_2 noradrenergic receptor agonist, completely blocked the activation of mesoprefrontal dopamine system by THC or PCP. In addition, the α_1 noradrenergic receptor antagonist prazosin blocked the PCP-induced increase in prefrontal cortical dopamine utilization. These data may provide new insights concerning pharmacological therapies for acute drug-induced psychoses and behavioral abnormalities in human PCP and THC abusers.
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INTRODUCTION

Exposure to the noncompetitive *N*-methyl-D-aspartate receptor antagonist phencyclidine (PCP) or the neuronal cannabinoid receptor agonist Δ^9-tetrahydrocannabinol (THC) can have psychotomimetic effects in humans (Javitt and Zukin, 1991; Thacore and Shukla, 1976). Both these agents can induce prefrontal cortical dysfunction, a symptom associated with schizophrenia (Goldman-Rakic, 1991), in rats, monkeys, and humans. The prefrontal cortex subserves several cognitive and executive processes, including working memory (Goldman-Rakic, 1987), and working memory has been shown to be disrupted by PCP, or its congener ketamine (Boyce et al., 1991; Krystal et al., 1994; Verma and Moghaddam, 1996), and by THC (Ferraro, 1980; Jentsch et al., 1997b; Molina-Holgado et al., 1994; Nakamura et al., 1991) in rats, monkeys, and humans. It now appears that the disrupting effects of THC and PCP on working memory function may involve a drug-induced dysregulation of the dopaminergic innervation of the prefrontal cortex.

The prefrontal cortex receives a prominent dopaminergic innervation arising from the ventral mesencephalon (Roth and Elsworth, 1995), and dopamine appears to provide a critical neuromodulatory influence on the cognitive functions of the prefrontal cortex (Goldman-Rakic et al., 1997). Destruction of the mesoprefrontal dopamine neurons or blockade of dopaminergic receptors within prefrontal cortex disrupts performance of tasks dependent on working memory in rats and monkeys (Brozoski et al., 1979; Bubser and Schmidt, 1990; Sawaguchi and Goldman-Rakic, 1991; Simon et al., 1980). In addition, recent data have shown that increased dopamine utilization in the prefrontal cortex induced by a pharmacologic stressor impairs spatial working memory (Murphy et al., 1996a).

Indeed, a hyperdopaminergic substrate may underlie the cognitive disrupting effects of THC and PCP. In-

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creases in prefrontal cortical dopamine release and utilization have been documented after THC (Bowers and Hoffman, 1986; Chen et al., 1990) and PCP (Bowers and Hoffman, 1984; Deutch et al., 1987; Hertel et al., 1996) in the rat and after PCP in the monkey (Jentsch et al., 1997a). These drug-induced increases in prefrontal cortical dopamine transmission appear to be responsible for the working memory deficits induced by acute THC and PCP, as the cognitive dysfunction can be ameliorated by agents that prevent the drug-induced activation of prefrontal cortical dopamine utilization (Jentsch et al., 1997b) or dopamine receptor antagonists (Verma and Moghaddam, 1996). As such, agents that prevent the increased dopaminergic transmission in the prefrontal cortex may prevent the clinical presentation of profound cognitive impairments in PCP- or THC-exposed subjects.

Both the α_2 agonist clonidine and the α_1 antagonist prazosin have been shown to affect midbrain dopamine neuron firing patterns (Grenhoff and Svensson, 1989, 1993). In addition, clonidine has been shown to prevent FG7142- and stress-induced activation of the mesoprefrontal dopamine system (Morrow et al., 1996; Murphy et al., 1996b; Tam, 1986). Thus, we hypothesized that clonidine may have an impact on the increases in prefrontal cortex dopamine utilization observed after THC and PCP. In the present study, the effects of drugs acting at α-noradrenergic receptors on THC- and PCP-induced increases in dopamine utilization in the prefrontal cortex and nucleus accumbens were examined. In addition, the effect of the α_{2a}-preferential agonist guanfacine on the THC-induced activation in prefrontal cortical dopamine utilization was also determined to identify the receptor subtype underlying any preventative effects of α_2 agonists.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley CAMM rats (Charles River Labs, Portage, MI) were used as subjects. All subjects were maintained under conditions consistent with the NIH "Guide for the Care and Use of Laboratory Animals," and all protocols were approved by the Yale University animal care and use committee. The rats were maintained on a 12-h light/dark cycle, with the light phase being 7:00 A.M. to 7:00 P.M. Food and water was provided ad libitum.

Drugs

PCP was administered at a dose of 10 mg/kg in sterile saline. THC (5 mg/kg) was dried down under a stream of purified nitrogen and suspended in a solution of 95% saline and 5% Tween 80 (a surfactant). Clonidine HCl (0.1 mg/kg), prazosin HCl (1 mg/kg), or guanfacine HCl (0.11 mg/kg) was delivered in saline 15 min before PCP administration. All injections were given at a volume of 1 ml/kg i.p. except THC, which was prepared and delivered at 2 ml/kg i.p. Vehicle treatments, in all cases, represented an injection of an equivalent volume of sterile saline. All drugs were obtained from Research Biochemicals Inc. (Natick, MA) except guanfacine, which was provided courtesy of A.H. Robins (Richmond, VA). All drugs weights were calculated as the salt.

Biochemistry

All rats were 250–275 g at the time of sacrifice. Sacrifices were performed during the animals' light phase. Rats were killed by rapid decapitation 1 h after PCP or 30 min after THC administration. The brains were quickly removed, and brain regions were dissected out on a thermostatically chilled platform. Samples were immediately frozen on dry ice and stored at −70°C until assayed.

Tissues were prepared with dihydroxybenzylamine as an internal standard. Samples were homogenized in 400 μl of ice-cold 0.1 M perchloric acid and centrifuged at 46,000*g*, and the supernate was analyzed directly with high pressure liquid chromatography (HPLC) using electrochemical detection with a glassy carbon electrode at +0.7 V (BAS, West Lafayette, IN) and a reversed-phase column (3-μm C18 beads, 100-Å diameter, 10-cm length; BAS, West Lafayette, IN). Pellets were analyzed for protein content according to Lowry et al. (1951).

Mobile phase used for HPLC was an 8% solution of acetonitrile containing 0.6% tetrahydrofuran, 0.1% diethylamine, 0.025 mM EDTA, 2.3 mM 1-octane-sulfonic acid, 30 mM sodium citrate, and 13.7 mM sodium dihydrogen phosphate (final pH 3.1).

Measurements of turnover were made as the ratio of tissue concentration (in ng/mg protein) of the primary metabolite, dihydroxy-*O*-phenylacetic acid (DOPAC), to the parent amine (dopamine).

Statistics

Statistical analysis was performed on a Macintosh IIcx running Statview II (Abacus Concepts, Berkeley, CA). Analysis of variance and post-hoc Scheffe's *F*-test were used to determine significance. All data are expressed as mean ± SEM.

RESULTS

Clonidine blocks PCP-induced activation of frontal cortical dopamine utilization

PCP (10 mg/kg i.p.) significantly increased dopamine utilization (DOPAC/dopamine) in the medial prefrontal cortex 1 h after administration (Fig. 1; $F_{(1,7)} = 26$; $P \leq .01$). This increase was prevented by pretreatment with clonidine (Fig. 1; $F_{(1,7)} = 47.3$; $P \leq .001$) at a dose (0.1 mg/kg) that did not alter dopamine metabolism on its own (Fig. 1; $F_{(1,7)} = 1.2$; $P > .05$). These changes in dopamine utilization after PCP and clonidine (either

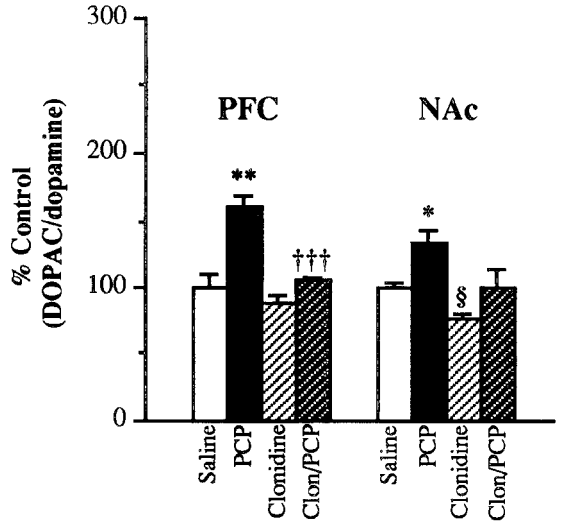

Fig. 1. PCP increases dopamine utilization in the prefrontal cortex (PFC) and nucleus accumbens (NAc), and this effect is significantly prevented by pretreatment with clonidine in the PFC. Clonidine reduces dopamine metabolism in the NAc on its own. Data represent mean ± SEM. $n = 4$ for PFC and $n = 6$ for NAc. **Significantly increased relative to control: $P \leq .01$. §Significantly reduced relative to control: $P \leq .05$. †††Significantly reduced relative to PCP: $P < .001$.

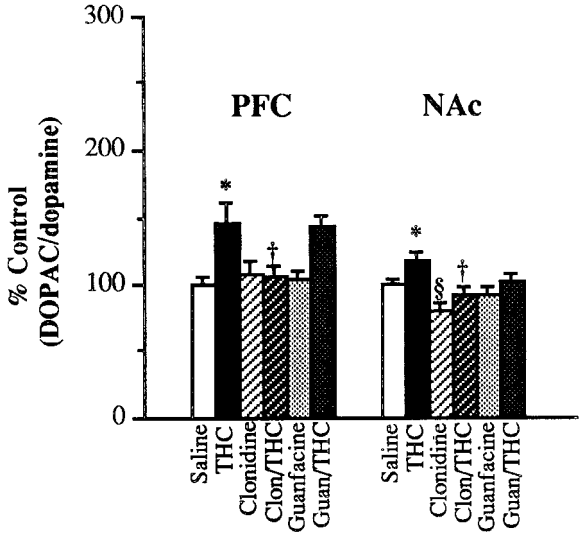

Fig. 2. THC increases dopamine metabolism in the prefrontal cortex (PFC) and nucleus accumbens (NAc). Clonidine but not guanfacine prevents this effect in the PFC and NAc while reducing NAc dopamine utilization on its own. Data represent mean ± SEM. $n = 7$ or 8 for all observations. *Significantly increased relative to control: $P \leq .05$. §Significantly reduced relative to control: $P \leq .05$. †Significantly reduced relative to THC: $P \leq .05$.

TABLE I. Absolute dopamine concentrations in prefrontal cortex after PCP, THC, clonidine, guanfacine, prazosin, and combinations[1]

Treatment	Vehicle	Clonidine	Guanfacine	Prazosin
Vehicle	0.40 ± 0.04 ($n = 11$)	0.38 ± 0.03 ($n = 12$)	0.38 ± 0.04 ($n = 7$)	0.39 ± 0.04 ($n = 4$)
PCP	0.39 ± 0.07 ($n = 4$)	0.36 ± 0.05 ($n = 4$)	n.d.	0.37 ± 0.03 ($n = 4$)
THC	0.36 ± 0.05 ($n = 7$)	0.39 ± 0.03 ($n = 8$)	0.45 ± 0.04 ($n = 8$)	n.d.

[1]No significant alterations in absolute dopamine concentrations (ng/mg protein) in rat prefrontal cortex after administration of vehicle, THC, PCP, clonidine, prazosin, guanfacine, or any combinations. Data represent mean ± SEM. n.d., Not done.

alone or combined) are independent on effects of absolute dopamine concentrations (in ng/mg protein) and, as such, are metabolite-driven (Table I).

PCP treatment also increased dopamine metabolism in the nucleus accumbens (Fig. 1; $F_{(1,11)} = 8.3$; $P \leq .05$). Clonidine significantly reduced dopamine utilization on its own in the nucleus accumbens (Fig. 1; $F_{(1,11)} = 17.9$; $P \leq .01$), but given as a pretreatment, clonidine produced only a nonsignificant trend for reversal of the PCP-induced activation in this region (Fig. 1; $F_{(1,11)} = 3.7$; $P = .08$).

Increased dopamine utilization in frontal cortex after THC is blocked by clonidine

THC administration increased dopamine utilization in the medial prefrontal cortex 30 min after administration (Fig. 2; $F_{(1,13)} = 7.4$; $P \leq .05$). Pretreatment with clonidine prevented this activation (Fig. 2; $F_{(1,14)} = 5.5$; $P \leq .05$) while, as in the previous experiment, having no significant effects on dopamine utilization on its own (Fig. 2; $F_{(1,14)} = 0.4$; $P > .05$). The effects of pretreatment with a dose of guanfacine equimolar to the clonidine dose were also examined; guanfacine (0.11 mg/kg i.p.) failed to alter dopamine metabolism on its own (Fig. 2; $F_{(1,14)} = 0.1$; $P > .05$) and, unlike clonidine, also failed to prevent the THC-induced activation of cortical dopamine utilization (Fig. 2; $F_{(1,14)} = 0.1$; $P > .05$). The observed effects in dopamine utilization are metabolite-driven; no significant alterations in absolute dopamine concentrations were detected after THC, clonidine, guanfacine, or combination administration (Table I).

THC also increased nucleus accumbens dopamine utilization, although the magnitude of the change was smaller (Fig. 2; $F_{(1,14)} = 6.8$; $P \leq .05$). Clonidine appeared to prevent the THC-induced rise in dopamine metabolism (Fig. 2; $F_{(1,14)} = 8.2$; $P \leq .05$), but as in the previous experiment, clonidine reduced dopamine utilization in the nucleus accumbens on its own (Fig. 2; $F_{(1,15)} = 7.6$; $P \leq .05$). Guanfacine failed to reduce dopamine metabolism on its own (Fig. 2; $F_{(1,14)} = 1.6$; $P > .05$) or to reduce the THC-induced activation of dopamine metabolism (Fig. 2; $F_{(1,14)} = 3.0$; $P > .05$) in the nucleus accumbens.

Prazosin prevents the PCP-induced activation in frontal cortical dopamine metabolism

Prazosin (1 mg/kg i.p.) had no significant effect on dopamine utilization in the frontal cortex on its own (Fig. 3; $F_{(1,7)} = 1.2$; $P > .05$), but it prevented the PCP-induced activation (Fig. 3; $F_{(1,7)} = 15.0$; $P \leq .01$) in dopamine utilization (Fig. 3; $F_{(1,7)} = 12.7$; $P \leq .01$).

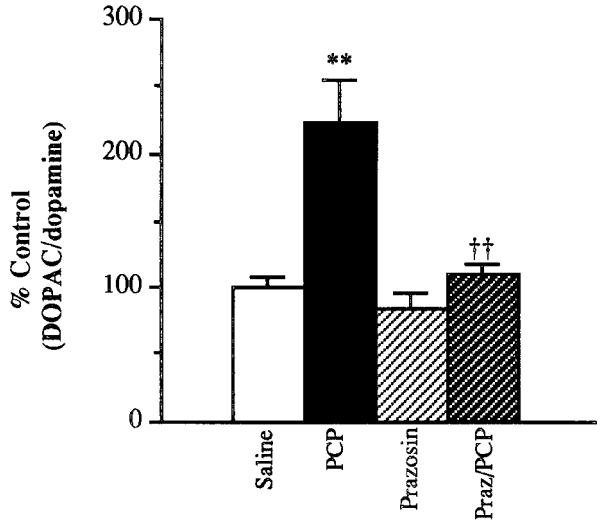

Fig. 3. Prazosin blocks the PCP-induced activation of dopamine utilization in the prefrontal cortex. Data represent mean ± SEM. n = 4 for all observations. **Significantly increased relative to control: $P \leq .01$. ††Significantly reduced relative to PCP: $P \leq .01$.

Again, this effect was metabolite driven (Table I). Finally, prazosin blocked the PCP-induced activation of dopamine utilization in the nucleus accumbens (data not shown; $F_{(1,7)} = 8.4$; $P < .05$) without having any effects on dopamine metabolism on its own (data not shown: $F_{(1,7)} = 0.5$; $P > .05$).

DISCUSSION

In this study, we show that α-noradrenergic receptors exert a potent regulatory influence over the activation of mesoprefrontal dopamine neurons by the psychotomimetic drugs PCP and THC. Clonidine, an α_2-agonist, and prazosin, an α_1-antagonist, prevented the psychotomimetic drug-induced rise in medial prefrontal cortical dopamine metabolism, while having no effects on mesocortical dopamine metabolism on their own. Clonidine also altered the PCP- and THC-induced mesolimbic activation, but these effects were seen at a dose of clonidine that significantly reduced dopamine utilization on its own.

By contrast, a dose of guanfacine, an α_{2a}-preferential agonist, equimolar to the clonidine dose did not reverse the THC-induced activation of cortical dopamine utilization. This dose range of guanfacine does appear to be relevant because it has been shown to prevent the stress-induced activation of the prefrontal cortical dopamine system (Morrow et al., 1996) and to enhance performance of a spatial memory task by young rats (Sirvio et al., 1991). These data suggest that the α_{2a} subtype may not be a critical mechanism by which clonidine modulates the THC-induced activation of the mesoprefrontal dopamine system and further implies that the stress- and THC-induced activation of the prefrontal cortical dopamine system may be differentially regulated.

These data are consistent with previous studies from this laboratory showing that clonidine can prevent the activation of dopamine metabolism in the frontal cortex induced by stress or the anxiogenic drug FG7142 (Deutch and Roth, 1990; Morrow et al., 1996; Murphy et al., 1996b; Tam, 1986). A possible substrate for these effects is based on the finding that clonidine and prazosin regulate the firing pattern of dopamine neurons within the ventral tegmental area (Grenhoff and Svensson, 1989, 1993), the principal nucleus providing dopaminergic innervation to the prefrontal cortex (Roth and Elsworth, 1995). Both clonidine and prazosin reduce firing rate and regularize firing pattern in ventral tegmental area neurons (Grenhoff and Svensson, 1989, 1993). In addition, α_2 receptors may have added benefits by acting as local heteroreceptors within prefrontal cortex, directly regulating dopamine release (Gresch et al., 1995).

The ventral tegmental area appears to modulated by a net excitatory noradrenergic drive, mediated by α_1 receptors. Stimulating the locus coeruleus excites midbrain dopamine neurons (Grenhoff et al., 1993), whereas lesioning the noradrenergic innervation of the ventral tegmentum reduces medial prefrontal cortical but not nucleus accumbens dopamine turnover (Herve et al., 1982). In addition, as previously stated, α_1 antagonists (which might block hypothesized postsynaptic receptors in the midbrain) and α_2 agonists (which reduce noradrenergic activity) reduce firing rate and regularize firing pattern in dopamine neurons (Grenhoff and Svensson, 1989, 1993). Finally, α_2 antagonists, which increase noradrenergic transmission, increase dopamine neuron burst firing (Grenhoff and Svensson, 1993) and prefrontal cortical dopamine release (Gresch et al., 1995).

The noradrenergic modulation of the PCP- and THC-induced increases in dopamine transmission can thus occur at the level of the midbrain. PCP has been consistently shown to activate or excite midbrain dopamine neurons (Freedman and Bunney, 1984; French, 1994; Pawlowski et al., 1990). Thus, the noradrenergic α_2 agonists and α_1 antagonists may block the PCP-induced activation of ventral tegmental area neurons. THC likewise activates dopamine neurons (French et al., 1977) and indeed, our pharmacologic data support the notion that THC increases impulse flow in dopamine neurons (Jentsch et al., in press).

The pharmacologic specificity of prazosin may be questioned because it has been observed to exhibit subtype-specific antagonistic effects on the α_{2b} and α_{2c} receptors (Bylund, 1985), in addition to its effects at the α_1 receptor. Nevertheless, the antagonistic effects of prazosin at α_2 receptors are unlikely to account for the

ability of this drug to prevent the PCP-induced rise in prefrontal cortical dopamine utilization because α_2 antagonists, as previously stated, *increase* dopamine neuron burst firing and transmitter release (Grenhoff and Svensson, 1993; Gresch et al., 1995). In this study, α_2 agonists prevented the PCP-induced increase in prefrontal cortical dopamine metabolism. Thus, the observed ability of prazosin to reverse the stimulatory effects of THC and PCP on dopamine utilization are more consistent with an α_1 effect.

In summary, drug-induced reductions in α-noradrenergic transmission appear to be effective in altering the activation of the mesoprefrontal dopamine neurons induced by the psychotomimetic drugs PCP and THC. An involvement of dopamine system dysregulation has been hypothesized in schizophrenia (Carlsson, 1988; Davis et al., 1990), and the PCP- and THC-induced activation of brain dopamine systems may be related to their psychotomimetic effects. Thus, in cases of acute drug-induced psychosis, α_2 agonists and α_1 antagonists may prove to have clinical benefits in ameliorating any dopamine-related psychotomimetic effects of PCP and THC.

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