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The 5-HT_{1A} receptor modulates the effects of cocaine on extracellular serotonin and dopamine levels in the nucleus accumbens

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Abstract

The regulation of extracellular levels of serotonin (5-HT) and dopamine in response to cocaine by 5-HT_{1A} receptors was examined using in vivo microdialysis and the 5-HT_{1A} receptor antagonist 4-(2′-methoxy-)-phenyl-1-[2′-(*N*-2″-pyridinyl)-*p*-fluorobenzamido-]ethyl-piperazine (*p*-MPPF). Pretreatment with *p*-MPPF significantly augmented the increase in extracellular levels of both 5-HT and dopamine in the nucleus accumbens produced by systemic administration of cocaine. Levels of 5-HT or dopamine were unaffected by *p*-MPPF given alone. Extracellular levels of 5-HT and dopamine were increased dramatically by cocaine infused locally into the nucleus accumbens. Systemic injection of cocaine given during the cocaine infusion reduced 5-HT and dopamine levels, presumably by activating inhibitory 5-HT and dopamine autoreceptors outside of the locus of infusion. The reduction of 5-HT and dopamine levels by systemic cocaine during accumbal infusion was blocked by pretreatment with the 5-HT_{1A} receptor antagonist *p*-MPPF. Taken together, these findings suggest that the 5-HT_{1A} autoreceptor acts to modulate the effects of cocaine on both 5-HT and dopamine levels in the nucleus accumbens.

Keywords: Substance abuse; Cocaine; Serotonin; Dopamine; Nucleus accumbens; Microdialysis

1. Introduction

Systemically administered cocaine binds at dopamine, serotonin (5-HT), and norepinephrine transporters (Ross and Renyi, 1967, 1969; Ritz et al., 1990), thereby blocking reuptake and increasing levels of the corresponding neurotransmitters in terminal regions, such as the nucleus accumbens (Bradberry et al., 1993; Essman et al., 1994; Chen and Reith, 1994; Rothman and Baumann, 2003). Evidence supports a predominate role for the mesolimbic dopamine system in the psychomotor stimulant and reinforcing properties of cocaine associated with its abuse (Koob and Nestler, 1997; Wise, 2004). Despite the evidence for a dopaminergic mechanism for many of the addictive effects of cocaine, it is clear that other neurotransmitters like 5-HT also play an important role in many of the behavioral effects of cocaine (Muller et al., 2003; Essman et al., 1994). The balance between the effects of cocaine on dopamine systems and other neurotransmitters like 5-HT may be a key factor in the development of medications that modify the abuse potential of cocaine.

In addition to its effects on monoamine transporters in forebrain terminals, the net effects of cocaine on monoamine neurotransmission are also dependent on feedback regulation of neurotransmitter release and interactions between different neurotransmitters. An important source of feedback regulation is provided by the activation of somatodendritic autoreceptors from increased neurotransmitter levels in the vicinity of monoamine cell bodies. Such autoreceptors, located in the ventral tegmentum (for dopamine) or

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raphe nuclei (for 5-HT), produce self-limiting effects by decreasing cell firing and neurotransmitter release (Rahman and McBride, 2000; Hjorth et al., 2000). Microdialysis studies have demonstrated that selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, produce self-limiting effects by increasing 5-HT levels and activating 5-HT_{1A} receptors in the dorsal raphe that regulate the net output of 5-HT levels in terminal regions (Hjorth et al., 1997; Romero and Artigas, 1997; Sprouse and Aghajanian, 1986; Becquet et al., 1990). The influence of autoreceptor regulation is easily apparent in microdialysis studies. Local infusion of SSRIs into terminal regions produces a greater increase in 5-HT levels than achieved by systemic administration of SSRIs, when somatodendritic autoreceptors would be activated (Kreiss and Lucki, 1995; Rutter et al., 1995; Romero and Artigas, 1997). These counteractive regulatory influences on net neurotransmitter output can be measured contiguously, when systemic fluoxetine administration causes a net decrease in 5-HT levels when given after terminal reuptake is first inhibited by the local infusion of fluoxetine (Rutter and Auerbach, 1993; Rutter et al., 1995). The reduction of 5-HT levels is blocked by 5-HT_{1A} receptor antagonists given systemically (Rutter et al., 1995) or locally into the raphe (Hjorth et al., 1997; Romero and Artigas, 1997). Finally, pretreatment with 5-HT_{1A} receptor antagonists augments the increase of extracellular 5-HT produced by SSRIs given systemically (Invernizzi et al., 1997; Knobelman et al., 2001; Romero and Artigas, 1997).

As essentially a monoamine reuptake inhibitor, the effects of cocaine are constrained by similar regulation from corresponding autoreceptors on 5-HT and dopamine neurons. For example, administration of i.v. cocaine dose-dependently inhibits dopamine cell firing in the ventral tegmental area region and 5-HT cell firing in the dorsal raphe (Einhorn et al., 1988; Cunningham and Lakoski, 1988, 1990). The effects in the dorsal raphe are mediated by 5-HT_{1A} receptors. Also, local infusion of cocaine in the nucleus accumbens produces greater increases of 5-HT and dopamine levels than systemic administration, and systemic injections of cocaine during cocaine infusion resulted in a reduction of both 5-HT and dopamine levels (Chen and Reith, 1994; Andrews and Lucki, 2001). The negative feedback effects of cocaine on 5-HT are more tightly regulated than for dopamine, and this may contribute to higher dialysis levels of dopamine than 5-HT in the nucleus accumbens after systemic injections of cocaine (Andrews and Lucki, 2001). Thus, the activation of 5-HT_{1A} autoreceptors by cocaine likely plays an important role in determining its effects on 5-HT levels and the relationship between 5-HT and dopamine. Other studies have also suggested an important role for 5-HT_{1A} receptors at regulating the effects of cocaine on extracellular 5-HT levels (Muller et al., 2002) and on the behavioral effects of cocaine (De La Garza and Cunningham, 2000; Carey et al., 2002).

4-(2′ -Methoxy-)-phenyl-1-[2′ -(*N*-2″-pyridinyl)-*p*-fluorobenzamido-]ethyl-piperazine (*p*-MPPF) is a 5-HT_{1A} receptor antagonist with high affinity and selectivity towards the 5-HT_{1A} receptor (Kung et al., 1996). Binding studies demonstrated high affinity and selectivity toward 5-HT_{1A} receptors (K_d=0.34±0.12 nM and B_{max}=145±35 fmol/mg protein in rat hippocampal membrane homogenates). The binding was not sensitive to 100 μM Gpp(NH)p; therefore, it is a pure antagonist for this receptor. Furthermore, autoradiographic studies of rat brain sections exhibited regional localization consistent with the known distribution of 5-HT_{1A} receptors. Behavioral and neurochemical studies have also shown that *p*-MPPF acts as a 5-HT_{1A} receptor antagonist both pre- and post-synaptically (Thielen et al., 1996). The present study used the 5-HT_{1A} receptor antagonist *p*-MPPF to examine the consequences of blocking 5-HT_{1A} receptors on the 5-HT and dopamine response to systemic and local cocaine administration. Also, in order to show that *p*-MPPF blocked the effect of cocaine on 5-HT_{1A} autoreceptors, *p*-MPPF was given in combination with systemic cocaine administered during the infusion of cocaine into the nucleus accumbens. Because 5-HT and dopamine levels in the nucleus accumbens were measured in the same dialysate sample, effects on the different neurotransmitters could be compared directly. Although it was expected that the 5-HT_{1A} receptor antagonist *p*-MPPF would increase the response on 5-HT levels to cocaine, it was unclear whether blockade of 5-HT_{1A} receptors could influence the balance between 5-HT and dopamine levels in the nucleus accumbens (Andrews and Lucki, 2001).

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighing between 250 and 350 g were housed two per cage on a 12-h light/dark cycle (lights on at 0700 h) in a temperature-controlled (22 °C) colony room. Rats were given access to standard rat chow and water ad libitum.

2.2. Microdialysis techniques

Custom-made concentric-style dialysis probes were constructed as described previously (Kirby et al., 1997). Filtered artificial cerebrospinal fluid (147 mM NaCl, 2.3 mM $CaCl_2$, 0.9 mM $MgCl_2$, and 4.0 mM KCl, unadjusted pH 6.3–6.5) was pumped through the probe at 0.6 μl/min with a syringe pump (Instech Laboratories, Plymouth Meeting, PA). The recovery characteristics of individual probes were determined as described in Andrews and Lucki (2001).

The microdialysis probes were implanted into the nucleus accumbens (1.5 mm anterior to bregma, 1.5 mm lateral to midline, and 8.5 mm ventral from dura; Paxinos and Watson, 1986) and secured to the skull with three skull screws and cranioplastic cement. After surgery, the rat was

placed into a 37.5-cm-high, clear polycarbonate cylindrical microdialysis apparatus with a counterbalance arm holding a liquid swivel and spring tether (Instech Laboratories, Plymouth Meeting, PA). During surgery and after placement into the awake animal apparatus, the probe was continuously perfused with artifical cerebrospinal fluid (aCSF) at a rate of 0.6 μl/min. The collection of dialysis samples began 20–22 h after probe implantation. Samples were collected at 20-min intervals into polypropylene microcentrifuge vials (Fisher Scientific, Pittsburgh, PA) containing 4 μl mobile phase yielding a total volume of 16 μl. Samples were stored at −80 °C until analysis (no more than 7 days after samples were collected). Serotonin and dopamine levels were measured in the same dialysis sample using high-pressure liquid chromatography, as described in Andrews and Lucki (2001).

On completion of each experiment, animals were euthanized and their brains were removed. Brains were sectioned with a refrigerated cryostat and stained with cresyl violet. Tissue was then examined for the location of the dialysis probe. Only data from animals with at least 75% of the probe membrane located in the nucleus accumbens were used.

2.3. Experimental design

2.3.1. Systemic cocaine administration

For each animal, the dopamine and 5-HT baseline was determined by averaging the three samples prior to drug administration. Following baseline sample collection, an i.p. injection of 30 mg/kg *p*-MPPF or an equal volume of saline was administered followed 5 min later by an i.p. injection of saline or 25 mg/kg cocaine and samples were collected every 20 min for another 3 h.

2.3.2. Direct cocaine infusion

Following collection of baseline samples, the perfusion media was switched from aCSF to 3 mM cocaine in aCSF using a liquid switch (Instech Laboratories). The infusion baseline was established for 3 h and then 30 mg/kg *p*-MPPF or saline was administered (i.p.) followed 5 min later by an i.p. injection of 25 mg/kg cocaine or saline and samples were collected for another 2 h.

2.4. Drugs

All drugs were prepared just prior to use and doses were calculated as the weight of the base. *p*-MPPF was synthesized according to a procedure published previously (Zhuang et al., 1994) and it was >95% pure. Cocaine hydrochloride was purchased from commercial sources (Sigma, St. Louis, MO) and used without further purification.

2.5. Data analysis

Absolute baseline values of 5-HT and dopamine (fmoles/sample) were determined for each rat from the mean of the dialysis samples collected during the hour before systemic injection. Absolute values were adjusted for individual probe recoveries. The 5-HT and dopamine content of the dialysate samples during and after cocaine administration were expressed as a percent change from baseline. The 5-HT and dopamine content of dialysis samples following systemic cocaine administration during cocaine infusion were expressed as a percent change from the cocaine infusion baseline, defined as the average of the samples from the hour just prior to systemic cocaine administration (hour 3 of the cocaine infusion). The effect of cocaine on 5-HT and dopamine levels was assessed by analysis of variance (ANOVA). The values of individual time points were compared with basal values using Dunnett's test, two-tailed. Comparisons between *p*-MPPF treated and saline-treated groups were made using the Student's *t*-test, two-tailed.

3. Results

3.1. Basal DA and 5-HT content in the nucleus accumbens

The mean baseline level of 5-HT in the nucleus accumbens across groups was 22.9±2.9 fmol/5.0 μl sample (n=48). The mean baseline level of dopamine in the nucleus accumbens across all groups was 70.7±11.8 fmol/5.0 μl sample (n=50).

3.2. Effect of p-MPPF on systemic cocaine on nucleus accumbens 5-HT and dopamine levels

In order to examine the effects of 5-HT_{1A} receptor blockade on 5-HT and dopamine levels in response to systemic cocaine, *p*-MPPF was administered just prior to the systemic injection of saline or cocaine. Fig. 1A shows the effect of 30 mg/kg *p*-MPPF and 25 mg/kg cocaine on 5-HT dialysate levels in the nucleus accumbens. Pretreatment with *p*-MPPF augmented the increase of 5-HT levels produced by cocaine. An overall two-way ANOVA indicated a significant effect of treatment ($F(3,198)=4.97$, $P<0.05$), time ($F(11,198)=9.27$, $P<0.001$) and an interaction ($F(22,198)=2.76$, $P<0.001$). Although 5-HT levels in the NAc were increased following cocaine injection in both the saline plus cocaine and the *p*-MPPF plus cocaine groups, *p*-MPPF produced significantly higher dialysate levels of 5-HT at 40, 60 and 100 min than cocaine alone ($P<0.05$). In the *p*-MPPF treated group, cocaine produced a significant increase in dialysate 5-HT at 20–100 min with the maximum increase of 584±106% occurring at 40 min post cocaine injection. In the saline plus cocaine group, cocaine produced a significant increase at 20 and 80 min following cocaine injection ($P<0.01$) with a maximum increase of 281±40% at 80 min post injection. There was no significant change from baseline 5-HT levels following *p*-MPPF plus saline.

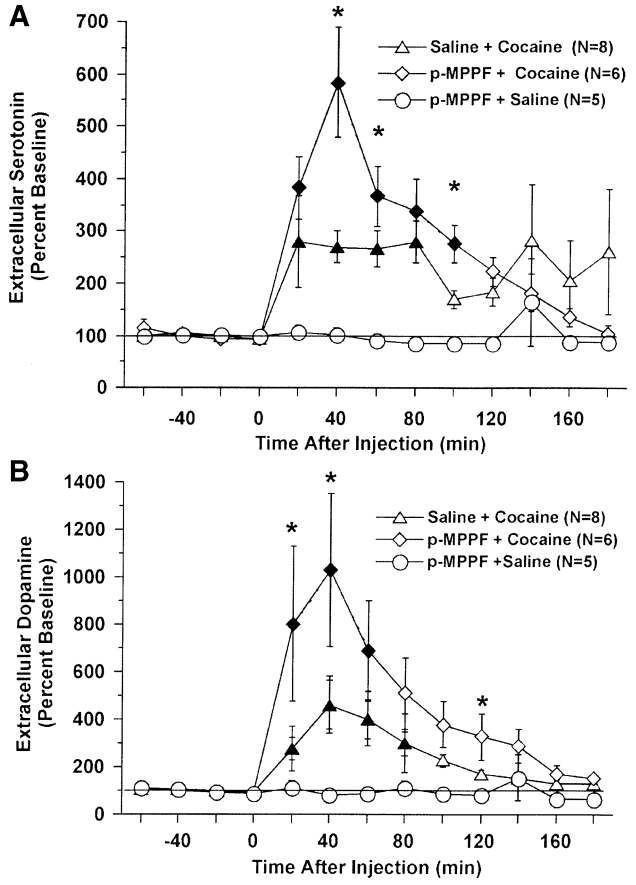

Fig. 1. The effects of systemic administration of the 5-HT_{1A} antagonist *p*-MPPF (30 mg/kg) or saline immediately prior to cocaine (25 mg/kg) or saline on 5-HT (A) and dopamine (B) dialysate levels in the NAc. *Filled symbols* represent a significant change from corresponding pre-injection baseline ($P<0.05$). Asterisks indicate time points at which dialysate levels are significantly higher in the *p*-MPPF and cocaine group than the cocaine alone group. See text for more details.

As shown in Fig. 1B, pretreatment with *p*-MPPF (30 mg/kg) also augmented the increase of dopamine levels produced by cocaine. An overall two-way ANOVA indicated significant effects for treatment ($F(3,198)=4.74$, $P<0.05$), time ($F(11,198)=13.96$, $P<0.001$) and their interaction ($F(22,198)=3.83$, $P<0.001$). Although both the saline plus cocaine and the *p*-MPPF plus cocaine groups showed a significant effect of the cocaine injection on dopamine dialysate levels in the nucleus accumbens, dopamine levels were significantly higher in the *p*-MPPF plus cocaine group when compared with the saline plus cocaine group at 20, 40, and 120 min after the cocaine injection ($P<0.05$). The *p*-MPPF plus cocaine group showed significant increases over baseline from 20 to 60 min after the cocaine injection ($P<0.01$) with a maximum increase of 1030±321% at 40 min post cocaine injection. In contrast, the saline plus cocaine group showed a significant difference from baseline at 20–80 min after the cocaine injection ($P<0.01$) with a maximum effect of only 462±102% at 40 min post injection. *p*-MPPF plus saline did not produce any significant changes from baseline dopamine levels.

3.3. Autoreceptor modulation of neurotransmitter levels in the nucleus accumbens

To examine if the attenuation of the increase in 5-HT and dopamine levels following systemic cocaine administration during cocaine infusion could result from activation of the 5-HT_{1A} receptor, *p*-MPPF was administered immediately prior to either saline of cocaine during the infusion of cocaine. Fig. 2A shows the effect of *p*-MPPF (30 mg/kg) or systemic cocaine (25 mg/kg) during infusion of 3 mM cocaine on dialysate concentrations of 5-HT in the nucleus accumbens. Fig. 2B shows the same data normalized to the cocaine infusion baseline. Systemic cocaine during infusion of 3 mM cocaine into the nucleus accumbens produced a significant decrease in 5-HT dialysate levels when compared to the cocaine infusion baseline ($F(5,48)=3.05$, $P<0.01$). This effect was significantly blocked by injection of *p*-MPPF 5 min prior to the systemic cocaine injection

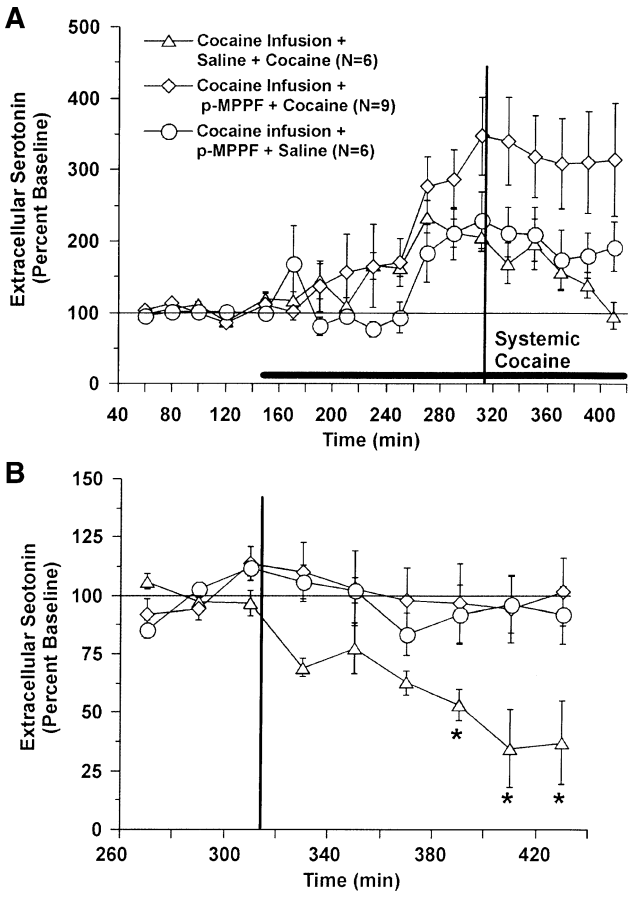

Fig. 2. The effects of systemic administration of the 5-HT_{1A} receptor antagonist *p*-MPPF (30 mg/kg) immediately prior to cocaine (25 mg/kg) or saline during local infusion of 3 mM cocaine on 5-HT dialysate levels in the NAc (Panel A). Panel B shows the same data normalized to the cocaine infusion baseline. In the cocaine alone group, there was a significant decrease in dialysate 5-HT levels following systemic cocaine at 370–410 min. Neither *p*-MPPF plus cocaine nor *p*-MPPF plus saline produced a significant change from the cocaine baseline. Asterisks indicate time points at which there is a significant difference between the cocaine alone and the *p*-MPPF and cocaine groups. See text for more details.

($F(3,96)=4.71$, $P<0.05$). There was a significant difference between the two groups at 370–410 min ($P<0.05$). Systemic treatment with 30 mg/kg *p*-MPPF plus a saline injection during 3 mM infusion of cocaine, as a control procedure, did not produce any change in 5-HT dialysis levels.

Fig. 3A shows the effect of systemic injection of 30 mg/kg *p*-MPPF plus 25 mg/kg cocaine during infusion of 3 mM cocaine on extracellular concentrations of dopamine in the nucleus accumbens. Fig. 3B shows the same data normalized to the cocaine infusion baseline. In the cocaine alone group, systemic injection of cocaine during the 3mM infusion of cocaine produced a significant decrease in dopamine dialysate levels in the nucleus accumbens ($F(5,48)=3.02$, $P<0.05$). This effect was significantly blocked by pretreatment with *p*-MPPF ($F(3,108)=3.63$, $P<0.05$) with significant differences between the two groups at 330–350 min ($P<0.05$). Systemic treatment with *p*-MPPF plus a saline injection during 3 mM infusion of cocaine, as a control procedure, did not produce any change in dopamine dialysis levels.

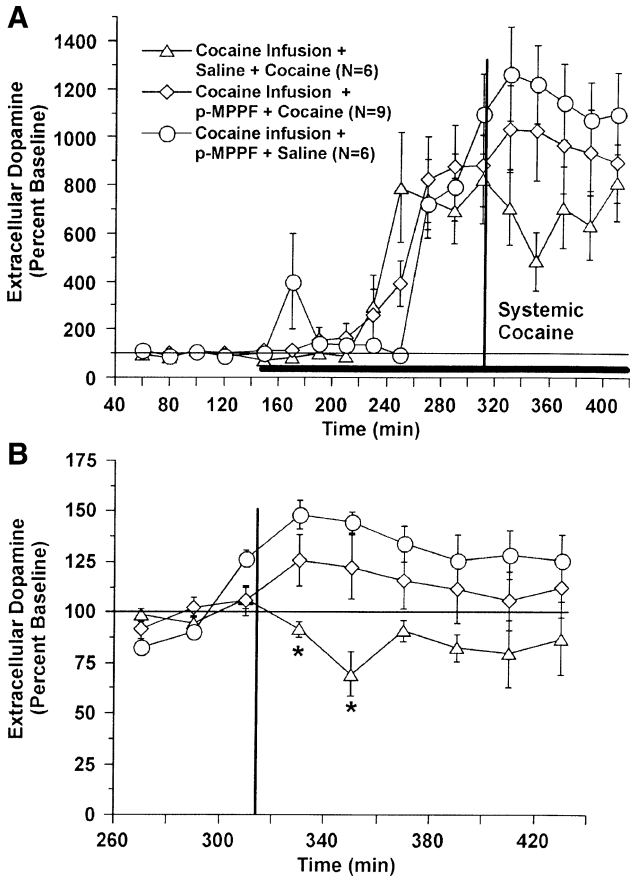

Fig. 3. The effects of systemic administration of the 5-HT_{1A} receptor antagonist *p*-MPPF (30 mg/kg) immediately prior to cocaine (25 mg/kg) or saline during local infusion of 3 mM cocaine on dopamine dialysate levels in the NAc (Panel A). Panel B shows the same data normalized to the cocaine infusion baseline. In the cocaine alone group, there was a significant decrease in dialysate dopamine levels following systemic cocaine at 330–350 min. Neither *p*-MPPF and cocaine nor *p*-MPPF and saline produced a significant change from the cocaine baseline. Asterisks indicate time points at which there is a significant difference between the cocaine alone and the *p*-MPPF and cocaine groups. See text for more details.

4. Discussion

Microdialysis studies have found that systemic administration of cocaine produces an approximately 3- to 5-fold increase in extracellular levels of 5-HT and dopamine in various regions throughout the brain (Chen and Reith, 1994; Essman et al., 1994; Parsons and Justice, 1993). In contrast, the local administration of cocaine into the nucleus accumbens can produce much greater increases in 5-HT and dopamine levels (Chen and Reith, 1994; Andrews and Lucki, 2001). Systemic administration of cocaine only modestly increases neurotransmitter output in the nucleus accumbens because of restraint imposed by the activation of autoreceptors that regulate neuronal discharge and neurotransmitter levels. The increase of 5-HT in the dorsal raphe nucleus, or the increase in dopamine levels in the ventral tegmental area, produced by systemic administration of cocaine would be expected to activate somatodendritic 5-HT_{1A} and dopamine $D_{2/3}$ receptors in these regions. These impulse-regulating autoreceptors decrease cell firing and extracellular neurotransmitter levels in corresponding terminal regions, such as the nucleus accumbens. Systemic cocaine, as well as local administrations of cocaine into the ventral tegmental area and dorsal raphe nucleus, has been shown to decrease cell firing in both of these regions (Cunningham and Lakoski, 1988, 1990; Einhorn et al., 1988; Lakoski and Cunningham, 1988; Pitts and Marwah, 1986). This decrease in cell firing restrains dopamine and 5-HT release in terminal regions, such as the nucleus accumbens (Parsons and Justice, 1993).

Restraint exerted by 5-HT_{1A} autoreceptors in the effects of cocaine on extracellular 5-HT levels in the nucleus accumbens was demonstrated in the present study by the 5-HT_{1A} receptor antagonist *p*-MPPF. A significantly larger increase in extracellular 5-HT levels in the NAc was produced in rats given *p*-MPPF just prior to systemic cocaine. The augmented response to cocaine is consistent with *p*-MPPF decreasing inhibitory autoreceptor feedback by blocking 5-HT_{1A} autoreceptors. The augmenting effects of *p*-MPPF on cocaine-evoked 5-HT levels is similar to those reported recently when the 5-HT_{1A} receptor antagonist WAY 100635 was administered in combination with cocaine (Muller et al., 2002). Extracellular 5-HT levels were also augmented when 5-HT_{1A} receptor antagonists were given just prior to systemic administration of selective serotonin reuptake inhibitors, such as fluoxetine or citalopram (Hjorth et al., 1997; Invernizzi et al., 1997; Knobelman et al., 2001; Romero and Artigas, 1997).

This interpretation was supported by measuring the effects of *p*-MPPF directly on a microdialysis response to cocaine mediated by 5-HT_{1A} autoreceptors. Systemic

cocaine causes a decrease in 5-HT levels (and dopamine levels) when terminal reuptake has been inhibited by the local infusion of cocaine (Andrews and Lucki, 2001), and this study contains a replication of that finding. While direct infusion of cocaine into the nucleus accumbens increases extracellular dopamine and 5-HT only in the area surrounding the probe and not in distal sites, systemic cocaine would be expected to increase extracellular dopamine and 5-HT levels throughout the brain, including areas such as the dorsal raphe nucleus or ventral tegmental area containing somatodendritic 5-HT_{1A} and dopamine D_2 autoreceptors, respectively. The inhibitory effects of cocaine are similar to inhibitory effects of systemic administration of selective serotonin reuptake inhibitors measured under similar circumstances and are mediated by 5-HT_{1A} autoreceptors (Rutter et al., 1995). In the present study, the inhibition of cocaine-elevated 5-HT levels by systemic injection of cocaine was blocked by *p*-MPPF, supporting its role as an antagonist of 5-HT_{1A} autoreceptors.

p-MPPF augmented extracellular 5-HT or dopamine levels in the nucleus accumbens when given in combination with systemic cocaine but not during the local infusion of cocaine. This indicates that local 5-HT_{1A} receptors in the nucleus accumbens were probably not involved in mediating the effects of cocaine since somatodendritic 5-HT_{1A} receptors were not activated during local cocaine infusion. Although there are 5-HT_{1A} receptors in both the terminal regions and the cell body regions, the 5-HT_{1A} receptor is located post-synaptically at terminal regions and does not act as an autoreceptor, while in the cell body regions, it is present on 5-HT neurons and acts as a somatodendritic autoreceptor (Blier and de Montigny, 1992).

It was possible that blockade of 5-HT_{1A} autoreceptors would selectively disinhibit the effects of cocaine on 5-HT relative to dopamine. However, *p*-MPPF administered prior to systemic cocaine also produced a larger dopamine response measured in the same microdialysis sample. There was no increase in extracellular dopamine levels by *p*-MPPF when administered prior to saline. There are two possible explanations for how *p*-MPPF could augment cocaine's effects on dopamine. The first is that by increasing the 5-HT response to cocaine, *p*-MPPF could indirectly increase the effects of cocaine on the dopamine system. There is ample evidence showing that 5-HT can modulate the release of dopamine but can exert different effects through distinct receptor mechanisms. Serotonin neurons from the dorsal raphe nucleus innervate regions where either dopamine cell bodies (ventral tegmental area and substantia nigra) or terminals (nucleus accumbens and striatum) are found (Dray et al., 1976; Herve et al., 1987; Fibiger and Miller, 1977). Infusion of 5-HT directly into the nucleus accumbens or striatum increases extracellular dopamine levels (Benloucif and Galloway, 1991; Parsons and Justice, 1993; West and Galloway, 1996), whereas reducing dorsal raphe nucleus discharge and 5-HT levels by local injection of the 5-HT_{1A} receptor agonist 8-hydroxy-2-di-*n*-propylamino-tetralin (8-OH-DPAT) decreased dopamine levels in the nucleus accumbens (Yoshimoto and McBride, 1992). Activation of 5-HT_{1A} receptors systemically or in the ventral tegmental area increases cell firing of these dopaminergic cell bodies thus increasing extracellular dopamine in the nucleus accumbens (Guan and McBride, 1989; Arborelius et al., 1993). Activation of 5-HT_{1B} receptors in the nucleus accumbens or the ventral tegmental area also increased extracellular dopamine in the nucleus accumbens (Yan and Yan, 2001). On the other hand, activation of 5-HT_{2C} receptors inhibits ventral tegmental area discharge and reduces extracellular dopamine in the nucleus accumbens (Prisco et al., 1994; De Deurwaerdere et al., 2004; Navailles et al., 2004). Thus, coadministration of a 5-HT_{1A} receptor antagonist could diminish the expected stimulatory influence of 5-HT_{1A} receptors on the cocaine-mediated dopamine response, but effects of greater levels of 5-HT acting at the remaining 5-HT receptors likely contributes to a net facilitation of dopamine levels in the nucleus accumbens.

A second explanation concerns a possible effect of *p*-MPPF on dopamine autoreceptors because *p*-MPPF has moderate binding affinity for the dopamine D_2 receptor (K_i=19 nM (D_2) vs. 0.34 nM (5-HT_{1A}; Kung et al., 1996). However, that *p*-MPPF does not increase extracellular dopamine levels in the absence of cocaine may indicate that its effects at dopamine D_2 receptors are not consequential, especially considering its higher affinity for 5-HT_{1A} receptors. In contrast, the selective dopamine D_2 receptor antagonist haloperidol increases extracellular dopamine levels when administered alone (Freeman and Tallarida, 1994).

Although much evidence supports the involvement of dopaminergic mechanisms in the reinforcing and addictive properties of cocaine, others have investigated whether modification of the serotonergic properties of cocaine may regulate its reinforcing effects. Pretreatment with the 5-HT_{1A} receptor agonist 8-OH-DPAT or the SSRI fluoxetine decreases self-administration of cocaine (Carroll et al., 1990; Peltier and Schenk, 1993) or cocaine-primed reinstatement (Burmeister et al., 2004). Other studies have reported that the discriminative stimulus effects of cocaine were unaffected by coadministration of 8-OH-DPAT (Przegalinski and Filip, 1997; De La Garza and Cunningham, 2000). Stimulation of 5-HT_{1A} receptors have been reported to enhance unconditioned locomotor responses to cocaine (De La Garza and Cunningham, 2000; Carey et al., 2002; Herges and Taylor, 1998), although 8-OH-DPAT inhibited cocaine-induced hyperactivity according to one study (Przegalinski and Filip, 1997). Based on the findings presented in this study, the influence of 5-HT_{1A} receptors on cocaine behavioral responses from systemic treatments would be complicated by direct effects on response measure and indirect influences by modulating the effects of cocaine on 5-HT and dopamine transmission. The enhancement of the stimulant effects of cocaine on locomotor activity by local blockade of 5-HT_{1A} autoreceptors in the dorsal raphe

nucleus (Herges and Taylor, 1999) provides an appropriate illustration of the ability of 5-HT_{1A} receptors to regulate the behavioral effects of cocaine by augmenting its effects on monoamine transmission.

In summary, these studies examined the involvement of 5-HT_{1A} receptors in modulating the ability of cocaine to increase extracellular levels of 5-HT and dopamine in the nucleus accumbens. Somatodendritic 5-HT_{1A} receptors act to limit the magnitude of the 5-HT response to cocaine, like other serotonin reuptake inhibitors, and extracellular 5-HT levels in the nucleus accumbens were augmented by blocking 5-HT_{1A} receptors with *p*-MPPF. However, coadministration of *p*-MPPF with cocaine produced a similar augmentation of extracellular dopamine levels. More studies are needed to evaluate whether other 5-HT ligands can produce selective modification of neuropharmacological responses to cocaine.

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