Interactions between Cocaine and Dopamine Agonists on Cardiovascular Function in Squirrel Monkeys


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ABSTRACT

Conscious squirrel monkeys were treated i.v. with cocaine and various dopamine agonist drugs. Cocaine produced a dose-dependent increase in blood pressure, heart rate, and the rate-pressure product (RPP). The dopamine D1 receptor agonist (±)-6-chloro-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF 82958) produced effects comparable to cocaine. The D1 agonist (±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF 81297) also produced increases in blood pressure and heart rate but was much less potent than either cocaine or SKF 82958. The partial D1 agonist (±)-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SKF 77434) did not significantly affect any cardiovascular parameters. The D2 agonist quinpirole slightly decreased blood pressure and increased heart rate. As such, the RPP only slightly increased. The selective dopamine uptake inhibitor 1-[2-[bis-(4-fluorphenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909) produced increases in blood pressure, heart rate, and RPP, but again these effects were smaller and only seen at doses higher than cocaine. Effects similar to those with GBR 12909 were seen with the dopamine autoreceptor antagonist cis-(+)-5-methoxy-1-methyl-2-(di-n-propy lamino)tetralin (UH 232). The combination of GBR 12909, SKF 82958, or SKF 77434 with cocaine produced effects that were clearly subadditive. The effects of quinpirole in combination with cocaine were comparable to, or lower than, those of cocaine alone on blood pressure and RPP. The effects on heart rate were additive. Only UH 232 produced additive effects with cocaine for all three measures. As dopamine agonists have been proposed as potential treatments for cocaine abuse, these results suggest that dopamine D1 agonists and uptake inhibitors can be used safely in combination with cocaine. Caution may be warranted, however, with the use of dopamine autoreceptor antagonists in the treatment of cocaine abuse.

Cocaine produces its reinforcing effects through an action on the dopamine system (Wise and Bozarth, 1987). In particular, the reinforcing effects of cocaine primarily result from blockade of the uptake of dopamine that increases the availability of dopamine in the synapse (Ritz et al., 1987). As a result, it has been suggested that dopamine agonists might be useful in the treatment of cocaine abuse (Caine et al., 1999; Katz et al., 1999; Negus et al., 1999; Childress and O’Brien, 2000) much like methadone is useful in the treatment of opioid abuse (Dole and Nyswander, 1965). A number of dopamine agonists have been shown to reduce cocaine self-administration in animals (Smith et al., 1995; Caine et al., 1999; Negus et al., 1999), supporting their further evaluation as medications in humans. However, because some individuals continue to use cocaine during treatment, it is important to evaluate the safety of potential treatment drugs in combination with cocaine. This is particularly true where agonists are concerned, as both drugs together might be expected to produce larger effects than either alone. Since many of the medical complications of cocaine are associated with the cardiovascular system (Karch and Billingham, 1988; Amin et al., 1990), supporting their further evaluation as medications in humans. However, because some individuals continue to use cocaine during treatment, it is important to evaluate the safety of potential treatment drugs in combination with cocaine. This is particularly true where agonists are concerned, as both drugs together might be expected to produce larger effects than either alone. Since many of the medical complications of cocaine are associated with the cardiovascular system (Karch and Billingham, 1988; Amin et al., 1990), the purpose of this study was to evaluate the effects of a variety of dopamine agonists on cardiovascular function in squirrel monkeys, both alone and in combination with

ABBREVIATIONS: RPP, rate-pressure product; AUC, area under the curve; SKF 82958, (±)-6-chloro-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide; SKF 81297, (±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide; SKF 77434 (±)-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride; GBR 12909, 1-[2-[bis-(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine; UH 232, cis-(+)-5-methoxy-1-methyl-2-(di-n-propy lamino)tetralin; SCH 23390, (+)-7-chloro-9-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride;
cocaine. The squirrel monkey has proven to be a reliable model for studying the cardiovascular effects of cocaine, because the effects of cocaine in the monkeys are similar to those in humans (Schindler et al., 1995; Schindler, 1996). Specifically, cocaine produces a prolonged increase in blood pressure and heart rate in both humans and monkeys.

Cocaine is also a potent uptake blocker for norepinephrine and serotonin as well as a potent local anesthetic (Jaffe, 1990). Therefore, the cardiovascular effects of cocaine may not be related to dopamine, and the impact of the dopamine agonist/cocaine combinations on the cardiovascular system may be minimal. In fact, several studies have suggested that dopamine plays little or no role in the cardiovascular effects of cocaine (Kiritis-Roy et al., 1990; Schindler et al., 1991), and regulation of the cardiovascular effects of cocaine by the noradrenergic system has been demonstrated (Schindler, 1996). However, other studies have shown an interaction between dopamine and dopamine antagonists on cardiovascular function (Tella and Goldberg, 1998).

Although the role of dopamine in cardiovascular regulation is minimal, evidence suggests that both peripheral and central dopamine contribute at least partially to cardiovascular regulation (van den Buuse and de Jong, 1991). In the periphery, dopamine is known to produce vasodilation by interacting with DA1 and DA2 receptors on smooth muscle fibers and at sympathetic nerve terminals, respectively (Kohli and Goldberg, 1990). Dopamine also inhibits stimulated release of norepinephrine from sympathetic nerve terminals via DA2 receptors (Brodde, 1990). Both of these actions might be expected to counteract cardiovascular effects of cocaine mediated by changes in noradrenergic neurotransmission. In brain, elevations in dopamine levels have been shown to both increase and decrease blood pressure, depending on the site studied (van den Buuse and de Jong, 1991). Chemical stimulation of the ventral tegmental area increases blood pressure, an effect that is antagonized by systemic administration of the dopamine D2 antagonist raclopride (Cornish et al., 1997; van den Buuse, 1997), suggesting the involvement of the mesolimbic dopamine system. Therefore, it is possible that dopamine agonists and cocaine may produce interactive effects on cardiovascular function.

For the current study, conscious squirrel monkeys were studied, because anesthesia severely lessens the effects of cocaine on cardiovascular function (Tella et al., 1990). First, the effects of cocaine were compared with those of D1 agonists, a D2 agonist, or indirect agonists. For D1 agonists, the agonists SKF 82959 and SKF 81297 were studied, as well as the partial D1 agonist SKF 77434. For a D2 agonist, quinpirole was studied. Finally, GBR 12909, a selective dopamine uptake blocker, and UH 232, a dopamine autoreceptor antagonist, were studied as examples of indirect agonists. GBR 12909 blocks the uptake of dopamine but is more specific for dopamine than cocaine. UH 232 produces central stimulation by an action at dopamine autoreceptors, which leads to an increase in dopamine synthesis and turnover (Svensson et al., 1986). After determining the cardiovascular effects of these D1 and D2 agonists and indirect agonists when given alone, some of the agonists were then given as pretreatments followed by administration of cocaine to assess possible interactions on cardiovascular function.

**Materials and Methods**

**Subjects.** Subjects were adult male squirrel monkeys (*Saimiri sciureus*) housed in individual cages in rooms in which light, temperature, and humidity were controlled. Fresh water was continuously available. The monkeys’ daily food intake was restricted to maintain a constant body weight throughout the course of the experiment (800–1000 g). Monkeys were implanted with both a venous catheter (internal iliac vein) for the delivery of drug and an arterial catheter (internal iliac artery) for the measurement of blood pressure. Catheters were implanted during a single sterile surgery. The general surgical procedure has been described in detail elsewhere (Herd et al., 1969). In brief, polyvinyl chloride catheters (inside diameter, 0.38 mm; outside diameter, 0.76 mm) were implanted during anesthesia with isoflurane-oxygen mixtures. The distal ends of the catheters were passed s.c. through the skin in the middle of the back. Monkeys wore nylon jackets at all times to protect the catheters. Following a 2-week recovery period, experiments were begun. Catheters were flushed with saline at least twice weekly and sealed with stainless steel obturators when not in use.

All animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. All procedures were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse/Intramural Research Program and the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

**Apparatus.** During experimental sessions, the monkeys sat in Plexiglas chairs (Hake and Azrin, 1953) and were loosely restrained in the seated position by a waist lock. The chairs were enclosed in ventilated, sound-attenuating chambers (model AC-3; Industrial Acoustics Co., Inc., Bronx, NY) that were provided with continuous white noise to mask extraneous sounds. The monkeys were fully adapted to the chair and acoustic chamber prior to surgery. The distal end of the arterial catheter was connected via polyethylene tubing to a blood pressure transducer (T42–20; Coulbourn Instruments, Lehigh Valley, PA). The transducers were calibrated regularly between experimental sessions with a hand-held manometer. During the sessions, the arterial catheter was continuously flushed with heparinized saline (5 units/ml) at a rate of 0.03 ml/min. The transducer was connected to an associated amplifier (ST2–25; Coulbourn Instruments) and blood pressure processor (ST7–24; Coulbourn Instruments) outside the experimental chamber. The blood pressure processor analyzed the raw transducer signal, giving analog outputs of systolic, diastolic, and mean pressure at the end of each cardiac cycle. The signal for the end of the cardiac cycle was fed into an Apple Macintosh computer (Apple Computers Inc., Cupertino, CA). For each cycle, the computer measured the time between cycles with a resolution of 1 ms and read the analog signals for pressure from the blood pressure processor with a resolution of 1 mm Hg. These values were summed and averaged over periods of 30 s for subsequent analysis. Only mean arterial pressure (diastolic + ((systolic – diastolic)/3)) and heart rate were used for statistical analysis.

The distal end of the venous catheter was passed outside the experimental chamber via polyethylene tubing and connected to a syringe for the injection of drugs. Needle electrodes (Grass Instruments, Quincy, MA) were used to collect ECGs. The ECG was recorded for 5 s at three different time points (1 min before the injection and 1 min and 5 min following injection). From the ECG signal, measures of P-R, QRS, and QT were taken and QT was corrected (cube root). Change scores were then calculated using the ECG values before drug injection as baseline. ECG was not systematically affected by any of the drugs or the drug combinations, so data are not reported here. This is consistent with previous results with lower doses of cocaine (cf. Schindler, 1996). Typically, changes in ECG are most evident at doses above 3.0 mg/kg.

**Procedure.** The subjects were placed in the chamber every weekday. Typically, injections of drugs were given on Tuesdays and Fri-
days, and saline vehicle was given on all other training days. The order of doses was nonsystematic. For all sessions, the subjects were placed in the chamber for a period of 90 min, with the i.v. injection of drug or saline (1.0 ml/kg) given, if scheduled, 30 min after the start of the session. For drug combination studies, the pretreatment drug was given i.v. 5 min prior to cocaine. There were also control sessions in which drug vehicle was given 5 min prior to cocaine and sessions in which a pretreatment drug was followed 5 min later by saline (the cocaine vehicle). These control sessions were no different from baseline drug or saline sessions, and therefore their results were combined for analysis.

**Drugs.** Cocaine hydrochloride (National Institute on Drug Abuse, Baltimore, MD) was dissolved in sterile, physiological saline. SKF 77434, SKF 82958, SKF 81297, GBR 12909 (Sigma/RBI, Natick, MA), and UH 232 (Tocris Cookson, Ballwin, MO) were dissolved in sterile water. The i.v. injections were given over a period not exceeding 15 s.

**Data Analysis.** Heart rate and blood pressure data were averaged over 1-min periods from the 30-s periods averaged by the computer. The use of 30-s means leads to a greater amount of variability in blood pressure and heart rate even following saline administration. This variability most likely reflects movement by the animal. Therefore, the use of the 1-min mean gives a more accurate measure of any drug-induced change in both the blood pressure and heart rate measures. The rate-pressure product (RPP) was calculated by multiplying systolic pressure and heart rate. Peak change effects were calculated using 5-min means with the 5-min period prior to the i.v. injection of saline or cocaine as baseline. Area under the curve (AUC) was calculated using the 1-min mean change scores, in which the 5-min period prior to drug administration was used as the baseline. As peak effects on blood pressure typically occurred within 5 min of drug administration and peak effects on heart rate typically occurred within 30 min, AUC measures are reported for the 30-min period following the last injection of the session. While some drugs had more persistent effects, the 30-min measure ensured that peak effects of both the treatment drug and cocaine were captured for the drug combination studies. Error bars are the standard error of the mean. Since peak effects were generally similar to the AUC effects, only the AUC measure is reported here. All data were subjected to a least-squares analysis of variance with Fisher follow-up tests to determine individual effects (Wilkinson, 1992). A linear regression was performed on the linear portion of the dose-effect function for cocaine and each pretreatment drug given alone. The effect for 1.0 mg/kg cocaine was then arbitrarily assigned the ED\textsubscript{100} value. Predicted additivity lines were constructed for drug combinations in which both drugs showed positive effects using dose-addition techniques (Woolverton, 1987).

**Results**

For saline-control sessions (n = 11), baseline blood pressure was 118.6 ± 3.6 mm Hg, and baseline heart rate was 252.1 ± 12.4 beats/min. Baseline blood pressure and heart rate did not differ significantly from these values for any of the drugs tested.

**Drugs Alone**

**Cocaine.** Figure 1 shows the AUC results for cocaine (n = 8–11/dose). Cocaine produced a dose-dependent increase in the blood pressure AUC (F\textsubscript{5,53} = 15.4, p < 0.001). The heart rate AUC values also increased at higher doses (F\textsubscript{5,53} = 7.1, P < 0.01), although the maximal heart rate effect was smaller at the highest dose. This decrease in the heart rate AUC at the highest dose also led to a decrease in RPP at this dose. At the lower doses, there was a clear relationship between dose and the RPP (F\textsubscript{5,54} = 10.4, p < 0.001). For all three measures, every dose above 0.03 mg/kg was significantly different from saline control (p < 0.01). The peak blood pressure effects were within 5 min of administration for all the doses tested and returned to near baseline by the end of the session (i.e., 60 min following administration). For heart rate, however, the peak effects usually occurred within 30 min of administration but persisted until at least the end of the session. There was also a tendency for the heart rate-increasing effect to be delayed at the higher doses, which accounted for the tendency of heart rate and RPP AUC to decrease at the higher doses.

**D1 Agonists.** Like cocaine, SKF 82958 (n = 3–6/dose) increased blood pressure (Fig. 1), which was reflected in an increase in the AUC (F\textsubscript{4,22} = 12.0, p < 0.001) measure.
that was similar to cocaine. The effects were significant at doses above 0.03 mg/kg (p < 0.001). None of the other D1 agonists, up to the highest doses tested, produced an increase in blood pressure that equaled that of cocaine. Nevertheless, the effects of SKF 81297 (n = 5/dose) on the blood pressure AUC were significant (F_{3,16} = 9.0, p < 0.01). The effect of SKF 77434 (n = 4/dose) was not significant. Except for SKF 77434, the D1 agonists tended to increase heart rate. The tendency was for SKF 77434 to decrease heart rate, although this effect was not significant. SKF 82958 again produced increases in the AUC (F_{3,22} = 10.9, p < 0.001) heart rate measure that were comparable to those with cocaine. The effects were significantly different from those with saline for the two highest doses (p < 0.001). The effects of SKF 81297 were also significant on the heart rate AUC (F_{3,16} = 4.9, p < 0.05), with the effect at the highest dose being significantly different from that of saline (p < 0.01). For the RPP, both SKF 82958 and SKF 81297 produced increases, whereas SKF 77434 tended to produce a decrease, although again the effect of SKF 77434 was not significant. SKF 82958 produced significant increases in RPP for the AUC (F_{3,22} = 14.1, p < 0.001) measure. These effects were comparable to those of cocaine, with all doses above 0.03 mg/kg being significantly different from saline control (p < 0.01). Likewise, the effect of SKF 81297 was significant for the AUC (F_{3,16} = 8.4, p < 0.01) measure, although SKF 81297 was clearly less potent than either cocaine or SKF 82958, with only the effect at 3.0 mg/kg being significantly different from that of saline.

Like cocaine, the D1 agonists produced immediate effects on blood pressure, with the peak effects for both SKF 82958 and SKF 81297 occurring within 5 min of administration. In contrast to cocaine, the peak heart rate effect also occurred within 5 min of administration for all doses of SKF 82958 and SKF 81297. The duration of action of the D1 agonists was also relatively short. The blood-pressure-increasing effect of SKF 82958 returned to baseline by 30 min after administration and the heart rate effect returned to baseline by 40 min. The blood pressure effect of SKF 81297 returned to baseline by 40 min, with the heart rate-increasing effect returning to baseline by 50 min. The partial agonist SKF 77434 produced a slight increase in blood pressure within 5 min of administration that reversed to a decrease in pressure that was most evident later in the session. The small decrease in heart rate also occurred later in the session.

**D2 Agonist.** The effect of quinpirole (n = 5/dose) on blood pressure (Fig. 1) was not significant, although quinpirole tended to decrease blood pressure. In contrast, quinpirole tended to increase heart rate, but again this effect failed to reach significance. This tendency for quinpirole to produce a decrease in pressure and an increase in heart rate led to only a small, nonsignificant change in the RPP. The decrease in blood pressure occurred within 10 min of administration and persisted for approximately 50 min. The heart rate increase also occurred within the first 5 min after drug administration and persisted longer than the blood pressure decreases.

**Indirect Agonists.** GBR 12909 (n = 5–8/dose) produced significant increases in the AUC (F_{3,24} = 3.9, p < 0.05) blood pressure measure (Fig. 1), but this effect was only significant at the 1.0 mg/kg dose (p < 0.01). The time course for GBR 12909, as expected, was longer than that for cocaine, but the peak effect of GBR 12909 on blood pressure still occurred at approximately 5 min following administration, similar to cocaine. The effects on blood pressure did persist until at least 60 min following administration. UH 232 (n = 4–7/dose) also produced significant increases in the AUC (F_{3,19} = 7.1, p < 0.01) blood pressure measure, with doses above 0.3 mg/kg being significantly different from those of saline (p < 0.05). The blood pressure-increasing effect of UH 232 also peaked within 5 min of administration and was returning toward baseline by 60 min. As with blood pressure, the effect of GBR 12909 on the heart rate AUC (F_{3,24} = 5.4, p < 0.01) measure was significantly different from saline only at the 1.0 mg/kg dose (p < 0.01). The effect of UH 232 on the heart rate AUC was also significant (F_{3,19} = 3.2, p < 0.05). The heart rate AUC measure for UH 232 was significantly different from saline for both the 1.0 and 3.0 mg/kg doses. The heart rate-increasing effects of both GBR 12909 and UH 232 occurred within 10 min of drug administration. Like cocaine, the effect of the higher dose of GBR 12909 was not as great as a lower dose. The effects of both drugs on heart rate persisted through the end of the session. GBR 12909 produced significant increases in the RPP AUC (F_{3,24} = 5.9, p < 0.01) measure, with the effect at both 1.0 and 3.0 mg/kg being significantly different from saline control (p < 0.05). Finally, the effect of UH 232 on the AUC RPP measure was also significant (F_{3,19} = 4.2, p < 0.05). Follow-up tests revealed that both the 1 and 3 mg/kg doses were significantly different from saline for the AUC measure (p < 0.05).

**Drug Combinations**

The different D1 and D2 agonists and indirect agonists were tested as pretreatments followed by at least 0.3 mg/kg cocaine, because this dose produced significant increases in both blood pressure and heart rate that were submaximal, leaving room to observe a potentiation. This dose of cocaine also falls within the range of doses abused by humans. Doses of the pretreatment drugs were chosen that appeared to have maximal effects on either blood pressure or heart rate. Since the significant effects of all the drugs occurred immediately after administration, a pretreatment time of 5 min was used before the cocaine administration. With the shorter duration of action of the D1 agonists, the AUC measures reflect the first 30 min after the cocaine administration when all drugs showed their largest effects. Although the possibility of delayed effects cannot be ruled out, this reflects the period of time when significant interaction between the drugs should be most likely.

**D1 Agonists.** Like cocaine, the D1 agonist SKF 82958 increased both blood pressure and heart rate. The dose of 0.1 mg/kg SKF 82958 produced a near maximal effect when given alone. When given in combination with cocaine, however, no potentiation was observed for any measure (Fig. 2). In fact, it appeared as though the two drugs together might have been mutually antagonistic because the effects at the higher dose appeared to be lower than the effects of either drug alone. This was reflected in significant pretreatment × dose effects for all three measures (F_{2,30} > 5.5, p < 0.01). For both heart rate and RPP, the effect of 0.1 mg/kg SKF 82958 combined with 0.3 mg/kg cocaine was significantly different from that of cocaine alone (p < 0.05). The solid line in Fig. 2 represents the dose-additivity line. At no time did the effects of the combination exceed additivity.

The partial D1 agonist had little effect on either blood pressure or heart rate, so the highest dose of SKF 77434 (3.0 mg/kg) was not significant. Follow-up tests revealed that the effect at the 3 mg/kg dose was significantly different from saline (p < 0.05).

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mg/kg) was given in combination with both 0.3 and 3.0 mg/kg cocaine (Fig. 2). The higher dose of cocaine produced a smaller increase in heart rate than did the lower dose, and for this subset of monkeys, the change in the heart rate measure was even more pronounced than that seen in Fig. 1. Nevertheless, when given in combination with cocaine, SKF 77434 clearly did not potentiate the effects of cocaine. In fact, at the lower cocaine dose, SKF 77434 appeared to antagonize the effect of cocaine. No significant pretreatment dose effects were observed; however, the pretreatment effect was significant for both the heart rate ($F_{1,12} = 7.7, p < 0.05$) and RPP ($F_{1,12} = 6.1, p < 0.05$) measures, indicating a significant reduction of these effects.

D2 Agonist. In contrast to cocaine, the D2 agonist quinpirole tended to decrease blood pressure. At a dose of 0.03 mg/kg, which produced maximal effects on both blood pressure and heart rate, the combined effect of quinpirole and cocaine (Fig. 3) approximated those of quinpirole on blood pressure. This was reflected in a significant pretreatment effect ($F_{1,16} = 9.9, p < 0.01$). For heart rate, the combined effect was elevated over that of cocaine alone, which was again reflected in a significant pretreatment effect ($F_{1,16} = 9.8, p < 0.01$). This effect appeared to be strictly additive, because the combined curve overlaps the additive line at every dose. Finally, the tendency for quinpirole to decrease blood pressure and increase heart rate produced wide variability for the RPP measure. Here the combined effect approached those of cocaine alone and no significant effects of pretreatment were observed.

Indirect Agonists. Both cocaine and GBR 12909 are potent dopamine uptake inhibitors. The 1.0 mg/kg dose of GBR 12909 produced a maximal effect when given alone. Figure 4 shows the effect of 1.0 mg/kg GBR 12909 given in combination with 0.03 and 0.3 mg/kg cocaine. Although GBR 12909 alone and cocaine alone both increased blood pressure and heart rate, when the two were given in combination, the effect observed was similar to that of cocaine alone. No significant pretreatment $\times$ dose or pretreatment effect was observed for any measure. At no time did the effect of the drug combination exceed additivity on any measure.
Finally, UH 232 had its maximal effects at 1.0 mg/kg, and like cocaine, UH 232 increased both blood pressure and heart rate. The combination of UH 232 and cocaine produced greater increases in every measure than cocaine alone (Fig. 4). This was reflected in a significant pretreatment effect at all three measures ($F_{1,29} > 4.7, p < 0.05$). However, as with quinpirole, the observed effects were generally no greater than additive. At the highest cocaine dose, the effect of the combination was actually below the additive line for each measure. The one point that appears to be clearly above the additive line is for the drug combination at the 0.1 mg/kg cocaine dose on RPP.

**Discussion**

Cocaine produced a dose-dependent increase in blood pressure that was highest at the highest doses tested. In contrast, the effects of cocaine on heart rate peaked at 1.0 mg/kg, with a smaller effect seen at the higher dose. These effects of cocaine were similar to previous results reported for squirrel monkeys (Tella et al., 1990; Schindler et al., 1995). Previous studies have suggested an involvement of noradrenergic mechanisms in these cardiovascular effects of cocaine (Kuhn et al., 1990; e.g., Branch and Knuepfer, 1992; Schindler et al., 1992a) but little or no involvement of dopaminergic mechanisms (Kiritsy-Roy et al., 1990; Schindler et al., 1991). Nevertheless, cocaine may interact with dopaminergic agonists on cardiovascular function because cocaine is a potent dopamine uptake blocker.

A number of the dopamine agonists tested produced effects similar to those of cocaine. In particular, both of the D1 agonists tested produced increases in blood pressure and heart rate, as did the indirect agonists GBR 12909 and UH 232. In contrast, whereas the D2 agonist quinpirole produced an increase in heart rate, blood pressure was decreased following quinpirole. The partial D1 agonist SKF 77434 had little effect on blood pressure and only a small tendency to decrease heart rate. These results suggest that if cocaine alters cardiovascular function through an action at dopamine receptors, it is most likely mediated by the D1 receptor. In previous studies, however, pretreatment with the specific D1 antagonist SCH 23390 did not antagonize the cardiovascular effects of cocaine in squirrel monkeys (Schindler et al., 1991) or rats (Kiritsy-Roy et al., 1990).

Action at peripheral dopamine receptors may complicate the role of dopamine D2 receptors in the cardiovascular effects of cocaine. Any action at these receptors would be expected to produce vasodilation (Kohli and Goldberg, 1990). As a decrease in blood pressure and an apparent reflex tachycardia were observed with quinpirole, peripheral DA2 receptor actions may predominate with quinpirole. In contrast, with cocaine central dopaminergic actions might predominate. When two animals were treated with the peripherally active DA2 antagonist domperidone (0.03 mg/kg) prior to quinpirole (0.03 mg/kg) administration, it appeared to block the depressor effect of quinpirole, but no evidence of a pressor effect was observed (blood pressure AUC = 27.1 mm Hg min). Therefore, the blood pressure-decreasing effect of quinpirole may be due to a peripheral mechanism. However, it is not clear whether central D2 receptors could potentially contribute to the effects of cocaine. Cocaine itself has little effect in the periphery as the quaternary derivative of cocaine, cocaine methiodide, does not produce profound effects on either blood pressure or heart rate (Schindler et al., 1992b).

The dopaminergic agonists and antagonists used in the present study have seldom been examined in previous studies of cardiovascular function in conscious animals, making comparisons difficult. Tella (1996) showed that GBR 12909 produced a prolonged increase in blood pressure and heart rate in conscious rats, although Knuepfer and Gan (1997) failed to show a similar effect. Quinpirole decreases blood pressure in a number of conscious animal models (e.g., Nagahama et al., 1986). However, in rat models where the central action of quinpirole predominates, blood pressure increases are observed (van den Buuse et al., 1996).

Given that the D1 agonists and the indirect agonists produced effects similar to those of cocaine, it was expected that additive effects would be observed in the drug combination studies. However, subadditive effects were observed with GBR 12909 and SKF 82958. The nature of this interaction is not clear, but the data suggest that the drugs are producing their effects through different mechanisms. For example, if the blood pressure-increasing effect of SKF 82958 and cocaine were both mediated through D1 receptors, then at submaximal doses, additive effects should have occurred. Similarly, if dopamine-uptake inhibition mediated the cardiovascular effects of cocaine, additive effects should have
occurred with GBR 12909. That this was not the case argues against a common mechanism. Thus, whereas both GRB 12909 and SKF 81297 produced effects similar to those of cocaine, the results of the drug combination studies suggest that the cardiovascular effects of cocaine are not mediated solely through an action at dopamine receptors, a conclusion in full agreement with previous work with dopamine antagonists (Kiritty-Roy et al., 1990; Schindler et al., 1991).

Interpretations of the fact that pretreatment with the D1 agonists and GBR 12909 did not lead to a potentiated cardiovascular effect of cocaine are complicated by the possibility of acute tolerance. It is known that repeated administration of cocaine over a short period leads to smaller cardiovascular effects with subsequent doses (Smith et al., 1993). Therefore, pretreatment with the dopamine agonists may have blunted the cardiovascular effect of cocaine through acute tolerance. However, shifting baselines are often used to calculate change scores (Pagel et al., 1994), complicating the importance of acute tolerance. In the current study, the baseline calculation was drawn from the time period prior to any drug administration.

Additive effects were observed with UH 232 and cocaine on both blood pressure and heart rate at the lower doses tested. Additive effects were also observed with quinpirole and cocaine on heart rate. Although additive effects would be expected if drugs were acting through a common mechanism, the finding of additive effects is subject to alternative interpretations. For example, the heart rate-increasing effect of quinpirole most likely results from a baroreceptor response to the decrease in blood pressure produced by the action of the quinpirole at peripheral DA2 receptors. In the two monkeys tested with quinpirole following domperidone, no change in heart rate was observed (AUC = 13.3 beats/min • min). In contrast, cocaine depresses baroreceptor function (Andresen et al., 1990). Likewise, it seems unlikely that the additive effects of UH 232 and cocaine result from a common mechanism of action. UH 232 increases dopamine function at some central sites through an antagonist action at presynaptic dopamine receptors (Svensson et al., 1986). As such, its agonist actions should be mediated through postsynaptic receptors that would be equally affected by GBR 12909. Since GBR 12909 did not produce additive effects with cocaine, it seems unlikely that any increase in dopamine function is responsible for cocaine’s prominent cardiovascular effects. Nevertheless, these results do not rule out the possibility that dopaminergic systems might contribute, at least partially, to cocaine’s overall cardiovascular effects.

In conclusion, the dopamine D1 agonists SKF 82958 and SKF 81297 and the dopamine uptake inhibitor GBR 12909 had cardiovascular effects that were similar to those of cocaine. Despite this similarity, these cardiovascular effects appear to be mediated via different mechanisms since SKF 82958 and GBR 12909 produced subadditive effects when combined with cocaine. The partial D1 agonist SKF 77434 had little effect on its own and appeared to antagonize the effects of lower doses of cocaine, and its cardiovascular effects in combination with higher doses of cocaine approximated those of cocaine alone. Thus, the use of D1 agonists in treatment for cocaine abuse should not be precluded by adverse cardiovascular safety concerns. Of course, in treatment, these drugs will be used chronically. Whether chronic use might reveal any additional adverse effects will need to be determined. The D2 agonist quinpirole produced a depressor effect that may be mediated by peripheral DA2 receptors. The heart rate-increasing effect of quinpirole most likely resulted from a baroreceptor response due to the decrease in pressure. When given in combination with cocaine, quinpirole reduced the pressor effect of cocaine, but an additive effect was observed on heart rate. Finally, the dopamine autoreceptor antagonist UH 232 increased blood pressure and heart rate as cocaine does, and additive effects were observed when it was given in combination with cocaine. These findings suggest caution when using D2 agonists or dopamine autoreceptor antagonists in subjects that might use cocaine.

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