Cocaine Potentiates Ethanol-Induced Excitation of Dopaminergic Reward Neurons in the Ventral Tegmental Area

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ABSTRACT

The coabuse of cocaine and ethanol is one of the most frequently used substance abuse combinations in the United States. The dopamine (DA) neurons in the ventral tegmental area (VTA) are important in the rewarding mechanism of these two substances. Cocaine is known to block the reuptake of DA and serotonin (5-HT). At concentrations below 1 μM, cocaine preferentially blocks the reuptake of 5-HT compared with DA. We have previously shown that ethanol increases the firing rate of DA neurons in the VTA, and that this excitation is enhanced by 5-HT. Extracellular single-unit recordings were made from VTA dopaminergic neurons in coronal brain slices from young adult Fischer 344 rats. Cocaine (1–10 μM) reduced the spontaneous firing rate in VTA dopaminergic neurons in a concentration-related manner. A lower concentration of cocaine (500 nM), which is a concentration that is pharmacologically relevant in addicts, produced only a very small decrease in the firing rate of VTA neurons but potentiated ethanol excitation of these neurons. Higher concentrations of cocaine (1 μM) did not enhance ethanol excitation. Ethanol-induced excitation was potentiated by the higher concentrations of cocaine (1 and 2 μM) in the presence of the D2 receptor antagonist sulpiride (1 μM). Furthermore, cocaine potentiation of ethanol-induced excitation was reversed by ketanserin (2 μM), a 5-HT2 antagonist. The enhanced ethanol excitation of VTA dopaminergic neurons caused by cocaine may partially explain the high incidence of the coabuse of these two substances.

In the United States, illicit drug abuse is a national epidemic with an estimated 13.9 million people using illicit drugs on a monthly basis in 1997 (SAMHSA, 1998). Alcohol remains the most popular substance of abuse; 111 million people currently drink alcohol on a monthly basis. The 1997 National Household Survey on Drug Abuse found that 1.5 million people in the United States currently use cocaine on a monthly basis, thus making alcohol and cocaine two of the most widely abused drugs. Coabuse of alcohol and cocaine is one of the most common illicit drug combinations used in the United States. A national survey found that 96.5% of cocaine users also report alcohol use over the same month period (concurrent use) and of these 85.7% took the two drugs together (simultaneous use) (Grant and Harford, 1990). Over the past decade, the Drug Abuse Warning Network report has stated that the combination of ethanol and cocaine is one of the top two drug combinations found in metropolitan emergency departments across the United States (DAWN, 1987; SAMHSA, 1998). The acute effects of simultaneous alcohol and cocaine use include gross impairment of judgment and psychomotor skills and increase the risk of traffic, occupational, and other accidents; overdose; and death (Grant and Harford, 1990).

The mesolimbic/mesocortical dopamine (DA) pathway is important for self-administration of cocaine and ethanol (Wise, 1987). Dopaminergic neurons in the ventral tegmental area (VTA) are the cells of origin of the mesolimbic/mesocortical DA pathways and provide dopaminergic innervation of the nucleus accumbens (Oades and Halliday, 1987). Disruption of central dopaminergic systems alters ethanol self-administration (Pfeffer and Samson, 1988; Sumson et al., 1993). Ethanol’s rewarding properties may be related to its ability to excite dopaminergic cell bodies in the VTA (Gessa et al., 1985; Brodie et al., 1990). Cocaine’s rewarding properties may be due to its blockade of DA reuptake in the nucleus accumbens, which increases and prolongs the effect of synaptically released DA (Ritz et al., 1987; Koob and Bloom, 1988). Disruption of central dopaminergic processes alters cocaine self-administration (Roberts and Koob, 1982; Pettit et al., 1984; Koob and Weiss, 1992). Rats will self-administer ethanol directly into the VTA (Gatto et al., 1994; Rodd et al., 1998) and will self-administer cocaine into the nucleus accumbens (McBride et al., 1999). These data indicate that although the rewarding effect of both of these drugs is mediated by the mesolimbic pathway, they are acting at different points in the pathway, ethanol at the dopaminergic cell

ABBREVIATIONS: DA, dopamine; VTA, ventral tegmental area; 5-HT, serotonin; aCSF, artificial cerebral spinal fluid.
bodies in the VTA and cocaine in the DA terminal fields in the nucleus accumbens.

Serotonergic neurons project from the median and dorsal Raphe nuclei, into both the VTA and nucleus accumbens (Herve et al., 1987). In addition to its blockade of DA reuptake, cocaine blocks the reuptake of serotonin (5-HT); the affinity of cocaine for the 5-HT transporter is higher than its affinity for the DA transporter (Ritz et al., 1987). At low concentrations (300 nM–1 μM), cocaine primarily enhanced 5-HT responses in the nucleus accumbens, indicating a greater effect on 5-HT reuptake than DA reuptake in this concentration range (Uchimura and North, 1990). Interestingly, these low concentrations of cocaine are clinically relevant because mean plasma cocaine concentrations in cocaine addicts at the time of maximum "high" were 370 to 570 nM after intranasal administration and 730 nM to 1 μM after i.v. injection of cocaine (Javaid et al., 1978). In vivo dialysis studies in rats estimate brain concentrations to be 1 to 2.5 μM 20 min after i.v. injection of 3 mg/kg cocaine (Pan et al., 1994).

Our previous studies in brain slices have shown that ethanol increases the firing rate of dopaminergic VTA neurons in a concentration-dependent manner over a behaviorally relevant range of ethanol concentrations (20–200 mM; see Materials and Methods) (Brodie et al., 1990). Application of 5-HT potentiates the ethanol-induced excitation of these neurons (Brodie et al., 1995). Furthermore, the monoamine reuptake blocker clomipramine potentiates ethanol-induced excitation of dopaminergic VTA neurons, and clomipramine enhances 5-HT-induced potentiation of ethanol excitation (Trifunovic and Brodie, 1996). The present study was undertaken to test whether cocaine, which also blocks 5-HT reuptake, modulates ethanol excitation of dopaminergic VTA neurons. Extracellular recording in brain slices was used to measure the effect of pharmacologically relevant concentrations of cocaine on ethanol excitation of dopaminergic VTA neurons. Some of the results have been previously reported in abstract form (Bunney et al., 1998).

Materials and Methods

Brain Slice Preparation. Fischer 344 rats (100–200 g) were sacrificed by cervical dislocation and the brain removed; this method of sacrifice is rapid and acceptable for rats of this size. Animals used in this study were treated in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The full methodology for our preparation of brain slices of the ventral tegmental area has been published previously (Brodie et al., 1990). Briefly, the rat brain was removed rapidly from the cranium and kept chilled and moist during dissection. A tissue block containing the VTA and substantia nigra was mounted in a vibratome and submerged in chilled, oxygenated artificial cerebrospinal fluid (aCSF). Coronal sections (400-μm thickness) were cut and the tissue was mounted directly in the recording chamber. Equilibration time of 1 h was allowed after placement of tissue in the recording chamber before recordings were made. The slice sat on a mesh platform, totally submerged in the recording chamber, and was weighted down with small platinum logs to increase the stability of recordings. A superfusion system maintained the flow of medium at 2 ml/min; the temperature in the recording chamber was ~35°C. The flow rate of fluid to the recording chamber was continuously monitored with a flowmeter, and adjustable valves were used to keep the rate constant. The small volume chamber (~300 μl) used in these studies permitted the rapid application and washout of drug solutions. The composition of the aCSF in these experiments was 126 mM NaCl, 2.5 mM KCl, 1.24 mM NaH2PO4, 2.4 mM CaCl2, 1.3 mM MgSO4, 26 mM NaHCO3, and 11 mM glucose. The aCSF was saturated with 95% O2, 5% CO2 at 35°C, pH = 7.4.

Cell Identification. We positioned electrodes into the VTA by visual guidance; the VTA is clearly visible in the fresh tissue as a gray area medial to the darker substantia nigra and separated from the nigra by white matter. Note that dopaminergic neurons have been shown to have electrophysiological characteristics very different from those of nondopaminergic cells in this region (Grace and Bunney, 1983). DA-containing neurons possess broad (>2.5 ms) action potentials often with an inflection or "notch" on the rising phase, fire spontaneously and regularly at 0.5 to 5 Hz, and show inhibition by DA (Bunney et al., 1973; Aghajanian and Bunney, 1977; Grace, 1987). Only neurons meeting these electrophysiological criteria were studied.

Drug Administration. Drugs were added to the aCSF by means of a calibrated infusion pump from stock solutions 100 to 1000 times the desired final concentrations. The addition of drug solutions to the aCSF was performed in such a way as to permit the drug solution to mix completely with aCSF before this mixture reached the recording chamber. Final concentrations were calculated from aCSF flow rate, pump infusion rate, and concentration of drug stock solution. Typically, drugs reach equilibrium in the tissue after 2 to 3 min of application. (−)-Cocaine HCl and (++)-sulpiride were obtained from Research Biochemicals International (Natick, MA). Cocaine effects required ~1 h of washout to fully reverse; therefore, lower concentrations of cocaine were always tested (in the absence and presence of ethanol) before higher concentrations of cocaine were administered. Each concentration of cocaine was applied for 20 min before ethanol responses in the presence of cocaine were tested.

A stock solution of 95% ethanol (v/v USP) was used in the pump, and infusion of ethanol never exceeded 1% of the flow rate of the aCSF. Ethanol was administered for 6 or 7 min to ensure that measurements were made after the full ethanol concentration was reached in the tissue and the peak drug effect was attained.

The behaviorally active range for blood ethanol concentrations in the rat extends from 40 mM (sedation) to 90 mM (loss of righting reflex) (Majchrowicz and Hunt, 1976); the lethal blood ethanol concentration in rats is ~200 mM (LD50 = 202 mM) (Haggard et al., 1940). The present study examined ethanol concentrations in the range of 40 to 120 mM, pharmacologically relevant, sublethal concentrations in the rat.

Extracellular Recording. Extracellular recording electrodes were made from 1.5-mm-diameter glass tubing with filament and were filled with 0.9% NaCl. Tip resistance of the microelectrodes ranged from 4 to 8 MΩ. The Fintronics amplifier used in these recordings includes a window discriminator, the output of which was fed to both a rectilinear pen recorder and a computer-based data acquisition system that was used for on-line and off-line analysis of the data. The multiplexed output of the Fintronics amplifier was displayed on an analog storage oscilloscope for accurate adjustment of the window levels used to monitor single units. An IBM PC-based data acquisition system was used to calculate, display, and store the frequency of firing over 5-s and 1-min intervals. Firing rate was determined before and during drug application. Firing rate was calculated over a 1-min interval immediately before drug administration and a 1-min interval during the peak drug effect; drug-induced changes in firing rate were expressed as the percentage change from the control firing rate according to the formula ((FRD – FRc)/FRc) × 100, where FRD is the firing rate during the peak drug effect and FRc is the control firing rate. The change in firing rate thus is expressed as a percentage of the initial firing rate, which controls for small changes in firing rate that may occur over time.

Statistical Analysis. Averaged numerical values were expressed as means ± S.E. The significance of firing rate changes before and after a single drug concentration was assessed with a paired t-test. For effects of multiple drug concentrations or more than one drug, an
appropriate one- or two-way ANOVA was used, followed by Student-
Newman-Keuls post hoc comparisons when needed (Kenakin, 1987).
Statistical analyses were performed with SigmaStat (SPSS, Chicago,
IL).

Results

In this study, extracellular single-unit recordings were
made from 64 VTA neurons (from 62 rats) that were identi-
fied as dopaminergic according to electrophysiological crite-
ria (see Materials and Methods). All neurons fired spontaneous
action potentials, with regular interspike intervals, at
rates ranging from 0.59 to 3.0 Hz; the mean ± S.E. firing rate
was 1.59 ± 0.07 Hz (n = 64).

Cocaine Concentration-Response Curve. The sponta-
neous firing rate of dopaminergic VTA neurons was reduced
by cocaine. In the dopaminergic VTA neuron illustrated in
Fig. 1A, increasing concentrations of cocaine (1–10 μM)
caused a concentration-dependent decrease in the firing rate
of the neuron. Figure 1B is the pooled data from 16 experi-
ments similar to the one shown in Fig. 1A. The mean per-
centage decrease in firing rate ranged from 3.9 ± 1.6% with
500 nM cocaine to 49.0 ± 8.2% with 10 μM cocaine. The
inhibition of dopaminergic VTA neurons by cocaine was con-
centration-dependent (one-way ANOVA, F = 9.35; df = 3,51;
P < .001).

A Low Concentration of Cocaine Enhances Ethanol
Excitation of VTA Dopaminergic Neurons. As discussed
above, ethanol increases the firing rate of dopaminergic VTA
neurons. In the present study, we found that the ethanol-
induced excitation of dopaminergic VTA neurons is enhanced
by a low concentration of cocaine (500 nM). Figure 2 illus-
trates a single VTA neuron’s response to ethanol, followed by

![Fig. 1.](image1.png)

Fig. 1. Cocaine inhibits the firing rate of dopaminergic VTA neurons in a
concentration-dependent manner. A, firing rate is plotted as a function of
time; each vertical bar represents the average firing rate over a 5-s
interval. The horizontal bars indicate the duration of bath application of
the concentration of cocaine noted above the bar. In this neuron the firing
rate was reduced by 1 μM cocaine (−10.7%), 2 μM (−15.5%), 5 μM
(−27.9%), and 10 μM (−49.3%). Note the inhibition reversed on wash-
out of cocaine. B, pooled concentration-response curve for cocaine re-
sponses measured from 16 neurons in experiments similar to those shown
in A. Mean percent inhibition is plotted as a function of cocaine concen-
tration. Points indicate mean responses of 8 to 16 neurons; error bars
indicate standard error. Firing rates before cocaine administration for
each group of neurons were 1.82 ± 0.21 Hz (500 nM; n = 9), 1.76 ± 0.15
Hz (1 μM; n = 16), 1.76 ± 0.15 Hz (2 μM; n = 16), 1.73 ± 0.13 Hz (5 μM;
N = 14), and 1.80 ± 0.17 Hz (10 μM; n = 8). The inhibition of firing
produced by cocaine was concentration-dependent (one-way ANOVA, P < .001).

![Fig. 2.](image2.png)

Fig. 2. Cocaine enhances ethanol-induced excitation of a dopaminergic
VTA neuron. A, firing rate is plotted as a function of time; each vertical
bar represents the average firing rate over a 5-s interval. The horizontal
bar indicates the duration of bath application of ethanol (80 or 120 mM).
In the control condition, these concentrations of ethanol increased the
firing rate by 36.5 and 49.1%, respectively. B, in the presence of 200 nM
cocaine, the same concentrations of ethanol excited the
firing of this cell by 48.4 and 80.0%, respectively. C, in the presence of 500
nM cocaine, the same concentrations of ethanol (80 and 120 mM) excited
the firing of this cell by 45.1 and 106.6%, respectively.
this cell’s response to ethanol in the presence of either 200 or 500 nM cocaine. In this cell before cocaine, 80 nM ethanol caused a 36.5% increase in firing rate and 120 nM ethanol caused a 49.1% increase; in the presence of 200 nM cocaine, 80 nM ethanol caused an increase of 48.4% and 120 nM ethanol caused an increase of 80.0% in firing. In 500 nM cocaine, 80 nM ethanol caused an increase of 45.1% and 120 nM ethanol caused a 106.6% increase in firing rate. Although burst activity is apparent during ethanol application to this neuron, no other cell in these studies exhibited any bursting activity in the absence or presence of cocaine or ethanol.

In the population of dopaminergic VTA neurons tested with cocaine and ethanol (Fig. 3), 200 nM to 1 μM cocaine alone produced very small (6–11%) but statistically significant decreases in the firing rate. The mean firing rate was decreased from 2.11 ± 0.28 to 1.98 ± 0.27 Hz by 200 nM cocaine (n = 11; paired t test, t = 3.09, df = 10, P < .02); 500 nM cocaine decreased the mean firing rate from 1.67 ± 0.12 to 1.53 ± 0.12 Hz (n = 20; t = 3.41, df = 19, P < .01); and 1 μM cocaine decreased the mean firing rate from 1.65 ± 0.12 to 1.47 ± 0.10 Hz (n = 19; t = 4.69, df = 18, P < .001).

The pooled data (Fig. 3) show a significant enhancement of ethanol-induced excitation by cocaine at 500 nM (Fig. 3B; n = 20; two-way ANOVA, F = 7.95; df = 2.90; P < .05). Potentiation was seen in 70% (14 of 20) of the neurons tested with 500 nM cocaine. Despite the example shown in Fig. 2B, the pooled data showed no significant enhancement of ethanol potency by cocaine at 200 nM (Fig. 3A; n = 11; two-way ANOVA, P > .05). Nor was significant enhancement of ethanol potency produced by 1 μM cocaine (Fig. 3C; n = 19; two-way ANOVA, P > .05). The effect of ethanol was concentration-dependent in the experiments with all three cocaine concentrations shown in Fig. 3 (two-way ANOVAs, P < .002).

**Higher Concentrations of Cocaine Enhance Ethanol Excitation of Dopaminergic VTA Neurons in the Presence of the D2 Receptor Antagonist Sulpiride.** The following experiments were performed to determine whether higher concentrations of cocaine (1 and 2 μM) would enhance ethanol excitation when D2 receptors were blocked by sulpiride. Excitation by 80 and 120 mM ethanol was measured in each dopaminergic VTA neuron in the control condition, again in the presence of sulpiride (1 μM), and after the subsequent additions of 1 and 2 μM cocaine with sulpiride still present; pooled data for 15 dopaminergic VTA neurons are shown in Fig. 4. In the presence of sulpiride, both 1 and 2 μM cocaine enhanced the ethanol excitation (see open triangles and open squares in Fig. 4). A two-way ANOVA indicated that the ethanol excitation was concentration-dependent (F = 11.73; df = 1,112; P < .001) and that there was a significant effect of the sulpiride-cocaine conditions (F = 9.36; df = 3,112; P < .001). Specifically, Student-Newman-Keuls post hoc comparisons showed that in the presence of sulpiride, both 1 and 2 μM cocaine significantly (P < .02 and P < .001, respectively) enhanced the ethanol responses compared with responses in sulpiride alone. Ethanol responses in sulpiride alone were not significantly different from control (P > .05). Note that in the absence of sulpiride, 1 μM cocaine did not significantly enhance ethanol excitation as shown in Fig. 3C, but in the presence of sulpiride this concentration of cocaine did significantly enhance ethanol excitation (Fig. 4 and ANOVA and above-mentioned post hoc tests).

Sulpiride alone did not change the spontaneous firing rate of VTA neurons; mean firing rate was 1.54 ± 0.18 Hz before sulpiride and 1.59 ± 0.17 Hz in the presence of 1 μM sulpiride (n = 15; paired t test, P > .05). In contrast to the inhibition of firing caused by 1 and 2 μM cocaine in Fig. 1, in the presence of sulpiride, cocaine (1 and 2 μM) did not significantly decrease the firing rate of VTA neurons, consistent with D2 receptor blockade. The mean firing rate in the presence of sulpiride (1 μM) just before the addition of 1 μM
Cocaine Enhances Ethanol Excitation in VTA Dopamine Neurons

**Discussion**

In the present study, 1 to 10 μM cocaine decreased the firing rate of dopaminergic VTA neurons in a concentration-dependent manner, in agreement with previous studies (Brodie and Dunwiddie, 1990; Lacey et al., 1990). This cocaine-induced inhibition is similar in magnitude to that seen previously (Brodie and Dunwiddie, 1990); inhibition of VTA neurons by cocaine also has been observed in vivo (Einhorn et al., 1988). Ethanol, when applied alone, produced a concentration-dependent excitation of dopaminergic VTA neurons, as previously reported (Brodie et al., 1990). A low concentration of cocaine (500 nM), which produced only a small decrease in the firing rate of dopaminergic VTA neurons, significantly potentiated the ethanol excitation. We have previously shown that 5-HT and the monoamine reuptake inhibitor clomipramine potentiate ethanol excitation (Brodie et al., 1995; Trifunovic and Brodie, 1995). We hypothesize that the potentiation of ethanol excitation by cocaine seen in the present study is due to cocaine’s blockade of the 5-HT transporter. Good potentiation of ethanol excitation was seen with 200 nM cocaine in a few cells, but this concentration was too low to routinely observe ethanol enhancement, whereas robust potentiation of ethanol excitation was seen with 500 nM cocaine.

As the concentration of cocaine was increased to 1 μM, the enhancement of ethanol excitation was lost. Concentrations of cocaine in the range of 1 to 10 μM block both DA and 5-HT reuptake, thus increasing the extracellular concentration of both neurotransmitters (Chen and Reith, 1994). The cocaine-induced increase in extracellular dopamine inhibits VTA neurons by acting on D₂ autoreceptors (Brodie and Dunwiddie, 1990; Lacey et al., 1990). We suspect that the loss of potentiation of ethanol seen with higher cocaine concentrations is due to the increasing blockade of the dopamine transporter on the dopaminergic VTA neurons as the concentration of cocaine increases. This blockade causes extracellular DA to accumulate, which then acts on D₂ autoreceptors on the dopaminergic VTA neurons to reduce their firing rate. We hypothesized that if a D₂ receptor antagonist (sulpiride)
was added to the cocaine and ethanol combination, then higher concentrations of cocaine (1 and 2 \( \mu \)M) might be effective in producing enhancement of ethanol excitation in VTA dopamine neurons. Indeed, we found that in the presence of sulpiride (1 \( \mu \)M) both 1 and 2 \( \mu \)M cocaine significantly enhanced ethanol excitation. Thus, it may be that at low concentrations of cocaine (<1 \( \mu \)M) inhibition of the 5-HT transporter predominates, and as the cocaine concentration increases, inhibition of the dopamine transporter becomes more apparent. Interestingly, it is the lower range of cocaine concentrations that may be most pharmacologically relevant to human cocaine abuse. Mean plasma cocaine concentrations measured in human subjects at the time of maximum subjective “high” were 570 nM at 20 min after intranasal administration of 96 mg cocaine, and 730 nM at 5 min after i.v. injection of 16 mg cocaine (Javaid et al., 1978). In the present study, potentiation of ethanol excitation of dopaminergic VTA neurons was seen with 500 nM cocaine.

If the cocaine-induced potentiation of ethanol excitation is mediated by 5-HT, then the effect should be blocked by a 5-HT receptor antagonist. We previously demonstrated that exogenously applied 5-HT potentiates ethanol excitation of VTA neurons by an action at 5-HT\(_2\) receptors (Brodie et al., 1995). In the present study, we antagonized the cocaine-induced potentiation of ethanol excitation with ketanserin, a 5-HT\(_2\) antagonist. This supports our hypothesis that potentiation of ethanol excitation by cocaine is mediated by 5-HT, and is therefore similar to the effects of 5-HT (Brodie et al., 1995) and clomipramine (Trifunovic and Brodie, 1996) that we have previously described.

The 5-HT transporter is blocked at lower concentrations of cocaine than is the dopamine transporter. The affinity of (\(-\))cocaine for binding to the 5-HT transporter is ~4.5 times higher than for the dopamine transporter (\( K_i \) for cocaine displacement of binding to the 5-HT transporter is 0.14 \( \mu \)M and for displacement of binding to the DA transporter is 0.64 \( \mu \)M) (Ritz et al., 1987). This difference in affinity could help to explain the predominance of effects on the 5-HT transporter with cocaine concentrations <1 \( \mu \)M in the present study and is consistent with cocaine effects on other electrophysiological responses in the literature. Cameron and Williams (1994) have shown that 0.1 to 1 \( \mu \)M cocaine reduces inhibitory synaptic potentials in the VTA via inhibition of the 5-HT transporter. Similarly, in the nucleus accumbens, Uchimura and North (1990) conclude that lower concentrations of cocaine (0.3–1 \( \mu \)M) effectively enhance the actions of 5-HT, whereas potentiation of DA responses requires higher cocaine concentrations.

In the present study, ~70% of the DA neurons tested exhibited cocaine enhancement of ethanol excitation compared with our previous work indicating that 80 to 90% of DA neurons were potentiated by application of exogenous 5-HT (Brodie et al., 1995). The cocaine potentiation of ethanol excitation is a more indirect effect, in that it requires the presence of 5-HT terminals and endogenous 5-HT in the slice. The degree of cocaine potentiation seen in each experiment would depend on the amount of endogenous 5-HT available in that brain slice. Slice-to-slice variation in the content of endogenous 5-HT most likely explains the 70% response rate.

In summary, dopaminergic VTA neurons have been implicated in the rewarding effects of drugs of abuse, including ethanol and cocaine (Roberts and Koob, 1982; Wise, 1987). Ethanol directly excites the cell bodies of dopaminergic neurons in the VTA (Brodie et al., 1990, 1999), which results in increased DA release in their terminal fields in the nucleus accumbens (Di Chiara and Imperato, 1988; Weiss et al., 1993). Cocaine inhibits the reuptake of DA, thereby increasing the amount of DA accumulating at synapses in the nucleus accumbens (Bradberry and Roth, 1989). These effects of ethanol and cocaine should act synergistically to increase the activity in the mesolimbic dopamine reward pathway. In addition, the present study shows that, at concentrations that are pharmacologically relevant in people self-administering cocaine (<1 \( \mu \)M), cocaine increases the amount of excitatory dopamine produced in dopaminergic VTA neurons by a given amount of ethanol. This enhancement of ethanol excitation was reversed by the 5-HT\(_2\) antagonist ketanserin, and is likely to be due to cocaine inhibition of the 5-HT transporter, which predominates in this lower range of cocaine concentrations. Although there may be other interactions of ethanol and cocaine that contribute to their coabuse liability (Farre et al., 1997; Cami et al., 1998; McCance-Katz et al., 1998), the potentiation of ethanol excitation by cocaine should certainly contribute to the rewarding effects of this drug combination. These data indicate that when taken together, ethanol and cocaine exert synergistic effects to increase the activity of the mesolimbic reward pathway. This synergistic effect may at least partially explain why the coabuse of cocaine and ethanol is so prevalent.

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References


Haggard HW, Greenberg LA and Rakieten N (1940) Studies on the absorption, distribution and elimination of alcohol. VI. The principles governing the concentration of alcohol in the blood and the concentration causing respiratory failure. J Pharmacol Exp Ther 79:252–265.


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