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Conditioned taste avoidance induced by the combination of heroin and cocaine: Implications for the use of speedball

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ABSTRACT

Speedball (heroin + cocaine) is a prevalent drug combination among intravenous drug users. Although its use is generally discussed to be a function of changes in the rewarding effects of either or both drugs, changes in the aversive effects of either drug may also be impacted (weakened) by the combination. To address this latter possibility and its potential role in the use of speedball, the present studies examined the interaction of cocaine and heroin in taste avoidance conditioning. In Experiment 1, male Sprague-Dawley rats were given access to a novel saccharin solution and then injected with either vehicle or heroin (3.2 mg/kg, IP) followed immediately by various doses of cocaine (10, 18 or 32 mg/kg, SC). At the two lowest doses of cocaine, only animals injected with the drug combination (H + C) displayed a taste avoidance relative to control subjects (taste avoidance was induced with both the combination and the high dose of cocaine). At no dose did animals injected with the combination of heroin and cocaine drink more than animals injected with cocaine alone. In Experiment 2, male Sprague-Dawley rats were similarly treated but injected with vehicle or cocaine (10 mg/kg) followed by injections of various doses of heroin (1.8, 3.2, 5.6 or 10 mg/kg). At the three highest doses of heroin, only animals injected with the drug combination (C + H) displayed significant avoidance relative to control subjects (no avoidance was evident with the combination of cocaine and the low dose of heroin). At no dose did animals injected with the combination of cocaine and heroin drink more than animals injected with heroin alone. Together, these results suggest that the aversive effects of heroin and cocaine are not attenuated by co-administration by cocaine and heroin, respectively. The importance of this for the use of speedball was discussed.

1. General introduction

Although the use of either heroin or cocaine occurs at levels considerably lower than that of a number of drugs of abuse (see Johnston et al., 2019; SAMHSA, 2017), each is associated with severe health complications, including fatal overdoses (see NIDA, 2019). In relation to the opiates, the occurrence of fatal overdoses for heroin and a variety of synthetic opioids has increased dramatically in the past 10–15 years. While the number of cocaine overdoses has remained relatively stable over this same period, the instances of psychostimulant overdoses involving opioids have more than doubled since 2007. Of the 47,600 reported opioid-related overdoses in 2017, 13,942 were related to cocaine/opioid use (NIDA, 2019; see also Coffin et al., 2003; Ochoa et al., 2001; Park et al., 2018; Rhodes et al., 2007). In this context, the concurrent administration of heroin and cocaine, known as “speedball”, is a prevalent combination in drug abuse (EMCDDA, 2018; UNODC, 2014), especially among opioid- and cocaine-dependent individuals who use the drugs intravenously (Colon et al., 2001; Roy et al., 2013; Schottenfeld et al., 1993). A recent survey on national drug use trends in high school seniors found that students who use heroin not only use cocaine, but upwards of five other drugs on average (Palamar et al., 2018). Epidemiological research on the frequency of non-fatal overdose in Baltimore, MD reported that 65.4% of all surveyed participants who used a syringe service program injected heroin + cocaine (Park et al., 2018; see also Leri et al., 2003; for studies of heroin/cocaine co-use in Montréal, Canada, see Roy et al., 2013). Accordingly, understanding the basis for the co-use of heroin and cocaine may inform prevention and treatment strategies aimed specifically at those who use this specific combination of drugs.

Consistent with the clinical and epidemiological studies assessing speedball use, a variety of species of animals have been reported to administer this drug combination as well and, in many instances, maintain responding at higher rates than either drug alone (see Cruz et al., 2011; David et al., 2001; Duvauchelle et al., 1998; Lacy et al., 2014; Martin et al., 2006; Mattox et al., 1997; Ranaldi and Munn, 1998; Ranaldi and Wise, 2000; Roberts et al., 1997; Rowlett et al., 1998;

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Smith et al., 2006). Further, in a drug choice procedure Ward et al. (2005) reported that rats self-administered speedball over cocaine by itself (although breakpoints for speedball on a progressive ratio schedule of self-administration were not greater than cocaine alone, and when rats were allowed concurrent access to cocaine and heroin alone, they generally self-administered cocaine exclusively rather than use the drugs serially).

Although the basis of the use of speedball has focused on its specific rewarding effects, the nature of these effects is not known (for a discussion, see Bilsky et al., 1992; Brown et al., 1991; Kantak et al., 1999; Lamas et al., 1998; Martin et al., 2006; Negus, 2005; Spealman and Bergman, 1992; Stevenson et al., 2004; Van Wolfswinkel et al., 1988; for a review of heroin and cocaine co-use, see Leri et al., 2003). For example, some have argued that the drug combination produces some unique rewarding effect, different from that of either drug alone, yet sufficient to maintain behavior (see Lamas et al., 1998; Mello and Negus, 1998; Walsh et al., 1996), whereas others have argued that the rewarding effects of the two drugs summate to produce a greater rewarding effect than either drug alone (Ward et al., 2005) or that one drug impacts the rewarding effect of the other, increasing the use of the drug combination (David et al., 2001; Mattox et al., 1997; Rowlett and Woolverton, 1997).

It is generally assumed that cocaine and heroin may be interacting to produce a more (or different) rewarding effect; however, it has also been argued that the aversive effects of these drugs might be impacted (in this case lessened) with the co-administration of the other. For example, cocaine may acutely reduce the sedation associated with heroin administration (Foltin and Fischman, 1992) or reduce any potential withdrawal effects associated with heroin dependence (for a discussion, see Leri et al., 2003). Conversely, heroin may reduce the intensity of cocaine-induced anxiogenic effects (Ranaldi and Munn, 1998; Rogerio and Takahashi, 1992; Simon et al., 1994). Under either of these conditions, the weakening of the aversive effects of one drug by the other might impact the use of the combination. In a direct test of the possibility that the two drugs may interact in a way to impact their aversive effects, Guzman and Ettenberg (2004) utilized the runway model of self-administration that allows a concurrent assessment of the rewarding and aversive effects of various drugs (for a description of this model, see Ettenberg, 2009). In this assessment, they examined the typical pattern of approach to and retreat from a goalbox in which rats were administered cocaine. Under conditions in which a single trial was given each day, the rats developed a pattern of behavior in which they would readily approach the goal-box but then immediately retreat from it as they got closer. According to Guzman and Ettenberg, this approach/retreat pattern represented “concurrent positive (reward) and negative (anxiety) associations with the goalbox…”. Interestingly, when heroin was given with cocaine on a test trial following chronic training (14 consecutive days), rats displayed fewer retreats that were suggested to be an indication of a possible anxiolytic effect of heroin. Thus, this preclinical model provides support for the position that speedball use may be a function, in part, of changes in the aversive effects of one of the two drugs, in this case cocaine.

The present series of studies extended this analysis of potential changes in the aversive effects of cocaine and heroin by examining their interaction in taste avoidance conditioning (Cunningham et al., 2003; Gaiardi et al., 1998; Riley and Simpson, 2001; Stolerman and D'Mello, 1981; for reviews, see Riley et al., 2009; Riley, 2011; Stolerman, 1985; see www.CTAlearning.com). In this design, animals are given limited access to a novel fluid to drink after which they are injected with one of a number of drugs. In a subsequent test, they generally avoid consumption of the drug-associated taste, indicative of its aversive effects (Riley and Tuck, 1985). Although initially demonstrated with radiation and classical emetics as the aversive agent (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Rozin and Kalat, 1971; for a review, see Freeman and Riley, 2009), such conditioned taste avoidance has now been reported for a variety of drugs of abuse, including cocaine (Ferrari et al., 1991; Freeman et al., 2005) and heroin (Davis et al., 2009). Although generally only a single drug is administered in this preparation, drug combinations have been studied and have allowed for assessments of the attenuating and potentiating effects of one compound on another (see Coil et al., 1978; Kunin et al., 2001; Loney and Meyer, 2019; Revusky and Martin, 1988; Rinker et al., 2008; Serafine et al., 2012). To assess the interaction of cocaine and heroin, animals in the present work were administered heroin alone and in combination with various doses of cocaine (Experiment 1) and cocaine alone and in combination with various doses of heroin (Experiment 2). If either drug weakens the other's aversive effects, it would be predicted that avoidance would be less in animals injected with the combination of heroin and cocaine than that of either drug alone.

2. General methods

2.1. Subjects

Subjects were 144 experimentally naïve, male Sprague-Dawley rats approximately 70 days of age and 230–350 g at the beginning of each experiment. All procedures adhered to the Guidelines for the Care and Use of Laboratory Animals (National Research Council, 2011) and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003) and were approved by the Institutional Animal Care and Use Committee at American University.

2.2. Apparatus

Subjects were housed in individual stainless-steel, wire-mesh cages on the front of which graduated Nalgene tubes were used to provide 20-min access to water or saccharin. Subjects were maintained on a 12 L:12 D cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. At the beginning of each experiment, fluid access was restricted to 20 min each day. Rat chow was available ad libitum.

2.3. Drugs and solutions

Cocaine hydrochloride (generously supplied by the National Institute on Drug Abuse) was dissolved in 0.9% physiological saline in a concentration of 10 mg/ml and injected subcutaneously (SC). Diacetylmorphine hydrochloride (heroin) (also generously supplied by the National Institute on Drug Abuse) was dissolved in 0.9% physiological saline in a concentration of 2.5 mg/ml and injected intraperitoneally (IP). Drug doses are expressed as the salt. Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

2.4. General procedure

Phase I: Habituation. Following 24-h water deprivation, all subjects were given 20-min access to water in their individual home cages. This limited-access procedure was repeated for 10 days to allow water consumption to stabilize (with animals approaching the drinking tube within 2 s with the average volume of water consumed not increasing or decreasing by more than 2 ml for 3 consecutive days).

Phase II: Taste Avoidance Conditioning. On the first day of this phase, all subjects were given 20-min access to a novel saccharin solution in their home cages during their normal fluid-access period. Immediately following saccharin access, subjects were ranked according to consumption and assigned to groups such that saccharin intake was comparable among groups. Subjects were then given an injection of cocaine or saline and varying doses of heroin (Experiment 1) or heroin or saline and varying doses of cocaine (Experiment 2). On the following three water-recovery days, subjects were given 20-min access to water during the fluid-access period. On the day following the

third water-recovery session, all subjects were again given 20-min access to saccharin after which they were injected with the drug or drug combination. Water was then given for three recovery days. This procedure of conditioning and water recovery was repeated for two additional cycles followed by a final aversion test in which saccharin was given but not followed by any injections.

2.5. Statistical analysis

For each experiment, differences in saccharin consumption were analyzed using a mixed model ANOVA with the between-subject factor of Drug (vehicle or Drug A in combination with Drug B at varying doses) and the within-subject factor of Trial (Trials 1–4; Aversion Test). In the instance of a significant two-way interaction between Drug and Trial, simple effects of Drug at each Trial were assessed (multivariate analysis) followed by Tukey's contrasts as warranted.

Statistical significance was set to $p \leq .05$.

3. Experiment 1

In Experiment 1, 64 male Sprague-Dawley rats were given 20-min access to saccharin followed immediately by an injection of vehicle or 3.2 mg/kg heroin (IP) and then either vehicle or varying doses of cocaine (10, 18 or 32 mg/kg, SC) to assess the effect of heroin on cocaine-induced taste avoidance. This procedure yielded the following groups: Groups VV, VC10, VC18, VC32, HV, HC10, HC18 and HC32 (n = 8 per group). The first letter in each group designates an injection of either vehicle (V) or heroin (H). The second letter/number refers to an injection of either vehicle (V) or cocaine (10, 18 or 32 mg/kg). The specific doses of heroin and cocaine used (as well as their specific routes of administration) were based on prior work reporting minimal to weak (heroin: Davis et al., 2009) and dose-related (cocaine: Freeman et al., 2005) taste avoidance.

3.1. Results

The mixed model ANOVA on saccharin consumption revealed a significant effect of Drug [$F(7,56) = 12.893$, $p < .0001$], Trial [$F(4,224) = 62.702$, $p < .0001$] and a significant Drug × Trial interaction [$F(28,224) = 12.581$, $p < .0001$]. Given that saccharin consumption was near completely suppressed after the second conditioning trial in drug-treated groups at the highest dose, a floor effect that precluded comparisons between those given cocaine alone vs heroin in combination with cocaine, only data from the second conditioning trial are described and compared to that prior to conditioning (i.e., Trial 1). Although there were no significant group differences on the initial exposure to saccharin [$F(7,56) = 0.013$, ns; see Table 1], a one-way ANOVA on saccharin consumption on Trial 2 revealed significant differences between groups [$F(7,56) = 7.726$, $p < .0001$]. Tukey's contrasts indicated that for all cocaine dose conditions, animals injected with the heroin + cocaine combination (Groups HC) drank significantly less saccharin than those injected with vehicle (Group VV), indicating acquisition of a taste avoidance for the combination groups. Subjects injected with cocaine alone at the two lowest doses (Groups VC10 and VC18) never differed significantly from the vehicle and combination groups, although at the highest cocaine dose (32 mg/kg) Group VC32 drank less than controls. Subjects injected with heroin alone (Groups HV) never differed from vehicle-injected subjects or those injected with the drug combination (see Fig. 1, Panels A, B and C).

Table 1
Mean and SEM for saccharin consumption (ml) during Experiment 1.

Trial 1			Trial 2		
Group	Mean	SEM	Group	Mean	SEM
VV	12.75	0.675	VV	16.375	0.557
HV	13.313	0.906	HV	11.438	0.952
VC10	13.313	0.79	VC10	15.313	1.214
VC18	12.813	0.719	VC18	11.688	1.172
VC32	12.75	0.675	VC32	7.875	0.817
HC10	13.563	1.588	HC10	11.188	1.056
HC18	13.625	1.448	HC18	10.563	1.63
HC32	13.5	1.056	HC32	7.5	1.275

Mean and SEM for saccharin consumption in milliliters during training (left) and testing (right) for each group during Experiment 1.

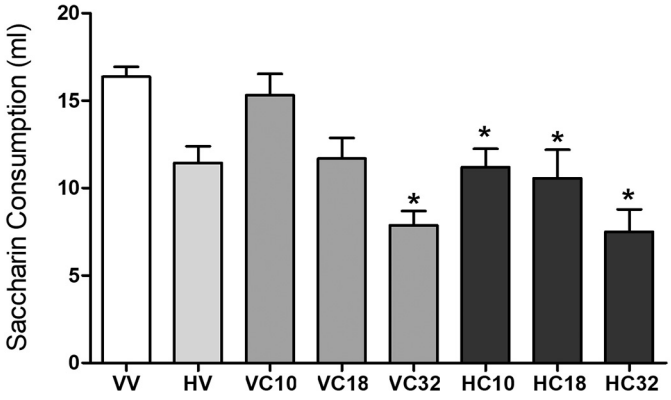

Fig. 1. The presentation of the mean (± SEM) absolute saccharin consumption for Groups VV, HV, VC10, VC18, VC32, HC10, HC18 and HC32 on the Aversion Test. *significant difference from Group VV.

4. Experiment 2

In Experiment 2, 80 male Sprague-Dawley rats were given 20-min access to saccharin followed immediately by an injection of either vehicle or 10 mg/kg cocaine (SC) and then injected with vehicle or varying doses of heroin (1.8, 3.2, 5.6 or 10 mg/kg, IP) to assess the effects of cocaine on heroin-induced taste avoidance. This procedure yielded the following groups: Groups VV, VH1.8, VH3.2, VH5.6, VH10, CV, CH1.8, CH3.2, CH5.6 and CH10 (n = 8 per group). The first letter designates an injection of either vehicle (V) or cocaine (C). The second letter/number refers to an injection of either vehicle (V) or heroin (1.8, 3.2, 5.6 or 10 mg/kg). The specific doses of cocaine and heroin and their routes of administration were based on prior work reporting minimal to weak (cocaine: Freeman et al., 2005) and dose-related (heroin: Davis et al., 2009) taste avoidance.

4.1. Results

The mixed model ANOVA on saccharin consumption revealed a significant effect of Drug [$F(9,71) = 4.480$, $p < .0001$], Trial [$F(4,284) = 47.336$, $p < .0001$] and a significant Drug x Trial interaction [$F(36,284) = 4.875$, $p < .0001$]. Although heroin alone did not suppress saccharin consumption as dramatically as did cocaine (described above), to allow for comparisons with Experiment 2 only data from Trials 1 and 2 were presented and compared. All analysis from these comparisons were the same for the remaining trials and test. As above, there were no significant group differences on the initial exposure to saccharin [$F(9,71) = 0.280$, ns; see Table 2]. A one-way ANOVA on saccharin consumption on the Trial 2, however, revealed significant group differences ($F(9,71) = 3.108$, $p = .0033$). Tukey's contrasts indicated that for all heroin dose conditions except the lowest dose examined (1.8 mg/kg), animals injected with the cocaine + heroin combination (Groups CH) drank significantly less saccharin than those injected with vehicle (Group VV), indicating acquisition of a taste avoidance for the combination groups. Subjects injected with heroin (Groups VH) alone at any dose never differed from the vehicle and combination groups. Subjects injected with cocaine alone (Groups CV)

Table 2
Mean and SEM for saccharin consumption (ml) during Experiment 2.

Trial 1			Trial 2		
Group	Mean	SEM	Group	Mean	SEM
VV	13.563	0.821	VV	16.5	0.726
CV	14.929	1.177	CV	15.786	1.439
VH1.8	13.438	0.918	VH1.8	12.563	0.952
VH3.2	13.25	0.896	VH3.2	11.688	1.302
VH5.6	13.5	0.881	VH5.6	10.938	1.159
VH10	13.688	1.451	VH10	11.625	0.811
CH1.8	13.813	1.085	CH1.8	12.188	1.363
CH3.2	14.5	0.881	CH3.2	9.25	1.524
CH5.6	13.556	0.911	CH5.6	10.667	1.71
CH10	13.333	0.712	CH10	10.5	1.323

Mean and SEM for saccharin consumption in milliliters during training (left) and testing (right) for each group during Experiment 2.

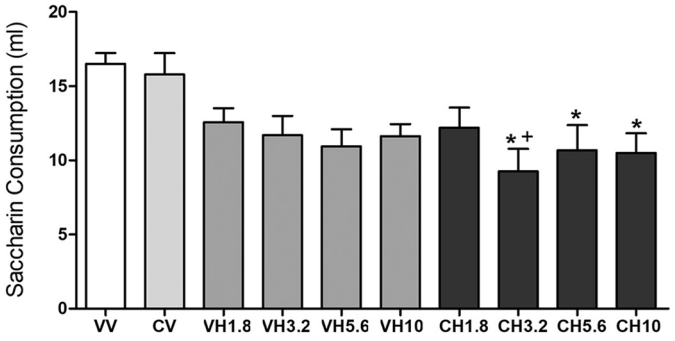

Fig. 2. The presentation of the mean (± SEM) absolute saccharin consumption for Groups VV, CV, VH1.8, VH3.2, VH5.6, VH10, CH1.8, CH3.2, CH5.6 and CH10 on the Avoidance Test. *significant difference from Group VV; $^{+}$significant difference from Group CV.

differed from the combination group only at the 3.2 mg/kg heroin dose at which Group CV drank significantly more than Group CH3.2 (see Fig. 2, Panels A, B and C).

5. General discussion

The combination of heroin and cocaine known as speedball is a prevalent combination in drug abuse. Although the mechanism for their co-use is unknown, several possibilities have been suggested, all of which have generally focused on changes in the rewarding effects with the combination (see General Introduction). A less considered possibility is that one drug might attenuate the aversive effects of the other (see Leri et al., 2003). Accordingly, the present series of studies assessed whether the aversive effects of cocaine or heroin were impacted by the concurrent administration of heroin and cocaine, respectively. Although either drug could decrease or increase the aversive effects of the other (or have no effect), given the extensive use of the combination, it was expected that each drug might have an attenuating effect on the aversive effects of the other, an attenuation that might mediate, in part, their co-use.

As reported, neither heroin nor cocaine when given in combination with the other attenuated its aversive effect as indexed by the acquisition of a taste avoidance. For example (see Experiment 1), for every combination of heroin and cocaine, animals injected with the drug combination did not differ from those injected with cocaine alone, suggesting that in this assessment heroin did not weaken cocaine's aversive effects. Interestingly, at the two lowest doses of cocaine (10 and 18 mg/kg), the combination of heroin and cocaine appeared more aversive than cocaine alone in that the combination induced an avoidance relative to vehicle, whereas subjects injected with cocaine did not differ from controls. At the highest dose of cocaine (32 mg/kg), both the combination group and subjects injected with cocaine alone differed from vehicle-injected subjects, but, as noted above, did not differ from each other. Similarly, in Experiment 2, for the combinations of cocaine and heroin at the three highest doses, animals injected with the combination did not differ from those injected with heroin alone, indicating that cocaine did not weaken heroin's aversive effects. As in Experiment 1, it appeared that the combination of cocaine and heroin was more aversive than heroin alone in that the combination induced an avoidance relative to vehicle, whereas subjects injected with heroin did not differ from controls. At 3.2 mg/kg heroin, the combination group also differed from subjects injected with cocaine alone.

The doses of heroin and cocaine used to examine their impact on taste avoidance induced by cocaine and heroin, respectively, were based on prior work in which these same drugs have been examined for their ability to induce a taste avoidance (Davis et al., 2009; Freeman et al., 2005). Although both drugs have been reported to be effective in this design, this avoidance is dose-dependent with the doses used here weak or minimal. The logic for such a choice was that the initial drug, e.g., heroin, could be assessed for its effects on the second or target drug, e.g., cocaine, without the potential confound of any suppression it might produce. As noted above, although neither heroin (Experiment 1) nor cocaine (Experiment 2) alone induced a significant taste avoidance, consumption for subjects injected with these drugs appeared to be less (although not significantly) than that of control subjects (31.38% less for heroin and 5.88% less for cocaine). It might be argued that it would be difficult to assess the effects of heroin on cocaine given that heroin alone suppressed consumption and that the aversive effects of the combination of heroin and cocaine was greater than cocaine alone because of the addition of heroin's effects (albeit nonsignificant) to those of cocaine. While possible, the decrease seen in each of the combination groups (data not shown) was less than the combined effects of heroin and cocaine (in terms of their decreases from controls), suggesting that if their effects were simply summating, such effects were infra-additive. Further, in Experiment 2, in which cocaine was assessed for its impact on heroin-induced taste avoidance, cocaine had a minimal effect on consumption (a reduction of less than 6% relative to controls) and the same pattern of results was seen, i.e., the combination appeared more (and clearly not less) aversive than the target drug, in this case, heroin. It might be argued that the dose chosen (10 mg/kg) in the examination of the effects of cocaine on heroin-induced avoidance was not behaviorally active. However, this dose (and for some preparations, even lower) has been reported to induce locomotor activity (Bedingfield et al., 1998; Bell et al., 1997), place preferences (Bedingfield et al., 1998; Bell et al., 1997; Russo et al., 2003; Zakharova et al., 2009) and taste avoidance (Freeman et al., 2008; Pomfrey et al., 2015; Wetzell and Riley, 2012) in other assessments.

The logic for the present series of studies was the possibility that changes in the aversive effects of either cocaine or heroin might mediate, in part, the use of their combination (either serially or concurrently). The present studies provide no support for this mediation. Together, the results from Experiments 1 and 2 demonstrate that when either heroin or cocaine is administered prior to taste avoidance conditioning with the other drug, no attenuation is evident. Although assessments of potential changes in the aversive effects with the combination are limited, work by Guzman and Ettenberg (2004) addressed this possibility by examining the effects of heroin on cocaine-induced approach/retreat in the runway model of self-administration (see above). In this test, heroin reduced the number of goalbox retreats produced by cocaine. Given that the retreats are associated with anxiety induced by cocaine, these results suggest that heroin reduced this anxiety, an effect that may be involved in the co-use of these drugs.

In this context, it is unknown why neither cocaine nor heroin attenuated the effects of the other drug in the present assessment. One possibility may be that the avoidance design is not amenable to attenuation given that conditioned taste avoidance is so rapidly acquired and generally quite robust (for a review, see Freeman and Riley, 2009).

Such a possibility is unlikely, however, given that other drugs have been reported to impact avoidance learning. For example, Freeman et al. (2008) demonstrated that non-aversive doses of the α_1 (prazosin) and β_2 (propranolol) noradrenergic antagonists increased cocaine-induced avoidance at doses comparable to those assessed in Experiment 1 (see also Rinker et al., 2008 for a report on the potentiating effects of nicotine on ethanol-induced taste avoidance). Conversely, cocaine-induced taste avoidance is attenuated by concurrent treatment with the D_2 antagonist haloperidol that had no aversive effects on its own (Serafine et al., 2012; see also LeBlanc and Cappell, 1975, for assessments of the attenuation of morphine-induced taste avoidance by the opiate antagonist naloxone). Secondly, the specific route of drug administration in the present work, i.e., heroin (IP) and cocaine (SC), are quite different from the intravenous route generally associated with speedball use and demonstrations in pre-clinical animal models. While these differences clearly exist, administration of drugs via the routes used here have been consistently reported to induce both rewarding and aversive effects with a wide variety of drugs, including cocaine and heroin, that are predictive of their self-administration (see Ettenberg et al., 2015; Hunt and Amit, 1987; Verendeev and Riley, 2012). Further, the effects of heroin on cocaine (and vice versa) have been reported in other preparations in which the drugs were not administered intravenously, suggesting that the absence of any attenuating effects in the present experiment is not likely a function of route of administration (see Cuhuna-Oliveira et al., 2010; Leri et al., 2003; Mori et al., 2004; Platt et al., 1999; see also Wang et al., 2001 for oral intake). Thirdly, it is important to note that in both experiments reported here animals were only briefly exposed to heroin or cocaine (in a single conditioning trial). It may also be the case that under conditions of human speedball use in which there is a history with one or both drugs prior to their co-administration, the two drugs would impact each other. It is interesting in this context that a history with a drug prior to taste avoidance conditioning with that drug (and others) significantly attenuates taste avoidance conditioning (for reviews see Randich and LoLordo, 1979; Riley and Simpson, 2001). Although such attenuating effects have been reported with both the opiates (Cappell et al., 1975; Dacanay and Riley, 1982; Simpson and Riley, 2005) and psychostimulants (Davis and Riley, 2007; Riley and Diamond, 1998; Riley and Simpson, 1999), no studies have directly assessed the cross-attenuating effects of heroin or cocaine history on avoidance conditioning with these same drugs (for an attenuating effect of amphetamine history on morphine-induced taste avoidance, see Cappell and Poulos, 1979; for examples of cross-drug effects with other compounds, see Riley and Simpson, 2001). Finally, the fact that there was no attenuation of the aversive effects of cocaine and heroin in the present experiment may not be inconsistent with the work of Guzman and Ettenberg (2004) in that it is not clear what role anxiety plays in taste avoidance learning. Although it has been suggested that stress and anxiety may be involved in its acquisition (see Gomez et al., 2000; Jensen et al., 1990; Parker, 2003; Smotherman et al., 1976; though see Bourne et al., 1992; Revusky and Reilly, 1989), anxiolytics themselves have been reported to induce avoidance. For example, such compounds as diazepam, midazolam, chlordiazepoxide and morphine (among others) are effective avoidance-inducing agents (for reviews, see Hunt and Amit, 1987; Verendeev and Riley, 2012). Consequently, it is unclear to what extent the taste avoidance design would be affected if anxiety is the component of cocaine impacted by the co-use of heroin.

Although the basis for the failure of heroin or cocaine to attenuate the aversive effects of each other in the taste avoidance design is not known, this drug combination remains prevalent and may be expanding as the types of opiates used in combination with cocaine increase (Kuczynska et al., 2018; Macmadu et al., 2017; Molina and Hargrove, 2011; Motta-Ochoa et al., 2017). Assessing the possible contributions to the use and abuse of speedball remains important in understanding the basis for its use and developing strategies for its prevention and treatment.

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Declaration of competing interest

None.

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