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Short communication

Ondansetron, given during the acute cocaine withdrawal, attenuates oral cocaine self-administration

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Abstract

We have previously shown that ondansetron, given 3.5 h after intravenous cocaine self-administration, can attenuate self-administration the following day. Here we tested ondansetron given either before or after a 14-h oral cocaine session in rats. Ondansetron (0.2 mg/kg sc) given 30 min before the cocaine session had no effect. However, when given 3.5 h after, ondansetron attenuated cocaine intake the following day while having no effect on water intake. Taken with our previous data in intravenous cocaine self-administration, we suggest that the acute cocaine withdrawal period may be an important treatment window and that ondansetron may be an effective cocaine abuse therapy.

Keywords: Cocaine; Ondansetron; Self-administration; Withdrawal

1. Introduction

Although the majority of cocaine abusers take cocaine via nasal or intravenous routes, the original route used by native South Americans was oral. Further, human studies are restricted to oral dosing (e.g., Fillmore et al., 2002). In rats, oral cocaine acts as an operant reinforcer (Miles et al., 2003) and evokes conditioned place-preference (Seidman et al., 1992). Thus, studies using oral cocaine self-administration in rats are useful when comparing with clinical studies and have the added advantage of not requiring animal surgery.

We have recently shown that ondansetron when given 3.5 h after either cocaine injections or intravenous self-administration sessions can reverse sensitization during withdrawal and attenuate cocaine self-administration on the following day (Davidson et al., 2002a). We were interested whether this effect was evident after oral cocaine self-administration.

2. Materials and methods

Six adult male Sprague–Dawley rats (Charles River) weighing ~420 g at the start of dosing were housed singly to allow accurate measurement of liquid consumption. A light–dark cycle (lights on: 7 AM–7 PM) was used, and food and water were restricted as described below and approved by Duke IACUC.

During the first 3 weeks (Monday–Friday) of cocaine dosing, rats were given a cocaine solution (0.2 mg/ml) for a 14-h period from 7 PM to 9 AM, with tap water available for 30 min thereafter. This 14-h period is similar to the average binge period in human abusers (Gawin and Ellinwood, 1988). During the first 2 weeks, food was freely available, and the single bottle was placed at the center of the cage to avoid conditioning effects. At the start of the third week, in an effort to increase cocaine solution intake, food was restricted to 20 g per day (polydipsia; Falk and Lau, 1993) given at the start of the dark period. At this stage, the rats' intake of cocaine doubled (see Fig. 1A). At the start of the 4th week, each rat was given a bottle with cocaine (0.2 mg/ml) and a bottle with tap water at the same time overnight 7 PM–9 AM, for the other 10 h/day no liquid

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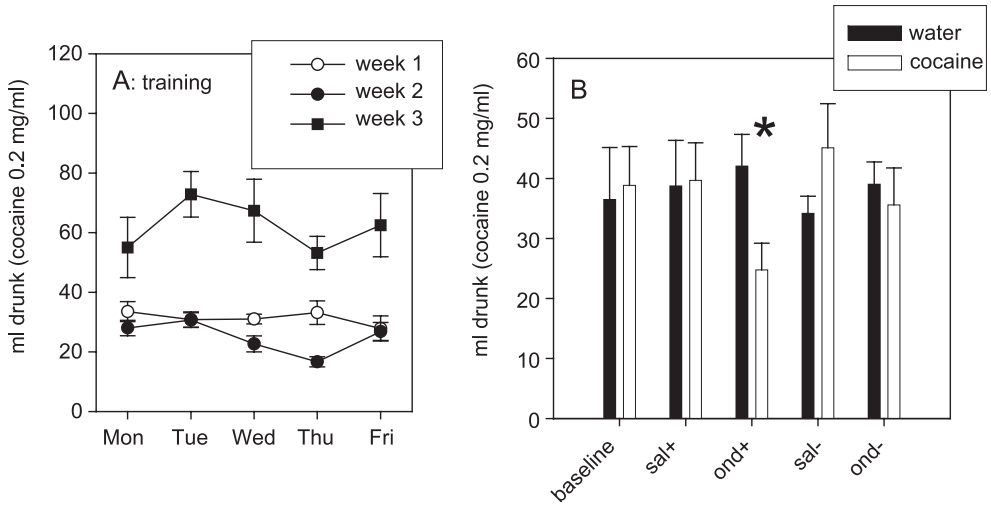

Fig. 1. Oral cocaine self-administration. (A) Cocaine training period. Rats drink relatively stable amounts of cocaine (0.2 mg/ml) for the first 2 weeks. Dosing was from Monday to Friday with withdrawal on the weekend. At the start of the third week, food was restricted and cocaine intake doubled. (B) Once a stable baseline was determined, rats were treated with either saline (sal) or ondansetron (ond) injections given either 30 min before (−) or 3.5 h after (+) the oral cocaine session. The ond+ treatment reduced cocaine intake while having no effect on water intake. The mean cocaine dose during the baseline period was 12.93±2.25 mg/kg. Values are means ±S.E.M.

was available. The bottles were placed at either side of the cage. This overnight presentation was used for the remainder of the experiment. Baseline (no injections) cocaine and water intake were measured for 3 days, then rats were injected on the following schedule: saline injection 30 min prior to session (sal−, 3 days), no injections (3 days), saline injection given 3.5 h after session (sal+, 2 days), ondansetron injection (0.2 mg/kg sc) 3.5 h after session (ond+, 3 days), sal+ (3 days), ondansetron injection given 30 min before the session (ond−, 3 days), sal− (3 days). The volume of cocaine solution or water drunk at the end of the 14-h session was measured each day. Body weights were measured daily to allow cocaine dose calculations. Data were analyzed with either one- or two-way repeated measure analysis of variance (ANOVA) where appropriate with post hoc Tukey's or Dunnett's tests.

3. Results

Animals quickly adapted to drinking the 0.2 mg/ml cocaine solution and often showed intense sniffing stereotypies at the cocaine bottle as well as a place preference by lying underneath the cocaine bottle. Drinking was relatively stable and food restriction doubled cocaine intake during the third week (Fig. 1A).

Overall, there was no preference for cocaine versus water (P=0.88), and no effect of the treatment injections (saline before or after; ondansetron before or after the drinking session) on the amount drunk although there was a trend (P=0.09). However, there was an interaction between the amount of cocaine or water drunk and treatment (F(59,4)=3.901; P=0.017). Post hoc Tukey's revealed no difference in the amount of water drunk after any of the treatments (P>0.4 for all), but the amount of cocaine drunk was affected by treatments. The ondansetron injection treatment given 3.5 h after oral cocaine (ond+) reduced the amount of cocaine drunk the following day versus baseline (P=0.02), sal−(P<0.001), sal+(P=0.014), and tended to reduce the amount of cocaine drunk versus the ond− treatment (P=0.125). There were no significant differences in the amount of cocaine versus water drunk for any treatment, although within the ond+ treatment

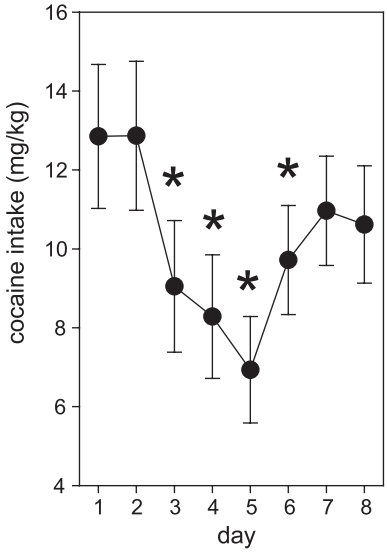

Fig. 2. Cumulative effect of ondansetron injections on cocaine intake. The cocaine dose self-administered over eight consecutive days is shown. Days 1 and 2 show cocaine intake the day after saline injections given 3.5 h after the cocaine session (sal+). Days 3–5 are cocaine intake the day after ondansetron injections, given 3.5 h after the session (ond+), and days 6–8 are cocaine intake after sal+. Cocaine intake was decreased versus day 2 on days 3–6 (p<0.05). Values are means ±S.E.M.

animals tended to drink less cocaine (P=0.126). Mean daily doses (mg/kg) under each treatment were baseline (12.93±2.25), sal+(13.09±2.03), ond+(8.10±1.46), sal−(15.12±2.31), and ond−(11.80±2.01). With regard to cocaine dose, only the ond+ treatment was significantly different from baseline (q=0.499, p<0.05). Thus, the ond+ treatment selectively attenuated cocaine intake on the following day while having no effect on water intake.

The data in Fig. 2 show cocaine intake over eight consecutive days when rats were first given sal+ and then ond+ injections. ANOVA showed that there was a difference in cocaine intake over this time period (F(41,6)=7.20; P<0.001), and Dunnett's test revealed that cocaine intake was attenuated on each day following ond+ and this effect persisted for a further day (P<0.05).

4. Discussion

We initially forced rats to drink a cocaine solution, as they had no other water available. After 3 weeks of cocaine with withdrawal periods, rats were given a choice of either cocaine (0.2 mg/ml) or tap water overnight during their active period. Despite having water freely available, rats still drank equivalent quantities of cocaine, consistent with Falk et al. (1996). The amount drank (~35 ml) corresponded to ~12 mg/kg/day. Injections of saline or ondansetron given 30 min prior to the overnight cocaine sessions had no effect on the amount of water or cocaine drunk that night, similarly saline injections given 3.5 h after the session were without effect the following day. However, ondansetron given 3.5 h after the session reduced cocaine intake on the following day while having no effect on water intake.

We have previously shown that this dose of ondansetron (0.2 mg/kg), when given 3.5 h after an intravenous cocaine self-administration session, can reduce the break point on a progressive ratio schedule of reinforcement (Davidson et al., 2002a). Similarly, ondansetron when given 3.5 h after a high dose (40 mg/kg sc) cocaine injection can reverse previously established sensitization (Davidson et al., 2002a). The present study extends this work by showing that ondansetron is also effective in an oral cocaine self-administration model. Further, the present study highlights the importance of treating the acute cocaine withdrawal period, i.e., ~3.5 h after cocaine; ondansetron injections 30 min prior to the cocaine session were ineffective. Another question is how long does this effect last? We found that cocaine intake tended to decrease over the 3 days for which ond+ was given (see Fig. 2) and that intake was still reduced 2 days after the last ond+ injection. These data are in agreement with our previous intravenous cocaine self-administration data that showed 5 days of ondansetron, given 3.5 h after the session, inhibited cocaine self-administration the following day and up to 3 days after the last ondansetron injection (Davidson et al., 2002a). King et al. (2000) have also shown that ondansetron, given during the first 5 days of withdrawal, reduced the expression of behavioral sensitization and that this effect was long lasting.

Ondansetron has previously been used in intravenous cocaine self-administration models with little effect (Peltier and Schenk, 1991; Lane et al., 1992; Depoortere et al., 1993), nor has it been shown to be effective in conditioned place-preference models (Cervo et al., 1996). However, in all of these cases, ondansetron was given 30 or 60 min prior to the test session. We believe that treatment prior to cocaine will be ineffective but that the acute cocaine withdrawal period represents a treatment window where, for example, consolidation of sensitization may be attenuated by disrupting certain as yet undefined neuroplastic mechanisms. These changes may include phosphorylation of the NR2B subunit of *N*-methyl-D-aspartic acid (NMDA) receptors or glutamate receptor-1 (GluR1) subunits of α-amino-3-hydroxyl-5-methyl-4-isoxazoleprropionic acid (AMPA) receptors in limbic brain regions that are markers of cocaine sensitization (Loftis and Janowsky, 2002). We have found ondansetron given in the acute cocaine withdrawal to reverse these phosphorylation changes (unpublished data). Further, it should be remembered that ondansetron has a short half-life in rodents (12 min; Saynor and Dixon, 1989), and thus if given 30 or 60 min prior to a test session, one may not expect it to have a great effect, especially when the session (e.g., intravenous cocaine self-administration) may last up to 5 h or more. Not only have we found ondansetron, a 5-HT_3 receptor antagonist, to be effective in attenuating cocaine self-administration, but we have also found 5-HT_2 receptor antagonists to be effective when these drugs are given during the acute cocaine withdrawal, e.g., 3.5 h after cocaine (Davidson et al., 2002b). Possible mechanisms behind these 5-HT_2 and 5-HT_3 effects could include attenuation of protein kinases (Blank et al., 1996) that may decrease NR2B or GluR1 subunit phosphorylation, but such a discussion is out of the scope of this paper.

Oral cocaine self-administration is a way of measuring cocaine self-administration without the need for surgery and subsequent adverse events. Here we show that the 5-HT_3 receptor antagonist ondansetron, when given during the cocaine withdrawal period, is able to attenuate cocaine intake the following day while having no effect on water intake. Taken together with our previous studies (Davidson et al., 2002a,b), we suggest that the acute cocaine withdrawal period may be an underexamined window for treatment and that ondansetron may be a useful pharmacotherapy in cocaine abuse.

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