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Effects of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and quipazine on heroin self-administration in rhesus monkeys

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Abstract

Rationale—The serotonin (5-HT) system is involved in pain modulation, and 5-HT receptor agonists can enhance antinociceptive effects of mu opioid receptor agonists. Less is known about the actions of 5-HT receptor agonists on other effects of opioids.

Objective—This study examined the effects of non-contingent and contingent administration of the 5-HT_{2A} receptor agonists DOM and quipazine on i.v. heroin self-administration in rhesus monkeys.

Results—Heroin (0.0001–0.1 mg/kg/infusion) generated an inverted U-shaped dose-response function. Non-contingent administration of DOM (0.1–0.32 mg/kg) flattened the dose-response function in three monkeys and eliminated heroin self-administration in a fourth monkey. Contingent DOM (0.0032–0.032 mg/kg/infusion) alone did not maintain responding above that maintained by saline, and, when added to self-administered heroin, monkeys responded less than for the same unit doses of heroin alone. Non-contingent (0.32–3.2 mg/kg) and contingent (0.0032–0.56 mg/kg/infusion) administration of quipazine flattened the dose-response function in two monkeys, increasing responding maintained by small unit doses of heroin and saline, but failed to enhance responding for heroin in two other monkeys.

Conclusion—This study shows that DOM does not enhance, and might attenuate, the positive reinforcing effects of the mu opioid receptor agonist heroin. Quipazine increased responding for saline and small doses of heroin; those effects were modest and observed in only two subjects. Taken together, these data suggest that 5-HT_{2A} receptor agonists do not significantly enhance the reinforcing effectiveness of mu opioid receptor agonists and support the view that administering 5-HT drugs in combination with opioids to treat pain might not enhanced abuse liability.

Keywords

heroin; DOM; quipazine; drug self-administration; rhesus monkey

Pain remains a serious clinical problem, and mu opioid receptor agonists (e.g., hydrocodone) are the most effective drugs for many pain conditions. However, the use of opioids for treating pain is limited both by unwanted side effects (e.g., constipation, abuse) and by their ineffectiveness in some patients (Gutstein and Akil 2005). Consequently, there is an unmet

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need to develop new approaches for treating pain by exploring novel mechanisms of action and/or new drug combinations.

Serotonergic (5-HT) systems can modulate pain, and some drugs acting on 5-HT systems have antinociceptive effects (Messing and Lytle 1978). For example, selective 5-HT reuptake inhibitors (SSRIs) have antinociceptive effects (Singh et al. 2001; Singh et al. 2003; Duman et al. 2004; Kesim et al. 2005) and selective 5-HT_{1A} receptor agonists are effective in various experimental pain conditions (see Colpaert 2006 for a review). Accumulating evidence suggests that drugs acting on 5-HT systems might be particularly useful for treating pain when they are used in combination with opioids. For example, the SSRIs fluoxetine and clomipramine potentiate the antinociceptive effects of morphine in rats and rhesus monkeys (Larson and Takemori 1977; Hynes et al. 1985; Gatch et al. 1998; Banks et al. 2010), and the 5-HT releaser fenfluramine increases the antinociceptive effects of morphine in monkeys (Li et al. 2011) and the analgesic effects of morphine in humans (Coda et al. 1993). Agonists acting selectively on 5-HT receptor subtypes have also been shown to enhance the antinociceptive effects of opioids. For example, 5-HT_{2A} receptor agonists significantly increase the potency of morphine to induce antinociception in rhesus monkeys; the same doses of 5-HT_{2A} receptor agonists attenuate the discriminative stimulus effects of morphine (Li et al. 2011).

Emerging evidence supports combining 5-HT drugs and opioids for pain treatment; however, little is known regarding possible unwanted effects of these drug combinations, particularly abuse-related effects. Drug combinations currently used to treat pain can be effective therapeutically, although abuse liability of opioids remains a significant problem. For example, some commonly prescribed analgesic preparations include both a mu opioid receptor agonist and a non-opioid drug (e.g. nonsteroidal anti-inflammatory drug; Vicodin®). However, Vicodin® has high abuse liability and is currently among the most widely abused prescription drugs (Manchikanti 2007). Several studies examined the effects of 5-HT drugs on the abuse-related effects of opioids, and the results were mixed. The 5-HT releaser fenfluramine decreased heroin self-administration in rats (Higgins et al. 1994; Wang et al. 1995). However, the SSRIs fluoxetine and fluvoxamine enhanced morphine-induced conditioned place preference (Subhan et al. 2000; Maleki et al. 2008) and morphine self-administration (Mosner et al. 1997) in rats.

The multitude of 5-HT receptor subtypes and the indirect mechanism of action of SSRIs (i.e., non-selective activation of all 5-HT receptor subtypes) complicate interpretation of the effects observed with combinations of SSRIs and opioids. One potentially useful strategy to identify the specific 5-HT mechanism(s) (e.g. receptor[s]) that modulate the actions of opioids is to examine the effects of selective direct-acting 5-HT receptor agonists in combination with an opioid receptor agonist. The effects of direct-acting 5-HT receptor agonists on the abuse-related effects of opioids are largely unknown. Some 5-HT_{2A} receptor agonists have hallucinogenic activity in humans and they are abused (e.g., see Fantegrossi et al. 2008; Nichols 2004 for reviews), yet 5-HT_{2A} receptor agonists are not reliably self-administered by non-human primates (e.g., Yanagita 1986; Fantegrossi et al. 2004). Moreover, it is unclear whether 5-HT_{2A} receptor agonists alter self-administration of opioids. The current study examined the effects of 5-HT_{2A} receptor agonists 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and 2-piperazin-1-ylquinoline (quipazine) on heroin self-administration in rhesus monkeys. Although the pharmacological profiles of DOM and quipazine are not identical (e.g., quipazine but not DOM has high affinity for 5-HT₃ receptors; Glennon et al. 1989), the both have prominent agonist activity at 5-HT_{2A} receptors. Moreover, both drugs modified the antinociceptive and discriminative stimulus effects of morphine in rhesus monkeys and those effects appeared to be mediated through 5-HT_{2A} receptors (e.g., Li et al. 2011). Because the conditions (e.g. contingency) of

drug administration can impact drug effects (Dworkin et al. 1995; Galici et al. 2000; Lecca et al. 2007), this study examined the effects of DOM and quipazine on heroin self-administration when the 5-HT receptor agonists were administered non-contingently (response-independently), as a pre-session treatment, and also when they were administered contingently (response-dependently), alone or together with heroin.

Materials and Methods

Subjects

Eight rhesus monkeys (*Macaca mulatta*), 4 males (JA, AB, PE, NE) and 4 females (MI, VO, MA, BE), weighed between 7 and 10 kg and were housed individually in stainless-steel cages with free access to water. Monkeys received primate chow (High Protein Monkey Diet; Harlan Teklad, Madison, WI), fresh fruit, and peanuts daily in amounts sufficient to maintain normal age- and gender-appropriate body weights. Monkeys were maintained under a 14/10 h light/dark cycle with lights on at 0600 h. Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and the 1996 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animals Resources on Life Sciences, National Research Council, National Academy of Sciences).

Surgery

Monkeys were anesthetized with 10 mg/kg of ketamine (*s.c.*, Fort Dodge Laboratories, Fort Dodge, IA) prior to intubation and maintenance of anesthesia by halothane (Butler Animal Health Supply, Grand Prairie, TX); oxygen was delivered at 2 l/min. A polyurethane catheter (SIMS Deltec Inc., St. Paul, MN) was implanted in the jugular or femoral vein and connected to vascular access ports (Access Technologies, Skokie, IL). The catheter and port were secured *s.c.* in monkeys all but one monkey (JA) according to methods described elsewhere (Wojnicki et al. 1994). The catheter was exteriorized in monkey JA who wore a jacket (Lomir Biomedical Inc., Malone, NY); for this monkey only an access port connected to the distal end of the catheter was stored and protected in a pocket of the jacket.

Apparatus

During experimental sessions, subjects were seated in commercially available chairs (Model R001; Primate Products, Miami, FL) that were placed in ventilated, sound-attenuating operant chambers. Response panels located in each chamber contained response levers and stimulus lights that could be illuminated red or green. Drugs were delivered *i.v.* by connecting vascular access ports to a 185-cm extension set (Abbott Laboratories, Stone Mountain, GA) via a 20-g Huber-point needle (Access Technologies, Skokie, IL). The opposing end of the extension set was connected to a 30-ml syringe that was mounted in a syringe driver (Razel Scientific Instruments, Inc., Stamford, CT) located outside the chambers. An interface (Med Associates, Inc., East Fairfield, VT) and a computer controlled experimental events and recorded data.

Self-administration procedure

All monkeys in this study had previously self-administered various drugs, including opioid receptor agonists. Monkeys did not receive drug for at least 3 weeks prior to the beginning of the study. Monkeys could lever press for infusions of *i.v.* heroin under a fixed-ratio 30 schedule. When the green light located above the active lever (right lever for VO, MA, and BE and left lever for other monkeys) was illuminated, 30 responses on that lever resulted in the illumination of a red light for 2 s and infusion of drug or vehicle followed by a 180-s

timeout. Responses on the inactive lever at any time and on the active lever during timeouts were recorded but had no programmed consequence. Sessions ended after 90 min.

Experiment 1: DOM

The acute effects of DOM on heroin self-administration were evaluated in 4 monkeys (JA, MI, AB, and PE) by determining dose-response functions for heroin alone and heroin following pre-session administration of DOM. A single dose of heroin (0.0001-0.1 mg/kg/infusion) or saline was available in each daily session, and this dose remained unchanged until it was studied in combination with both doses of DOM (0.1 and 0.32 mg/kg). Tests with a particular dose of heroin began with at least three consecutive sessions during which that dose was available in the absence of other treatment (i.e., to establish a baseline). When the number of infusions received for each of three consecutive sessions did not exceed $\pm 20\%$ of the average number of infusions received during the same three sessions, monkeys received a single dose of DOM s.c. 5 min before the session. During subsequent sessions, the same dose of heroin was available in the absence of other treatment, and the criterion described above had to be satisfied again before another dose of DOM was studied. Once each dose of DOM had been studied with a particular dose of heroin, saline was available in daily sessions until eight or fewer infusions were obtained for three consecutive sessions. Subsequently, a different dose of heroin was available for self-administration, and that remained available until it was studied in combination with both doses of DOM. The order in which monkeys were tested with the two doses of DOM was mixed. Each dose of DOM was also studied when only saline was available for self-administration. The effects of each dose of DOM were determined twice in two different (nonconsecutive) sessions.

Two monkeys that were studied in the non-contingent DOM study (JA and PE) and two additional monkeys (VO and NE) participated in the contingent DOM study. For this study, the experimental design and the stability criteria were identical to those employed in the non-contingent DOM study. The only exception was that different unit doses of DOM (0.0032, 0.01, 0.032 mg/kg/infusion) were available alone or in combination with a dose of heroin and studied for at least three consecutive sessions. After a dose of DOM was tested for three sessions, heroin again was available alone until responding stabilized and then another dose of DOM was tested in combination with that dose of heroin.

Experiment 2: Quipazine

The effects of non-contingent quipazine on heroin self-administration were evaluated in 4 monkeys (MA, BE, NE, and PE) by determining dose-response functions for heroin alone and heroin following a pre-session administration of quipazine. Initially a single dose of heroin was available in each daily session until the stability criteria were met (i.e., no more than 20% variation in infusions obtained per session for three consecutive sessions; see Experiment 1). Then saline was available until eight or fewer infusions were obtained for three consecutive sessions. The effects of non-contingent quipazine (0.32, 1.0, 1.78, and 3.2 mg/kg) were assessed in the same manner except that quipazine was administered i.v. 5 min prior to the start of the session. After at least three sessions of stable responding, saline was available until eight or fewer infusions were obtained for three consecutive sessions followed by the next test. Doses of quipazine were tested in ascending order. Initially, for all subjects, the effects of quipazine were determined with the dose of heroin that produced the maximum number of infusions or highest response rate (0.0032 mg/kg for MA, BE, and PE, 0.01 mg/kg for NE). Then the same dose of quipazine was studied in combination with each dose of heroin comprising the ascending limb of the dose-response function and saline. After a single dose of quipazine was studied in combination with each dose of heroin, the next larger dose of quipazine was studied in the same fashion. For each monkey, the dose of

quipazine was increased until a dose was reached that either completely suppressed responding (1.78 mg/kg for PE) or precluded further testing.

The effects of contingent quipazine were evaluated in the same group of monkeys that participated in the non-contingent quipazine study. Each heroin plus quipazine dose combination was studied for at least three consecutive sessions until responding was deemed stable, and each test was preceded by at least three consecutive sessions in which saline was available and fewer than eight infusions were obtained. A dose of quipazine (0.0032, 0.01, 0.032, 0.1, 0.32, and 0.56 mg/kg/infusion) or a combination of quipazine and heroin was then made available for self-administration. Quipazine was studied first in combination with the dose of heroin that produced the maximum number of infusions or highest response rate, then with other doses in descending order, and finally with saline (i.e. self-administered or quipazine alone).

Data analyses

The mean ($\pm$ SEM) number of infusions received per session in each experimental condition and the mean ($\pm$ SEM) rate of lever pressing (responses/second on the active lever when infusions were available) were plotted as a function of the unit dose of heroin for individual monkeys. In Experiment 1, control (heroin alone) dose-response functions were obtained by averaging the number of infusions and the rate of responding from the three sessions immediately prior to the start of DOM treatment. For the non-contingent study, the dose-response functions of heroin with DOM pretreatment represent the average number of infusions and the average response rate from two determinations. For the contingent DOM study, the dose-response functions of the DOM plus heroin mixture represent the average of number of infusions and the average response rate from three consecutive sessions for each dose combination. For Experiment 2, the number of infusions and response rate were averaged across the last three sessions of each test condition. Data obtained in individual monkeys were analyzed using GraphPad Prism version 5.0 for Windows (GraphPad Software, Inc., San Diego, California, USA) for two-way analysis of variance (ANOVA), with the dose of heroin and the treatment dose of DOM (Experiment 1) or quipazine (Experiment 2) as the two factors, followed by a Dunnett's test to compare the effects of each treatment dose of DOM or quipazine with control data (saline or each unit dose heroin when it was available alone).

Drugs

Diacetylmorphine hydrochloride (heroin) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) were both obtained from The Research Technology Branch, National Institute on Drug Abuse (Rockville, MD), and 2-piperazin-1-ylquinoline (quipazine) maleate salt was obtained from Sigma-Aldrich (St. Louis, MO). Heroin and quipazine were always administered i.v. DOM was administered s.c. for the non-contingent experiment and i.v. for the contingent experiment. All drugs were dissolved in sterile 0.9% saline, and doses are expressed as the forms listed above in mg per kg of body weight.

Results

Experiment 1

Non-contingent DOM—For all monkeys in the non-contingent DOM study, heroin produced an inverted U-shaped dose-response function for the number of infusions received (circles, Fig 1A) and for the rate of responding (circles, Fig 1B), each plotted as a function of unit dose. The number of infusions and the rate of responding increased then decreased with larger unit doses of heroin. The highest number of heroin infusions was observed with a unit dose of 0.0032 mg/kg/infusion in two monkeys (AB and PE) and 0.01 mg/kg/infusion

in two other monkeys (JA and MI), with monkeys receiving an average of between 20 (PE) and 27 (JA) infusions per session (circles, Fig 1A). When saline was available, the average number of infusions was 2 (JA), 7(MI), 4 (AB), and 1 (PE). Similarly, the highest rate of lever pressing (ranging from 0.42 responses/second in PE to 3.73 responses/second in JA) occurred at unit doses of 0.0032 mg/kg/infusion in monkeys AB and PE and 0.01 mg/kg/infusion in monkeys JA and MI (circles, Fig 1B).

Non-contingent administration of DOM prior to the session flattened the heroin dose-response function for the number of infusions delivered per session plotted as a function of dose (Fig 1A). For three monkeys (JA, MI, AB), DOM tended to increase the number of infusions of saline and small doses of heroin and decrease the number of infusions of larger doses. For MI and AB, DOM significantly (filled symbols denote significant differences from heroin or saline alone) increased the number of infusions of 0.0001 mg/kg/infusion heroin. When administered alone, this unit dose of heroin resulted in a number of infusions that was not different from the number of infusions received when only saline was available; however, after pre-session administration of 0.1 mg/kg DOM, monkeys MI and AB received an average (+ SEM) of 21.5 ± 4.5 and 11.5 ± 1.5 infusions of 0.0001 mg/kg/infusion heroin and after 0.32 mg/kg DOM they received an average of 24.0 ± 2.0 and 15.5 ± 0.5 infusions of heroin, respectively (Fig 1A). Rate of responding for 0.0001 mg/kg/infusion of heroin also was increased by pre-session administration of DOM in monkeys MI and AM (Fig 1B), although this increase did not reach statistical significance. In monkey JA, DOM tended to increase the number of infusions received for saline and small doses of DOM and decrease the number of infusions received for intermediate doses of DOM; for example, the decrease in number of infusions was statistically significant for 0.01 and 0.032 mg/kg/infusion of heroin in combination with 0.32 mg/kg DOM (filled squares, Fig 1A). A dose of 0.1 mg/kg DOM significantly increased the number of saline infusions received from 2 to 17.5 in monkey JA; similarly, a dose of 0.32 mg/kg DOM significantly increased the number of saline infusions received in monkey AB. For monkey PE, both doses of DOM significantly decreased responding for all doses of heroin (Fig 1A).

An overall flattening of the dose-response function, including increased self administration of saline and small unit doses of heroin, was also apparent for the same data in terms of responses per second plotted as a function of unit dose (Fig 1B). Some dose combinations, that were not significantly different from heroin alone in terms of the number of infusions received, were significantly different in terms of rate of responding (e.g. 0.0032 mg/kg/infusion heroin in combination with 0.32 DOM in monkey AB and 0.01 mg/kg/infusion heroin in combination with 0.32 DOM in monkey MI; compare Figs 1A and 1B).

Contingent DOM—For the two monkeys that participated in the contingent and non-contingent studies with DOM (JA and PE), the control heroin dose-response functions obtained during the non-contingent study were used as control data for the contingent study (circles; Fig 1A, 1B, 2A and 2B). For the two monkeys that did not participate in the non-contingent experiment (NE and VO), heroin also produced an inverted U-shaped dose-response function for the number of infusions received (Fig 2A) and for the rate of responding (Fig 2B). The number of infusions received and the rate of lever pressing increased then decreased with larger unit doses of heroin. The maximum average number of infusions was obtained at a unit dose of 0.01 mg/kg/infusion of heroin for VO (24.7) a unit dose of 0.032 mg/kg/infusion for NE (27.0); the average number of saline infusions received per session was 5 and 9 for VO and NE, respectively.

DOM alone (squares and triangles above “V”, Figs 2A and 2B) did not maintain responding that was significantly different from responding maintained by saline. In all four monkeys, dose-response functions for combinations of DOM and heroin were shifted to the right and

downward as compared with self-administration of heroin alone (Fig 2A and 2B). At least one dose of DOM significantly decreased the number of infusions received (Fig 2A) and the rate of responding (Fig 2B) in all four monkeys (filled symbols denote significant difference from heroin or saline alone). Self-administration of the drug combination resulted in maximum intake (for the entire session; inverted triangles, all panels, Figs 2A and 2B) of DOM as follows: 0.65 mg/kg for JA and 0.17 mg/kg for PE at unit doses of 0.032 mg/kg/infusion DOM and 0.032 mg/kg/infusion heroin; 0.78 mg/kg for NE and 0.46 mg/kg for VO at unit doses of 0.032 mg/kg/infusion DOM and 0.01 mg/kg/infusion heroin. For both the number of infusions received (Fig 2A) and response rate (Fig 2B), the heroin dose-response function was not shifted significantly upward or leftward for any dose combination of heroin and DOM.

Experiment 2

Non-contingent quipazine—For all the monkeys studied in Experiment 2, heroin produced an inverted U-shaped dose-response function for the number of infusions received (Fig 3A) and response rate (Fig 3B). The number of infusions and response rate increased and then decreased with larger unit doses of heroin. The highest number of heroin infusions was observed with a unit dose of 0.0032 mg/kg/infusion in three monkeys (MA, BE, and PE) and 0.01 mg/kg/infusion in monkey NE, with monkeys receiving between 12 (MA) and 26 (NE) infusions per session. The highest response rates at these unit doses ranged between 0.1 (MA) and 2.8 (NE) responses/second. When saline was available (circles above “V”, Fig 3A) the average number of infusions decreased to 1 in PE, NE, and MA, and to 4 in BE.

In two monkeys (MA and BE), non-contingent quipazine significantly increased the number of infusions obtained and response rates maintained by saline and small unit doses of heroin (Fig 3A). For MA, pre-session administration of 1.78 or 3.2 mg/kg quipazine significantly increased the number of infusions of 0.00032 and 0.001 mg/kg/infusion heroin to between 9.0 ± 0.5 and 10.7 ± 0.3 (filled squares and diamonds, Fig 3A). These unit doses of heroin alone resulted in no more than 1 infusion per session which was not different from the number of infusions obtained with saline alone. The largest dose of quipazine tested in this monkey (3.2 mg/kg) significantly increased the number of saline infusions obtained (from 0 to 12.0 ± 0.3) and the rate of responding for saline (filled diamonds above “V”, Figs 3A and 3B). For BE, pre-session administration of 1.0 or 1.78 mg/kg quipazine significantly increased the number of infusions of 0.001 mg/kg/infusion of heroin from 5.0 to 12.3 ± 1.0 and 15.7 ± 2.3 , respectively (filled triangles and squares, Fig 3A). The same doses of quipazine failed to increase the number of infusions obtained at a smaller unit dose of heroin (0.00032 mg/kg/infusion). However, 1.0, 1.78, and 3.2 mg/kg quipazine significantly increased the number of infusions of saline from 4 ± 0.5 to 10 ± 1.0 , 10 ± 1.0 , and 9 ± 0.5 , respectively (Fig 3A).

In two other monkeys (PE and NE), non-contingent quipazine did not substantially alter the number of infusions obtained of any unit dose of heroin; though, there were several statistically significant differences in each monkey. In PE, 0.32 mg/kg quipazine increased the number of infusions of 0.001 mg/kg/infusion heroin from 1.3 ± 1.0 to 8.3 ± 1.0 (triangles, Fig 3A). In NE, non-contingent administration of 1.0 mg/kg quipazine (inverted triangles, Fig 3A) significantly increased the number of infusions of 0.00032 mg/kg/infusion heroin from 3 ± 1.0 to 8.7 ± 1.0 . In both monkeys, there was no increase in the number of saline infusions received or in the rate of responding for saline after non-contingent administration of DOM.

Contingent quipazine—For individual monkeys, the effects of contingent quipazine were similar to the effects of non-contingent quipazine. For MA and BE, at least one dose of

contingent quipazine increased responding for small unit doses of heroin and for saline. For MA, 0.32 mg/kg/infusion quipazine (filled squares, Fig 4A) increased the number of infusions obtained with saline, and with 0.00032 and 0.001 mg/kg of heroin from an average of 1.0 ± 0.7 infusion per session to 6 ± 0.7 , 12 ± 1.0 , and 12 ± 1.0 , respectively. The same dose of quipazine significantly decreased the number of infusions of 0.0032 mg/kg/infusion of heroin from 11.7 ± 0.5 to 7.7 ± 1.0 . In BE, 0.1 mg/kg/infusion quipazine (triangles, Fig 4A) increased the number of infusions of 0.001 mg/kg from 5.0 to 14.3 ± 0.7 . In the same monkey, the next larger dose of quipazine, 0.32 mg/kg/infusion, failed to increase responding for saline or any unit dose of heroin; however, this unit dose of quipazine modestly but significantly decreased the number of infusions of 0.0032 and 0.01 mg/kg/infusion of heroin (filled squares, Fig 4A).

For monkeys PE and NE, contingent quipazine (i.e. quipazine in combination with heroin) did not significantly increase the number of infusions received. For NE, rate of responding was significantly increased for one unit dose of quipazine (0.32 mg/kg/infusion) in combination with 0.0032 mg/kg/infusion of heroin (squares, Fig 4B); however, this increase did not impact the number of infusions obtained (Fig 4A). In monkey PE, the largest dose of quipazine tested (0.01 mg/kg/infusion) in combination with 0.0032 mg/kg/infusion of heroin produced a significant decrease in both number of infusions and response rate (filled triangles, Figs 4A and 4B).

Self-administration of the quipazine in combination with heroin resulted in maximum intake (for the entire session, Fig 4A) of quipazine as follows: 0.08 mg/kg for PE (crossed circles) at unit doses of 0.0032 mg/kg/infusion quipazine and 0.0032 mg/kg/infusion heroin; 10.45 mg/kg for NE (diamonds) at unit doses of 0.56 mg/kg/infusion quipazine and 0.001 mg/kg/infusion heroin; 4.16 mg/kg for BE (squares) at unit doses of 0.32 mg/kg/infusion quipazine and 0.0032 mg/kg/infusion heroin; and 4.16 mg/kg for MA (squares) at unit doses of 0.32 mg/kg/infusion quipazine and both 0.00032 and 0.001 mg/kg/infusion heroin.

Discussion

There is a need for more effective and safer treatments for pain and one potentially fruitful approach combines drugs with different mechanisms of action; drugs administered together have the potential to be more effective than one drug administered alone and relatively smaller doses of each drug might be necessary to obtain adequate analgesia, thereby reducing the likelihood of adverse effects. Some drugs acting on 5-HT systems can enhance the antinociceptive effects of opioids and the current study examined whether two such drugs, the 5-HT_{2A} receptor agonists DOM and quipazine, altered the positive reinforcing effects of heroin in rhesus monkeys.

Contingent (response-dependent) administration of DOM in combination with heroin attenuated the positive reinforcing effects of heroin in all monkeys, shifting the heroin dose-response functions to the right and down. Non-contingent (response-independent) administration of DOM and quipazine (in two monkeys) flattened the heroin dose response function by increasing responding for saline and small doses of heroin. In addition, DOM but not quipazine decreased responding for intermediate doses of heroin. In neither experiment was there a clear indication of a shift to the left in the heroin dose-response function that might indicate either DOM or quipazine was enhancing the positive reinforcing effects of heroin.

Some 5-HT₂ receptor agonists (e.g., LSD and DOM) have hallucinogenic activity in humans and they are abused. However, these drugs are not reliably self-administered by non-humans under typical experimental conditions and are generally considered to be relatively weak

reinforcers (Yanagita 1986; Fantegrossi et al. 2004; Nichols 2004). Consistent with previously published studies, DOM failed to maintain self-administration in any monkey, and quipazine maintained modest levels of self-administration in only two monkeys (MA and BE). Overall, 6 of 8 monkeys did not self-administer a 5-HT₂ receptor agonist at levels above what was obtained with saline.

When administered non-contingently, DOM and quipazine decreased the dose-relatedness of the typically inverted U-shaped heroin dose-response function. That is, in some cases pre-session administration of DOM (MI and AB) and quipazine (MA and BE) increased responding for small unit doses of heroin and decreased responding for larger unit doses (DOM; JA and AB). The mechanisms underlying these effects remain unclear. Given that responding for saline was also increased, it appears unlikely that this effect of DOM is related to enhancement of the positive reinforcing effectiveness of heroin.

In addition to functioning as positive reinforcing stimuli, drugs can also (and at the same time) serve as discriminative stimuli that set the occasion for drug-associated behavior (e.g., lever pressing to obtain infusions of drug). Thus, drugs that share discriminative stimulus properties with heroin might evoke self-administration behavior even in the absence of heroin. This possibility seems unlikely in light of the fact that 5-HT_{2A} receptor agonists such as DOM and quipazine do not occasions drug-lever responding in monkeys discriminating morphine and, in the same monkeys, they attenuate rather than enhance the discriminative stimulus effects of morphine (Li et al. 2011).

It might be the case that DOM and quipazine generally increase low rates of responding (e.g., rates maintained by saline and small doses of heroin) and decrease high rates of responding (e.g., rates maintained by larger doses of heroin) in a rate-dependent fashion (cf., Dews and Wenger 1977), and thus the effects observed were non-specific changes in response rates. However, this interpretation seems unlikely because experiments designed specifically to detect rate-dependent effects have typically not found such effects with 5-HT receptor agonists like quipazine (e.g. Brady and Barrett 1985; Harris et al. 1978).

Finally, it is possible that DOM and quipazine stimulate responding in monkeys with a history of heroin self-administration by enhancing the reinforcing effectiveness of stimuli that were paired with heroin infusions (e.g. by enhancing conditioned reinforcement). For example, some drugs (e.g. direct-acting dopamine D2/D3 receptor agonist quinpirole) that alone do not reliably maintain self-administration in drug-naïve animals can maintain responding in the presence of stimuli previously paired with reinforcing drugs like cocaine (Collins and Woods 2009). In the current study, in all sessions the response period was signaled by a green light, and completion of the ratio requirement resulted in brief illumination of a red light followed by an i.v. infusion. DOM and quipazine might have enhanced the response-evoking effects of these stimuli, thereby reducing control by the dose of heroin and increasing control by the common discriminative stimuli. It remains unclear if this effect would be the direct result of activation of 5-HT receptors or the result of downstream interactions between 5-HT and dopamine systems.

It is well established that under some conditions the contingency of drug administration significantly impacts the effects obtained (Dworkin et al. 1995; Galici et al. 2000; Lecca et al. 2007). The effects of quipazine did not depend on the response contingency of drug administration; for individual monkeys, similar effects were obtained in the non-contingent and contingent studies with quipazine (compare Figs 3 and 4). However, the effects of DOM differed across studies. In contrast to increases in responding for saline and small doses of heroin that were observed in some monkeys after the non-contingent administration of DOM (Figs 1A and 1B), only decreases in responding were observed when DOM was

administered together with heroin, as compared to what would be expected with heroin alone (Figs 2A and 2B). Notwithstanding a different route of administration in the two conditions (s.c. for non-contingent DOM and i.v. for contingent DOM), a markedly different interaction occurred between DOM and heroin after the administration of similar doses of both drugs. The unit doses of heroin were the same in the two experiments and the total dose of DOM was also similar between the two experiments (0.1 and 0.32 mg/kg in the non-contingent experiment and 0.17-0.78 mg/kg in the contingent experiment). Together these results provide another example of a difference in drug effect depending on the contingency of administration – in this case the nature of interaction between two drugs. Thus, self-medication for pain might significantly influence the interaction between opioids and drugs acting on 5-HT systems, perhaps reducing the abuse liability of the opioid component of the drug mixture.

In summary, the 5-HT_{2A} receptor agonists DOM and quipazine failed to produce clear enhancement of the positive reinforcing effects of the mu opioid receptor agonist heroin. Both drugs tended to reduce the dose dependency of heroin self-administration as evidenced by a flattening of the heroin dose-response function. The relative potencies of DOM and quipazine in the current study were similar to those reported previously, with DOM being approximately 10-fold more potent than quipazine (see Li et al. 2011). In some cases, the flattening of the curve was the result of increased responding for small doses of heroin, suggesting that it might enhance the reinforcing effects of heroin; however, concomitant increases in responding for saline suggest that these effects are likely not due to enhanced reinforcing effectiveness of heroin per se. Thus, DOM and quipazine enhance the antinociceptive effects and attenuate the discriminative stimulus effects (Li et al. 2011) of mu opioid receptor agonists without enhancing their positive reinforcing effects. It remains to be seen whether drug combinations, such as those examined in this study, translate to more effective pain treatment, whether the administration of smaller doses of each drug results in a reduced adverse effect profile, and whether interactions that are observed under acute dosing conditions persist under repeated (chronic) dosing conditions.

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A

B

Fig 1.

Self-administration of saline (circles above “V”) or heroin (i.v.) alone (circles) and after a non-contingent pre-session administration of 0.1 (triangles) or 0.32 (squares) mg/kg DOM (s.c.) 5 min prior to the session in 4 rhesus monkeys responding under a fixed ratio 30 schedule. Fig 1A shows the number of infusions ($\pm$ SEM) received in the 90-min session (ordinate) and Fig 1B shows the rate of lever pressing (in responses per second when infusions were available; note different ranges among ordinates), each plotted as a function of the unit dose of heroin (abscissae) expressed in mg/kg/infusion. Filled symbols indicate

that the number of infusions (Fig 1A) or the rate of responding (Fig 1B) was significantly different ($p < 0.05$) as compared to the effects obtained with saline alone or heroin alone at that unit dose per infusion. “V” = vehicle.

A

B

Fig 2.

Self-administration of saline alone or with DOM (above “V”) and self-administration of heroin alone or with DOM in 4 rhesus monkeys. Fig 2A shows the number of infusions received per session and Fig 2B shows the rate of responding (note different ranges among ordinates). See Fig 1 for other details.

A

B

Fig 3.

Self-administration of saline (circles above “V”) or heroin (i.v.) alone (circles) and after a non-contingent pre-session administration of 0.32 (triangles), 1.0 (inverted triangles), 1.78 (squares), or 3.2 (diamonds) mg/kg quipazine (i.v.) 5 min prior to the session in 4 rhesus monkeys responding under a fixed ratio 30 schedule. Fig 3A shows the number of infusions ($\pm$ SEM) received in the 90-min session (ordinate) and Fig 3B shows the rate of lever pressing (in responses per second when infusions were available. See Fig 1 for other details.

Fig 4.

Self-administration of saline alone or with quipazine (above “V”) and self-administration of heroin alone or with quipazine in 4 rhesus monkeys. See Figs 1 and 3 for other details.