Abstract  Rationale and objectives: Opioid agonists frequently have been reported to share discriminative stimulus (DS) effects with cocaine; however, the pharmacological basis of these shared effects is not understood completely. The present study assessed the ability of heroin and its deacetylated metabolites, 6-monoacetylmorphine (6-MAM) and morphine, to engender cocaine-like DS effects and investigated the role of opioid receptor subtypes in modulating these DS effects. Methods: Squirrel monkeys were trained to discriminate 0.3 mg/kg cocaine (i.m.) from vehicle under a 10-response fixed-ratio schedule of food reinforcement, and responding on the drug lever was assessed after varying i.m. doses of heroin, 6-MAM, and morphine. The potential role of opioid receptor mechanisms in modulating the cocaine-like DS effects of heroin and its metabolites was assessed with the mixed mu/kappa opioid antagonist naltrexone, the delta-selective antagonist naltrindole, and the kappa-selective antagonist nor-binaltorphimine. Results: Heroin, 6-MAM, and morphine engendered dose-related increases in responding on the cocaine lever in three of four monkeys. Naltrexone shifted the dose–response functions for heroin and its metabolites to the right, and in vivo apparent pA2 analyses revealed that naltrexone antagonized the effects of the opioids in a manner consistent with mu receptor antagonism (apparent pA2 values ranging from 8.20 to 8.47). Naltrindole only minimally altered the dose–response functions of heroin, 6-MAM, and morphine, whereas nor-binaltorphimine did not block the cocaine-like DS effects of the three opioid agonists, suggesting that neither delta nor kappa receptors played a prominent role in the cocaine-like DS effects of heroin and its metabolites. Conclusions: These results suggest that heroin and its deacetylated metabolites engendered cocaine-like DS effects in a similar fashion. Furthermore, the cocaine-like DS effects of these opioids were modulated by a predominantly mu-opioid receptor mechanism.

Key words Heroin · 6-Monoacetylmorphine · Morphine · Speedball · Drug discrimination · Squirrel monkey (Saimiri sciureus)

Introduction

Many polydrug abusers use cocaine in combination with heroin by mixing the drugs and injecting them simultaneously. This combination is referred to as a “speedball”, and abuse of speedballs is prevalent worldwide along with cocaine and heroin abuse (Kosten et al. 1986; Darke and Hall 1995; Frank and Galea 1996). Efforts to identify the pharmacological basis for speedball abuse have yet to reveal clear mechanisms underlying this form of addiction. For example, some drug abusers have reported that cocaine–heroin combinations produce greater euphoric effects than either drug alone, whereas others have reported that the combination ameliorates certain undesirable effects of the individual drugs (Kosten et al. 1986). Controlled laboratory studies with polydrug abusers have also revealed varying results, with some studies demonstrating that the subjective effects of cocaine–opioid combinations differ qualitatively from either drug alone, while others have found that the combination results in enhanced subjective effects of the individual drugs (Foltin and Fischman 1992, 1994; Strain et al. 1994; Preston et al. 1996; Walsh et al. 1996). Whether the different findings from human laboratory studies are due to factors such as properties of the opioid agonist, degree of opioid dependence, and/or tolerance has yet to be resolved.

Consistent with the above findings, preclinical experiments have revealed individual differences in the interaction of cocaine and opioids. For example, studies using drug discrimination procedures have found that co-
caine and opioids share discriminative stimulus (DS) effects in some subjects but not others. In this regard, various opioid agonists (e.g., heroin, fentanyl) engendered a majority of responses on the drug-appropriate lever in a subset of monkeys trained to discriminate cocaine from vehicle (Mello et al. 1995; Negus et al. 1998). Conversely, cocaine and related stimulants have been shown to substitute in a subgroup of monkeys trained to discriminate morphine from vehicle (Platt et al. 1999). At present, the pharmacological basis of the shared DS effects of stimulants and opioids in some subjects but not others is not known.

The present study examined the ability of heroin to engender cocaine-lever responding in squirrel monkeys. Heroin was chosen because it is a primary constituent of speedball combinations used by polydrug abusers. Because heroin is rapidly deacetylated to 6-monoacetylmorphine (6-MAM) and morphine after administration (Way et al. 1960; Inturrisi et al. 1983), a goal of this study was to assess whether the active metabolites of heroin differed in their ability to engender cocaine-like DS effects. Although the effects of heroin are thought to reflect primarily the action of these metabolites, notable differences in the behavioral effects of 6-MAM and morphine compared with heroin have been identified. For example, the antinociceptive effects of 6-MAM may be mediated by delta-opioid receptors (Rady et al. 1994, 1997), whereas the effects of heroin and morphine are generally attributed to mu receptor stimulation (Martin et al. 1976; Woods et al. 1992).

The present report also sought to identify potential mechanisms underlying the shared stimulus effects of cocaine and heroin. Converging evidence has suggested a role for mu-opioid receptor stimulation in the ability of opioids to either reproduce or enhance the DS effects of cocaine and related stimulants (Spealman and Bergman 1992; Negus et al. 1998; Rowlett and Spealman 1998; Platt et al. 1999). In addition, we recently demonstrated that delta receptor stimulation can enhance the DS effects of cocaine (Rowlett and Spealman 1998). These findings raise the possibility that both mu- and delta-opioid receptor stimulation may play a role in the shared DS effects of stimulants and opioids. To assess this possibility, antagonism of the cocaine-like DS effects of heroin and its metabolites by the mu/kappa-opioid antagonist naltrindole was compared with antagonism by the selective delta-opioid receptor antagonist naltrindole. Finally, in addition to mu and delta receptors, the metabolites of heroin also bind to kappa receptors; for example, morphine is only about tenfold less selective for kappa than mu receptors (Emmerson et al. 1994). Selective kappa receptor agonists, in general, have been shown to have effects opposite to those of mu and delta agonists when combined with cocaine (Spealman and Bergman 1992). However, the kappa agonist U-50488 engendered a majority of responses on the drug lever in more than half the monkeys trained to discriminate a low dose of cocaine (Spealman and Bergman 1994). In the present study, the kappa-selective antagonist nor-binaltorphimine was used to assess potential kappa receptor involvement in the cocaine-like DS effects of heroin and its metabolites.

Materials and methods

Subjects

Four adult male squirrel monkeys (Saimiri sciureus) were studied in daily experimental sessions (Monday–Friday). Between sessions, the monkeys lived in individual home cages, where they had unlimited access to water. Each monkey was maintained at 85–90% of its free-feeding body weight (0.70–0.94 kg) by adjusting its access to food (Purina monkey chow, Teklad monkey diet, fresh fruits) in the home cage. All animals were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare Publication No. (National Institutes of Health) 85–23, as revised in 1996. Research protocols were approved by the Harvard Medical School Institutional Animal Care and Use Committee.

Apparatus

During experimental sessions, monkeys were seated in a Plexiglas chair identical to the one described by Rowlett and Spealman (1998). Two response levers (BRS/LVE, model 121–05; Beltsville, Md.) were mounted 15 cm apart on the wall of the chair in front of the monkey. A press of either lever with a minimum downward force of 0.25 N produced an audible click and was recorded as a response. Food pellets (Noyes, 190 mg, Formula L; Lancaster, N.H.) could be delivered to a tray located between the levers. Red lights, mounted at eye level above the levers, were illuminated during the session except during timeout periods (see below). The chair was enclosed in a ventilated, sound-attenuating chamber, which was provided with white noise to mask extraneous sounds.

Drug discrimination procedure

Before the present study began, each monkey had been trained to discriminate 0.3 mg/kg cocaine from saline (Rowlett and Spealman 1998), and these training conditions continued during the present study. Briefly, after i.m. injections of cocaine, ten consecutive responses (FR 10) on one lever produced food; whereas, after i.m. injections of saline, FR 10 on the other lever produced food. Responses on the incorrect lever (e.g., the saline-associated lever when cocaine was injected) reset the FR requirement. Training sessions consisted of a variable number of components (n=1–4) of the FR schedule. Each component ended after the completion of the tenth FR 10 or after 5 min had elapsed, whichever occurred first. A 10-min timeout period, during which the lights were off and responses had no programmed consequences, preceded each component. During most training sessions, saline was injected during timeout periods preceding the first n–1 components, and cocaine was injected before the last component of the session. Periodically, saline was injected before all components of a training session to prevent an invariant association between the last component and cocaine. Injections of cocaine or saline were made in a thigh or calf muscle of either leg during the fifth minute of the 10-min timeout periods.

Drug testing procedure

Test sessions were conducted once or twice per week with training sessions scheduled on intervening days. Test sessions were conducted only if ≥90% of the total number of responses were made...