Abstract  Rationale: The nonpeptidic compound SNC80 [(+)-(αR)-(2S, 5R)-4-allyl-2, 5,-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide], has a high degree of selectivity for delta opioid receptors. Moreover, compounds with delta opioid activity have been shown to enhance the effects of mu agonists under certain conditions. Objectives: The present study examined the effects of SNC80 alone and in combination with the mu opioid agonists, morphine, butorphanol, and buprenorphine to determine whether SNC80 would enhance their antinociceptive effects. Methods: In the squirrel monkey shock titration procedure increasing levels of shock are delivered to the monkey's tail in incremental steps and responses on a lever decrease shock intensity. The level at which monkeys maintain the shock (median shock level, MSL) and rate of responding (RR) are examined. Results: SNC80 alone did not consistently alter responding under the titration procedure; however, morphine, butorphanol, and buprenorphine increased MSL without decreasing RR markedly. SNC80 (0.1–3.0 mg/kg) enhanced the effects of single doses of morphine, butorphanol, and buprenorphine that either did not increase or produced very small increases in MSL when administered alone. Interestingly, SNC80 enhanced the effects of morphine, butorphanol, and buprenorphine on MSL without decreasing RR. Conclusions: SNC80 does not produce antinociceptive effects in the squirrel monkey titration procedure but can enhance the effects of selected doses of morphine, butorphanol, and buprenorphine on MSL without decreasing RR. These data suggest that SNC80-induced enhancement of the antinociceptive effects of mu opioids is dependent on dose, time, and method of administration and is not the result of sedation or motor dysfunction.

Keywords  SNC80 · Delta opioids · Mu opioids · Morphine · Buprenorphine · Butorphanol · Antinociception

Introduction

There are numerous reports that delta opioid peptides increase the analgesic potency of morphine (Adams et al. 1993; Horan et al. 1992; Jiang et al. 1990; Porreca et al. 1987; Malmberg and Yaksh 1992). Moreover, the non-peptidic delta opioid BW373U86 increases the analgesic potency of l-methadone and fentanyl (Dykstra et al. 1993; O’Neill et al. 1997) and also attenuates some of the behaviors associated with morphine dependence (Lee et al. 1993).

Recently investigators have developed a series of nonpeptidic compounds with a high degree of selectivity for delta opioid receptors. One very interesting compound in this class is SNC80, an O-methylated derivative of BW373U86, which is reported to have greater than 500-fold selectivity for delta vs. mu opioid receptors (Calderon et al. 1994, 1997). In vivo studies indicate that SNC80 can produce antinociceptive properties in both rodents and nonhuman primates under certain conditions (Bilsky et al. 1995; Brandt et al. 2001a; Butelman et al. 1995; Negus et al. 1998; Stewart and Hammond 1994). The fact that the antinociceptive effects of SNC80 are antagonized by delta-selective antagonists provides additional evidence that the antinociceptive actions of SNC80 are mediated by delta opioid action. Moreover, investigations of the discriminative stimulus and rate-decreasing effects of SNC80 in monkeys also suggest that the effects of SNC80 are selective for delta opioid systems (Brandt et al. 1999, 2001b; Platt et al. 1999).

In order to characterize the antinociceptive effects of SNC80 further and to determine whether it potentiates the effects of other opioid agonists, the squirrel monkey titration procedure was used (Dykstra and Massie 1988; Dykstra et al. 1993; Pitts et al. 1998). The present study examined the effects of SNC80 in combination with the
mu opioid agonists morphine, butorphanol, and buprenorphine. Previous investigations indicate that each of these agonists is active in the titration procedure; however, they differ in efficacy in this procedure with morphine having the greatest degree of efficacy, followed by buprenorphine and then butorphanol (Dykstra 1985, 1990; Negus and Dykstra 1988). Moreover, the parent compound of SNC80, BW373U86, has been shown to enhance the effects of a range of opioid agonists under the titration procedure (Dykstra et al. 1993).

One advantage of the shock titration procedure is that it allows the simultaneous measurement of response rate and antinociception. Increasing levels of shock are delivered to the monkey’s tail in incremental steps and responses on a lever decrease shock intensity. Because termination of shock requires an operant response, the rate of responding on the lever is recorded along with a measure of shock intensity. After extensive training monkeys generally allow the shock to increase several steps and then maintain the shock at a predictable level, measured as the median shock level. It has been shown that monkeys allow shock to increase to a higher intensity (as reflected by an increase in median shock level) when opioid analgesics such as morphine are administered. Therefore alterations in the discriminative aspects of the analgesic response are indicated by changes in median shock level which are measured separately from rate of responding.

Research in our laboratory has shown that opioid analgesics increase median shock levels over a range of doses that do not produce marked decreases in rates of responding; however, rates of responding are decreased when very high doses of opioids are administered. This observation strengthens the notion that opioids can alter the discriminative aspects of nociceptive processing, and that these alterations do not simply reflect sedation or motor dysfunction. The ability to make this distinction is an important advantage of the titration procedure, especially given previous research indicating that both the discriminative stimulus and rate-decreasing properties of a drug are important determinants of its behavioral effects (Dews 1974; Kelleher and Morse 1964).

Methods and materials

Subjects

Eight adult male squirrel monkeys (Saimiri sciureus) were pair-housed in a climate controlled colony room, maintained on a 12-h light/dark cycle (7:00 a.m. to 7:00 p.m.). All monkeys had free access to water and were maintained at their free-feeding weights (650–1050 g) through a high-protein monkey diet supplemented with fresh fruit. Four of the monkeys had extensive histories while the other four were experimentally naive. No monkey had received any drugs in the 2 months prior to beginning these experiments.

Apparatus

Each monkey was seated in a Plexiglas primate restraint chair and held in place by a waist support with its tail secured by a small stock (Dykstra 1985). Electrical shock was administered via two hinged brass plates that rested on a shaved portion of the monkey’s tail which was coated with a noncorrosive electrode paste (EKG Sol). Each chair was enclosed within a ventilated sound-attenuating chamber, illuminated by a 10-W bulb. A lever was positioned on the right side of the front panel. When the lever was pressed with a downward force of at least 0.15 N, an audible click was heard and the response was recorded. Experimental events were controlled using software and hardware from Med Associates (St. Albans, VT, USA).

Behavioral procedure

The shock titration procedure previously described by Dykstra and Massie (1988) was used. At the start of each experimental session the shock intensity began at 0.01 mA and increased in 30 intervals to a maximum shock level of 2.0 mA. Monkeys received continuous shock during 15-s trial periods. If a monkey did not respond five times (FR5) during that 15-s period, the shock was increased one increment and maintained at that level for another 15-s period. When a monkey met the FR5 requirement, the shock was immediately terminated for a 15-s time-out period after which the shock resumed at the next lower intensity. During time-out periods chamber lights stayed on but responding had no experimental consequence. If at the highest shock intensity the FR5 requirement was not met in any of five consecutive 15-s shock periods, the session was automatically terminated.

Each session consisted of four 15-min periods during which the shock titration procedure was in effect. A 10-min interval preceded each 15-min shock period during which the chamber was dark and responding had no consequence. Control sessions were typically conducted on Monday, Wednesday, and Thursday with test sessions on Tuesdays and Fridays. For test sessions the inter-component interval was extended to 20 min, and a fifth component was added.

Pharmacological procedure

All compounds were dissolved in distilled water, and, when necessary, a few drops of lactic acid were added to the SNC80/water mixture. Injections were intramuscular in a volume of 0.5 ml/kg. Morphine sulfate, buprenorphine hydrochloride, and SNC80 were obtained from NIH (Bethesda, Md., USA) and butorphanol tartrate was obtained from Sigma Aldrich (St. Louis, Mo., USA).

Dose-effect curves for SNC80, morphine, butorphanol, and buprenorphine were first obtained using a cumulative dosing procedure. Under this procedure vehicle (sterile water) was injected 20 min before the first FR5 period. On completion of the first FR5 period the lowest dose of SNC80, morphine, butorphanol, or buprenorphine was injected, and its effects were assessed in the following FR period. At the onset of each subsequent period an amount of drug that increased the cumulative dose by 0.25–0.5 log unit was injected. Injections continued in this manner for three or four dose increments. The dose-effect curves for morphine, butorphanol, and buprenorphine were then redetermined in the presence of a range of acute doses of SNC80. In this situation a dose of SNC80 was given prior to the first FR5 period, and this was followed by redetermination of dose-effect curves as described above.

Time-effect curves for SNC80, morphine, butorphanol, and buprenorphine alone were obtained by administering a selected dose of each compound 20 min before the first FR period. On completion of the first and all subsequent FR5 periods, vehicle was injected. The total time period examined was 175 min. Time-effect curves were then redetermined in the presence of a range of acute doses of SNC80. In this situation a dose of SNC80 was administered along with a dose of morphine, butorphanol, or buprenorphine 20 min before the first FR period, followed by the assessment of time-effect curves as described above.