Buprenorphine is a partial opioid agonist derived from thebaine and has high affinity for μ and κ opioid receptors. The present study investigated dose-response (0.03, 0.15, 0.3, 3 mg/kg) and time-dependent effects of buprenorphine (1.5 or 4 h post-treatment) on EtOH self-administration in outbred Sprague-Dawley rats. Freely feeding and drinking rats were trained to initiate EtOH self-administration for 1 h daily using the ascending concentration procedure, wherein they were provided with increasing concentrations of EtOH at 2, 5, 7, 9 and 11% (v/v), respectively. Water was concurrently available with each concentration. Animals were maintained on a given concentration of EtOH for 5 days. By day 21, animals began their stabilization on the 11% regimen and remained on this concentration throughout the remainder of the study. EtOH and water consumption were recorded daily at both 10- and 60-min intervals. At 1.5 h post-buprenorphine, all test doses greatly suppressed both EtOH and water intake at the 10-min interval. At the 60-min interval, all but the lowest dose (0.03 mg/kg) significantly suppressed EtOH intake, while only the highest dose (3 mg/kg) suppressed water intake. In contrast to the suppressant profile observed at 1.5 h post-buprenorphine, at 4 h post-buprenorphine the lower doses (0.03 and 0.15 mg/kg) significantly increased EtOH intake while the higher doses (0.3 and 3 mg/kg) continued to suppress intake. None of the doses of buprenorphine altered water intake 4 h post-buprenorphine. The results support previous research demonstrating the utility of low doses of buprenorphine in suppressing behavior rewarded by a non-opioid drug.

**Abstract**

Buprenorphine is a partial opioid agonist derived from thebaine and has high affinity for μ and κ opioid receptors. The present study investigated dose-response (0.03, 0.15, 0.3, 3 mg/kg) and time-dependent effects of buprenorphine (1.5 or 4 h post-treatment) on EtOH self-administration in outbred Sprague-Dawley rats. Freely feeding and drinking rats were trained to initiate EtOH self-administration for 1 h daily using the ascending concentration procedure, wherein they were provided with increasing concentrations of EtOH at 2, 5, 7, 9 and 11% (v/v), respectively. Water was concurrently available with each concentration. Animals were maintained on a given concentration of EtOH for 5 days. By day 21, animals began their stabilization on the 11% regimen and remained on this concentration throughout the remainder of the study. EtOH and water consumption were recorded daily at both 10- and 60-min intervals. At 1.5 h post-buprenorphine, all test doses greatly suppressed both EtOH and water intake at the 10-min interval. At the 60-min interval, all but the lowest dose (0.03 mg/kg) significantly suppressed EtOH intake, while only the highest dose (3 mg/kg) suppressed water intake. In contrast to the suppressant profile observed at 1.5 h post-buprenorphine, at 4 h post-buprenorphine the lower doses (0.03 and 0.15 mg/kg) significantly increased EtOH intake while the higher doses (0.3 and 3 mg/kg) continued to suppress intake. None of the doses of buprenorphine altered water intake 4 h post-buprenorphine. The results support previous research demonstrating the utility of low doses of buprenorphine in suppressing behavior rewarded by a non-opioid drug.

**Key words**

Buprenorphine · Opioids · Ethanol · Self-administration · Rat

**Introduction**

The role of opioids in modulating EtOH self-administration has been demonstrated in outbred rats (Reid and Hunter 1984; Linesman 1989; Linesman and Harding 1990; Weiss et al. 1990) and genetically selected rats bred for high voluntary EtOH intake (for review see Froehlich 1993; also see Weiss et al. 1990). This work has typically shown that low doses of opioid agonists (e.g., morphine, methadone, etc.) increase EtOH self-administration, while non-selective opioid antagonists such as naloxone and naltrexone decrease intake (Altshuler et al. 1980; Reid and Hunter 1984; Froehlich et al. 1988). More recently, selective δ and μ opioid receptor antagonists have also been shown to suppress EtOH intake (Krishnan-Sarin et al. 1995a,b, 1998) and EtOH-maintained responding (unpublished observation) in rats bred for high voluntary EtOH intake. However, the exact mechanism(s) by which opioids modulate EtOH self-administration remains unclear. It has been postulated that EtOH’s reinforcing effects may be mediated in part by activation of endogenous opioid systems, and opioid antagonists may attenuate the reinforcing effects of EtOH by blocking opioid receptors and preventing EtOH from activating these endogenous opioid systems (Reid 1990). Alternatively, EtOH-induced activation of endogenous opioid systems may attenuate the aversion to high dose effects of EtOH (Froehlich 1993). In either case, both of these actions could serve as a strong motivator to initiate and maintain moderate-high EtOH drinking behavior (Froehlich 1993).

Buprenorphine is a low efficacy μ-opioid agonist derived from thebaine, and is approximately 25–50 times more potent than morphine (Cowan et al. 1977). In binding studies, buprenorphine demonstrates high affinity for μ and κ receptors, and less for δ receptors (Dum and Herz 1981; Villiger and Taylor 1981; Lewis 1985). Pre-
Materials and methods

Subjects

Subjects were 48 experimentally naive male Sprague-Dawley rats approximately 4–5 months of age, weighing between 301 and 355 g at the start of the experiment. Animals were individually housed in wire mesh stainless steel cages at an ambient temperature of 22°C on a 12:12 reversed light:dark cycle, with the dark period beginning at 0700 hours. All test sessions were conducted during the dark phase of the light:dark cycle between 1000 and 1500 hours. A single red light bulb illuminated the experimenters’ corner of the colony room to aid in data collection. All animals were given ad libitum access to both food (Purina Rat Chow) and water throughout the experiment, except during the self-administration sessions.

Drugs and solutions

Buprenorphine hydrochloride was prepared by a mechanical mixer (Fisher Scientific) in 0.9% sodium chloride in an injection volume of 1 ml/kg. All buprenorphine solutions were made immediately prior to injections. The doses of buprenorphine and injection intervals were selected based on the work of previous investigators (Myers et al. 1984; Brown et al. 1991) and preliminary work from our laboratory (J. W. Lewis and H. L. June, unpublished observation). All injections were given intraperitoneally (IP). The EtOH solution used was 2–11% v/v prepared by mixing 100% pure EtOH (USP) with tap water. Fresh stock solutions of EtOH were prepared daily.

Apparatus

Each cage contained two 7 cm diameter openings (spaced approximately 10 cm apart) to accommodate presentation of the EtOH in one bottle and water in another. Stainless steel sipper tubes protruded 2.5 cm into the cage from 100 ml drinking tube (Farnam Products, Huntsville, Md., USA). All sipper tubes were equipped with ball-bearings to minimize spillage.

Procedures

Training phase

Following acclimation to the colony room for 14 days, non-food or water deprived animals were trained to consume EtOH and water solutions using a modification of the MacDonnell and Marcucella (1979) procedures as previously described (Linesman 1989; Linesman and Harding 1990; for details see June et al. 1994). Specifically, animals were provided with increasing concentrations of EtOH at 2, 5, 7, 9 and 11% (v/v), respectively, for 1 h daily. Water was concurrently available with each concentration. Animals were maintained on a given concentration of EtOH for 5 days. Thus, by day 21, animals had begun their stabilization on the 11% regimen. EtOH and water consumption were recorded daily at both 10- and 60-min intervals.

Experimental treatment phase

Following the 5-day stabilization period on the 11% v/v regimen of EtOH and water (days 21–25), animals were further maintained on this regimen for 7 additional days. On day 32, 36 animals were