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Effects of morphine on circadian rhythms of motor activity and body temperature in pig-tailed macaques

Michael R. Weed *, Robert D. Hienz

Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical School, Baltimore, MD 21224, USA

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Abstract

Previous studies of the effects of opiates on motor activity and body temperature in nonhuman primates have been limited in scope and typically only conducted with restrained animals. The present study used radio-telemetry devices to continuously measure activity and temperature in unrestrained pig-tailed macaques for 24 h following morphine administration. Two dose–response functions (0.56 to 5.6 mg/kg, i.m.) were determined, one with morphine administered at 9 a.m. and one with morphine administrated at 3 p.m. Under both the 9 a.m. or 3 p.m. administration schedules, body temperature and activity were increased acutely. Activity was also reduced the following morning after morphine administered at either time. In other regards, morphine's effects on both temperature and activity differed between 9 a.m. and 3 p.m. injection, including periods of decreased activity immediately after the acute increases after 9 a.m. but not 3 p.m. administration. Surprisingly, motor activity also increased 9–12 h post-injection following morphine administered at 9 a.m., but not at 3 p.m. These results clearly show an interaction between timing of morphine administration and effects on temperature and activity. These results also underscore the fact that single injections of drugs may have multiple and delayed effects on circadian rhythms in macaques.

Keywords: Morphine; Pig-tailed macaque; Motor activity; Body temperature; Radio-telemetry; Circadian rhythm

1. Introduction

Morphine administration affects locomotion in several species and generally has biphasic effects on locomotor activity (Swerdlow et al., 1986; Uhl et al., 2002). Low and moderate doses of morphine stimulate locomotor activity while higher doses of morphine produce sedation (Swerdlow et al., 1986; Uhl et al., 2002). The vast majority of data on locomotor activity come from rodents where simple and inexpensive techniques for locomotor measurement are common, and where some species differences are known to exist. In rats, for instance, higher doses of morphine produce acute decreases in activity followed by delayed periods of hyperactivity 3–5 h after injection (Browne and Segal, 1980; Dafters and Taggart, 1992). In mice, however, morphine's effects may be strain-dependent with some strains demonstrating dose-related increases in motor activity (e.g. C57BL/6J) (Browne and Segal, 1980), and other strains demonstrating decreased activity following morphine administration (e.g. DBA/2J) (Frischknecht et al., 1988). Biphasic responses, with decreases followed by increases, are also common in mice (Belknap et al., 1998; Patti et al., 2005). In contrast to rodents, few studies have investigated the effects of morphine on locomotor activity in nonhuman primates. Morphine has been shown to increase activity in an observational study of freely moving marmosets (Guard et al., 2002). Additionally, the long-acting opiate acetylmethadol (LAAM) given every other day, has been shown to increase motor activity on drug days and decrease activity on non-drug days in pig-tailed macaques (Crowley et al., 1985).

Morphine and other opiates also affect thermoregulation, and these effects are distinct from the effects of increased activity on body temperature (Adler et al., 1988; Dafters and Taggart, 1992; Baker and Meert, 2002). In rodents, morphine can produce hypothermia or hyperthermia depending upon dose, species, methodologies and ambient temperature (Clark, 1979; Adler et al., 1988; Gonzalez, 1993). Despite the variation in the literature, most often, hyperthermia occurs at low to moderate doses and

* Corresponding author. Fax: +1 410 550 2780.
E-mail address: mweed@jhmi.edu (M.R. Weed).

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hypothermia at higher doses (Clark, 1979; Adler et al., 1988; Dafters and Taggart, 1992). Hyperthermic and hypothermic actions of low and high doses of morphine and other opioids in rats are likely due to predominately mu-opioid receptor influences at lower doses with higher doses having kappa-opioid, hypothermic, effects (Geller et al., 1983; Clark and Lipton, 1985; Adler et al., 1988; Spencer et al., 1988).

One possible reason for the varied reports in the effects of opiate on thermoregulation is that the measurement of body temperature is typically invasive and stressful to the animal, causing heart rate and body temperature changes (Chen and Herbert, 1995). Procedures used to measure temperature range from mildly stressful restraint and infrared measurement of ear canal temperatures to highly stressful restraint and rectal temperature measurement (Clark, 1979; Adler et al., 1988). Restraint equipment may also vary from study to study, and the type of equipment may interact with the effects of drugs such as morphine to significantly alter its pharmacologic effects (McDougal et al., 1983). Reports vary as to whether restraint alters the effects of drugs on temperature due to the inducement of stress, or to procedural factors such as insufficient heat dissipation (McDougal et al., 1983; Wright and Katovich, 1996); duration of restraint is typically short, however, and therefore measurement of body temperature over long periods of time is less common than acute measurements.

Studies of opiate effects on body temperature have been more prolific with rodents than with nonhuman primates. The published nonhuman primate studies have the potential confounds of chair restraint and rectal temperature measurements and the stress associated with these procedures (Holtzman and Villarreal, 1969). The development of radio telemetry procedures has allowed for the determination of both locomotor activity and body temperature in freely moving animals (Essler and Folk, 1961; Winget and Fryer, 1966). In addition to the removal of confounds such as restraint stress, telemetric measurement allows for convenient measurement over longer periods of time. For animals living in cages equipped with telemetry receivers, activity and temperature can be measured continuously for many months, enabling time course studies of longer-term changes in circadian rhythms. Given the frequency of species differences reported previously among rodents, and the dearth of data from primates, the present studies were designed to investigate the effects of morphine on activity and temperature over a full 24-h circadian period.

2. Methods

Four male pig-tailed macaques (3–5 kg) were subjects in this study. The monkeys were implanted with radio telemetry transmitters (TA-D70, Data Sciences International, St. Paul, MN) that transmitted body temperature and locomotor activity. Using aseptic surgical techniques in anesthetized animals, the transmitters were placed in the inter-peritoneal (i.p.) cavity, secured to the right front abdominal wall in 3 monkeys. Due to surgical complications following initial i.p. placement, a transmitter was placed subcutaneously (s.c.) in 1 monkey. For the s.c. placement, the

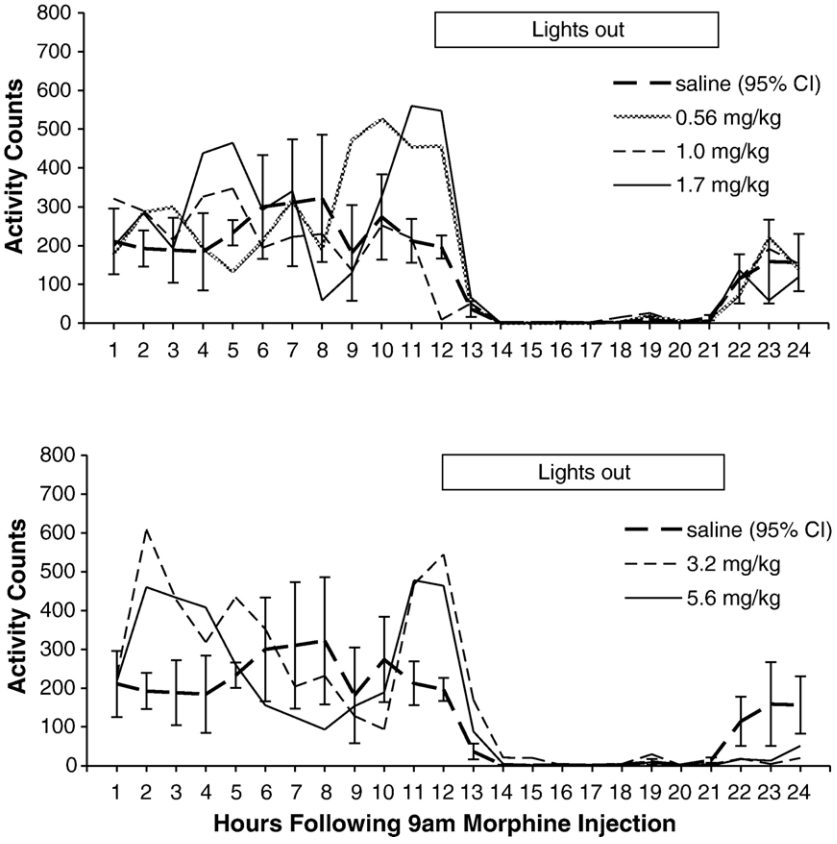

Fig. 1. Circadian patterns of locomotor activity following 9 a.m. injections of morphine. Group means (N=4) are represented on the Y-axis and hours following injection are represented on the X-axis. Error bars around saline means are 95% confidence intervals.