Abstract Rationale: Despite the widespread popularity of opioid analgesics, significant differences in the potency and effectiveness of these drugs are often observed across age groups. Objectives: The purpose of this investigation was to examine age-related differences in sensitivity to the antinociceptive effects of mu opioids and to identify the conditions under which these differences are most apparent. Methods: In a warm-water tail-withdrawal procedure, young (3 months) and aged (24 months) male rats were habituated to restraint and the latencies to remove their tails from 50°C (low nociceptive intensity) and 55°C (high nociceptive intensity) water were measured. Opioids possessing a range of intrinsic efficacy at the mu receptor (morphine, levorphanol, buprenorphine, butorphanol, nalbuphine, nalorphine) were examined. Results: Young and aged rats were equally sensitive to the antinociceptive effects of morphine, levorphanol, and buprenorphine when tested at the low nociceptive intensity. When these drugs were tested at the high nociceptive intensity, differences between the two age groups became apparent, such that aged rats were significantly more sensitive to the antinociceptive effects of these drugs than young rats. Differences between age groups were most apparent when butorphanol, nalbuphine, and nalorphine were tested, in that each of these drugs produced maximal levels of antinociception in aged rats under conditions in which they failed to produce antinociceptive activity in young rats. Under conditions in which lower efficacy opioids failed to produce antinociceptive activity in young rats, they antagonized the effects of morphine in drug combination tests. Conclusions: These data may be taken as evidence that aged male rats are more sensitive to the antinociceptive effects of mu opioids than young male rats, and that age-related differences in opioid sensitivity are most apparent when lower efficacy opioids and higher nociceptive intensities are employed during behavioral testing.

Keywords Age · Analgesia · Antinociception · Intrinsic efficacy · Opioid · Pain

Introduction

Opioid analgesics are the primary treatment option for the clinical management of moderate to severe pain. Despite their popularity, large differences in the potency and effectiveness of these drugs are often observed across clinical populations that differ in age. For example, relative to their younger cohorts, older patients require less morphine to achieve equivalent levels of analgesia (Macintyre and Jarvis 1996; Vigano et al. 1998) and report greater pain relief for a given intramuscular dose of heroin and hydromorphone (Wallenstein et al. 1990). Complete consensus for the relationship between aging and opioid sensitivity has yet to be achieved, as some studies have failed to observe a consistent correlation between these two variables (McQuay et al. 1988; Lubenow et al. 1994). Such findings have prompted some investigators to conclude that this relationship is likely modulated by additional factors, such as the intensity of the pain-inducing stimulus (Sidebotham et al. 1997) and the type of opioid administered (Woodhouse and Mather 1997).

Previous studies examining the relationship between aging and opioid sensitivity in experimental animals have produced a complex pattern of results that depends on the species and gender of the subject tested. Studies conducted in mice, for example, report that sensitivity to the antinociceptive (i.e., analgesic) effects of opioids decreases as a function of age in the hot-plate test (Kavaliers et al. 1983), the radiant-heat, tail-flick test...
was high and the intrinsic efficacy of the test drug was most pronounced when the nociceptive intensity was low (i.e., in 50°C water). These findings mirror those from several recent studies indicating that within- and between-group differences in opioid sensitivity are most apparent when lower efficacy opioids and higher nociceptive intensities are employed during behavioral testing. For example, Negus and Mello (1999) recently examined gender-related differences in sensitivity to the antinociceptive effects of mu opioids in rhesus monkeys. Under conditions in which male and ovariectomized female monkeys were equally sensitive to the high-efficacy mu-opioid fentanyl, male monkeys were significantly more sensitive to the low-efficacy mu-opioids butorphanol and nalbuphine, and these differences were more pronounced when the nociceptive intensity was high (i.e., in 54°C water) than when the nociceptive intensity was low (i.e., in 50°C water). These findings mirror those from several recent studies indicating that within- and between-group differences in opioid sensitivity are most apparent when lower efficacy opioids and higher nociceptive intensities are used during behavioral testing (Morgan and Picker 1996; Morgan et al. 1999; Cook et al. 2000).

The purpose of the present investigation was to examine age-related differences in sensitivity to the antinociceptive effects of mu opioids and to identify the conditions under which these differences are most apparent. To this end, the antinociceptive effects of various mu opioids were examined in young (3 months) and aged (24 months) male rats in a warm-water, tail-withdrawal procedure. In order to identify the conditions under which age-related differences were most apparent, opioids possessing high (morphine, levorphanol, buprenorphine) and low (butorphanol, nalbuphine, nalorphine) intrinsic efficacy at the mu receptor were examined at both low (50°C water) and high (55°C water) nociceptive intensities. It was predicted that age-related differences in opioid sensitivity would be most apparent under conditions in which the intensity of the nociceptive stimulus was high and the intrinsic efficacy of the test drug was low.

Materials and methods

Animals and apparatus

Six young (3 months) and six aged (24 months) virgin, male, experimentally naive Fischer 344 rats were obtained from the National Institute on Aging (Bethesda, Md.). Fischer 344 rats were chosen due to the commercial availability of aged rats from this strain and because the effects of opioids have been well characterized in this subject population (Gosnell and Krahn 1993; Mayo-Michelson and Young 1993; Woolfolk and Holtzman 1995). The two age groups selected reflect the two ends of the adult developmental continuum in this strain and species. Small differences in body weight were observed between the groups at arrival (young 320–340 g; aged 350–370 g), and these differences remained consistent throughout the duration of the study. Over the course of behavioral testing, two aged rats died for reasons unrelated to drug administration. Rats that died prematurely were replaced by new, 24-month-old subjects. No mortality was observed in young rats over the course of testing. Throughout the study, subjects in both age groups were housed individually in a colony room maintained on a 12-h/12-h light/dark cycle with food and drinking water available ad libitum in the home cage. All rats were tested and maintained in accordance with the guidelines of the Institutional Animal Care and Use Committee of Davidson College and the “Guide for the Care and Use of Laboratory Animals” (Institute of Laboratory Animals Resources, National Academy Press 1996).

During antinociceptive testing (see below), rats were restrained in plastic restraint tubes (Fischer Scientific, Pittsburgh, Pa.) and tail-withdrawal latencies were measured with a hand-operated digital stopwatch with a time resolution of 0.01 s. Water was maintained at either 50°C or 55°C via thermostat-controlled water baths (Fisher Scientific).

Behavioral testing

Beginning 1 week prior to the first scheduled test session, individual rats were gentled each day for a minimum of 5 min. On the day immediately preceding the first test session, rats were habituated to the testing apparatus by being placed in the restraint tubes for approximately 30 min. This habituation session was conducted in order to minimize the influence of restraint-tube confinement on behavioral testing (Calcagnetti and Holtzman 1990). Antinociceptive testing was conducted between 1300 hours and 1600 hours, with at least 7 days separating each test. During testing, rats were removed from their home cages and placed in restraint tubes with their tails hanging freely off the edge of a table. Taking into consideration differences in tail lengths between young (16–18 cm) and aged (18–20 cm) rats, the distal 8–10 cm (young rats) or 10–12 cm (aged rats) of the tail was immersed into an insulated mug containing water maintained at either 50°C or 55°C, and the latency for each rat to withdraw its tail from the water was recorded. A 15-s cut-off latency was imposed in all tests to prevent tissue damage. Antinociceptive testing commenced only when a rat kept its tail submerged in room temperature water (24°C) for 15 s (i.e., the cut-off latency) for two successive determinations. This criterion was met in all rats prior to each test session, and, in 92 of 96 instances (95.8%), this criterion was met during the first two determinations. Following these tests, baseline latencies were recorded for each rat at both the 50°C and 55°C temperatures, with the order of testing counterbalanced across rats. During these tests and during all subsequent tests conducted during the session, approximately 3 min separated the two stimulus presentations. No order effects were observed under baseline conditions or after drug administration.

All drugs were administered under a cumulative dosing procedure. In this procedure, each rat was removed from its restraint tube, injected i.p. with the lowest dose of the test drug, and immediately returned to the tube. After a 30-min pre-treatment interval, the latency for each rat to withdraw its tail from the 50°C and 55°C water was determined. Immediately following testing at both...