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Evaluation of Prescription Opioids Using Operant-Based Pain Measures in Rats

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Abstract

Opioids are the most effective compounds available for the relief of pain, yet there are a number of side effects that are of great concern to clinicians. For example, opioids are powerful reinforcers, and the treatment of pain using opioids could lead to the development of addiction. In addition, there is an increasing body of literature demonstrating that the repeated administration of opioids could lead to a phenomenon called opioid-induced hyperalgesia (i.e., increased sensitivity to painful stimulation). Studies examining these potential adverse effects are necessary in the development of novel analgesics. Furthermore, most studies of pain sensitivity and pain relief use reflex-based procedures to identify analgesics; however, it is argued here that operant-based procedures provide measures that are more analogous to the human condition (i.e., the mechanisms of pain are similar to those in humans) and should be useful in the assessment of novel analgesics. A series of studies examining the effects of opioids and the influence of variables such as age are discussed to demonstrate the utility of this approach.

Keywords

operant; reflex; opioid-induced hyperalgesia; thermal escape; thermal preference

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The use of opioids is becoming more accepted as a treatment option for acute and chronic pain in a variety of medical conditions and across an ever-expanding population of individuals. On the one hand, this development may be seen as a positive shift toward providing ubiquitous improvements in pain management in the clinical setting. However, from a public health perspective, real questions still exist as to whether this trend will also lead to an increase in the number of individuals who become vulnerable to the abuse potential of these medications or whether those suffering from other comorbidities may have further exacerbation of their symptoms in response to this treatment.

In the last 50 years, the use of animal models has been integral in determining the efficacy of this class of compounds with regards to both their analgesic effects and abuse potential. However, these models are limited in their scope because they use young, healthy animals as subjects, most often under the conditions of experimentally induced pain, and out of the “natural” history of disease conditions in which these conditions are reported clinically. In addition, traditional modeling often relies on the use of a limited number of behavioral procedures in order to address the analgesic effects of a particular treatment. For example, the most common procedures employed use reflexive measures of antinociception. Although reflexive procedures allow for a high-throughput, simple systems approach for identifying the effects of opioid receptor occupancy, these behaviors are not necessarily indicative of pain or pain relief (Cooper & Vierck, 1986a, 1986b; King, Devine, Vierck, Mauderli, & Yezierski, 2007; Vierck, Hansson, & Yezierski, 2008; Vierck, 2006; Vierck, Kline, & Wiley, 2003; Vierck, Kline, & Wiley, 2004).

In this review, we provide a brief overview of the use and efficacy of opioids in the clinical management of pain and their potential abuse liability. We then describe the benefits and shortcomings of using established pre-clinical models to provide insight into the translation of experimentally induced pain and treatment strategies across a wide variety of clinical conditions and patient populations. Finally, we present preliminary data using the variable of aging as a special example of the possible complexities revolving around the development of useful translational models for testing pain and its treatment in divergent conditions of pain.

Opioids Are Effective Pain Relievers for the Management of Pain

Opioids are the mainstay of pain management. Opioids are used for acute and chronic pain conditions, for cancer and nonmalignant sources of pain, before, during and after surgical procedures, and for virtually any other pain condition described in humans. Morphine and many other opioids have been studied in nearly every preclinical model of acute and chronic pain developed for testing in rodents and primates, and decades of research have

demonstrated that opioids useful in the treatment of pain in humans are effective antinociceptive agents in nonhuman animals (e.g., Vierck, Acosta-Rua, Nelligan, Tester, & Mauderli, 2002; Yeomans, Cooper, & Vierck, 1995). Opioids used as analgesics clinically include morphine, hydromorphone, oxymorphone, levorphanol, methadone, meperidine, fentanyl, sufentanil, codeine, hydrocodone, drocodone, oxycodone, propoxyphene, buprenorphine, pentazocine, tramadol, nalbuphine, and butorphanol (Reisine & Pasternak, 1996). An interesting aspect of this list of drugs is that it covers nearly the entire spectrum of intrinsic efficacy, these drugs have a wide range of onsets and durations of action, and there is a range of selectivities among these drugs for different opioid receptor subtypes. Opioids are used to treat moderate to severe pain, and several advantages of opioid use are that there appears to be no ceiling effect, no major organ dysfunction, and generally manageable side effects (Przewlocki & Przewlocka, 2001; Zollner & Stein, 2007). The side effects of most interest to clinicians appear to be constipation, the possibility of long-lasting sedative and cognitive effects, opioid-induced hyperalgesia (increases in pain sensitivity), and the potential for iatrogenic opioid addiction (see, e.g., Ballantyne, 2007; Højsted and Sjøgren, 2007).

Opioids Are Powerful Reinforcers

Opioids can function as powerful reinforcers, and the study of their reinforcing effects has been extensively investigated in the laboratory using drug self-administration procedures (e.g., Ator & Griffiths, 2003; Collins, Weeks, Cooper, Good, & Russell, 1984; Epstein, Preston, & Jasinski, 2006). In fact, the earliest laboratory studies of self-administration were conducted using morphine as a reinforcer in physically dependent chimpanzees (Spragg, 1940). The first intravenous self-administration studies also studied morphine in physically dependent animals (e.g., Collins & Weeks, 1965; Thompson & Schuster, 1964; Weeks, 1962), although contemporaneous publications demonstrated that physical dependence was not a necessary condition for opioid self-administration (Deneau, Yanagita, & Seevers, 1969; Schuster, 1970). Subsequent research initially focused specifically on heroin and morphine, but many opioids have been investigated and likely neuropharmacological substrates have been identified; the receptor subtypes involved in each instance are primarily μ opioid receptors. Unfortunately, the primary receptor sites associated with analgesia and antinociception are also μ opioid receptors, a fact that has led many researchers to search for opioids that produce analgesic effects without the almost inevitable, abuse-related behavioral effects. To date, few candidate medications meet this desirable pharmacological and behavioral profile.

Nonmedical Use of Opioids Is Increasing

Epidemiological evidence indicates that the nonmedical use and abuse of prescription opioids is on the rise in the United States. Data from the 2006 National Survey on Drug Use and Health (SAMHSA, 2006) show the second most popular category of illicit drug use after marijuana is the nonmedical use of prescription pain-relievers. Approximately 5.2 million people are currently misusing prescription opioids. The survey estimates that 4.1 million persons aged 12 or older used OxyContin nonmedically at least once in their lifetimes. The National Institute of Drug Abuse's 2006 Monitoring the Future survey found that 9.7% of

12th graders reported using Vicodin for nonmedical reasons and 4.3% of 12th graders reported using OxyContin without a prescription (Johnston, O'Malley, Bachman, & Schulenberg, 2007). Important data from the National Survey on Drug Use and Health also show that there are more first-time pain reliever users ("initiates") than all other drugs; 2.2 million new users of opioids last year compared with 2.1 million new users of marijuana (the second highest drug). These epidemiological data suggest that the nonmedical use of prescription opioids is on the rise, and constitutes a growing problem (see also CASA, 2005; Cicero, Inciardi, & Muñoz, 2005; Gilson, Ryan, Joranson, & Dahl, 2004; McCabe, Teter, Boyd, Knight, & Wechsler, 2005; Morgan et al., 2006; Woolf & Hashmi, 2004; Zacny et al., 2003)—one potential conclusion is that the search for effective pain relievers without the associated abuse liability profile are still necessary.

The Need for Different Kinds of Pain Assessment Strategies to Evaluate Models of Antinociception

In the quest for effective analgesic compounds, it is critical to identify the appropriate experimental pain models and outcome measures. For this reason, applying various methodologies can be useful in identifying the crucial parameters that determine whether a particular animal model is appropriate for the question at hand. Most experimental models used to study pain and its relief have used assessment strategies that measure various kinds of reflexive responses (e.g., tail withdrawal, tail flick, paw licking, and guarding) induced by aversive stimulation (through the application of particular thermal, electrical, mechanical, and chemical stimuli). In each of these cases, the presumably painful stimulation determines the latency, duration, or magnitude of the reflexive response. Stevenson and colleagues (2006) made an important contribution to the field with the development of a procedure to examine the restoration of a stimulus-induced suppression of behavior. In these studies, the administration of acetic acid to trained mice decreased feeding, and the ability of opioids to reinstate that feeding was examined. The prototypical opioid morphine was successful, and it was also demonstrated that haloperidol failed to do so. Because drugs such as haloperidol produced generalized decreases in many behaviors, it could show up as a "false-positive" in tests where a decrease in behavior is taken as evidence of "antinociception." Along similar lines, Matson et al. (2007) examined locomotor activity and rearing (vertical activity) following injury (inflammation induced by complete Freund's adjuvant administration). Pain-induced suppression of rearing was found to be reversed by presumed analgesics (e.g., morphine) but not by other compounds (e.g., amphetamine). Martin and colleagues (Martin, Buechler, Kahn, Crews, & Eisenach 2004; Martin, Kahn, & Eisenach, 2005) examined the effects of various surgical manipulations on positively reinforced operant responding (maintained by sucrose pellets). These studies showed a disruption of behavior that could last for weeks, depending on the "magnitude" of the surgery (e.g., incision of the skin, incision of the abdominal musculature, manipulation of the gut), and this disruption could be prevented by administration of analgesics such as morphine. Concurrent measurements of both pain-induced and pain-suppressed behaviors, as well as the measurement of responses that are not reflexive, is a step in the right direction in the search for novel analgesic medications, in the development of appropriate animal models to study pain and its relief,

and to more closely emulate the types of pain conditions experienced in humans (for review, see Negus et al., 2006; Vierck et al., 2008).

The Need for the Inclusion of Additional Behavioral Measures

Along with the development of more sophisticated experimental procedures to identify the potential usefulness of a medication with regards to pain relief, it is imperative to determine potential side effect profiles for prescription opioids. For example, Meert and Vermeirsch (2005) demonstrated nociceptive reflex suppression by several opioids, while concurrently determining unwanted, adverse effects including respiratory depression, motor incoordination, and inhibition of gastrointestinal activity. Along similar lines, while developing operant-based procedures to study potential antinociceptive agents, we include an assessment of overall physical performance that would provide information regarding side effects as well as performance decrements that could influence measures of nociception.

The Need for the Ability to Detect Both Increases and Decreases in Sensitivity

Evidence from both the laboratory and the clinic has demonstrated that an increased sensitivity to pain is a potential consequence of opioid administration. This phenomenon, termed opioid-induced hyperalgesia (OIH), would clearly impact the effectiveness of using opioids to treat pain and has been demonstrated in many subsets of human patients (Angst & Clark, 2006; Mao, 2002). Because all of the factors that influence the risk of developing hyperalgesia are not completely known (Angst & Clark, 2006; Chu, Clark, & Angst, 2006; Mao, 2002; Ossipov, Lai, King, Vanderah, & Porreca, 2005), it is important to assess the likelihood and magnitude of OIH that may develop when testing potential new analgesics, and to use experimental procedures which allow an assessment of such changes in sensitivity following chronic or repeated administration of opioids. From a clinical perspective, distinguishing between OIH and simple tolerance (i.e., a decreased sensitivity to drug following repeated administration) to the administered opioid is critical—primarily because these two interpretations of a decreased opioid effect could lead to opposite recommendations for further treatment (e.g., elimination or decrease in administered dose vs. increases in opioid administration).

Operant-Based Models of Pain Assessment

In addition to the pain-suppressed operant behavior described earlier, there are several operant-based models of nociception and antinociception that are being developed by various laboratories. For example, Neubert and colleagues (Neubert, Rossi, Malphurs, Vierck, & Caudle, 2006; Neubert et al., 2005) use an operant orofacial assay wherein rats have access to a reinforcer (e.g., sweetened condensed milk), but their face makes contact with a thermal stimulus (this is essentially a positive punishment contingency). Baliki et al. (2005) used a procedure in which rats can escape from a thermal stimulus (changing temperatures on the floor) to other side of an apparatus— by dynamically controlling the temperature, multiple escape latencies and the temperature at which escape occurs can be determined. LaBuda and Fuchs (2000) used a preference procedure where mechanical

stimulation is applied to the rat's paw repeatedly. When a paw is injured, rats learn to avoid the compartment in which mechanical stimulation of the injured paw occurs.

What follows is a description of two operant-based procedures that are being used in our laboratories to study both the mechanisms of pain sensitivity and the influence of various pharmacological and environmental manipulations.

Thermal Escape

In the thermal escape procedure, animals are faced with a choice between two situations—to remain on a temperature-controlled floor that can be maintained at different temperatures, or to escape from this stimulation by climbing onto a temperature-neutral but brightly lit platform (the light makes escape somewhat aversive to rats). Details of the procedure and equipment have been described previously (Mauderli, Acosta-Rua, & Vierck, 2000; Vierck et al., 2002). Briefly, a Plexiglas chamber surrounds an aluminum plate containing channels for the circulation of water maintained at a particular temperature. By altering the temperature of the plate, stimulus-response functions can be generated to show that as the hot temperatures increase or cold temperatures decrease the cumulative escape durations get longer. Manipulations can then be introduced to study changes in thermal sensitivity. Extensive parametric evaluations were initially conducted to identify the influence of floor temperature, the role of the aversive illumination, and the training protocol. In general, rats are trained over several weeks to escape from the thermal stimulation. Rats are initially placed in a chamber with a floor maintained at 36°C to equilibrate paw temperatures and habituate animals to the chamber. Following 10 minutes of acclimation, rats are placed into the test chamber for a 10- or 15-min trial. Initial training consists of testing temperatures in an ascending order (e.g., 39°C, 41°C, 43°C, 45°C, 47°C, then 49°C across days) with access to the unlit escape platform. Subsequently, the same series of tests are conducted with the escape platform brightly lit (creating a choice between two aversive conditions). Test sessions are then conducted until baselines are stable (consistent measures of escape duration, latency to escape, and number of escapes). At this point, manipulations such as drug administration can be introduced.

Thermal Preference

A second procedure that has been used involves preference measures between two plates that are maintained at different temperatures (e.g., hot, 45°C vs. cold, 10°C). The equipment consists of two plates surrounded by Plexiglas that contains a partition with a cut-out to allow movement between the two compartments. Stability in this task is reached relatively quickly (i.e., within several weeks), and it has been demonstrated that female Long-Evans rats will spend approximately 50% of the 10-min trial on each side with an average of 12 to 13 crossings (e.g., Vierck et al., 2002).

Physiological Relevance of These Tasks

In humans, the types of pain that are attenuated by opioids are primarily sensations dominated by input from unmyelinated (C) nociceptors (Cooper, Vierck, & Yeomans, 1986). Relatively low nociceptive thermal stimuli (e.g., 45°C) that can be used in operant studies

results in a slow rate of heat transfer to the rats' paws that primarily activates unmyelinated (C) nociceptors. In contrast, reflex studies using thermal stimulation in rodents (e.g., tail withdrawal, hot plate, tail flick procedures) use high temperatures (e.g., 50–55°C) that result in a rapid rate of heat transfer that primarily stimulates myelinated (A-8) nociceptors (Yeomans, Pirec, & Proudfit, 1996; Yeomans & Proudfit, 1996). If a goal of these preclinical studies is to discover compounds (e.g., opioids) that might be useful for treating pain in humans, it is important to use an animal model and experimental conditions that closely mimic the human condition. An additional concern of using extraordinarily high temperatures is the potential tissue damage that occurs with pro- longed and/or repeated testing. Using these thermal escape and preference measures, long duration trials can test effects of prolonged stimulation. Also, testing can be conducted over months to years—this allows for the development of longitudinal studies of changes in pain sensitivity (e.g., the influence of aging), the ability to examine the consequences of chronic administration of drugs (e.g., opioid-induced hyperalgesia), and the effects of injury (e.g., formalin administration, spinal cord damage) and the time course of recovery. Descriptions of some of the findings using these procedures, including differential modulation of reflex and operant-based measures, the effects of injury, administration of drugs, and the influence of restraint stress, along with additional characteristics to be considered in the development of assessment methods are addressed in a recent review (Vierck et al., 2008).

Effects of Opioids in the Thermal Escape and Preference Procedures

There have been several studies using the thermal escape and preference procedures to assess the effects of opioids. In most of our studies, measures of escape/preference are determined in parallel with reflex-based measures of nociception (e.g., paw lick/guard latencies, counts and durations). For example, Vierck et al. (2002) and King et al. (2007) directly compared the effects of opioid agonism and antagonism across reflex and operant-based measures of pain sensitivity.

Under baseline conditions, there are temperature-appropriate increases in escape duration; for example, 36°C, 44°C, 47°C, and 50°C floor temperatures result in escape durations of 10%, 50%, 75%, and 90% of the session time. Under these conditions, low to moderate doses of morphine (0.5, 1.0, and 1.5 mg/kg) result in decreases in escape duration (i.e., antinociception). Conversely naloxone increased escape duration suggesting that behavior under these conditions is extraordinarily sensitive to opioid modulation. In the thermal preference procedure, morphine (0.5 mg/kg) produced a dramatic increase in the amount of time spent on the “hot” side of the chamber, suggestive of either an antinociceptive effect (for the heat) or an increase in the aversiveness of the cold stimulation. Additional studies are needed to examine the effects of other opioids and to establish dose-effect curves, to identify whether tolerance and/or opioid-induced hyperalgesia occurs, and to conduct more extensive and parametric manipulations in the thermal preference task to determine how the baseline preference (based on the two floor temperatures) influences sensitivity to opioids.

Preliminary Data With Morphine and Naloxone Across Ages

Pain is a common problem among elderly people (Bernabei et al., 1998; Brattberg, Parker, & Thorslund, 1997; Brochet, Michel, Barberger-Gateau, & Dartigues, 1998; Chodosh et al., 2004; Clark, 2002; Crook, Rideout, & Browne, 1984; Davis & Srivastava, 2003; Freedman, 2002; Landi et al., 2001; Nikolaus & Zeyfang, 2004). This is of increasing concern in the clinical geriatric community given: (1) that the absolute and relative number of people >65 years is projected to dramatically increase over the next decade (for a summary, see He, Sengupta, Velkoff, & DeBarros, 2005), and (2) pain reduces function, quality of life, the ability to engage in activities of daily living, among other detrimental effects (Cavalieri, 2002; Chodosh et al., 2004; Devulder, Richarz, & Nataraja, 2005; Freedman, 2002; Hadjistavropoulos et al., 2007; Weiner et al., 2003; Won et al., 1999, 2006). Therefore, the medical use of opioids will continue to increase in proportion to the ever-increasing prevalence of pain in this population, and older people experience chronic pain for a longer duration. Given the immediacy of this dilemma, the development of animal models of chronic pain associated with aging are needed to provide a platform for assessing the efficacy and safety of opioid treatment strategies.

The literature is replete with contradictory findings demonstrating increased, decreased, or no difference in sensitivity to opioids across ages, depending on sex, species, stimulus modality and intensity, and behavioral measure (e.g., Chan & Lai, 1982; Crisp et al., 1994; Hoskins, Burton, & Ho, 1986; Islam, Cooper, & Bodnar, 1993; Kavaliers & Hirst, 1983; Kramer & Bodnar, 1986; Raut & Ratka, 2007; Saunders, Paolino, Bousquet, & Miya, 1974; Smith & Gray, 2001; Webster, Shuster, & Eleftheriou, 1976). In our laboratory, preliminary data suggest little difference in baseline sensitivity and sensitivity to fentanyl in rats across age groups (8-, 18-, 24-, and 30-month-old rats) when assessed using the reflex-based, warm-water tail withdrawal procedure (Figure 1, left panel). In this study, male Fischer F344 x Brown Norway crosses (F344xBN) were exposed to various water temperatures and the latency until tail withdrawal was recorded.

Because humans are administered analgesics repeatedly, oftentimes for chronic pain conditions, it is imperative to examine the long-term effects of drug administration (e.g., Wang et al., 2005). In an attempt to examine this question across a wide breadth of ages, the effects of chronic fentanyl administration and withdrawal were examined using osmotic minipumps over a 4-week period. Fentanyl produced hyporeflexia (increase in latency) the day following implantation of the minipump (Figure 1, right panel)—an increase in the area under the curve (AUC) indicates an upward shift in the temperature-effect curve. During chronic administration, a tolerance-like phenomenon was observed after 7 days and a hyperreflexic response (perhaps opioid-induced hyperalgesia) was noted following 28 days of administration. Upon withdrawal from fentanyl, there was a return toward baseline levels of performance. These data are too preliminary to conclude whether there were age-related differences in this pattern or magnitude of effects, but are included to show a reversal in opioid effects (e.g., tolerance, opioid-induced hyperalgesia, and recovery) on behavior with long-term application. It is also important to note that the “tolerance” observed at Day 7 could be the result of a summation of an antinociceptive response and an opioid-induced hyperalgesic response. It is too early to draw conclusions about these two phenomena, and

additional behavioral testing would be needed to dissociate them. However, these are phenomena being encountered in the clinic and fortunately are recently receiving more attention from experimental researchers.

Regarding testing in our operant-based models, there are clear differences in baseline sensitivity across female F344xBN rats aged 14, 20, and 28 months (see Figure 2). In contrast to reflex measures, operant escape from both heat and cold is enhanced (hyperalgesia) with age. All age groups showed opposite effects produced by morphine and naloxone; that is, morphine decreased the amount of time spent on the platform, and naloxone increased this duration. These preliminary results indicate that morphine does not lose effectiveness with age; however, a more thorough approach is needed to determine whether there are age-related differences in sensitivity to opioid modulation. An important aspect of these procedures is that there are baseline differences across populations (e.g., ages) that could be manipulated by altering stimulus conditions; that is, the effects of opioids on different baselines could be studied, or the thermal stimulation could be altered across groups to equalize the baselines and then look at sensitivity to opioid modulation.

The Need to Evaluate Changes (Deficits) in Physical Performance

As with all behavioral procedures, it is critical to know whether an animal is capable of making the response of interest. This is especially important in studies examining drug administration and with the induction of acute or chronic pain. As noted with haloperidol earlier, this concern is important in reflex-based studies of nociception, but also in operant-based procedures. In general, administration of drugs could influence behavioral functioning in a manner that is not related to pain or pain relief (for discussion, see Vierck et al., 2008). In our studies, the effects of pain, age and/or drug administration are concurrently assessed using a battery of physical performance measures, which includes grip strength, inclined plane, rotarod, and locomotor activity. Performance in these procedures decreases in older animals when examined either longitudinally or in a cross-sectional manner. Data in Figure 3 show that performance in both the grip strength and inclined plane assessment decreases in female F344xBN rats. It is therefore important to consider how these performance deficits would influence operant behavior in the escape and thermal preference tests. Both of these tests involve a choice in occupancy of either of two compartments. For thermal preference, the compartments are identical, except for floor temperature, and motor performance is not relevant to a preference for cold or heat stimulation. For the escape test, the thermally neutral escape platform is inclined slightly (10°), so that a motor deficit would favor more time on the heated or cooled plate. The fact that older animals remain on the escape platform longer across several conditions suggests that if this type of physical performance is an influence on escape duration, the overall age effects are being underestimated.

Overall Implications

It is clear that animal models are still important to the development of novel analgesic compounds for use in humans. Important to note, the animal models in use today are becoming more sophisticated, in part to make them more relevant to the “real world” and are based on the same biological mechanisms responsible for pain sensation and relief in

humans. Just as in the human clinical situation, basic researchers need to understand the particular experimental question being addressed when using a particular animal model (is this acute or chronic pain, what are the underlying mechanisms of pain being examined, are there other influences on measurement of pain sensitivity and relief, etc.). The operant-based techniques described in the present paper are proposed as an alternative to many of the reflex-based tasks that are commonly being used as a screen in preclinical laboratories to discover and/or develop analgesics that are more effective or have lower abuse liability (resulting in an overall increased effectiveness in pain management).

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Figure 1.

Baseline pain sensitivity and the effects of chronic fentanyl administration across ages. Nociception and the effects of fentanyl (1.0 mg/kg/day) were assessed using a standard warm-water tail withdrawal procedure in which the latency to tail withdrawal was measured following immersion in water maintained at various temperatures. Following baseline assessment, osmotic minipumps filled with fentanyl were implanted subcutaneously and left in place for four weeks. Under baseline conditions, tail withdrawal latency varied inversely with water temperature and was similar across all age groups. Data in the right panel represent the area under the temperature-effect curve assessed at various times during and following fentanyl administration. Increases in this measure indicate an antinociceptive response. Data from only the youngest and oldest group are shown for clarity. Fentanyl produced antinociception, followed by the development of tolerance. By the 28th day, there was a trend toward hyperalgesia (increased sensitivity), especially in the oldest rats. Following discontinuation of fentanyl administration, sensitivity returned to baseline levels.

Figure 2.

Effects of morphine and naloxone on escape durations across age groups. Under baseline conditions, there were age-related differences in the time spent on the platform with the oldest rats escaping for the longest duration. When morphine (1.0 mg/kg, i.p.) was administered, there were decreases in these durations suggesting that the plate was less aversive; that is, there was an antinociceptive response. When naloxone (3.0 mg/kg, i.p.) was administered, there were increases in these durations, demonstrating that escape duration can be modulated by both agonist and antagonist activity at opioid receptors.

Figure 3. Age-related differences in physical performance. Animals of various ages were tested in both the escape procedure and assessed for physical performance. Older rats' performance was decreased in both grip strength and inclined plane procedures.