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Operant nociception in nonhuman primates

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ABSTRACT

The effective management of pain is a longstanding public health concern. Morphine-like opioids have long been front-line analgesics, but produce undesirable side effects that can limit their application. Slow progress in the introduction of novel improved medications for pain management over the last 5 decades has prompted a call for innovative translational research, including new preclinical assays. Most current in vivo procedures (eg, tail flick, hot plate, warm water tail withdrawal) assay the effects of nociceptive stimuli on simple spinal reflexes or unconditioned behavioral reactions. However, clinical treatment goals may include the restoration of previous behavioral activities, which can be limited by medication-related side effects that are not measured in such procedures. The present studies describe an apparatus and procedure to study the disruptive effects of nociceptive stimuli on voluntary behavior in nonhuman primates, and the ability of drugs to restore such behavior, through their analgesic actions. Squirrel monkeys were trained to pull a cylindrical thermode for access to a highly palatable food. Next, sessions were conducted in which the temperature of the thermode was increased stepwise until responding stopped, permitting the determination of stable nociceptive thresholds. Tests revealed that several opioid analgesics, but not d-amphetamine or Δ^9-THC, produced dose-related increases in threshold that were antagonist sensitive and efficacy dependent, consistent with their effects using traditional measures of antinociception. Unlike traditional reflex-based measures, however, the results also permitted the concurrent evaluation of response disruption, providing an index with which to characterize the behavioral selectivity of antinociceptive drugs.

1. Introduction

The effective management of pain remains an important public health concern. Although morphine-like opioids have long been front-line analgesics for most painful conditions, their clinical utility is restricted by well-recognized liability for side effects, including dependency/addiction, respiratory depression, and sedation [3]. Despite the clear need for improved analgesics, progress in the discovery and development of novel candidate medications for pain management over the last 5 decades has been slow. This has provoked well-publicized concern [7,23], leading to the suggestion that traditional nociception assays might be inadequate for the task of identifying novel candidate medications for pain management, and, correspondingly, that new animal models are needed for translational pain research [27,29,32,33,44].

Currently, analgesiometry in laboratory animals primarily uses thermal, electrical, chemical, and mechanical nociception to assay the antinociceptive effects of candidate analgesics [28]. Most commonly used approaches (eg, tail flick, hot plate, acid-induced writhing, warm water tail withdrawal), use simple spinal reflexes or unconditioned behavioral reactions to nociceptive stimuli. These approaches present both conceptual and experimental limitations. From a conceptual standpoint, simple reflex measures fail to adequately capture any involvement of supraspinal areas of the central nervous system in pain-stimulated responses [5,8,31,44]. Therefore, preclinical animal models of nociception are needed to assay behavioral responses that clearly involve higher-order cortical function. From an experimental standpoint, conventional assays usually rely on a decrease in response (eg, longer latency to tail flick, decreased writhing, etc). Therefore, it is often difficult to distinguish the role of nonspecific depression of behavior in candidate analgesics. For example, morphine has sedative effects over the same range of doses that increase the latency to tail flick, and the interaction of these effects is uncertain.

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One way to address the above issues is to establish an index of antinociception that relies on the restoration, rather than suppression, of a response under otherwise nociceptive conditions. Operant-based tasks, unlike assays of reflexive or unconditioned behavioral responses, involve the subject engaging in a volitional response that necessarily involves centrally mediated processes. Thus, such tasks provide an important alternative approach for the evaluation of candidate analgesics. The utility of an operant-based approach has received some attention [27,29,33,44]; however, few studies have been conducted to examine the effects of antinociceptive drugs under operant contingencies. Notable exceptions, however, include the operant orofacial apparatus [2,35,36,40] and operant escape procedure [6,43,49].

The present report describes an apparatus and operant procedure to examine both the disruptive effects of nociceptive stimuli on voluntary responses in nonhuman primates and behaviorally restorative effects of analgesics. Squirrel monkeys were trained to respond (by pulling down a cylindrical thermode) for a palatable food reinforcer. Next, experiments were conducted in which the temperature of the thermode was increased stepwise until responding stopped. This permitted the determination of nociceptive thresholds, which proved to be highly stable over time and sensitive to varying parameters of the response requirement. Finally, tests with several types of drugs purported to produce analgesia were conducted to assess their antinociceptive effects under these conditions.

2. Methods

2.1. Subjects

Four adult male squirrel monkeys (*Saimiri sciureus*) were individually housed in a temperature- and humidity-controlled vivarium with a 12-hour light/dark cycle (7 AM–7 PM). Subjects had unlimited access to water in the home cage and were maintained at approximate free-feeding weights by post-session access to a nutritionally balanced diet of high-protein banana-flavored biscuits (Purina Monkey Chow, St. Louis, MO). In addition, fresh fruit and environmental enrichment were provided daily. Experimental sessions were conducted 5 days per week (Monday–Friday). The experimental protocol for the present studies was approved by the Institutional Animal Care and Use Committee at McLean Hospital. Subjects were maintained in a vivarium licensed by the U.S. Department of Agriculture and in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research [34].

2.2. Apparatus

Fig. 1 shows a drawing of the operant nociception chamber. A custom-built Plexiglas chair measuring 25 cm × 25 cm × 40 cm was housed in a 50 cm × 50 cm × 75 cm sound- and light-attenuating enclosure. A digital video camera was mounted in the inside upper-right corner of the enclosure for real-time session monitoring and an infusion pump (PHM- 100-10; Med Associates, St. Albans, VT) was mounted outside the left wall of the enclosure for the delivery of liquid reinforcement. Briefly, each operation of the pump delivered 0.15 mL of 30% sweetened condensed milk (70% water) via Tygon Microbore tubing (0.40 inner diameter, 0.70 outer diameter; Saint-Gobain Performance Plastics, Paris, France) into an easily accessible shallow well (2.5 cm in diameter) of a custom-designed Plexiglas fluid dispenser (5 × 3.5 × 1.27 cm) mounted to the inside front wall of the chair. Previous studies in our laboratory have found that a small volume (0.15 mL) of this liquid serves as a powerful reinforcer for squirrel monkeys that is very resistant to satiation even under free-feeding conditions

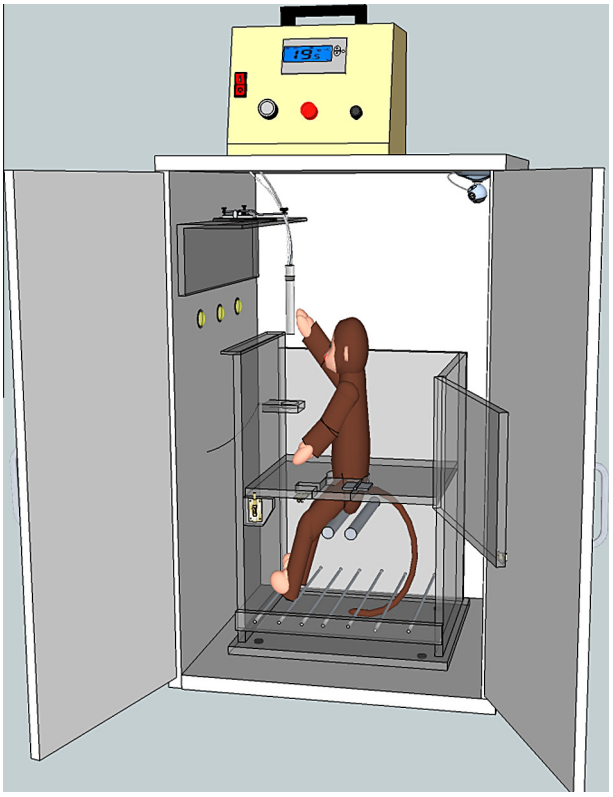

Fig. 1. Schematic representation of the operant nociception chamber (see Apparatus section for additional details).

[19]. Three horizontally arrayed white stimulus lights (2.5 cm in diameter) were mounted 50 cm above the enclosure floor, spaced 10 cm apart and centered above the fluid dispenser. A telegraph key was secured to a shelf 15 cm above the stimulus lights, and a custom-built stainless steel 500 w/120 v thermode (1.27 cm in diameter; 15.24 cm in length) with fiberglass leads hung from the telegraph key button via a 5-cm chain. A downward pull of the thermode closed the telegraph key circuit, making an electrical contact that could serve as a response. A temperature sensor (TBC-72.OG, Convectronics, Haverhill, MA) was attached to the upper end of the thermode, which also was attached via the fiberglass leads to a 120 v, 15 amp temperature control unit (Control Console 006-12015, Convectronics, Haverhill, MA). This unit served as a thermostat and controlled the temperature of the thermode with a resolution of ±1°C. All temperature settings and adjustments were made by the experimenter. Other experimental events (ie, pull detection, operation of stimulus lights, milk delivery) and data collection were controlled by Med Associates (St. Albans, VT) interfacing equipment and operating software.

2.3. Procedure

2.3.1. Pull training

During experimental sessions, subjects were seated in the chair. Each subject was trained with response shaping [4], first to drink from the milk well and then to pull the thermode downward to close the telegraph key. Trials began with illumination of the left and right stimulus lights. Thermode pulls with a force of at least 2.78 N closed the telegraph key circuit and were recorded as responses. During initial training, each circuit closure immediately extinguished the left and right stimulus light and illuminated the center stimulus light for 2 seconds, delivered 0.15 mL of milk into the well, and was followed by a 10-second intertrial interval (ITI)

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