Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 84 (2006) 148–157
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Nociceptive threshold and analgesic response to morphine in aged and young adult rats as determined by thermal radiation and intracerebral electrical stimulation

Steven J. Crosby [a], Clifford M. Knapp [a], Conan Kornetsky [a,b,*]

[a] Department of Psychiatry, Boston University School of Medicine, 715 Albany Street, R-620, Boston, MA 02118, USA
[b] Department of Pharmacology, Boston University School of Medicine, 715 Albany Street, R-620, Boston, MA 02118, USA

Received 1 February 2006; received in revised form 18 April 2006; accepted 26 April 2006
Available online 8 June 2006

Abstract

The present experiment compared the nociceptive threshold and analgesic response to morphine in young (4–5 months) and aged (24 months) rats using peripheral thermal stimulation and intracerebral electrical stimulation. Responses to thermal stimuli were assessed using both the classical tail-flick procedure in which latency of response is the dependent variable and a new method in which threshold in calories of heat is the dependent variable. In the intracerebral nociceptive threshold procedure, electrical stimuli were delivered via an electrode implanted in the mesencephalic reticular formation (MRF), a pain pathway, and the animals were trained to terminate the stimulation by turning a cylindrical manipulandum embedded in one wall of the experimental chamber. For the classical tail-flick method, the aged rats required a greater intensity of stimulation to produce a basal response latency that was between 2.5 and 3.5 s. Using the new psychophysical method for determining the tail-flick threshold, the aged rats' basal thresholds were significantly higher than that of the young rats. However, the basal thresholds obtained by direct stimulation of the MRF failed to show a significant age effect, suggesting that the registration of pain is not different between young and aged rats. These age-related differences in baseline tail-flick response may be due to changes in the spinal reflex associated with aging. Although, there was no difference in the analgesic effects of morphine between young and aged rats using the latency of the tail-flick response, evidence for decreased analgesic response was seen using the tail-flick threshold measure and the intracerebral stimulation threshold method.

Keywords: Nociception thresholds; Pain; Tail-flick; Brain stimulation; Analgesia; Morphine aging

1. Introduction

There has been concern that pain is undertreated in the elderly (Ardery et al., 2003; Gagliese and Melzack, 1997; Sauaia et al., 2005). This problem may arise, in part, from a limited understanding of the actions of opioid analgesics in the elderly. There is a common belief held by many clinicians, supported, for the most part, by considerable clinical experimental evidence, that aged patients have higher pain thresholds than the young and are more responsive to the analgesic action of opiate drugs (Gibson and Helme, 2001; Macintyre and Jarvis, 1995). However, Gaston-Johansson et al. (1999) in reviewing pain management in older adults, concluded that the undertreatment of pain in the older patient is a significant problem. The extent of the difference between the aged and young is often a function of the type of clinical pain (Helme et al., 2004) or pain scale used (Gagliese and Katz, 2003). In the evaluation of the intensity of clinical pain patients are often asked to judge the intensity of their pain on a 10 point scale with a score of 10 being the worst pain they ever felt or could imagine. This makes the assumption that a score of 10 in the aged is equal to 10 in the young. Given these problems, greater experimental evidence is needed before the actions of opiate drugs in the aged can be considered to be adequately characterized.

Animal models of the effects of aging on opioid analgesia have been used to determine if the efficacy and potency of opioid agents such as morphine are altered with age. However, these experiments have given mixed results (Gagliese and Melzack, 2000). Differences obtained are often a reflection of

* Corresponding author. Tel.: +1 617 638 4320; fax: +1 617 638 5254.
E-mail address: ckornets@bu.edu (C. Kornetsky).

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.04.021

the pain model used. Although a variety of nociceptive stimuli are used, (e.g., thermal radiation, mechanical pressure, electrical stimulation) most studies of responses to nociceptive stimuli use an unconditioned withdrawal response as the dependent variable. The two most common experimental procedures for the study of pain and analgesia are the "tail-flick" (D'Amour and Smith, 1941; Ness and Gebhart, 1986) and the "hot-plate" procedure (Eddy and Leimbach, 1953). In the former, radiant heat is focused on the tail of a rodent and the latency of a reflexive withdrawal of the tail is the dependent variable. In the latter, rodents are placed on a "hot-plate" and the latency of a withdrawal response (e.g., raising a rear paw) is the dependent variable. In both of these procedures a fixed nociceptive intensity is used. The tail-flick response is believed to involve both spinal (Borszcz et al., 1990; Douglass and Carstens, 1997; Irwin et al., 1951; Kauppila et al., 1998; King et al., 1997; Ness and Gebhart, 1986), and supraspinal levels (Carstens and Douglass, 1995; Jensen and Yaksh, 1986; Kauppila et al., 1998; King et al., 1997) of the central nervous system.

In determining the analgesic effects of drugs using the tail-flick procedure, the stimulus intensity is typically adjusted for each animal so that the baseline latencies are approximately equal for all animals (Crisp et al., 1994; Kramer and Bodnar, 1986; McLaughlin and Dewey, 1994; Sawamura et al., 2002). This adjustment of the intensity may have its limitations in comparisons between experimental groups with significantly different baseline intensity thresholds. In an experiment where baseline latency levels of response, using the tail-flick procedure, were reported, an increase in response latency was found in 25 month old rats compared to three month old rats (Akunne and Soliman, 1994). However, Islam et al. (1993) found six month old rats had longer latencies versus 12, 18, and 24 month old rats. Results from an experiment by Crisp et al. (1994) indicated that 25–26 month old rats had shorter latencies than 15–16 month old rats but no difference from five to six month old rats. Further, some experiments have found no differences in assessments of baseline response latency with age (Hamm and Knisely, 1986; Hamm et al., 1986). An additional experiment, in which pain thresholds were determined by electric shock stimuli and vocalization, rather than thermal radiation, found no significant age differences (Goicoechea et al., 1997).

Regarding the analgesic response to morphine, a number of investigators have reported diminished analgesia in older rats and mice (Kavaliers et al., 1983) as measured by the tail-flick method (Kramer and Bodnar, 1986; McLaughlin and Dewey, 1994), the "hot-plate" procedure (Kavaliers et al., 1983), tail immersion in warm water (Jourdan et al., 2002), and jump-threshold to electric shock (Kramer and Bodnar, 1986). In one of these experiments, the direction of the difference depended on the post-injection time of testing (Kramer and Bodnar, 1986). The direction of an age-related difference has also been shown to depend on the dose of the drug (Spratto and Dorio, 1978). Results in which aged animals were consistently more sensitive to morphine than younger cohorts were reported by Islam et al. (1993) and Spratto and Dorio (1978) using the tail-flick procedure and Saunders et al. (1974), using response to foot-shock. Other investigators have found no age-related differences between young and aged rats (Akunne and Soliman, 1994; Van Crugten et al., 1997a).

Almost all of the previous tail-flick experiments comparing analgesic responses of young and aged rats used a fixed intensity of thermal radiation with latency of response as the dependent variable. However, the integrity of the tail-flick reflex response may be compromised in the aged rat, and consequently latency of response may not be a valid measure for the comparison of the sensitivity of animals in different age groups to painful stimuli. Because of this possibility we employed a threshold method that was independent of speed of response. This new tail-flick method varied the intensity of stimulation and the dependent variable was the absolute psychophysical threshold in units of heat (cal). Both baseline sensitivity to thermal radiation and the analgesic effects of morphine were examined in this study using this threshold procedure. The results of this approach were compared with those obtained using the classic tail-flick approach.

Another issue that has not been addressed by prior studies is whether there are age-related differences in sensitivity to nociceptive stimuli and to the analgesic actions of morphine at the supraspinal level as compared to differences that might exist at lower levels of the nervous system. In order to bypass the possible differences in response to peripheral stimulation between young and aged rats, an additional experiment was performed employing a method in which aged and young rats were intracerebrally implanted with stimulating electrodes in the mesencephalic reticular formation (MRF), a pain pathway, and the psychophysical thresholds for centrally delivered electrical stimuli were determined. In this experiment the analgesic effects of morphine also were determined in both the aged and young rats. Thus, the combined experiments allowed a comparison of peripheral and central nociceptive stimulation as well as the analgesic response of morphine in young and aged rats.

2. Materials and methods

All procedures used in this study were approved by the Boston University School of Medicine Institutional Animal Care and Use Committee (IACUC).

2.1. Animals

Male Brown Norway/Fischer 344 F1 hybrid rats (F344/BNF1) (Harlan Sprague Dawley, Indianapolis, IN) were used in these experiments. Responses to peripherally delivered stimuli were evaluated in two tail-flick experiments in which either tail-flick latencies or tail-flick thresholds were determined. A brain-stimulation escape paradigm was employed for the third experiment, evaluating analgesic responses using intracerebral stimulation.

Sixteen animals were used in the completion of the tail-flick stimulus intensity threshold ($n=8$/group) experiment. These animals were also used in the tail-flick latency experiment, but because of the loss of two animals only 7 animals were used per