Novel Animal Paradigms for Analgesic Screening  (3-Dec-2002)

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Introduction
The discovery of novel therapeutics for the treatment of chronic pain depends largely upon the development of not only clinically-relevant animal models but also clinically-relevant quantitative nociceptive assays. While several animal models resembling human clinical pain syndromes (e.g. neuropathy and arthritis) have been developed in the last two decades, most assays continue to rely on traditional procedures that involve high-intensity, phasic end-points to quantify changes in nociception and determine analgesic efficacy. Indeed, allodynia and hyperalgesia are hallmark signs of chronic pain. However, pain assays overlook other important clinical signs of pain syndromes such as the negative affective states and functional disability that accompanies chronic pain. Thus, one challenge facing pain researchers is the development of animal pain paradigms that more closely approximate these other important signs in human clinical populations.

A major research effort of my laboratory is in the development of novel animal paradigms that attempt to quantify features of chronic pain and properties of analgesic drugs not captured by traditional procedures. In one line of research, we have used the place preference paradigm to assess the affective properties of analgesic drugs under conditions of chronic pain. This paradigm is important because pain involves both sensory and affective components, each of which can be modulated by analgesic drugs. In a second line of research we have used the operant response paradigm to quantify both functional motor deficits that accompany chronic pain and recovery of function afforded by analgesic drugs. This second paradigm is important because functional disability is a significant clinical parameter of pain and pain relief.

Place Preference Paradigm
The place preference paradigm is commonly used to evaluate the affective/motivational properties of drugs. This paradigm, based on traditional learning principles, involves the pairing of a drug state with environments having distinctive stimuli (i.e., place). Following several drug-place conditioning trials, an animal's place preference is ascertained by observing the probability that the animal will approach or maintain contact with the drug-paired environment. This paradigm has become a standard method in behavioral pharmacology for determination of the positively reinforcing properties of drugs of abuse. And while a number of analgesic drugs possess positively reinforcing properties, by definition, all analgesics possess potent negatively reinforcing properties where negative reinforcement is defined as an increase in response strength due to the reduction or elimination of an aversive stimulus. We reasoned that animals in chronic pain receiving analgesic drugs should display enhanced place preference scores compared to no-pain controls, because analgesics modulate the negative-affective component of chronic pain. In a series of experiments using the unilateral hindpaw CFA model of chronic inflammatory nociception and the place preference procedure, we sought to measure the negatively-reinforcing properties of a diverse number of compounds with known antinociceptive properties. The compounds we selected included the opioid receptor agonist morphine, the non-competitive NMDA receptor antagonist MK-801, and the bradykinin B1 receptor antagonist des arg9, (Leu8)-BK. Over an eight-day period, animals received alternating exposures of a drug paired with the S+ chamber and vehicle paired with the S- chamber. Preference was determined by scoring approach behaviors on six choice trials over the next 3 days. Morphine produced place preference in both inflamed and non-inflamed groups. However, preference scores for inflamed rats were significantly greater than non-inflamed rats. MK-801 produced a dose-dependent place aversion in non-inflamed groups. However, in inflamed rats MK-801 produced low dose place preference and high dose place aversion. Finally, des arg9, (Leu8)-BK produced place aversion in non-inflamed rats and place preference in inflamed rats. An important feature of analgesic drug effects is the ability to modulate both the affective and sensory components of pain processing. Traditional animal paradigms in pain research have been limited to analysis of analgesic drug action on the sensory component of pain processing. These studies demonstrate that the place preference paradigm can quantify analgesic drug modulation of the affective component (i.e., negative reinforcement) of chronic pain and suggest that this paradigm may...
be a promising analgesic assay in pain research.

Operant Response Paradigm
Functional disability is an important clinical parameter of pain and pain relief and several animal paradigms have been developed to assess motor impairment (locomotion) under conditions of chronic inflammatory pain. These paradigms, which simulate some of the clinical features of chronic pain, have been successful in screening various analgesic drugs. It is interesting that operant response paradigms, which are the mainstay of behavioral pharmacology, have not been incorporated into pain research paradigms. With recent advances in instrumentation and measurement of operant responding, the operant response paradigm seems well-suited for examining functional disability that accompanies chronic pain. In a second series of experiments, we incorporated the CFA model of chronic inflammatory pain (bilateral forelimb into a standard operant response paradigm to determine whether chronic pain would produce deficits in operant responses, and, if so, whether morphine or the NSAID indomethacin would provide for recovery of function on operant tasks. The operant apparatus used in these studies was typical of others with the exception replacing the traditional lever with a force-sensing manipulandum. Rats were autoshaped to use forelimb extension to operate this force-sensing manipulandum to receive water reinforcement. The schedule of water reinforcement (3-sec dipper access) was FR1. The force criterion for a response was set at 8 g and the peak force of each response was measured by a computer equipped with custom-designed software. A session mean of the individual peak forces that met an 8-g criterion was used as the force value for each subject in data analyses; response rates were also included as a second dependent measure. In these experiments, CFA inflammation produced a deficit in response rate and response force that persisted up to four days post-inflammation. Vehicle-treated rats displayed a modest recovery of functioning on the response rate measure. However, response force never fully recovered throughout the testing period. Rats that received indomethacin or morphine exhibited an accelerated recovery of function on both the response rate and the response force measures. Recovery of response rate preceded recovery of response force. These observations highlight an important difference between the response rate and response force measures. The response rate measure seems to indicate a willingness to respond, and as responding is reestablished following inflammation, it provides a gross indicator of the capacity to respond. On the other hand, the response force measure cannot indicate anything about ability to respond until some responses are actually made. Once responding is reestablished, either through analgesic treatment or through the recovery/healing process, the response force measure may provide information about subtle deficits not detectable with the grosser response rate measure. Collectively, this paradigm may provide a measure of functional disability that successfully models recovery of function in human clinical populations.

Summary
The discovery of novel therapeutics for the treatment of chronic pain depends largely upon the development of clinically-relevant animal models and quantitative methods for determination of drug efficacy. Research from this laboratory demonstrates that the place preference and operant response paradigms serve as important assays for the evaluation of unique and clinically-relevant aspects of analgesic drug efficacy in models of chronic inflammatory pain. We hope that these and other novel paradigms will provide researchers with the necessary tools to discover new pharmacotherapeutics that will improve the quality of life in people suffering from chronic pain syndromes.

References

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