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Assessing the aversive nature of pain with an operant approach/avoidance paradigm

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ABSTRACT

Preclinical pain assessments can be criticized for failing to adequately characterize the human clinical pain experience. Although recent assessments have improved upon this shortcoming, there are still significant limitations. One concern is that current procedures fail to examine underlying motivational drives related to pain. Therefore, we used a novel approach-avoidance paradigm that allowed a rat to either satisfy hunger or avoid noxious stimulation to reveal prioritizing of motivational drives. The operant paradigm utilized a single lever that the animal pressed for appetitive reward (approach). The lever press was associated with mechanical stimulation of an inflamed paw induced by subcutaneous injection of carrageenan (avoidance). The results revealed that carrageenan-injected animals had a significant suppression of lever pressing and, in addition, had a longer latency to approach and press a lever for appetitive reward. The pattern of operant behavioral responses indicates that the motivation to avoid pain superseded the motivation to alleviate hunger. Utilization of approach-avoidance paradigms, such as this one, can allow researchers to unravel the complexities of the pain experience with the goal of enhancing translation to clinical efficacy.

1. Introduction

Pain is a subjective phenomenon consisting of sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions [21]. Despite this complex experience, preclinical pain models have focused primarily on quantifying the sensory component of pain via mechanical and thermal responses. Although reflexive and stimulus-evoked behaviors reflect clinical allodynia and hyperalgesia, these models have been limited in accurately modeling the overall pain experience [11,12]. Failure to incorporate all components of pain in preclinical testing allows for only a partial understanding of the phenomena and likely has a negative impact on translation to clinical realms. Paradigms that quantify the affective component of preclinical pain via mechanical or thermal stimuli like the Place Escape/Avoidance paradigm [17], two-temperature choice [20] and condition place aversion [15] as well as conditioned place preference using analgesics [31,32] have improved on these shortcomings. Although these assessments quantify pain affect by measuring escape and avoidant behaviors that can be interpreted as an indicator of the unpleasantness of pain [1,19], these paradigms may still be inconclusive since the ability to escape and/or avoid pain may not always be possible.

Much like hunger and thirst, pain can be viewed as a homeostatic emotion that creates an unpleasant state motivating an organism to maintain internal stability and react in favor of its survival [7,10]. However, other factors, including hunger and thirst, also subserve processes of homeostasis and can influence pain-related behavior [3,16]. According to drive reduction theory, organisms have a basic biological need to reduce tension of unsatisfied needs. As a result, these motivational drives (e.g. pain, hunger, or thirst) can compete to resolve each state (e.g. relieve pain, satisfy hunger, or quench thirst) [14]. Previous studies that have explored these competing motivational drives using operant methodology suggest pain can suppress reward-seeking behavior in animals [9,18,23,24,26,29,30]. In one study, LaGraize et al. [18] observed suppression of lever responses for food reinforcement in rodents during the first phase of the formalin test and an increase in lever responses during second phase. The results suggested that animals chose to attend to one of the competing motivational drives at a time, with attention given to the most aversive drive. Similar findings also suggest that pain suppresses reward-seeking behavior in animals [9,24,26,29,30].

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In order to better characterize and evaluate the pain experience, such operant approach/avoidance models may be valuable. Approach-avoidance models typically present a conflict such that obtaining a desired goal (i.e. food) is associated with a negative outcome (i.e. evoked pain). Existing studies have explored this type of reward-conflict with orofacial thermal [23] and orofacial mechanical stimulation [26,30]. In the following experiment, rodents on a food controlled diet to induce "hunger" also experienced pain as a result of an inflammatory agent, carrageenan. Behaviorally, animals were allowed to "choose" to lever press for appetitive reward and receive noxious mechanical stimulation of the carrageenan-induced inflamed paw or avoid noxious stimulation by not pressing the lever and consequently, foregoing appetitive reward. Therefore, the purpose of this study was to investigate the effectiveness of an operant approach/avoidance paradigm in quantifying the affective and motivational components of pain through competing motivational drives of pain and hunger.

2. Methods

All procedures for this experiment were approved by the University of Texas at Arlington Institutional Animal Care and Use Committee and in accordance with the guidelines of the International Association for the Study of Pain.

2.1. Materials and methods

2.1.1. Animals and procedures

Twenty-six male adult Sprague Dawley rats (400–600 g) were randomly chosen from the University of Texas at Arlington vivarium and single housed in a separate colony room on a 12:12 dark/light cycle. Animals were placed on a food-controlled diet with a variable time feeding schedule until 85% of original weight was achieved and water ad libitum.

Once at 85% of original weight, animals were subjected to a mechanical paw withdrawal threshold (MPWT) testing. In this test, animals were placed into Plexiglas chambers atop a mesh floor providing access to the plantar surface of the hind paws for mechanical stimulation. After 10 min of habituation, mechanical sensitivity was measured using a set of von Frey monofilaments (3.85, 5.68, 9.74, 18.39, 39.42, 77.3, 135.3, and 251.34 mN). In order to quantify mechanical withdrawal thresholds, the up/down method was used [8]. Each trial of testing began with the 9.74 mN von Frey filament delivered to the left hind paw for approximately 1 s, then to the right paw. If no withdrawal response was observed (i.e. paw withdrawal or licking), the next highest force was used, while the next lower force was delivered if a response was observed. This procedure was repeated until no response was made at the highest force (251.34 mN) or until five stimuli were administered in total. The 50% paw withdrawal threshold for each trial was calculated using the following formula: $[Xth]\log = [vFr]\log + ky$, where [vFr] is the force of the last von Frey used, k = 0.2593 is the average interval (in log units) between the von Frey monofilaments, and y is a value that depends upon the pattern of withdrawal responses. If an animal did not respond to the highest von Frey monofilament (251.34 mN), then y = 1.00 and the 50% mechanical paw withdrawal response for that paw was calculated to be 456.63 mN. This test was conducted three times and the scores from each trial were averaged to determine the mean threshold to tactile stimulation for the right and left paws for each animal [8].

If animals displayed no tactile sensitivity, they were trained to lever-press for appetitive reward. Animals varied on the number of training days that were required to reach criteria for test day (80% response rate), but had a minimum of four days. Training occurred once daily on a variable schedule in standard operant chambers (Med Associates, Inc.) and animals were shaped through successive approximations to press a single lever for appetitive reward (45 mg grain based pellet).

Day one of training consisted of a manual training phase, where animals were exposed to the paradigm. Every 20 s, the lever was presented, then retracted, which matched the left lever light turning on and off, respectively. When the lever was retracted back in, the food hopper dispensed one food pellet. Inclusion criteria to meet the next training phase occurred when animals successfully associated the lever retraction with appetitive reward, which was signified by the consumption of all 60 pellets from the training. On the second phase of training, animals were subjected to another manual training where the lever remained out until the animal successfully lever pressed, at which, one pellet would be dispensed. Animals who successfully lever-pressed for 40 times or more met criteria to move onto the next phase of training. On the third phase of training, animals were subjected to an automatic phase where every 20 s, the lever was presented and remained out for 10 s. If the animals lever-pressed or the time exceeded 10 s without a lever press, the lever was retracted, and animals would have to wait another 20 s for a new trial to begin. Animals had to successfully lever-press at least for 80% of trials, i.e. lever-pressed for at least 48 out of the 60 trials or omitted no more than 12 trials to move onto test day.

2.1.2. Test day

On the test day, animals were randomly assigned to receive a subcutaneous injection into the plantar surface of the hindpaw with either 1% carrageenan lambda (Sigma) (n = 13) or normal saline (n = 13). A MPWT test was performed 30-min later to ensure the effectiveness of carrageenan to induce hypersensitivity. Animals were then placed in the operant approach/avoidance paradigm (AAP) to quantify the animal's approach/avoidance behavior associated with the presentation of a noxious stimulation. To produce the AAP box, a standard operant chamber (MedPC) was removed from the sound attenuating box hub and the steel rod floor was removed. The chamber was fixed atop a mesh floor PVC platform so that a mechanical stimulus could be applied to the plantar surface of the hindpaws. The transparent outside walls of the chamber were covered in black contact paper. Essentially, this test utilized a modified operant chamber that allowed stimulation of the plantar surface of the hind paws.

Before testing, animals were subjected to a priming, where animals had to successfully lever-press for 10 consecutive times. This was to ensure the animal was able to transfer performance of the task learned in the standard operant chamber used during lever press training to the modified operant chamber. During the test session, a lever was presented for 10 s at 20-second intervals for a total of 30 min for a total of 60 trials. Animals were able to lever press once during this 10 second interval, at which the lever would retract back in and one pellet would be dispensed. The single pressing of the lever signified the end of the trial and a new trial would start 20 s later. If the animal did not lever-press within the 10 second interval, the trial would end, be considered an omission, and a new trial will commence in another 20 s. This allowed for a minimum of 0 pellets and a maximum of 60 pellets within the paradigm, in which the number of lever-presses correlated with the number of pellets received. Lever presses for appetitive reward were immediately followed by paw stimulation of the injected left paw (associated with either carrageenan or saline injection) with a suprathreshold (465 mN) Von Frey filament. This presented the rat with an approach-avoidance conflict in which appetitive reward (i.e. lever press) was associated with noxious mechanical stimulation to the injected carrageenan or saline paw. The animals could also forego appetitive reward and avoid noxious mechanical stimulation. Thus during testing, animals were presented with two behavioral choices: (1) press the lever and receive noxious stimulation to the inflamed left paw or (2) not press the lever, avoid noxious stimulation and forego appetitive reward. Suppression of reward seeking would be viewed as an indication of the unpleasantness of the noxious stimulation. The number of trials yielding a response as well as latencies to lever-press were recorded via MED-PC operant coding by Med Associates for each trial.