Developing Improved Translational Models of Pain: A Role for the Behavioral Scientist

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Abstract

The effective management of pain is a longstanding public health concern. Although opioids have been frontline analgesics for decades, they also have well-known undesirable effects that limit their clinical utility, such as abuse liability and respiratory depression. The failure to develop better analgesics has, in some ways, contributed to the escalating opioid epidemic that has claimed tens of thousands of lives and has cost hundreds of billions of dollars in health-care expenses. A paradigm shift is needed in the pharmacotherapy of pain management that will require extensive efforts throughout biomedical science. The purpose of the present review is to highlight the critical role of the *behavioral scientist* to devise improved translational models of pain for drug development. Despite high heterogeneity of painful conditions that involve cortical-dependent pain processing, current models often feature an overreliance on simple reflex-based measures and an emphasis on the absence, rather than presence, of behavior as evidence of analgesic efficacy. Novel approaches should focus on the restoration of operant and other CNS-mediated behavior under painful conditions.

Keywords Opioids · Nociception · Antinociception · Pain · Analgesia · Animal models

The failure to develop better analgesics for the management of pain has resulted in a profound predicament with consequences that relate to several major public health concerns. Although opioids can provide effective pain management, they also have

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well-known undesirable effects that hamper their clinical utility. Two of the most problematic are respiratory depression, which is the primary cause of fatality in opioid overdose, and high abuse liability, which is expressed in alarmingly high rates of addiction and dependence. Abuse of prescription opioids has risen dramatically throughout the last decade and more than half of fatal drug overdoses were attributed to prescription and illicitly manufactured opioids, accounting for the deaths of nearly 50,000 Americans in 2017 (Ahmad, Rossen, Spencer, Warner, & Sutton, 2018). As the prevalence of opioid use has significantly increased in recent years, so too have concerns regarding the *undertreatment* of pain, likely representing an overcorrection in the response to the opioid abuse problem (Tompkins, Hobelmann, & Compton, 2017; Seers, Derry, Seers, & Moore, 2018). For example, although overprescribing practices warrant tough scrutiny, so too does underprescribing, especially as it has been shown to disproportionately affect certain patient populations, such as racial and ethnic minorities, those with previous drug abuse histories, and the elderly (e.g., Shavers, Bakos, & Sheppard, 2010; da Cunha, 2015; Hemmingsson et al., 2018). Taken together, it is estimated that pain affects more than 100 million people in the United States and costs \$600 billion a year in lost work productivity and health-care costs (Gaskin & Richard, 2011), whereas opioid overdoses claim the lives of more than 130 Americans each day (Ahmad et al., 2018) and prescription opioid abuse alone costs the United States \$78.5 billion a year in health care, lost productivity, addiction treatment, and criminal justice efforts (Florence, Zhou, Luo, & Xu, 2016).

This well-publicized state of affairs has recently been promoted to epidemic status (see Christie et al., 2017). To be sure, the failure to develop better analgesics has not gone unnoticed within the biomedical research community. However, despite highly active laboratory and clinical research efforts over many decades, there have been limited successes in the development of new forms of analgesic drugs (reviewed in Corbett, Henderson, McKnight, & Paterson, 2006; Kissin, 2016). A dramatic shift in the pharmacotherapy of pain management appears necessary and will require extensive efforts from multiple diverse disciplines working together to reach a common goal. This will include *physiologists* identifying novel ways to attenuate activation of pain pathways within the central and peripheral nervous system, *neuroscientists* employing advanced electrophysiological and neuroimaging techniques to identify localization of pain perception, *biologists* discovering ever-elusive objective biomarkers of acute and chronic pain syndromes, *physicians* delineating functional categories of clinical pain, and *medicinal chemists* developing improved candidate molecules.

The purpose of the present article, however, is to outline the essential role of the *behavioral scientist* in this endeavor, namely, to develop better in vivo assays that permit more effective preclinical appraisals of analgesic action. As detailed below, model development must reflect the heterogeneity of painful conditions and consequent need to tailor assays to emulate such distinct conditions. Of course, there are phenotypic complexities and important ethical concerns that need to be considered in this pursuit. However, the behavioral scientist is exceptionally qualified to devise and empirically validate candidate models given repeated success in effective assay development for laboratory animals across diverse fields of study, including economics, learning and memory, drug abuse and addiction, and choice and decision making (reviewed extensively in Madden, Dube, Hackenberg, Hanley, & Lattal, 2013).

Nociception vs. Pain

To understand the requirements of developing translational models, it is important to note the fundamental distinction between nociception and pain (Mao, 2012). Put simply, nociception is to pain what sensation is to perception. Nociception is the *neural process* of encoding noxious stimuli, resulting in the neural responses associated with resultant nocifensive behavior and pain perception (reviewed in Sneddon, 2018). Pain is a multidimensional *subjective experience* comprising sensory, motor, cognitive, autonomic and affective responses, and it is often reported by patients with reference to such responses (Rainville, Feine, Bushnell, & Duncan, 1992; Kunz, Lautenbacher, LeBlanc, & Rainville, 2012; Davis et al., 2017). In addition, pain perception may vary among individuals due to idiosyncratic histories of painful experience, sex differences, or clinical comorbidities (Edwards, 2005; Peacock & Patel, 2008; Bartley, Fillingim, Colvin, & Rowbotham, 2013). Adding additional layers of complexity, it has become increasingly recognized that there are multiple neurobiologically and phenomenologically distinct categories of pain and the pathophysiological mechanism of many pain syndromes remains unknown.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,” a definition that accommodates several types of pain (IASP, 2017). *Acute pain* is provoked by a specific injury or disease and acts as a protective mechanism initiated by the nociceptive system (Grichnik & Ferrante, 1991). In contrast, *chronic pain* is defined as pain that persists beyond normal tissue healing time that may not serve an apparent biologic purpose (Davis et al., 2017; Grichnik & Ferrante, 1991). Chronic pain is associated with a wide range of pathological conditions. Pain that results in damage to the somatosensory nervous tissue is referred to as *neuropathic* (Finnerup, 2017). Swelling of tissue that applies pressure to sensitive areas, especially joints, is characterized as *inflammatory pain*. Diseases such as cancer, arthritis, fibromyalgia, diabetes, and acquired immunodeficiency syndrome produce pain comprising a complex, temporally changing constellation of symptoms; such pain can involve inflammatory, neuropathic, ischemic, and compression mechanisms at multiple sites (British Pain Society, 2010).

Although the categories of pain described above have inherent heterogeneity with respect to their causes, the first-line approach in many cases has been to treat the symptom (pain) rather than the underlying problem. That is, many of the currently available treatments target only the nociceptive component while ignoring—or at least not intentionally altering—other variables that control pain. The same treatments (e.g., opioids) are often prescribed regardless of the specific syndrome or pathophysiological mechanism. A “one-size-fits-all” approach in some cases may result in more harm than benefit. For example, people suffering from chronic pain may be prescribed opioids, despite no scientific evidence supporting any benefit of such treatment beyond 12 weeks, and thus the symptoms persist or even worsen (Tompkins et al., 2017). Therefore, developing assays to comprehensively study different pain types and tailored preclinical models targeting particular pain syndromes will be required.

Ethical Considerations

Discussion of the current state of affairs and suggestions for potential improvements in pain research requires careful consideration of ethical issues and constraints. In this regard, it is generally accepted that experiments designed to further our understanding of the mechanisms of nociception and pain are essential to ameliorating both the unmet public health concern of problematic pain management therapies and the related epidemic of prescription opioid abuse. No matter how pressing the issues may be, however, in order to carry out such experimental work in laboratory animals within an ethical and moral framework, several important principles must be considered carefully. First, established guidelines related to best practice procedures that emphasize ethical factors in pain research are available and should be consulted (e.g., Morton & Griffith, 1985; Zimmerman, 1983; National Research Council, 2011). Second, ethics committees consisting of scientists, veterinarians, and lay members of the community should be assembled to review experimental protocols and provide recommendations to be adhered to by scientists studying nociception and pain (e.g., institutional animal use and care committees). Third, pain research, like all endeavors in biomedical science, requires active participation of society on the local, national, and international level to consider the problem at hand and the role that both human and nonhuman animal subjects can play in finding solutions to unsolved public health concerns. A critical evaluation of potential benefits in relation to risk should ultimately guide the nature of all scientific pursuits.

Current Animal Models of Pain

Advancing a therapeutic to the clinical trial phase requires demonstration of effectiveness in preclinical models. Models that are more predictive of analgesic effects in the relevant patient population are critical to the clinical success of novel pharmacotherapies. Current models vary in the topography of nocifensive responses elicited and the noxious stimuli used to induce such behaviors. First, some responses that are measured in extant assays occur in spinalized animals and therefore are thought to be spinal withdrawal reflexes, whereas other induced behaviors involve the recruitment of supraspinal central nervous system (CNS) regions. Second, depending on the type of pain one is attempting to model, there is a broad range of nociceptive stimuli available to induce pain states; however, certain stimuli may be preferred to model a particular pain condition (see Gregory et al., 2013). Many early models of nociception employ short duration noxious stimuli (i.e., thermal, electrical) to study acute pain. Mechanical and chemical stimuli subsequently became more prevalent, in particular in efforts to model chronic pain states. In general, nociceptive stimuli activate distinct nociceptors in the nervous system and can be grouped into four categories: *thermal*, *electrical*, *mechanical*, and *chemical*. Nociception assays employing each of the four stimuli offer several advantages including the simplicity of the equipment, little or no training required, rapidity of measurement, and the ability to precisely control the stimulus intensity. The uses of each are briefly reviewed below as more extensive reviews of nociception models in nonhuman animals have been published (e.g., Vierck & Cooper, 1984; Chapman et al., 1985; Franklin & Abbott, 1989; Vierck, Hansson, & Yezierski, 2008; see especially Le Bars, Gozariu, & Cadden, 2001).

Thermal

Studying behavioral responses produced by the application of thermal stimuli forms the basis of many preclinical models of nociception. The use of thermal stimuli has numerous advantages, including translatability across species and reproducibility within- and between-subject responses, in part due to sharply defined sensory thresholds of thermal pain. In an early study by Hardy, Wolff, and Goodell (1940), radiant heat was applied to the blackened forehead of human subjects, and the intensity of the light was increased periodically until the subject reported pain. The final light intensity, defined as a pain threshold, was highly consistent both within and between subjects. The principles of this procedure contributed to the development of the *tail-flick* assay, which has since been one of the most commonly used assays of nociception in rodents (e.g., D'Amour & Smith, 1941; Kimura, Mattaraia, & Picolo, 2019; Silva, Silva, & Prado, 2013). In these assays, a fixed-intensity radiant light heat stimulus is focused on the subject's tail, and the latency to displace it serves as the primary dependent measure. Highly reliable thermal thresholds can be obtained and augmented in a dose-dependent manner following administration of opioid analgesics (e.g., D'Amour & Smith, 1941; Manning & Mayer, 1995). In a derivative of the tail-flick procedure, the *warm water tail-withdrawal* assay, the subject's tail is immersed in hot water which, under baseline conditions, provokes rapid withdrawal of the tail. The latency to tail-withdrawal is a highly reliable and pharmacologically sensitive measure in both rodents (Janssen, Niemegeers, & Dony, 1963) and nonhuman primates (Dykstra & Woods, 1986). In another thermal assay, the *hot-plate test*, a subject is placed on a warm metal surface, and the latency to either withdraw the paw from a hotplate or lift and lick the paw is measured (Woolfe & Macdonald, 1944; Eddy & Leimbach, 1953; Tjølsen, Rosland, Berge, & Hole, 1991). Utilizing similar principles, the *Hargreaves Test* (Hargreaves, Dubner, Brown, Flores, & Joris, 1988) involves the precise application of radiant heat to the target hind paws, allowing assessment of antinociceptive effects of drugs in normal and targeted paws. It is interesting that although cold thermal stimuli are commonly used in the assessment of acute pain thresholds in humans (Olesen, van Goor, Bouwense, Wilder-Smith, & Drewes, 2012; Lue, Wang, Cheng, Chen, & Lu, 2018), they are rarely used to study acute pain in nonhuman animals. One exception is work examining cold allodynia in models of neuropathic pain, using methods similar to those that involve heated thermal stimuli, that is, immersion of the tail into cold water or lifting paws from a cold surface (e.g., Choi, Yoon, Na, Kim, & Chung, 1994; Wang, Ho, Hu, & Chu, 1995; Atwal, Casey, Mitchell, & Vaughan, 2019).

Electrical

Like the studies reviewed above using thermal stimuli, experiments utilizing electrical stimuli require simple apparatus, and the stimulus intensity can be adjusted in a highly controlled manner. Electrical stimuli can be applied in several ways, including long-lasting trains of increasing intensity that continue for hundreds of milliseconds via subcutaneous electrodes attached to the tail (Carroll & Lim, 1960; Paalzow, 1969; Paalzow & Paalzow, 1975; Levine, Feldmesser, Tecott, Gordon, & Izdebski, 1984; Borszcz, Johnson, & Fahey, 1994). As an alternative, single shocks or very short trains lasting 10–20 ms can be applied multiple times with increasing intensities to measure

responses including twitching, escape behaviors, vocalizations, and biting. Some studies have used an operant-based shock titration procedure to characterize analgesic effects of different classes of drugs (e.g., Weiss & Laties, 1964; Dykstra & Mcmillan, 1977). The paw or dental pulp can also be electrically stimulated (see Le Bars et al., 2001). With increasing intensity, thresholds are reached at which the subject displays nocifensive behavior that can correlate with the degree of cortical involvement (Borszcz, 1995). First, there is a reflexive tail movement that is followed by characteristic vocalizations that occur for the duration of stimulation, and distinct vocalizations that continue beyond the period of stimulation. Such complex vocal behaviors emitted during and following electrical stimulation have been characterized in rats, for example, peeps, chatters, ultrasonic vocalizations (Ardid, Jourdan, Eschaliere, Arabia, & Le Bars, 1993; Jourdan, Ardid, Chapuy, Eschaliere, & Le Bars, 1995). Opioid analgesics have been shown to modify vocal pain behaviors, and each component of the vocalization pattern is differentially sensitive to the effects of opioids (Jourdan, Ardid, Chapuy, Le Bars, & Eschaliere, 1998). Taken together, the potency of opioids to produce antinociception in response to electrical stimulation assays increases with the hierarchy of cortical involvement in each of the observed responses (i.e., motor responses < vocalization < vocalization after discharge; Paalzow & Paalzow, 1975; Borszcz et al., 1994; Jourdan et al., 1998).

Mechanical

Tests utilizing mechanical stimuli in the study of nociception often involve applying increasing pressure to an appendage and, using standardized instruments, measuring the applied pressure (weight in grams) to generate precise stimulus–response functions. Mechanical stimulation can be used to induce both analgesia and hyperalgesia (increased pain sensitivity to a stimulus that normally provokes pain). Similar to electrical stimulation, the application of increasing pressure produces a chained response, that is, attempts to release appendage, visible struggle, vocalizations. This may vary depending on the type of assay used and may involve both spinal and supraspinal structures. The most commonly used assay that employs mechanical stimuli is the *Von Frey test*, which utilizes nylon fibers of varying diameters to test sensitivity to mechanical stimulation (Lambert, Mallos, & Zagami, 2009). Because the parameters of this specific assay allow for measuring allodynia (pain following exposure to a stimulus that does not normally provoke pain) and hyperalgesia, it is particularly useful for modeling clinical conditions with enhanced cutaneous sensitivity (e.g., neuropathic pain, osteoarthritis, inflammation) using increasing diameter filaments or repeatedly applying the same filament. Other instruments used for mechanical stimulation include calibrated forceps to induce deep but not cutaneous pain (Skyba, Radhakrishnan, & Sluka, 2005), and a dolorimeter or Randall-Selitto analgesiometer to decrease pain threshold in the attempt to mimic conditions such as fibromyalgia or myofascial pain (Bennett, 2007; Gregory et al., 2013; Hsu et al., 2010; Finan et al., 2013).

Chemical

The application of algogenic chemicals offers several advantages when modeling certain pain syndromes. First, the severity of chemical stimuli can be controlled and

altered by increasing concentration, volume, or route of application (e.g., dermal application or injection). Furthermore, chemical administration often leads to two phases of nocifensive behaviors. The first is an initial response resulting from nociceptor activation, and the second phase reflects inflammation (Dubuisson & Dennis, 1977). The biphasic response allows researchers to study acute and longer-lasting tonic pain following a single noxious insult. For example, opioids can effectively suppress both acute and tonic pain, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) suppress only the tonic phase (Jourdan et al., 1997). Depending on the type of pain one is attempting to model, the route of administration and the noxious agent can be altered. Diluted formalin can be injected into the surface of the rodent's hind paw, and resulting behaviors (e.g., flinching, licking, biting at affected paw) are tallied. The formalin-orofacial test involves the injection of formalin into the upper lip to study nociception in the trigeminal region, a model for neuropathic trigeminal pain (Raboisson & Dalle, 2004). Intraperitoneal administration of chemical agents induce stereotyped behaviors in the writhing test (Niemegeers, Van Bruggen, & Janssen, 1975; Murray & Miller, 1960; Collier, Dinneen, Johnson, & Schneider, 1968). Finally, algogenic substances also can be injected directly into hollow organs (e.g., colon, bladder, uterus) to model visceral pain to produce complex pain behavior patterns, such as body contortions (Miampamba, Chery-Croze, Gorry, Berger, & Chayvialle, 1994; Craft, Henley, Haaseth, Hruby, & Porreca, 1995; Pandita, Persson, & Andersson, 1997; Wesselmann, Czakanski, Affaitati, & Giamberardino, 1998).

Limitations of Current Models of Nociception

Although observable behavior such as paw- or tail-withdrawal, licking, and guarding posture may appear to reflect volitional attempts to escape or attenuate painful conditions, interpretive caution is required. Accumulating evidence using functional imaging techniques has made it increasingly clear that the experience of pain has high heterogeneity and involves supraspinal regions in the modulation of pain processing (e.g., Martucci & Mackey, 2016; Moisset & Bouhassira, 2007). Therefore, consideration of central circuitry involved between the sensory inputs and motor outputs generated in response to noxious stimuli is required in the evaluation of nociceptive tests. This has usually been investigated by severing the neuraxis to disrupt pain signal transmission. For example, the tail-flick, tail-withdrawal, and paw-withdrawal responses can be elicited in spinalized animals (e.g., Dewey, Harris, Howes, & Nuite, 1970; Franklin & Abbott, 1989) and as such are thought to represent segmental spinal reflexes without the involvement of cortical function. Likewise, paw licking and vocalization in the hot-plate test have been elicited in decerebrate rats (e.g., Carroll & Lim, 1960; Woolf, 1984; Berridge, 1989; Matthies & Franklin, 1992; Sandkühler & Gebhart, 1984; Cooper & Vierck, 1986; Dubner & Hargreaves, 1989). Therefore, when designing preclinical models of pain, it is important to distinguish between unconditioned responses that could be segmental (spinal) reflexes and those that are operant (conditioned) responses that necessarily employ learned behavior that requires cortical function. Moreover, pain occurs in an environmental and historical context that can be manipulated experimentally. To be clear, the contribution of preclinical models that investigate drug effects on segmental reflexes as a measure of antinociception has proven instrumental in

developing our understanding of opioid analgesics. However, to increase the likelihood of novel nonopioid therapeutics advancing from bench to bedside, preclinical analyses of antinociceptive compounds should assess more than a drug's effect on simple nociceptive reflexes. That is, more sophisticated methods of analgesimetry, expressly designed to incorporate cortical-dependent responses, likely will be required to develop currently elusive pain management treatments (Vierck et al., 2008).

Another significant limitation inherent in the extant models described above is that they are all susceptible to false positives. This is due to the fact that the models are arranged such that the *nonoccurrence* of a response (e.g., failure to flick the tail, withdraw the paw, or vocalize) following a nociceptive stimulus is the primary evidence of antinociception. However, the *selectivity* of drug effect needs to be determined. For example, if a drug is administered and a particular nocifensive response does not occur following a noxious stimulus that reliably produced it under control conditions, it remains unclear the extent to which the drug selectively blocked the response via reduction of sensory sensitivity to the nociceptive stimulus (i.e., analgesia) or, as an alternative, if it induced sufficient motor impairment to physically impair the response despite a full subjective experience of the painful condition. This is especially problematic when the candidate analgesic has known behaviorally disruptive effects, for example, sedation, muscle relaxation, stupor—effects that are commonly produced following administration of opioid analgesics.

Desirable Features of Translational Models of Pain

With the limitations of current models in mind, there are several desirable features that should be considered in the development of improved translational models of pain. 1) *CNS-dependent response as evidence of antinociception*. As discussed above, it is increasingly clear that the experience of pain has high heterogeneity and involves supraspinal regions in the modulation of pain processing. As such, measurement of a response that requires CNS activation would be beneficial. 2) *Restoration of function*. Translational models could benefit from measures of antinociception that are evident via the presence of a response rather than its absence. This will reduce the false-positive risk of confusing analgesia with behavioral disruption. 3) *Efficacy requirements*. All drugs, including pharmacotherapies, can be characterized with respect to their *efficacy*, that is, their maximum possible effect on a particular endpoint. High-efficacy opioid agonists (e.g., fentanyl, morphine) may have antinociceptive effects regardless of the magnitude or intensity of nociceptive stimuli, whereas low-efficacy opioid agonists (e.g., buprenorphine, nalbuphine) may display antinociceptive effects only when stimulus intensity is low (Morgan, Cook, Smith, & Picker, 1999; Cook, Barrett, Roach, Bowman, & Picker, 2000). Models of nociception that allow for a range of stimulus intensities to be examined will be beneficial to the pharmacological characterization of candidate analgesics. For example, opioid analgesics are likely too efficacious for some painful conditions in which they are prescribed (del Portal, Healy, Satz, & McNamara, 2016). Therefore, having the ability to tailor efficacy requirements in a nociception assay would provide important flexibility in drug screening and allow for the targeted development of lower efficacy analgesics. 4) *Cross-species comparisons*. As with all pursuits in preclinical pharmacology and drug development, testing candidate

therapeutics requires coordinated translational procedures across human and nonhuman laboratory subjects to best predict clinical utility.

Recent Advances in Model Development

Despite a paucity of models that embrace the features described above, the need for more translational models has been considered for some time (Barrett, 2015; Mao, 2012; Mogil, 2009; Negus, 2019; Vierck et al., 2008) and has inspired some advancement. One recent approach expressly designed to incorporate a *CNS-dependent response* was the inclusion of operant behavior within a well-established reflex-based model of nociception. In this regard, Withey, Paronis, and Bergman (2018) modified the warm water tail-withdrawal assay in nonhuman primates described above to also incorporate operant behavior between tail-withdrawal latency measurements. In particular, the effects of a variety of opioid analgesics were examined during 10 alternating components of lever responding (fixed-ratio 10) reinforced with food followed by short timeout periods (30 s) during which the subject's tail was immersed in water that varied in temperature. This arrangement allows for sequential assessment of the behaviorally disruptive *and* antinociceptive effects of candidate analgesic drugs. This is vital because as described above, existing frontline opioid analgesics are well-known to produce analgesia and behavioral disruption at similar doses. It is important to note, however, that there are circumstances in which sedation is a desirable effect (e.g., post-operative recovery). Therefore, this assay allows for the quantitative characterization of drugs with regard to their behavioral selectivity (i.e., ratio of behaviorally disruptive to antinociceptive effects) that may allow for more effective selection of analgesic drugs in accordance with individual treatment goals.

Other recent efforts in model development have emphasized *restoration of function*. For example, operant models have been developed to characterize orofacial pain in mice and rats (Neubert et al., 2005; Ramirez et al., 2015; Rohrs et al., 2015). In these assays, rodent subjects are trained to press a shaved portion of their face against a noxious stimulus (thermal or mechanical) to earn a food reinforcer. These contingencies produce *conflict* between appetitive and nociceptive stimulation and allow for assessment of candidate analgesics to increase a subject's threshold of nociceptive stimulation to earn a reward. In a related assay that examines the ability of candidate analgesics to restore operant responding in the presence of nociceptive conditions, Kangas and Bergman (2014) designed a procedure in which nonhuman primates were trained to pull down a cylindrical thermode for a brief duration (2, 3, or 5 s) to earn food reinforcers. The temperature of the thermode was increased across trial blocks until the subject failed to complete a response within 10 s of trial initiation. The highest temperature at which the subject was able to successfully complete a response defined a thermal threshold, and subsequent assessments could be conducted to evaluate the ability of candidate analgesics to increase a subject's thermal threshold. It is important to note that, unlike the extant assays described above in which analgesia is inferred via the absence of a response, analgesia in both the rodent orofacial assay and nonhuman primate thermal pull assay is inferred by the ability of a candidate therapeutic to *increase* the probability of responding during nociceptive conditions that are otherwise too aversive for the subject without drug treatment (i.e., restoration of function).

Although the recently developed models described above emphasize the use of schedule-controlled operant behavior, examination of naturalistic behavior via observational methods has also provided a fruitful approach. For example, Negus et al. (2015) examined the effects of nociceptive stimuli on naturally occurring and adaptive nesting behavior in mice. When provided with squares of cotton material in their home cage, mice consistently shred the cotton and build organized nests (Jirkof et al., 2013). However, administration of diluted lactic acid depresses this nesting behavior in a concentration-dependent manner. It is important to note that pretreatment with low doses of opioid analgesics and NSAIDs can block the depressant effect of the chemical nociceptive stimulus and thus provides evidence of construct validity. Similar to the schedule-controlled operant tasks described above, strengths of this procedure using naturalistic behavior include an emphasis on the restoration of CNS-mediated behavior in the presence of a painful condition (Negus, 2018).

Volitional wheel running in the rodent is another naturalistic behavior that is susceptible to pain-induced changes and has been used to model conditions such as inflammatory pain following injection of Complete Freund's Adjuvant (CFA) into the hind paw(s) (Kandasamy, Calsbeek, & Morgan 2016), osteoarthritis-related pain following injection of monosodium iodoacetate into the knee joint (Stevenson et al., 2011), as well as migraine pain induced by injection of allyl isothiocyanate onto the dura (Kandasamy, Lee, & Morgan, 2017). Under baseline conditions, rodents will engage in long periods of wheel running, and the duration of this behavior can be systematically reduced following administration of a noxious stimulus as described above. It is important to note that pain-induced decreases in wheel running can be dose-dependently reversed by both anti-inflammatory and analgesic drugs such as naproxen, ibuprofen, and morphine (Cobos et al., 2012). Similar to the nesting model described above, wheel running relies on pain-depressed rather than pain-evoked measures and, therefore, success of an analgesic agent is measured by its ability to restore CNS-mediated behavior. It is interesting that systematic differences have been reported between the duration of CFA-induced depression of wheel running and CFA-induced allodynia (Kandasamy et al., 2016), which suggests that the two models may be assaying different aspects of pain. For example, allodynia assayed via Von Frey can persist for a 14-day experimental condition, whereas wheel running behavior fully returns to baseline activity at Day 12, and as early as Day 2 subjects begin engaging in wheel-running albeit while guarding the injected hind paw. Perhaps in a similar way, humans will often return to daily behaviors (e.g., work or socializing) before the symptoms of pain are completely relieved. These findings should encourage the development of models that allow for the investigation of novel treatments that restore daily function rather than simply eliminate hypersensitivity and also highlights the benefit of combining multiple models to investigate different aspects of pain.

Additional Benefits of Developing Translational Models of Pain

In addition to contributing to the development of better analgesics, there are other important reasons to study behavioral processes related to nociception and pain. Despite the fact that responses to nociceptive stimuli are fundamental and adaptive, many basic functional relations are poorly understood (Dews, 1974). An understanding

of the environmental determinants that modulate the expression of pain is currently limited; however, examining the ability of contingencies and contextual/historical aspects of stimulus control to regulate these subjective effects could inform the development of *nonpharmacological* adjunct treatments for certain types of painful conditions (e.g., Nahin, Boineau, Khalsa, Stussman, & Weber, 2016; Qaseem, Wilt, McLean, & Forciea, 2017). Indeed, basic behavioral principles have already proven to be effective in this domain. For example, contingent praise and feedback can increase physical activity in patients with chronic lower back pain (Cairns & Pasino, 1977), which in turn can speed recovery and improve treatment outcomes (Searle, Spink, Ho, & Chuter, 2015). Likewise, scheduled access to exercise can alleviate behavioral disruptions due to various types of chronic pain in rats (e.g., Bement & Sluka, 2005; Kuphal, Fibuch, & Taylor, 2007; Stagg et al., 2011; reviewed recently by Pitcher, 2018). In addition, recent research examining the ability of environmental enrichment to modulate pain sensitivity had demonstrated some promising effects across nociceptive stimulus types in rodent models (e.g., Kimura et al., 2019; Parent-Vachon & Vachon, 2018; Tai, Yeung, & Cheung, 2018; Wang et al., 2019.)

Because nociception is necessarily an interoceptive phenomenon (private event) yet often produces reliable observable responses (public accompaniments), the study of pain could also provide a fertile research domain to empirically examine private events. This should be of particular interest to many behavioral scientists, given that the inclusion of private events is a defining feature of radical behaviorism (Skinner, 1945). Indeed, notwithstanding copious conceptual and theoretical treatises, there have been relatively few controlled laboratory studies examining private events. One exception that has proven fruitful is the use of behavioral techniques to bring operant behavior under the control of interoceptive events produced by drug treatment, with drug discrimination being one of the most prominent examples (reviewed in Kangas & Maguire, 2016). Other studies have used drug treatment in human subjects to produce equivalence relations between interoceptive (drug) and exteroceptive (visual) stimuli (DeGrandpre, Bickel, & Higgins, 1992) and in pigeons to model interpersonal communication of private events produced by distinctive interoceptive effects associated with different drug classes (Lubinski & Thompson, 1987). Similar procedures could be employed to establish discriminative control of operant behavior using the presence or absence of a painful stimulus, which would permit rigorous examination of various dimensions of painful stimuli (e.g., Grilly & Genovese, 1979; Miksic, Shearman, & Lal, 1980). Such experiments would likely provide valuable insight into the nature of painful stimuli and analgesic drug action, for example, by exploring the generality across various pain modalities. An interpretive system that embraces the examination of controlling variables that govern private events may generate novel perspectives regarding the relations between nociception and pain (see Rachlin, 1985).

Conclusion

The behavioral scientist has made numerous contributions to model development in a variety of diverse disciplines and is well-suited to design and empirically validate highly translational models of pain. As reviewed above, most extant models suffer from limitations including, 1) an overreliance on reflex-based measures that ignore

cortically mediated pain processing, and 2) an emphasis on evaluating the absence of a response under painful conditions rather than its restoration. Improved translational models that embrace the restoration of CNS-dependent behavior have been recently developed and can be improved upon. It is important to note, however, that the recommendations offered in the present review should inform future efforts but not constrain them. Given the well-documented heterogeneity of painful conditions, model development should prioritize diversity in approach that would allow for innovative appraisals of nonopioid candidate therapeutics.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to report.

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