Commentary

Translational challenges and analgesic screening assays

Progress in the development of novel treatments for chronic pain syndromes relies, in part, on both clinically-relevant animal model simulations and analgesic screening procedures [5]. Simulations purport to mimic the features of a clinical syndrome and screenings are geared towards drug discovery. The validity of any animal model simulation is based on how well that model fits the human clinical syndrome in terms of etiology, symptomatology, pathophysiology and response to treatments [9]. The validity of any screening assay requires that it correctly identify compounds that have clinical benefits, screens out compounds that do not and avoids false positives and false negatives [10].

In this issue of Pain, Gutierrez et al. [2] performed a series of well-designed studies to examine cannabinoid (CB) 2 receptor-mediated modulation of neuropathic pain. One interesting aspect of this research, beyond that of showing that the CB2 receptor may be a viable target for analgesic drug development, is their use of a more clinically relevant analgesic screening procedure. Such advances in screening protocols may facilitate drug discovery efforts.

Research has shown that both CB1 and CB2 receptors are potential targets for novel analgesics. However, CB1 receptor activity is also associated with an abuse liability, making this receptor less than an ideal target for analgesic drug development. Using a variety of assessment procedures including a self-administration (SA) paradigm, Gutierrez et al. offers evidence that rats will self-medicate a CB2 receptor agonist to reduce allodynia in a nerve injury model of neuropathic pain and that this effect is mediated by CB2 receptor activation alone. Moreover, they demonstrate that CB2 receptor agonism does not support self-administration in sham-operated controls. This latter finding suggests that CB2 receptor agonists are unlikely to possess an abuse liability. The incorporation of self-administration procedures in pain protocols is an important step in developing novel therapeutics in pain models.

Concerns have long been raised over the clinical relevance of traditional analgesic screening assays that use high intensity phasic stimuli to elicit reflex responses. Among these assays include the hot-plate test with thermal stimuli, paw-pressure test with mechanical stimuli and abdominal constriction test with chemical stimuli. The introduction of animal model simulations of chronic pain syndromes represents a significant advance. Among these simulations include arthritic models using complete Freund's adjuvant, urate crystals or carrageenan, neuropathic models using various procedures of sciatic nerve ligation, and cancer models using tumor implantation. While evidence exists that increased nociceptive activity and central sensitization is long lasting, current analgesic screening assays continue to rely on evoked responses to noxious (i.e., hyperalgesia) and non-noxious (i.e., allodynia) stimuli. Perhaps certain challenges in translational pain research might be addressed by new screening protocols that better parallel the clinical syndrome [4]. Below, I mention two such protocols that seem to avoid the concerns raised by existing analgesic screening assays. Both paradigms move beyond simple reflex responses and entail well-organized (supra-spinal) behavioral responses to quantify analgesic drug effects.

The conditioned place preference (CPP) paradigm is commonly used to study the affective and motivational properties of drugs. This paradigm involves pairing a drug state with environments that have distinctive stimuli. Animals prefer environments previously paired with positively reinforcing drugs and, as such, the paradigm is traditionally used to study the abuse liability of drugs. It is also the case that animals prefer environments paired with negatively reinforcing stimuli. Negative reinforcement is a conditioning paradigm whereby behavior is increased if its consequence removes, diminishes or postpones an aversive stimulus. For example, we have shown that animals in chronic pain (arthritic and cancer models) display CPP to morphine and other drugs possessing antinociceptive activity [6–8]. The theory behind this finding is that analgesic drugs, by definition, are negatively reinforcing through their ability to lower the aversive state in chronic pain simulations. More recent work shows CPP's findings generalize to neuropathic pain simulations [3].

Operant response paradigms are the mainstay in behavioral pharmacology and are based on traditional learning principles. Animals are trained to operate a lever to receive positively reinforcing stimuli such as food, water or drugs. Like CPP, SA paradigms can be used to evaluate a drug's abuse liability. Also like CPP, animals experiencing persistent pain should self medicate analgesic drugs because of their negatively reinforcing properties (i.e., ability to reduce the aversive state). The incorporation of an SA paradigm in pain research is not without significant challenges. However, the excellent study by Gutierrez et al. [2] details the SA protocols necessary to control for a number of potentially confounding variables that do or may occur in a chronic pain model. While the use of SA as an analgesic screening assay will require much validation, the protocol is a significant advance in that it mirrors well clinical populations permitted to self-medicate opioids to control pain levels following heart surgery [1].

Conflict of interest statement

I have no conflicts of interest to report.

References

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