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Human models of pain for the prediction of clinical analgesia

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ABSTRACT

Human experimental pain models are widely used to study drug effects under controlled conditions. However, efforts to improve both animal and human experimental model selection, on the basis of increased understanding of the underlying pathophysiological pain mechanisms, have been disappointing, with poor translation of results to clinical analgesia. We have developed an alternative approach to the selection of suitable pain models that can correctly predict drug efficacy in particular clinical settings. This is based on the analysis of successful or unsuccessful empirical prediction of clinical analgesia using experimental pain models. We analyzed statistically the distribution of published mutual agreements or disagreements between drug efficacy in experimental and clinical pain settings. Significance limits were derived by random permutations of agreements. We found that a limited subset of pain models predicts a large number of clinically relevant pain settings, including efficacy against neuropathic pain for which novel analgesics are particularly needed. Thus, based on empirical evidence of agreement between drugs for their efficacy in experimental and clinical pain settings, it is possible to identify pain models that reliably predict clinical analgesic drug efficacy in cost-effective experimental settings.

1. Introduction

Experimental human pain models (Box 1) have improved our understanding of the physiology and pathophysiology of clinical nociception, inflammation, and analgesia [6,17]. They represent sophisticated tools to assess the efficacy of analgesic dugs in humans. They also have the potential to limit the costs of analgesic drug development by predicting clinical success with fewer resources than are needed for large clinical trials. However, correct prediction of clinical analgesia in experimental studies crucially depends on the correct choice of the pain model for the relevant clinical pain target [38].

In biomedical pain research environments, the classical approach to model selection is based on the knowledge of pathophysiological mechanisms involved in both experimental and clinical pain settings. For example, the analgesic efficacy of the TRPV1 antagonist, AZD-1386, has been shown to be related to excitation of TRPV1 by painful heat [9,27]. Based on this mechanism, AZD-1386 should also be effective in osteoarthritic and postoperative pain, both shown to involve TRPV1 [3,53]. However, AZD-1386 failed in these clinical settings [42,51]. This failure could have been predicted by the negative data obtained with the experimental blunt pressure test [27]. But the mechanism-based selection approach provided no basis for disregarding heat in favor of pressure as a predictor of the analgesic efficacy of the TRPV1 antagonist.

Such failures indicate that mechanism-based model selection, although completely reasonable and in accordance with biomedical scientific principles, has its limitations. This has resulted in frequent disappointment and doubts about experimental pain models [36] and to a decrease in their use (Fig. 1). A reason for these failures is incomplete understanding of the mechanisms on which basis the model is chosen. This hampers mechanism-based model selection. Although more research on the underlying mechanisms will undoubtedly reduce this handicap, immediate enhancement of the predictive nature of pain models is needed to exploit their potential in drug development. Hence, we have developed an alternative means for choosing the relevant model, based on empirical evidence of agreement between analgesic drugs for their effects in experimental and clinical settings. Statistical methods were applied to identify the most predictive experimental pain models or combinations of models. We finally show that this approach

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Box 1 Structure and function of experimental human pain models.

Experimental pain models share 3 separate main components: the subject, the assay, and the measure.

Subject	Assay (pain stimulus)	Measure (readout)
• **Sex** • **Age** • **Health status** • **Genetics** • **Epigenetics** • **Social factors** • **Testing conditions** • **Body part** ○ Cutaneous ○ Muscular ○ Orofacial ○ Visceral	• **Etiology** ○ Nociceptive ▪ Electrical ▪ Thermal (heat, cold) ▪ Mechanical (blunt, punctate pressure) ▪ Chemical (intranasal CO_2, nociceptive substances, capsaicin, menthol, hypertonic saline) ○ Inflammatory ▪ Freeze lesion ▪ Intranasal dry air ○ Reflex • **Time point** ○ Single/Repetitive ○ Short/long lasting	• **Psychophysics** ○ Visual analog scales ○ Numerical rating scales ○ Questionnaires ○ Pain threshold ○ Pain tolerance • **Non-verbal** ○ Behavior (mimics, vocalization) ○ Autonomic parameters (heart rate, skin temperature, electrical skin resistance) ○ Microneurography ○ Reflex ○ PET ○ fMRI ○ Cortical event-related potentials ○ Peripheral nociceptive responses (NMP)

In human experimental pain models, subjects can be selected for age, sex, body measures, ethnicity, genetic and epigenetic background, health, or disease. The assay by which pain is assessed involves the pain stimulus, which can be electrical, thermal, mechanical, and chemical. This can be applied to different body parts to evoke superficial, muscle, or visceral pain. Common criteria apply to the use of the stimuli [4]. These include administration to body parts exhibiting minimal interindividual variation in terms of neuronal histological characteristics; ability to provoke minimal or no tissue damage; correlation between stimulus strength and perceived pain; and differential discrimination between strong stimuli with high resolution. In addition, the responses to stimuli should be largely time-invariant to allow for repeated measurements. The stimuli should evoke responses that can be measured by a variety of readouts. The measure of pain involves surrogate markers, as pain cannot be measured directly, being a subjective phenomenon defined as "unpleasant sensory and emotional experience associated with actual or potential tissue damage" (International Association for the Study of Pain; http://www.iasp-pain.org). The measures by which pain is quantitatively determined [17] range from psychophysical responses, obtained by questionnaires during most experimental pain studies or by measuring the length of visual rating scales or the number of items describing pain [34], to cortical evoked potentials [10], magneto-encephalographic, positron emission, and functional magnetic resonance tomographic assessments of the brain representation of pain [41].

Experimental human pain models, like all models, provide a limited reflection of reality [50]. This reality is clinical pain, which is the most frequent reason for visits to a doctor and chronically affects one-fifth of adults in Europe, North America, and Australia (http://www.iasp-pain.org). Why, then, should analgesic efficacy be studied with models and not directly? In contrast to spontaneous clinical pain, experimental pain is controllable with regard to its spatial (localization), temporal (duration), quantitative (intensity), and qualitative (eg, "pricking" or "pressing" [5]) properties. Major confounders, such as analgesic therapy, can be avoided, and placebo-controlled cross-over designs can be applied to healthy subjects. Withholding analgesic therapy would be unethical in pain patients. However, models capture not all attributes of the original pain but only those considered as relevant [50], and these obviously vary in their ability to reflect clinical pain. This is the background to the present comparative analysis that made use of a further characteristic of models, which can itself be subject to modeling [50]: namely, the agreement between analgesic efficacy under experimental and clinical conditions.

would have predicted the recent clinical failure of TRPV1 antagonists. Prediction of clinical drug efficacy at an early stage of development is, therefore, already possible.

2. Methods

2.1. Data acquisition and compilation

A review in July 2012 of the available literature on analgesic efficacy in either clinical or experimental settings [38], which was updated on May 30, 2013, provided a data set of n = 22,644 items that was sufficiently detailed to allow generation of a set of predictive experimental pain models applicable to future drug development for various clinical pain settings. Evidence for analgesic drug efficacy in clinical settings was obtained by a Cochrane library search for "pain" and "analgesia," which yielded 126 hits. This led to the identification of 37 clinical pain settings for which the analgesic efficacy of 18 different drug classes had been tested (for details, see Table 1 in the supplementary materials). Analgesic drug efficacy in clinical settings was assessed based on primary outcomes such as changes in pain intensity by at least 50%, ratings of pain intensity on visual analog or categorical scales, or third-party pain scoring. Secondary outcomes were opioid dosing requirements for breakthrough analgesia, the time elapsed until