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Identifying biological markers of activity in human nociceptive pathways to facilitate analgesic drug development

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1. Introduction

Nearly 20% of the adult population in Europe suffers from moderate to severe chronic pain and only half receive beneficial treatment [8]. In US, 37% of younger adults and 57% of older adults suffer with pain lasting at least a year [9]. Despite the significance of this problem and advances in our understanding of pain mechanisms, the pace at which new treatments become available to chronic pain patients has been very slow. In recent decades, successful novel analgesics have been mostly found through serendipity or refinement of existing approaches (e.g., gabapentin, cyclooxygenase-2 and monoamine reuptake inhibitors). Analysis of drug development failures indicates that they occur primarily in clinical phases, and are mostly due to a lack of translation of efficacy in animal models to patients [7,22]. Although a comprehensive analysis of problems in analgesic development is beyond the scope of this review, we hypothesise that the preclinical to clinical transition can be facilitated by a rational use, in early drug development stages, of biological markers of activity in human nociceptive pathways. We also propose that such markers could have translational value if adapted for animal studies to provide efficacy measures more clinically relevant than withdrawal reflexes, see [29].

2. Prediction of pharmacological activity and efficacy in humans

There are valid concerns about animal models of pain and how measurements of nocifensive behaviour in animals relate to human pain [29]. However, there are not many published examples of animal models being undoubtedly wrong in predicting clinical efficacy. The

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NK1 antagonist mechanism was tested in the clinic with several potent, selective compounds able to achieve near-maximum receptor occupancy in the CNS [6] and active in other indications, yet efficacy in preclinical pain models did not translate into humans [7]. This target has therefore been fully tested and invalidated for a range of human pain states; with many other targets one cannot be so certain. Analyses of pharmacokinetic/pharmacodynamic (PK/PD) relationships for established analgesics indicate that there can be large differences between efficacious systemic drug exposure levels in rats and humans [31]. While the limits of drug exposure in humans are based on toxicology, safety and tolerability in Phase I, evidence for target-related pharmacological activity in humans may not be obtained before clinical efficacy trials (proof-of-concept, PoC). This carries a high risk of failure to reach pharmacologically active concentrations in the relevant tissues in humans, and it is likely that a lack of target engagement is a frequent reason for a lack of clinical efficacy. This is one area where quantitative sensory assessments and biomarkers, e.g. in experimental PD models, could provide important information in early clinical stages to guide larger scale clinical trials.

3. Pain heterogeneity and alignment of mechanisms in pain models and patients

Mechanisms of pro-nociceptive sensitisation evoked in animal models of chronic pain may be different from those in humans. Even the more 'realistic' animal models of pain that attempt to mimic the aetiology of human clinical conditions are unlikely to fully reflect the complexity of pain pathophysiology in patients. Healthy volunteer models can be used in Phase I and serve to cross the species barrier as well as provide evidence of PD actions; negative findings however may be inconclusive as these models may only reflect specific aspects of mechanisms occurring in chronic pain patients, e.g. central sensitisation, inflammatory hyperalgesia, disinhibition [18,20]. On the other hand, in patients, even within a single aetiologically defined group, the basic mechanisms underlying clinical symptoms (such as central sensitisation, ectopic discharge, disinhibition, sensory loss/deafferentation, glial activation and peripheral sensitisation), may vary considerably. This leads to a mechanistic disconnect between preclinical, human experimental and clinical studies of new analgesics. To overcome this problem, attempts have been made to come up with a mechanism-based classification of pain [32], but it is still far from clinical implementation. If robust tools were available to quantitatively assess mechanisms in animals and humans, efficacy trials could be conducted in mechanistically-defined patient groups, guided by information obtained in preclinical and human volunteer models. Measurements of activity in nociceptive pathways may provide such tools.

4. The role of sensory marker assessments in humans: how could they help solve the drug development problems?

4.1. Pharmacodynamic markers and pain models: Focus on translation

Human PD markers and models may be able to provide quantitative information about target engagement in the relevant pathways, and confirm in humans the pharmacology predicted from preclinical data. One can consider several examples where such translational efforts

could be particularly useful. Transient receptor potential (TRP) receptors have attracted a lot of interest, and several selective ligands are being developed for pain indications [16]. Their well-defined temperature sensitivity makes it possible to use responses to controlled thermal stimuli as PD markers. Indeed, the first report on the activity of a TRPV1 antagonist in humans described sensory effects (increased heat pain threshold and tolerance in normal and inflamed skin) consistent with the preclinical pharmacological profile [10]. This indicates a level of TRPV1 blockade in humans, although it remains to be established whether it is sufficient for clinical efficacy. If translational markers could be used, a more direct comparison of PK/PD relationships in animals and humans would be possible, allowing prediction of the efficacious exposure levels in humans. What could serve as such translational markers? Cortical activity plays a key role in the experience of pain, and neurophysiological techniques such as EEG and MEG can directly assess pain-related responses [3]. Synchronised brain activity (evoked potentials, EPs) evoked by noxious stimuli, including controlled heat (e.g. laser- or contact heat), reflects processing of nociceptive information [3]. Studies in humans and animals have shown that the amplitudes of EPs elicited by noxious stimuli are correlated to the intensity of pain perception, pain-related behaviours and/or other nociceptive markers, and modulated by analgesics [21,27]. In addition, functional brain imaging measures (PET, fMRI) can provide signals of thermosensitively driven brain activity with considerable spatial resolution. Many human volunteer studies documented the ability to measure intensity-dependent responses from several cortical regions likely to be important for pain perception [3]. Apart from temperature sensitive TRP receptors, other examples for which heat-evoked responses could serve as translational PD markers include targets modulating the cannabinoid, opioid and several other systems. For targets along inflammatory cascades, several models exist, but only UV-evoked inflammatory hyperalgesia has been established in both humans and rats, and shown to involve similar inflammatory mediators found in clinical inflammatory pain states, including IL-1 β , IL-6, TNF α , etc. [2,25]. If controlled heat [15] or mechanical stimuli [17] were used to record evoked cortical activity under conditions of inflammatory sensitisation, the range of potential analgesic mechanisms that would be expected to modulate such responses will be even wider. Other objective markers of nociceptive activity should also be considered. Thus, laser-doppler assessments of nociceptive axon-reflex flare have shown utility for detecting activity of TRPV1 and CGRP antagonists, and sodium channel blockers in humans [10,12,30], allowing prediction of clinically efficacious doses. In some circumstances, positron-emission tomography (PET) studies may be useful for quantifying the level of receptor occupancy in the brain required to achieve a pharmacological effect. However, development of a PET ligand can be long and expensive, and the cost/benefit may be unclear, particularly for novel targets.

Thus, translational PD markers can provide tools for ensuring continuity of drug development by demonstrating target engagement in animals and humans. Such markers will be target-specific and their selection should be guided by the preclinical pharmacological profile of the target. One basic principle is that pain-related PD markers are more likely to be relevant for predicting clinically efficacious doses than non-nociceptive ones, e.g. ex-vivo blood assays, because they can provide a measure of target engagement in the relevant pathway or tissue.

4.2. Mechanistic markers

In clinical settings, simple, unidimensional pain intensity scales are most often used for pain assessments (i.e., category or visual analogue scales). These measures are clearly important indicators of clinical efficacy accepted by the regulators; however, they do not provide insight into underlying mechanisms and cannot be used in animals. Objective markers of activity in nociceptive pathways could become useful complementary tools; these may include PET, fMRI, neurophysiological (EEG, MEG) and similar techniques, as discussed below. Additionally, more sophisticated use of psychophysical measures can also identify pathophysiological mechanisms underlying chronic pain [5]. Related to this objective, some of these tests have been included in guidelines on assessment of neuropathic pain [11].

4.2.1. Explorations of mechanisms of chronic pain—It will be important to identify critical neurobiological determinants of chronic pain in humans and confirm their clinical significance and underlying mechanisms in animal studies. Imaging techniques such as PET, fMRI, MR spectroscopy and others seem to be particularly informative; examples include exploration of the role of glial mechanisms in human pain states, unravelling the circuitry underlying endogenous pain inhibition and mechanisms of placebo response, characterisation of dynamic changes in specific neurotransmitter/modulator systems in pain states (reviewed in Refs. [23,28]), etc.

4.2.2. Stratification of patient groups on a mechanistic basis—To be useful in clinical trials, mechanistic markers of pathophysiological processes such as central or peripheral sensitization, sensory denervation or disinhibition must be relatively simple bedside tests that could be applied reliably in many different clinical settings. Neurological observations of allodynia, hyperalgesia and other pain descriptors could provide insight into the underlying pathophysiology; however, it is first necessary to establish firm links between such observations and specific mechanisms. If validity is established, these links would facilitate a mechanistic continuity of drug discovery and development from animal studies to clinical trials that is most appropriate for a particular target. Psychophysical measures (quantitative sensory testing) and physiological markers may provide complementary mechanistic information. They may also have a translational value, as some tests may be used both in humans and animals. For example, nociceptive EPs have utility as markers of function in nociceptive pathways of pain patients. Heat EPs have been shown to be reduced in patients with peripheral neuropathy; the reduction in the response amplitude correlated with the loss of small fibre counts in the skin, indicating a loss of function of nociceptive fibres [4]. Potentials evoked by noxious stimulation of the skin or viscera are augmented in patients with chronic pain syndromes such as fibromyalgia and irritable bowel syndrome [13,24]. Habituation of evoked responses may also serve to assess hyperexcitability due to impairment of endogenous inhibitory mechanisms [1]. Additionally, functional brain imaging can localize brain activity changes associated with chronic pain conditions, such as central pain [19] and fibromyalgia [14], allowing for more precise anatomic specificity of neuropathological processes. For more complex central mechanisms, more sophisticated imaging techniques may be required, e.g. those able to detect pain-related glial activation (PET or MR spectroscopy, [28]). This may not be currently practical to be performed on a large scale, but may change as these methods become more established.

4.3. Quantification of pain response for efficacy assessment

One can argue that subjective pain scales are definitive measures of pain perception. However, their context-dependence contributes to large between and within-subject variability. This means that for clinical trials to be robust they have to be large – and expensive, which limits the number of attempts any pharmaceutical company will support. However, markers of activity in nociceptive pathways may detect clear signals of treatment efficacy in small numbers of patients even if standard clinical efficacy measures are not sufficiently sensitive. Obtaining this information prior to PoCs may increase the confidence required for moving forward with expensive studies. It has been suggested that some imaging and electrophysiology tools may be able to provide such information [26,28], however, the cost/benefit balance of such approaches needs to be demonstrated. Where the value is less questionable is in translational research. Thus, ‘back-translation’ of objective markers of human nociceptive activity into animals could provide valuable preclinical tools.

5. Conclusions and perspectives

There is an urgent need to change the way new analgesics are discovered and developed, as the failure rate is currently high and may not be sustainable [22]. Physiological biomarkers of pain may be able to serve as a bridge between preclinical and clinical studies. Although pain is subjective and cannot be measured by physiological responses, objective quantitative measures of activity in nociceptive pathways may be used at early stages of clinical development to detect PD activity in humans and help stratify patients on a presumed mechanistic basis. Such markers may serve as early indicators of treatment efficacy when clinical scales are not sufficiently sensitive. The additional value of such markers is that they could potentially be back-translated into animals, to provide efficacy measures more relevant for the clinic than withdrawal reflexes.

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