1. Introduction

A large body of knowledge has been generated on human pain modulation when pain-free and when experiencing pain on the basis of, among other tools, psychophysical dynamic stimulation protocols, which utilize a spatial and/or temporal array of stimuli in order to evoke an experimental process of pain modulation. Protocols designed to evoke inhibition or facilitation of pain are believed to better depict the clinical pain experience than the classical static parameters, such as pain thresholds. A commonly used protocol for pain inhibition is based on the diffuse noxious inhibitory control (DNIC) effect, typically using 2 remote painful stimuli, whose interaction generates, in most cases, pain inhibition [12] (for review, see Pud et al. [21]). The term conditioned pain modulation (CPM) was coined for the psychophysical protocols that explore DNIC in humans [28]. The protocols for pain facilitation use temporal summation (TS), where pain reports are obtained along a series of identical stimuli [19]. The common response is an increase in pain ratings along the series representing the physiological phenomenon of windup. Evaluation of response to these arrays of experimental pain can be a useful clinical tool; it can predict future pain [27] and predict the efficacy of analgesics [29]. Although the current data do not allow practical implementation, the following hypothesis may carry the translation of pain modulation into practice.

2. Hypothesis

Lab-based pain modulation, for which the term pain modulation profile (PMP) is suggested, ranges between inhibitory and facilitatory ends. We propose that on the basis of CPM and/or TS responses, which indicates the inhibitory/facilitatory balance, individuals can be positioned on a clinical spectrum between pronociception and antinociception. Thus, an individual expressing low-efficiency CPM and/or enhanced TS positioned on the pronociceptive side of the spectrum would express a higher pain phenotype, resulting, for example, in higher risk of pain acquisition. In turn, an individual expressing efficient CPM and/or nonenhanced TS located on the antinociceptive side would express a lower clinical pain phenotype (Fig. 1).

3. Evidence

Convincing evidence associates pain-lab-based altered pain modulation and clinical pain morbidity, mostly describing a pronociceptive pain modulation in pain patients compared to controls. For CPM, less efficient inhibitory pain modulation was reported for several pain syndromes, including fibromyalgia [7,10], irritable bowel syndrome [2], migraine [22], tension headache [18], temporomandibular disorder [14], osteoarthritis and muscle pain [8], and whiplash [3] (see also review in [13]). For TS, enhanced pain facilitation has been documented in fibromyalgia [20], osteoarthritis [1], migraine [25], and temporomandibular disorder [23]. Several articles have also reported co-occurrence of both enhanced TS and less efficient CPM in pain patients, such as osteoarthritis [1], cluster headache [17], and chronic postmastectomy pain [4]. Thus, a pronociceptive profile seems to be associated with pain morbidity. It is noted that in most of the above articles, assessment of pain modulation was performed in unaffected body areas, thus representing the generalized pain modulation rather than the modulation of data transmitted from a specific painful region. Notably, pronociceptive profile was reported in widespread pain disorders such as fibromyalgia.

The above-mentioned cross-sectional studies do not reveal whether the interrelations between the modulation profile and the presence of the various pain syndromes are causative, and if so, which is primary to the other. It could be, on the one hand, that a preexisting facilitatory modulation state leads to the establishment of the pronociceptive profile and the acquisition of the idiopathic pain syndromes; on the other hand, it could be that...
the presence of the pain syndrome consumed the antinociceptive capacity and led to a pronociceptive profile. We explored these relationships in a prospective study, where prethoracotomy pain-free patients were examined for their pain modulation and were followed up for acquisition of chronic pain after surgery [27]. CPM efficiency was found to predict chronic postthoracotomy pain; patients with less efficient CPM had a higher risk of developing chronic pain, and vice versa. This reasonably establishes causative relations suggesting pronociceptive PMP as a pathogenetic factor for future clinical pain. Similar results were later found by Landau et al. [9] and Wilder-Smith et al. [26] for cesarean section and abdominal surgery, respectively.

A second key question pertains to the intraindividual plasticity of the PMP. Two studies on osteoarthritis patients indicated that PMP is plastic; Kossek and Ordberg [8] found that less efficient CPM obtained in patients with painful hip osteoarthritis improved after total hip replacement surgery in parallel with pain alleviation. Similar results have been reported by Graven-Nielsen et al. [6] for knee osteoarthritis. Yarnitsky et al. [29] and Niesters et al. [16] showed that pharmacological alleviation of polyneuropathy pain improved CPM in proportion to the extent of pain alleviation. In line with this, parallel reduction of pain and TS response was reported for patients with complex regional pain syndrome after sympathetic blockade [15]. Thus, PMP seems to change in conjunction with changes in clinical pain.

A third and pertinent issue, one that provides the main motivation for the use of PMP, is its relevance for pain treatment. By being involved in pain pathogenesis, it is likely that PMP also plays a role in its alleviation. Targeting a dysfunctional mechanism of pain modulation by a drug capable of rectifying that dysfunction will achieve the best pain alleviation. This way, patients with less efficient CPM should benefit more from serotonin norepinephrine reuptake inhibitors that augment descending inhibition by spinal monoamine reuptake inhibition than patients whose CPM is already efficient. Similarly, those with enhanced TS should benefit more from gabapentinoids or NMDA blockers such as ketamine, which inhibit neuronal sensitization, than those with nonenhanced TS did not benefit from the drug. It thus seems that identifying the dysfunctional modulation state can be the key to the choice of drug for pain alleviation. This is a step forward toward individualized pain medicine.

4. Discussion

On the basis of the described evidence, and in conjunction with our hypothesis, we suggest the following scenario for the clinical relevance of pain modulation. (i) A pain-free individual expresses a certain PMP, be it eu-, pro-, or antinociceptive. Higher expressions of clinical pain and higher chances of acquiring pain characterize pronociceptive individuals, and vice versa. (ii) When experiencing a substantial nociceptive event, modulation is shifted, and an altered pain modulation of pronociception develops. (iii) Use of pain-modulating drugs, as is routinely done for neuropathic pain and often for other sorts of pain, may rectify the dysfunctional parameter or parameters of PMP; thus, an individual-based coupling of drug and modulation dysfunction can be established. (iv) Preventive treatment (e.g., migraine prevention or preoperative preemptive analgesia) shifts the profile toward antinociceptivity and lowers the pain phenotype (Fig. 2).

A few practical points need to be further clarified to ease clinical application of PMP: clinical experimental data should be strengthened; better test-to-test reliability of these psychophysical protocols should be obtained by improving them; and further studies should use various test modalities (i.e., thermal, electrical, mechanical) and types of stimuli (i.e., phasic, tonic, repetitive) because results seem to depend on these factors. Further, the scientific basis of the relevant pain modulation paradigms, mainly CPM, could be widened, clarifying the relations with other top-down pain-regulating mechanisms, including cognitive and emotional factors such as stress and anxiety. In addition, the interrelations between the facilitatory and inhibitory factors and the relative weight of each in construction of the PMP need further clarification.

Pain modulation is, of course, not a single player on the stage of clinical pain, which is affected by the causative diseases in addition to many genetic and environmentally influenced psychological and cognitive factors. The alleviation of pain and rectifying of the pronociceptive profile is also influenced by pharmacogenetic factors and drug interactions. For example, the association between CPM and pain was found to be mediated by pain catastrophizing [5].
Further, TS was positively associated with anxiety [24]. Therefore, an assessment of pain-related personality parameters may reveal their role in determining pain modulation.

A major limitation of the currently proposed easy-to-use single-axis psychophysical-based scale of pain modulation is that it might be too simple. Future experience will tell us whether it should be supplemented by additional factors to potentially achieve more precise correlates of clinical pain. Another limitation relates to the prediction of drug efficacy: an attempt was made to couple the principle mode of action of specific drugs to the patient’s dysfunctional mechanism, but the coupling might be unclear for drugs with multiple modes of action.

The concept of antinociceptive pain modulation deserves additional attention. Though reasonable, it is currently unknown whether efficacy of pain prevention, such as in migraine, depends on achievement of an antinociceptive modulation profile, and consequently whether testing for PMP should become a tool to assess efficacy of preventive treatment. Further, the notion should be entertained that achieving an antinociceptive PMP should be the target of pain therapy for patients with ongoing pain because it may indicate a more radical change in the pain perceiving system—and possibly one of longer durability—than the standard, more fragile target of pain reduction.

Conflict of interest

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References