Scandinavian Journal of Pain 2 (2011) 105–107

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

The pain modulatory cocktail

Siri Leknes*

University of Oslo, Forskningsveien 3A, Postboks 1094 Blindern, Oslo, Norway

Pain is the subject of a vast field of neuroscientific and medical research. A particular challenge in the study of pain is the subjective and changeable nature of this sensation. The International Association for the Study of Pain (IASP)'s definition of pain highlights its subjective quality:

> 'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.

Pain is reliably induced by stimuli which activate nociceptive receptors in the skin, muscle, and gut. Although sensory pains vary qualitatively (consider a sharp pin-prick pain vs. a dull muscle ache), these feelings are similar enough to be classified as pain both in subjective and physiological terms [14,40,44,42]. Chronic pain syndromes such as post-stroke and phantom pain are examples of painful conditions where the pain is not caused by stimulation of peripheral nociceptors. Nevertheless, the subjective hedonic feeling of these pain syndromes mimics sensory pains, and central pain syndromes are encompassed by the IASP definition of pain.

As reviewed by Knudsen et al. [47] in this issue, pain is highly changeable. Somatosensory, affective and cognitive factors have repeatedly been shown to alter both subjective and objective measures of pain. For instance, anxiety can greatly enhance pain and suffering [1,36,24], while expectation of treatment can dramatically reduce pain [41,7,46]. The cognitive context in which pain is perceived also affects the subjective interpretation of a nociceptive event [30,21]. Research on the modulation of pain has mainly concerned itself with pain caused by nociceptive stimulation. The 'pain modulatory cocktail,' i.e. the interaction of nociception and cognitive, affective and other factors, determines the *meaning* of a painful sensation.

1. Measuring pain

Within the neuroscientific and medical communities, numerous approaches exist that use objective measures of pain. Animal pain research largely relies on measures of avoidance behaviours such as tail flick latency. Some research also aims to quantify suffering behaviour, such as licking of the injured paw and reductions in eating [11,37,34]. Many human pain studies use subjective pain ratings to indicate the level of pain. The perhaps most common rating scales for pain are the 11-point pain intensity numerical rating scale (NRS), and visual analogue scales (VAS) anchored "no pain" and "intense pain." These subjective measures are in turn used to inform the interpretation of objective measures of pain-related neural activity, such as functional imaging measures or direct measures of electrical activity from peripheral neurons [28]. An alternative approach relies solely on objective measures of pain-related activity, for instance the quantification of reflexes [19].

With the advent of functional brain imaging, many hope that a technique which will provide a conclusive objective measurement of pain has been found, obviating the need to rely on subjective measures. A large number of brain regions are activated in most neuroimaging studies of pain. Some, notably the insula, thalamus, and dorsal anterior cingulate cortex (ACC), are reported with great consistency [38]. More than a decade ago, Rainville and colleagues [27] used hypnotic suggestion to show that activity in the ACC varies with the affective component of pain processing. This left the thalamus and the insula as the main candidate regions for an objective marker of nociceptive input. Direct electrical stimulation of insular cortex in epilepsy patients causes intense feelings of pain [22]. Interestingly, however, both the insula and the thalamus have recently been shown to activate during hypnotic suggestion of pain in the absence of nociceptive stimulation [26]. That no brain region has been identified unequivocally as *the* objective marker of nociceptive input after a more than decade of functional imaging research of pain highlights the complexity of the perceptual decision underpinning the pain experience.

2. The descending pain modulatory circuit

Animal research has greatly enhanced our knowledge about the mechanisms involved in modulation of pain. The well-described descending pain modulatory circuit in the brainstem consists of excitatory and inhibitory cells, and communicates with neurons in the prefrontal cortex, anterior cingulate cortex (ACC), hypothalamus, and amygdala to control the nociceptive afferent pathway in the spinal and trigeminal dorsal horn [16,39]. This decision circuit exerts bidirectional control over pain [15]. The circuit consists of ON- and OFF-cell populations in midbrain and medullary pain-modulatory nuclei, notably the periacqueductal grey (PAG) and the rostro-ventral medulla (RVM). Cells within this circuit have a

DOI of refers to article:10.1016/j.sjpain.2011.05.005.
* Tel.: +47 92622872.
E-mail address: siri.leknes@psykologi.uio.no

doi:10.1016/j.sjpain.2011.05.007

reciprocal activity pattern where OFF-cell silence *permits* a pain response and ON-cell activity facilitates it. Conversely, OFF-cell activity reduces responses to noxious stimuli [15].

It is likely that opiate drugs and endogenous opioids act on this descending system to produce pharmacological, placebo, stress-induced and pleasure-related analgesia [37,12,17,18,23,29,45,15,16,39]. Neuroimaging studies of various factors which modulate pain have implicated brainstem regions within this circuit during up- and down-regulation of pain [40,44,3,13,42,10,43].

3. Why is pain so changeable?

Unpleasant sensations such as pain, itch and nausea have probably evolved as homeostatic alarm signals, notifying us of imbalances in the mechanical, thermal or chemical status of the tissues of the body [33]. Pain encourages the constant optimization of our internal homeostatic balance. The notion of homeostasis was first introduced in relation to automatic regulatory processes such as thermoregulation [6]. Later findings have highlighted the relationship between homeostasis and subjective experience. Cabanac showed that the subjective experience of an event depends on how the event affects homeostasis [5]. For instance, when someone's core temperature is abnormally low, cool stimuli become unpleasant, whereas stimuli which would normally feel too hot (and activate nociceptors) become pleasant [4]. In other words, homeostatic utility or disutility determines the subjective value of a stimulus. This effect is well-documented for primary rewards such as food and drink, which are more pleasurable when relieving a hunger or thirst state [31,9,20]. Since a painful experience constitutes a deviation from homeostatic balance [8], the same principle can be applied to pain. When the perceived threat to the organism becomes greater, pain unpleasantness increases, enhancing defensive and avoidance mechanisms [25].

According to Fields' Motivation-Decision model of pain, the processes underlying the subjective interpretation of a nociceptive stimulus can be understood as the manifestation of an unconscious decision process [15,16]. The decision process requires information about the homeostatic state of the individual (inflammation, hunger, etc.), sensory input, and knowledge about impending threats and available rewards. The basic premise for the decision process is that anything potentially more important for survival than pain should assert antinociceptive effects. This allows the animal to ignore the pain and attend to the more important event. One answer to why pain should be so malleable therefore directly relates to survival. Essentially, pain caused by nociception should be down-regulated if this stimulus occurs in competition with an even which is more important for survival, such as a worse pain or other stressful events, a salient reward, or during goal-related movement. Conversely, pain can be upregulated due to increased attention in contexts where it is the most important event or there is a bias towards negative aspects of the pain experience for reasons such as anxiety, catastrophizing, or depression. Such a negative bias can be transient or due to personality traits [35,2].

Neuroimaging studies of pain modulation in humans have often, but not always implicated the descending pain modulatory circuit in the brainstem. In addition, as reviewed extensively by Knudsen and colleagues in this issue, a number of cortical and subcortical brain regions are thought to play a role in determining the subjective experience of pain. The studies reviewed demonstrate clearly that no region within the 'pain neuromatrix' is consistently unaltered by factors which modulate the experience of pain. Therefore, a putative primary nociceptive cortex in the human brain which reflects only nociceptive input irrespective of factors relating to homeostasis, has yet to be identified. In fact, primary sensory cortices such as visual area 1 (V1) are also modulated by attention and other factors [32]. Whether the changeability of pain is unique is thus uncertain. Importantly, however, the 'pain modulatory cocktail' reviewed by Knudsen and collegues forms the basis of the challenge as well as the promise of many treatments of chronic pain.

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