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Editorial comment

CNS-mechanisms contribute to chronification of pain

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In this issue of the *Scandinavian Journal of Pain*, Per Brodal, professor of neurobiology at the Institute of Basic Medical Sciences, University of Oslo, Norway, publishes a topical review of how our central nervous system (CNS) handles sensory impulses from the peripheral nervous system [1]. Per Brodal is highly qualified to write such a review: he is the author of the outstanding textbook *The Central Nervous System*, now in its 5th Edition [2].

1. What is pain?

The IASP definition of pain from 1994:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Amanda C. de C. Williams and Kenneth D. Craig recently proposed a new definition, mainly because they feel it is necessary to emphasize the psychosocial aspects of the experience of pain [3]:

"Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components."

Per Brodal emphasizes that…"pain is a sensation, an experience, and common with other sensations, e.g. itching, it has a bodily location". Pain felt in an arthritic knee joint exists only when the person experiences it. The MRI image of the knee joint can give the observer an impression of a badly pathological knee, but the person imaged can be pain-free.

The burden of suffering caused by a pain condition depends critically on how the person or patient perceives the situation that brought on the pain experience and the perceived disruption of their life due to the pain. This is why Amanda Williams and Kenneth Craig want to emphasize the cognitive and psychosocial aspects of the pain experience [3].

Nociceptors are sensors that can identify tissue injury, a noxious event, can send impulses via peripheral nerves, rapidly through A_{delta}, and more slowly via C-fibres, to the CNS, where appropriate reactions occur to motivate the body/person to react to maintain homeostasis. A pain experience can be initiated by processes that are still not an actual tissue injury, but homeostasis is disturbed and there is potential tissue damage. Per Brodal therefore proposes to use homeoceptors for such sensors that can initiate a CNS-process when homeostasis is being disturbed, a process that eventually leads to a pain experience [1].

2. A salience network in our brain monitors and reacts to homeostatic disturbances that can be potential tissue-injury

A *pain network in CNS* with interconnected nodes (*the anterior cingular gyrus, the insula, the second somatosensory area, and the thalamus*) is active when a person feels pain, see Fig. 1 in Per Brodal's article [1,4,5]. By "node" Brodal means a locus that potentially connects to a variety of other brain structures. But this network can be activated by non-painful stimuli. Depending on the importance for homeostasis, this salience network is there to enable the person to react appropriately and optimally to a stimulus from several possible different modalities. Because a pain stimulus, at least from an acute pain evoking tissue injury, normally is a highly salient alarm signal, this network may most often serve and react to impulses from sensors that detect early changes that can develop to a tissue injury [1].

3. A sensitive pain network insures that all harmful events are detected and reacted to appropriately.

Per Brodal emphasises the wise arrangement with a very sensitive sensor system that rapidly reacts to any potential tissue injury so that homeostasis is protected and well preserved. However, it is conceivable that such a sensitive, even hypersensitive, system can be overloaded by false alarms, malfunctions and causes pain experiences when no tissue damage has happened, or it keeps reacting to impulses that are not initiated by potential tissue damage [1]. This

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could explain how a patient can experience pain where the medical doctor or nurse cannot find any tissue damage, i.e. the patient will be diagnosed with having a pain condition without any obvious somatic cause, referred to as primary pain, or even "functional pain", almost implying malingering. This can also be the case when aggravating a minor pain condition can provoke severe pain.

4. Pain and pleasure – our two most powerful teachers of behaviour

From a young age, we rapidly learn to avoid painful and potentially pain-provoking situations. This is life-protecting knowledge. However, this can be overdone; the patient can develop "fear-avoidance", avoiding behaviours that they feel may be damaging. The patient may stop using an injured limb, something that makes sense immediately after an injury or after surgery [6], and even a few weeks after a fractured wrist or ankle. However, when this continues long after the injury has healed completely, then all the negative effects of a passive, inactive limb, will appear. Eventually the patient develops a neglect-like phenomenon; the inactive limb loses the normal sensorimotor signalling between CNS and muscles and joints in the limb. The patient will gradually feel that this painful and useless limb does not belong to the patient; the patient neglects the limb: "That foot does not belong to me anymore". This is similar to what hemiplegic post-stroke patients experience.

This behaviour is typical of an injury where appropriate teaching about reactivation is neglected and, in extreme cases, gradually leading to disuse atrophy of muscles, contractures of joints, painful allodynia to touch and to cold. This produces a painful, useless limb with the symptoms and signs of Complex Regional Pain Syndrome (CRPS) [7]. In a young patient, this is a sad and tragic sight, and fate. This is a difficult-to-treat pain condition.

Effective prevention and treatment are so simple: Inform, motivate, instruct to activate the patient – early on it is not so difficult but delays make it more difficult. Fortunately, this situation is very rare but once it develops, most frequently in young people, treatment becomes complicated. This is an example of what Brodal calls "network locking" [1].

5. Pain-prone personality? Or personality coloured by pain?

Why is there such a very wide difference in pain sensitivity and pain tolerance between persons of the same ethnicity and living in apparently similar conditions? Christopher S. Nielsen documented in his twin-studies how genes determine about 50% of sensitivity to pain [8]. This means that there is a lot the health care providers can do to motivate patients who appear to be on the slippery road to chronic pain [8].

It is therefore not difficult to imagine that our complex pain modulating, pain experience regulating mechanisms can vary tremendously between persons, leaving some of us at higher risk of CNS network malfunctioning, or at least having such highly sensitive sensors and salience networks that the normal pain hypersensitive state after surgery or injury [6] does not return to the pre-operative/preinjury state but keeps on accepting and reacting to peripheral innocuous stimuli (= false alarms) as if they are real tissue-injury-signals. This creates a persistent pain experience, Brodal's "network locking" [1].

And an ongoing, never ending, persistent pain experience is highly stressful, causing all the well-known somatic, mental, psychosocial and economic miseries of a chronic pain state.

6. The role of peripheral input in maintenance of chronic pain

The debate on the importance of peripheral input is far from settled. Recently Harutinian and colleagues in Aarhus, Denmark, documented how a peripheral nerve block can relieve chronic neuropathic pain [9]. It is a pity they did not cite one of the important research reports published in PAIN 27 years ago [10]. The famous "Karolinska Pain Troika", Staffan Arnér, Bjørn Meyerson, Ulf Lindblom published an observational study in 1990 documenting that peripheral blocks with a local anaesthetic could relieve chronic pain [10]. Not only that, but after repeated blocks, the relief could last for a considerable, and for the patient with chronic pain, clinically meaningful time. Pat Wall's editorial comment to their paper was supportive and he recommended strongly "more research on peripheral nerve blocks for chronic pain" [11].

7. Is there hope for prevention of persistent pain?

Some time ago we thought that we could predict who is at higher risk of developing persistent postsurgical pain (PPP) by looking for certain risk factors [12]. By taking extra care of patients with risk factors when they have to undergo an elective operation, such as treating their pain optimally during and after surgery as well as continuing to give such patients continued pain relief after discharge from the hospital, and by bringing them to the chronic pain clinic early on, rather than waiting till they have developed a difficult to treat PPP [12–15]. The results have not been too encouraging to date and we need to learn much more about the phenomenon of "network locking" [1]. No doubt, there is more we all can do here and, hopefully further research will show the way.

8. Conclusions

The eminently experienced brain neurobiologist, Professor Per Brodal, in this topical review of pain modulating systems in our CNS, has increased our knowledge and understanding of these fantastically complex [1] neurobiological systems that regulate our pain experiences. He points out that nociception and pain optimally function as the most important salience stimulus in the homeostatic systems in the CNS. However, the system can "go awry" and understanding that phenomenon is difficult [1]. We are beginning to understand why some persons are more prone to develope persistent pain than others are. In due time we should be able to take advantage of this deeper knowledge and take better care of those who are at higher risk of developing persistent pain, rather than trying to relieve it once persistent pain has fastened its claws in our sensitive CNS.

Conflicts of interest

None declared.

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