Neuroplasticity – an important factor in acute and chronic pain

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The nociceptive system is not just a system for the conduction of pain impulses from the periphery to the brain. We now know that plastic changes can take place in the periphery, the spinal cord and also in higher brain centres following injury or inflammation. These changes may increase the magnitude of the perceived pain and may contribute to the development of chronic pain syndromes. Although our knowledge is growing, we are now almost more confused as to how we should intervene in order to attenuate or inhibit neuroplasticity. The present review examines the current knowledge on mechanism, clinical significance and prevention of neuroplastic changes.

Key words: neuroplasticity; chronic pain

Introduction

Traditionally the nociceptive system was considered a "hard-wired" system. Stimulation of a peripheral pain receptor started an impulse that travelled via the spinal cord to the brain. Here a sensation of pain would be perceived, and appropriate action started. In 1965 Melzack and Wall [1], with their famous "Gate Control Theory", indicated that the nociceptive system is not a "hard-wired" system but can undergo modulation. Their theory stated that afferent nociceptive input could be modulated at the dorsal horn level by afferent input in larger non-nociceptive fibres. This served as a regulatory or "gating" mechanism for the afferent input to the cerebrum where pain was perceived.

We now know that not only modulation but also plastic changes may take place at the level of peripheral receptors, at the spinal cord, or at higher cerebral centres [2]. Due to different receptor populations with different response mechanisms and response times, the induced changes can be of short duration, last days, months, or may potentially be irreversible [3].

Mechanism of pain modulation

Peripheral modulation

Tissue injury caused by trauma or surgery will lead to an inflammatory response with the liberation of several substances at the site of injury. These include potassium ions, substance P, bradykinin, prostaglandins, etc. (often termed the "inflammatory or sensitising soup") [4]. The inflammatory response can induce a sensitisation of peripheral receptors with changes in the response characteristics of primary afferent fibres. Prior activation of the nociceptor may also contribute to a decrease in the response threshold [2]. Both result in an increased input to the spinal cord [5].

Spinal modulation

Normal afferent input will lead to a fast postsynaptic potential that usually signals the onset, intensity and location of a noxious stimulus. An increased afferent input will lead to a modulation which is a reversible change in the excitability of peripheral and central sensory neurones. The modulation is enhanced by the peripheral inflammatory response, and an activation of further receptor systems in the dorsal horn (mainly via the N-methyl D-aspartate (NMDA) receptor) results. This induces a hyperexcitability of dorsal horn neurones [6]. The peripheral sensitisation and the central hyperexcitability decrease the threshold for Aδ- and C-fibre pain, both within the injured area

(primary hyperalgesia) but also in the surrounding uninjured tissue (secondary hyperalgesia). Activation of normally non-painful Aβ-fibres by thermal or mechanical stimuli may then be perceived as painful (allodynia) (for review see Woolf and Salter [2] and Coderre et al. [7]). The peripheral sensitisation and the central hyperexcitability also lead to an expansion of the receptive fields (the cutaneous area which is innervated by a single spinal neurone) of individual dorsal horn neurones. Inflammation may induce a gene expression with increased synthesis of peripheral receptors. This contributes to the increased sensitivity of the peripheral nociceptor [8]. Longer lasting modulation may lead to a potentially irreversible modification. A-fibres may start synthesising receptors that are normally only found in C-fibres, thus simulating a phenotype shift with the A-fibre adopting C-fibre characteristics [9]. Recently the glia cells, which were earlier regarded as purely supportive, have become implicated in exaggerated pain states [10]. They may be activated by infection or by excitatory neurotransmitters, and then contribute to the maintenance of the sensitisation and hyperexcitability.

Supraspinal modulation

Research into nociceptive system plasticity has mainly concentrated on the peripheral receptor and the spinal cord. Descending facilitatory and inhibitory pathways may influence spinal cord hyperexcitability caused by tissue injury due to trauma, inflammation or surgery (for review see Dubner and Ren [11]). Already in 1967 Wall [12] demonstrated that stimulation of brainstem structures could inhibit spinal cord nociceptive neurones. The periaqueductal grey and endogenous opioid peptides play a central role in this inhibition of spinal cord neuronal responses [13, 14]. Noxious stimulation may evoke the release of encephalin at supraspinal and spinal levels [15, 16]. Further inhibitory modulation is exerted by serotonergic [17] and noradrenergic systems [18, 19]. In patients with phantom limb pain a reorganisation of the cortical body map has been demonstrated, and if the phantom limb pain is treated with opioids it may reduce the cortical reorganisation [20, 21]. Sandkühler [22] has in a recent review pointed at the striking similarities between central sensitisation and the processes of learning and memory, a further indication that long lasting plastic changes are possible.

Clinical significance of peripheral sensitisation and central hyperexcitability

Acute pain

Tissue injury caused by surgery or trauma will lead to a fast, early but short lasting increase in afferent nociceptive input. This may induce a first wave of central hyperexcitability. Due to the development of an inflammatory reaction to the tissue injury, with sensitisation of peripheral receptors, a second wave of longer lasting afferent input will kindle a new increase in central hyperexcitability [23]. The resulting hyperalgesia and allodynia can lead to increased postoperative and posttraumatic pain and maybe increase the likelihood of chronic pain (see later).

Concept of pre-emptive analgesia

Attempting to block or attenuate the peripheral sensitisation and the central hyperexcitability would therefore seem logical. Early animal experiments showed that an analgesic administered before trauma resulted in less posttraumatic pain then when the same analgesic was administered after the trauma [24]. This was later termed pre-emptive analgesia. A natural step was therefore to transfer the concept of pre-emptive analgesia into the human postoperative setting. An early study by McQuay and Caroll [25] showed that morphine premedication and local anaesthetic nerve blocks reduced postoperative pain after orthopaedic surgery, indicating that if the afferent traffic is blocked or attenuated this might reduce central hyperexcitability. In a famous and much quoted study Bach et al. [26] demonstrated that phantom pain after lower limb amputation could be reduced if an epidural anaesthesia blocked the limb pain before amputation. This indicated that preventing central hyperexcitability induced by surgical trauma might even prevent the development of chronic pain syndromes. However a later study [27] could not confirm these results. Later Katz [28] showed that epidural fentanyl administered before the start of surgery compared to after surgery reduced postoperative morphine consumption after thoracotomy. Multiple studies, both positive and negative, followed (for a review see Woolf and Chong [23]). A Medline search using the search term "pre-emptive analgesia" resulted in over 200 citations for the last 10 years. However, none of these studies have had a significant impact on our clinical practice. Why is this so? Firstly, most studies on pre-emptive analgesia just looked at short-term outcome, e.g. postoperative morphine consumption during the first postoperative days. Is this a clinically relevant outcome? Only if the reduced morphine consumption leads to a reduction in postoperative complications or length of hospital stay, and this is very seldom recorded in studies on pre-emptive analgesia. Secondly, opiates may not be an ideal drug for preventing central hyperexcitability (see later). Thirdly, many studies have probably used inadequate doses, or have had a faulty study design because the pre-emptive interventions were not extended into the postoperative period. Thereby, the "second wave" of nociceptive input due to an inflammatory response in the injured tissues was not attenuated (see Woolf and Chong [23]).

Chronic pain

Direct measurements of spinal cord neurons cannot be made in patients. However, hypersensitivity can be investigated by quantitative sensory tests. For instance, hypersensitivity is detected when sensory stimulation evokes pain at stimulus intensities that do not induce pain in normal subjects. If hypersensitivity is observed after sensory stimulation of healthy tissues its cause must be a hyperexcitability of the central nervous system (central hypersensitivity).

Using the above methodology, central hypersensitivity has been observed in different chronic pain syndromes such as neck pain after whiplash injury [29–31], fibromyalgia [32], osteoarthritis [33], tension-type headache [34], temporomandibular joint pain [35], and post-mastectomy pain [36]. In these investigations hypersensitivity was observed after stimulation of areas surrounding the site of pain, as well as after stimulation of areas that are distant from the painful areas. For instance, in chronic neck pain after whiplash in-jury, hypersensitivity has been found not only at the neck but also at the leg [29]. These data show that central hypersensitivity may be a condition that is present in several, and possibly in all, chronic pain syndromes. Central hypersensitivity is not just confined to the painful areas, but may involve the whole central nervous system.

Central hypersensitivity may have an important role in the determination of the pain complaints. In the presence of central hypersensitivity, either no or minimal and undetectable tissue damage is required to induce pain. In other words, innocuous sensory stimulation or minimal nociceptive stimulation of peripheral tissues would be able to evoke exaggerated pain. This may provide a neurobiological explanation for the discrepancy between extent of tissue damage and pain complaints that is frequently found in chronic pain patients. Furthermore, therapies that treat or prevent central hypersensitivity could be an important part of the therapeutic approach to chronic pain syndromes.

Prevention and treatment of peripheral sensitisation and central hyperexcitability

Most of our knowledge on peripheral, spinal and central modulation of nociception is based on animal research. But can we directly transpose animal studies to the clinical situation in humans? Species differences may be important, and due to ethical reasons, animal studies are seldom performed in intact, awake animals. The animals are either under an anaesthetic, have been spinalized, or isolated spinal cord slices or cells are studied. Thereby, the important interaction of the different components of the nociceptive system may be influenced or obliterated. In order to systematically investigate therapeutical regimes in humans we need to develop relevant human experimental models.

Further problems are what drugs should we use, what are the optimal combinations, and where in the nociceptive pathway should we intervene. Should we inhibit sensitisation of the peripheral receptor, block afferent nociceptive input, spinal hyperexcitability, or central modulation? A recent study [37] showed that a combination of an opioid receptor agonist and NMDA-receptor antagonist was necessary to inhibit sensitisation. We most probably need to use a combination of drugs with effect at different levels and receptors – the concept of balanced analgesia [23, 38].

Role of the opioid receptor in central hyperexcitability

Opioids are still our mainstay in the treatment of acute and some forms of chronic pain. However, recent studies have shown that the role of opioids may not be as simple as we have thought [39]. It has been shown that acute tolerance to opioids may develop very quickly [40], and that NMDA recep-tor antagonists (see later) may reverse this acute tolerance [41, 42]. If acute tolerance also develops in humans, a large pre-emptive dose of opioids administered before surgery might induce an acute tolerance. This would lead to a decreased effect of opioids and therefore an increased consumption of postoperatively administered opioids. Chia et al. [43] have shown that women receiving a large dose of fentanyl at induction of anaesthesia had more intense pain and larger opioid requirements in the first postoperative hours compared to those receiving a small dose at induction. Development of acute tolerance to opioids could be an explanation for the negative pre-emptive analgesic studies using opioid consumption as outcome parameter. Further confusion as to the role of opioids has been added by Celerier et al. [44] in an animal study. They showed that fentanyl may induce a hyperalgesia lasting days! The hyperalgesia was dose dependent: the more fentanyl the more hyperalgesia. Interestingly the development of hyperalgesia could be prevented by pre-treatment with the NMDA receptor antagonist ketamine.

Role of the NMDA receptor in central hyperexcitability

Early animal studies showed an important role of the NMDA receptor in the development of central hyperexcitability, and that NMDA-receptor antagonists may attenuate hyperexcitability in both animals [45, 46] and humans [47–50]. Although the pharmaceutical industry has worked for several years on developing NMDA receptor antagonists for human use, none have until now reached clinical trials. For human use we are lim-

ited to ketamine, dextromethorphan, and amantidine. The two last drugs are "dirty" drugs with mixed effects other than NMDA receptor antagonism. Ketamine is a relatively selective NMDA receptor antagonist, but has severe psychometric side effects limiting its use in humans. However, ketamine has been shown to reduce hyperexcitability in experimental human pain models [51, 52], and to reduce chronic neuropathic pain in patients [49, 53, 54]. Considering the multitude of receptors involved in the nociceptive system, it may be a too simplistic approach to just concentrate on the NMDA receptor. It might be more fruitful to look for a more basic general mechanism that is common for several receptor types (Andy Dray, 2002, personal communication).

Role of local anaesthetics in inhibiting peripheral sensitisation and central hyperexcitability

A logical approach would be to block afferent nociceptive traffic. This could be performed as wound infiltration, peripheral nerve blocks or central neural blockade (spinal or epidural blocks). Many studies have used this approach but with conflicting results (for a review see [23]). Wound infiltration has only a short effect and does not block the secondary hyperalgesia [55, 56]. But why does epidural blockade not produce consistent results [57, 58]. It is a common assumption that epidural anaesthesia produces a total blockade of afferent impulses. Lund et al. [59], however, showed that somato-sensory evoked potentials could be recorded during epidural anaesthesia, and Curatolo et al. [60] showed that epidural blockade does not inhibit spinal temporal summation (increased pain response to repeated stimuli) indicating that afferent impulses may reach the spinal cord even during an epidural anaesthesia sufficient for surgery. Therefore, local anaesthetics may provide an incomplete prevention of hyperexcitability of the central nervous system.

Is preventing peripheral sensitisation and central hyperexcitability clinically relevant?

Although there is ample evidence that peripheral sensitisation and central hyperexcitability is present in animals and that indirect evidence indicates they have a role in human acute and chronic pain, we still have not answered the question of whether this is clinically relevant in humans.

We have stated earlier several reasons why the concept of pre-emptive analgesia has not changed clinical practice. One reason was that most studies only examined short-term outcome. However, many chronic pain syndromes develop after surgery or trauma. The problems of phantom pain after amputations and chronic pain after traumatic whiplash neck injuries are well known. Prolonged postoperative pain after thoracic surgery may be experienced by 45% of the patients. Recently, evidence for central sensitisation in patients with neck pain after whiplash injury [29–31] and in patients with fibromyalgia [32] has been demonstrated. This indicates that central hyperexcitability may be an important factor in patients with chronic pain.

If inhibiting or preventing peripheral sensitisation and central hyperexcitability could decrease the incidence of chronic pain syndromes this would have an immense socio-economic impact. Only recently have studies been published examining long-term outcome after pre-emptive interventions aimed at inhibiting hyperexcitability. Stubhaug et al. [50] have published a very interesting and elegant study. They demonstrated that patients receiving low dose ketamine (a NMDA-receptor antagonist) during the operation and the first 2 postoperative days exhibited almost no hyperalgesia around the surgical incision compared to a placebo control group. Interestingly, the reduced hyperalgesia was present not only during the ketamine infusion, but also several days after the ketamine infusion had been stopped. Obata et al. [61] found that epidural block during and after a thoracotomy reduced long-term pain by about 50% compared to patients who only received the epidural postoperatively. Both studies indicate that a perioperative inhibition of peripheral and central sensitisation may have long-term consequences, and that sensitisation could therefore be very important clinically.

Conclusions and future perspectives

There is ample evidence that peripheral sensitisation and central hyperexcitability are important factors for postoperative and posttraumatic pain in animals. The sparse evidence in humans is mainly due to methodological problems in measuring peripheral sensitisation and central hyperexcitability. The few published human studies, however, indicate that also in humans these may be important determinants for acute and chronic pain. However, we still do not know how to optimally inhibit peripheral sensitisation and central hyperexcitability. Where in the pain pathway should we concentrate our efforts, what drugs should we use and in what combinations and concentrations, still remains to be investigated.

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