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Chapter 1

Introduction
PERIPHERAL AND CENTRAL MECHANISM IN CHRONIC PAIN

The pain system has long been regarded as a simple connection between a peripheral sensor sending information, and the brain as the awareness center interpreting this information. This basic description of the perception of pain as proposed by Descartes in the 17th century, has evolved into an elaborate system involving much more than sensory information alone. We have come to understand that pain is a complicated experience integrating prior exposures, expectations, attention, mood, genetics, peripheral and central nervous system physiology as well as neurochemical and anatomical variation 1-3 (Figure 1).

During the previous century elaborate research on nerve fiber morphology, velocity of signal conduction and neuronal responses to thermal, mechanical and noxious stimuli in both animals and humans has unveiled some of the mysteries of how the peripheral and central nervous system are wired to generate and control pain 4-6. The peripheral

![Figure 1. The view on pain perception in the 16th century has evolved into our current understanding of the complexity of pain perception in the 21st century. (With permission from: Tracey, I. & Mantyh, P.W. The cerebral signature for pain perception and its modulation. Neuron 55, 377-391).]
nervous system consists of first order neurons that have their cell bodies in the dorsal root ganglia and end at sensory receptors in the skin or in the visceral organs. Nociceptors are small unmyelinated (C) or thinly myelinated (Aδ) fibers that respond to thermal, mechanical or chemical stimuli \(^7\)\(^-\)\(^10\). Peripheral nerves first connect to the central nervous system in the dorsal horn of the spinal cord. Nociceptive signals that pass the dorsal root ganglion, synapse onto a second order neuron as soon as they arrive in the spinal cord and the second order neuron further conveys the pain signal to several brain regions involved in pain perception, such as the thalamus, the insula and the somatosensory cortex \(^3\). From the cortical regions, multiple descending pathways involving the periaqueductal grey and the nucleus raphe magnus send signals back to the spinal cord, where incoming pain signals are modulated. When this central modulation of pain is inhibitory it is known as descending inhibition \(^11\)\(^,\)\(^12\). To the contrary, a pain amplifying mechanism is central sensitization or facilitation of pain signaling: the amplification of incoming signals from primary nerves at synapses in the spinal cord or at supraspinal sites \(^13\)\(^,\)\(^14\). Sustained afferent nociceptive input can induce a long-term increase in excitability of second order neurons which may lead to hypersensitivity and hyperalgesia \(^15\). Both the increase in facilitation of pain and a disruption of descending inhibition are thought to play a major role in the chronification of pain.

Chronic pain is usually preceded by a focal lesion or trauma or may be a consequence of systemic diseases that disrupt peripheral small nerve fiber function and/or central modulation of nociception. When the lesion or disease causing the pain is affecting the somatosensory system, the disorder is classified as neuropathic and may be manifested as large and/or small fiber pathology \(^16\)\(^,\)\(^17\). In contrast to large fiber neuropathy, the exact mechanism of the degeneration of nerve fibers in small fiber neuropathy is still unknown, even when it is present as a complication of diseases such as diabetes and sarcoidosis \(^18\)\(^-\)\(^20\). However, decreased nerve fiber density in the skin or cornea and functional impairment can be clearly demonstrated in patients with small fiber neuropathy.

**FIBROMYALGIA**

Fibromyalgia is a disorder of unknown etiology mainly defined by widespread pain and fatigue, and was previously considered to be caused predominantly by central nervous system dysfunction. This idea is supported by the observation that patients with fibromyalgia often suffer from additional centrally mediated problems such as sleep disturbance, irritable bowel syndrome, depression and mild cognitive symptoms, *i.e.* forgetfulness and verbal memory problems. However, in 2013, two separate research groups \(^21\)\(^,\)\(^22\) showed decreased intraepidermal nerve fiber density in skin biopsies, a capital sign of small fiber pathology, in cohorts of fibromyalgia patients. Ramirez and
colleagues 23 were the first to demonstrate the presence of small fiber pathology in patients with fibromyalgia by use of cornea confocal microscopy, a relatively new method to quantify and qualify small nerve fibers. These studies imply that besides central mechanisms, peripheral nerves are also involved in the generation of pain in fibromyalgia (this view is explored in chapter 5).

MEASURING PAIN PERCEPTION AND MODULATION

For the measurement of pain a number of instruments are available. A distinction needs to be made between measuring chronic pain and acute, or experimental pain. For the evaluation of chronic pain, its occurrence and intensity, quality and impact on daily life, several questionnaires exist such as the brief pain inventory 24, PainDetect 25, DN4Q 26, the RAND-36 27 and the Neuropathic Pain Symptoms Inventory 28. In most of these questionnaires, at least one of the questions concerns rating daily pain on a numerical rating scale, usually from 0 to 10, 0 representing no pain and 10 the worst pain imaginable (chapter 2 explores the complexities of pain rating).

In most experimental studies, acute pain perception is evaluated by means of psychophysical tests: applying various pain stimuli, such as electrical, ischemic, heat, cold and pressure pain and recording individual’s responses to these stimuli, also known as quantitative sensory testing (QST). Often, the lowest intensity of a stimulus that elicits a feeling of pain, i.e. the pain threshold, or the highest endurable pain, i.e. pain tolerance, is recorded. As it is known which kind of small nerve fibers (C or Aδ fibers) are responsible for conduction of signals from cold, warm and mechanical stimuli and because normative values are available, the class of dysfunctional nerve fibers can be identified by the modalities that show abnormal test results. Moreover, some tests can specifically identify peripheral or central sensitization 29,30.

In contrast to static tests, dynamic tests give an indication of the status of the endogenous pain modulatory system. Examples of such pain modulation tests are conditioned pain modulation (CPM) and offset analgesia (OA). CPM is performed by application of two noxious stimuli at two separate sites on the body, during which the second stimulus reduces the perception of pain evoked by the primary stimulus. This test represents endogenous modulation of pain based on spatial signal integration in the spinal cord 31. OA, on the other hand, represents a temporal integration of signals. OA is the rapid onset and large reduction in pain perception after a small reduction in temperature during a noxious heat stimulus 32 (these two paradigms are explored in chapter 3 and 4).

Apart from psychophysical testing and questionnaires, two objective measurements can be used to assess the state of the small sensory nerve fibers specifically. Skin biopsies and cornea confocal microscopy allow the determination of nerve fiber density
and morphology of small nerve fibers. Skin biopsies are usually taken from the thigh or lower leg and the number of small nerve fibers per mm of epidermis, the intraepidermal nerve fiber density (IENFD), is measured. This technique is currently the gold standard to confirm the diagnosis of small fiber pathology. Alternatively, a confocal microscopic technique called cornea confocal microscopy (CCM) can be used to visualize small nerve fibers that innervate the cornea. Corneal nerve fiber density, corneal nerve fiber length, and corneal branching density (i.e., the number of smaller nerves branching from main nerve fibers) can be determined by this technique allowing the assessment of small fiber pathology rapidly, repetitively and non-invasively. With all these tests at our disposal, it is possible to apply these in characterization of chronic pain patients and combine the results to construct a somatosensory phenotype of an individual patient. Analysis of these phenotypes can be used to divide the heterogeneous groups of chronic pain patients, even within a disease entity, into more homogeneous cohorts. Treatment regimens may subsequently be based on the characteristics present in each cohort (phenotype analysis was performed for fibromyalgia patients in chapter 5 and for diabetes mellitus type 2 and sarcoidosis patients in chapter 6).

**THESIS OUTLINE**

In Chapter 2 the ability of chronic and acute pain patients and healthy volunteers to grade experimental painful stimuli on a number based scale is evaluated. Additionally it is described how opioids affect the ability to rate painful stimuli.

Chapter 3 compares the response of patients with fibromyalgia to several offset analgesia paradigms with the response of healthy volunteers, and describes the influence of impaired OA responses on the onset and offset of pain.

In Chapter 4 a novel contact heat thermode device, the Q-sense CPM, is evaluated for its ability to induce a sufficiently large CPM effect. Moreover, several CPM paradigms are compared to explore which model generates the optimal CPM effect.

In Chapter 5 CCM is performed to assess small nerve fiber morphology of patients with fibromyalgia. The results are used in combination with QST and questionnaires to construct phenotypes of patients.

Chapter 6 describes phenotypes of patients with diabetes mellitus type 2 and patients with sarcoidosis based on CCM and QST.
REFERENCES


