Chapter 1

Introduction

1

Pain modulation

Pain is a complex sensation influenced by biological, emotional, cognitive and behavioral factors. Early important evidence for this is described in a study by Beecher in 1946.[1] Beecher was an surgeon who worked for the US Army during World War II and during this time treated many wounded soldiers suffering from acute and severe pain. He observed that only a quarter of severely injured soldiers with penetrating traumas and long bone fractures (while mentally healthy) reported severe pain and requested analgesics. This indicated that strong emotions as experienced in the battlefield could block pain perception. Another interesting observation made by Beecher was the effect of placebo in severely injured soldiers. Due to shortages of medical supplies including strong analgesics like morphine, Beecher was forced to treat his patients with placebo substances. In several studies he performed, involving over 1,000 patients, he observed an average analgesic effect of placebo of about 35%.[2] These studies indicated that the human body is capable of modifying painful sensations and underlie the development of theories regarding endogenous control of pain.

The first clearly articulated concept of a pain modulatory system was described in 1965 by Melzack and Wall in the gate control theory.[3] In this theory a gating mechanism within the dorsal horn of the spinal cord of rodents was proposed which determined whether signals were sent to the brain based on the type of activated nerve fibers. Supraspinal influences on this system were suggested, although no clear evidence was present at that time for descending pathways (from the brain to the spinal cord) that could influence pain perception. Evidence for this concept was provided by Wall in 1967 who demonstrated that the blockade of descending impulses from the brain stem by spinal cord lesions spontaneously activated dorsal horn neurons.[4] This indicated that projections from the brain stem were able to inhibit neurons at the level of the dorsal horn in the spinal cord which was the basis for the current understanding of descending control of pain. In the beginning of the 1970s several regions of the brain stem in animals such as the periaquaductal gray (PAG) and rostral ventromedial medulla (RVM) were shown to be involved in the initiation of descending inhibitory pathways as electrical stimulation of these regions induced analgesia, inhibition of withdrawal reflexes and inhibition of dorsal horn neurons sensitive to noxious stimulation. The administration of morphine in these regions provided similar observations and currently we know that these pain modulatory pathways are the central substrate for the analgesic actions of opioids and endorphins.[5,6] In 1979 Le Bars et al. demonstrated in rats that afferent noxious information from various parts of the body was able to inhibit activity of nociceptive neurons in the dorsal horn which simultaneously received afferent noxious information from a different part of the body. This phenomenon was called diffuse noxious inhibitory controls (DNIC). In animals DNIC involves a spinal-bulbo-spinal feedback loop where afferent noxious pathways are able to activate descending inhibitory pathways originating in the brain stem to inhibit nociceptive neuronal activity at the level of the dorsal horn.[7,8] In the late 1980s, DNIC was demonstrated to also

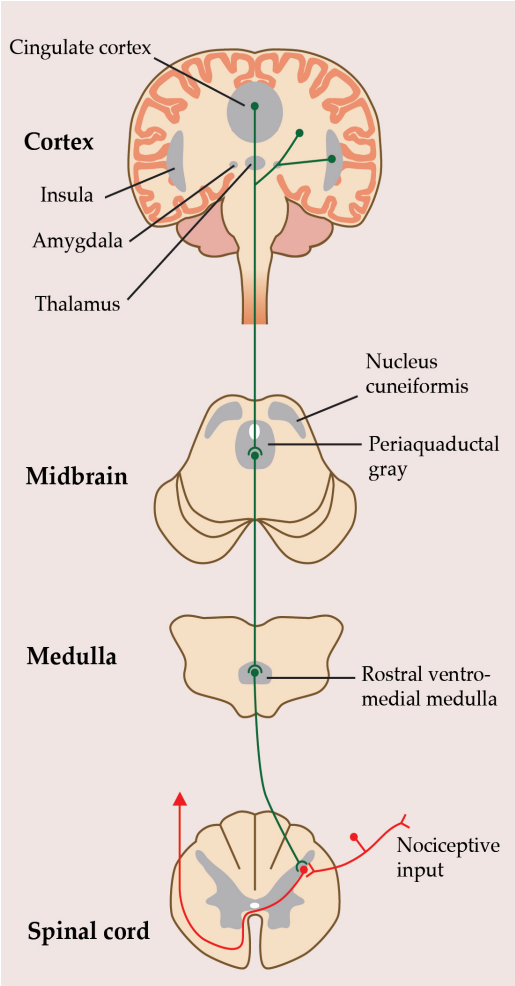

Figure 1. *Schematic illustration of the pain modulatory pathways. Nociceptive input reaches the brain via an afferent pathway (red). Next, the descending pain modulatory pathway is activated by several higher cortical sites that project to the brainstem to modulate nociceptive input at the level of the dorsal horn. This descending pathway can be either facilitatory or inhibitory. (adapted from: Dahan A, Niesters M, Sarton E. Endogenous modulation of pain is visible in the brain. Clin Neurophysiol. 2012; 123: 642-3).*

be present in humans.[9] However, imaging studies demonstrate that in humans descending control of pain also involves higher cortical areas, such as the amygdala, the thalamus, the insula and the anterior cingulate cortex (ACC).[10,11] The current understanding of nociceptive modulatory pathways in humans involves an afferent pathway for nociceptive input to several areas of the cortex and brain stem for pain perception and interpretation. Descending pathways, either facilitatory or inhibitory, can modulate this afferent noxious information at the level of the dorsal horn of the spinal cord as illustrated in figure 1.

Conditioned pain modulation

The biology of the DNIC-like effect in humans is more complex compared to rodents, for instance due to the involvement of higher cortical centers. Therefore, new terminology has been proposed to refer to the DNIC-like effect in humans to discriminate between the brain stem mediated inhibitory effect in rodents and the complex facilitatory and inhibitory pain modulatory properties present in humans. Two noxious stimuli are required during psychophysical research to explore descending control of pain in humans, which are referred to as the test stimulus and the conditioning stimulus. The test stimulus is the stimulus on which the conditioning effect is evaluated; the conditioning stimulus is the stimulus that induces the change in pain perception. The effect of the conditioning stimulus on the test stimulus is called “Conditioned Pain Modulation” (CPM)

which is the net effect of the facilitatory and inhibitory mechanisms of pain processing.[12]

In the current thesis CPM was evaluated using heat pain as test stimulus and cold pain as conditioning stimulus (Fig. 2A). Heat pain was administered on the lower part of the dominant arm using a 30-second stimulus during which the test subject continuously rated pain intensity. The test stimulus was applied with and without the conditioning stimulus, which was administered on the lower leg During effective descending inhibitory control of pain, as observed in healthy volunteers, the conditioning stimulus will decrease the pain intensity of the test stimulus (Fig. 2B).[9]

Offset analgesia

More recently, a novel model of endogenous inhibitory control of pain has been proposed that produces temporal alterations in pain processing named offset analgesia (OA).[13] OA is the perception of profound analgesia during a slight decrease of a noxious heat stimulus, which is more pronounced than would be predicted by the rate of the temperature decrease. Although a peripheral origin of OA is not excluded (*e.g.* related to primary afferent neurons within the dorsal horn), OA is generally considered an example of central inhibitory modulation of pain probably induced by neuronal circuits similar to CPM. A schematic illustration of a normal OA response as observed in healthy volunteers is shown in figure 3.

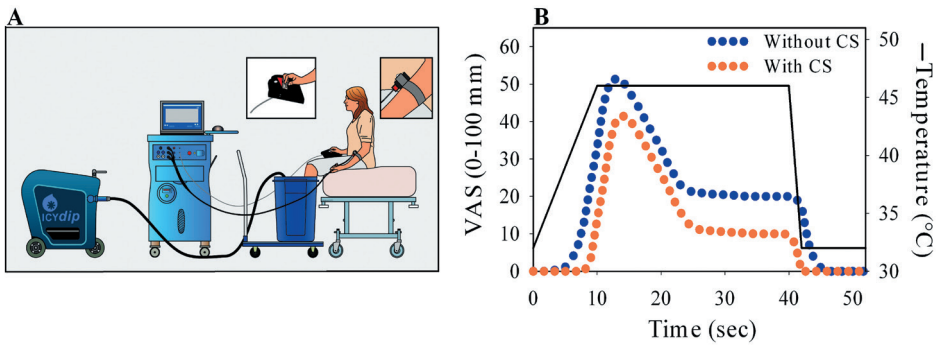

Figure 2. A. *Schematic presentation of the experimental set-up to evaluate conditioned pain modulation (CPM). Heat pain (test stimulus) was applied using a 3 x 3 cm peltier element on the lower part of the dominant arm while the subject rated pain intensity using a slide on a potentiometer using the other arm. Cold pain (conditioning stimulus) was applied using a cold water bath (6-12 °C) in which the lower leg and foot was immersed.* ***B.*** *Schematic illustration of CPM as observed in healthy volunteers. The dotted lines represent the pain intensity scores during the 30-second heat stimulus (straight black line) on the lower part of the arm without (blue line) and with (orange line) the conditioning stimulus. The difference between the two dotted lines represents the CPM effect. CS: conditioning stimulus; VAS: visual analogue scale.*

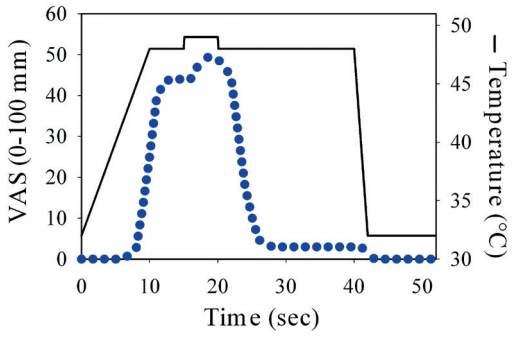

Figure 3. *Schematic illustration of offset analgesia (OA) as observed in healthy volunteers. The dotted line represents the pain intensity scores during a 30-second dynamic heat stimulus applied on the skin. Heat stimulation consists of 3 phases: 1) a ramp to the target temperature that is kept constant for 5 seconds; 2) a 1 °C temperature increase that is also kept constant for 5 seconds; 3) a 1 °C temperature decrease (back to the target temperature) that is kept constant for 20 seconds followed by a quick return towards the baseline temperature. OA is seen in response to the 1 °C temperature drop observed as a profound decrease in pain intensity.*

Outline of this thesis

The aim of the current thesis was to evaluate the effect of central-acting drugs on endogenous control of pain in healthy volunteers and patients with chronic neuropathic pain using psychophysical research and functional magnetic resonance imaging (fMRI).

In **chapter 2** the effect of short-term treatment with the analgesic ketamine on CPM and OA is evaluated in healthy volunteers in a placebo-controlled cross-over study.

Chapter 3 describes the presence of OA in a large group of healthy volunteers in the age range 6-80 years and a group of chronic neuropathic pain patients. Furthermore, the effect of short-term treatment with the analgesics ketamine, morphine and placebo on OA responses in neuropathic pain patients is evaluated.

In **chapter 4** the effect of short-term treatment with ketamine, morphine and placebo on CPM responses in chronic neuropathic pain patients using a cross-over study is described.

Chapter 5 describes the effect of a 4-week treatment with the new analgesic tapentadol on CPM and OA in patients with painful diabetic neuropathy in a double-blind, placebo-controlled study.

In **chapter 6** the effect of ketamine and pain perception during ketamine infusion on large-scale network interaction in the brain measured by resting-state fMRI is evaluated. We aimed to identify changes in brain connectivity for (1) brain areas involved in ketamine's pharmacodynamic profile with respect to intended (analgesia) and side effects (most importantly psychedelic effects) and (2) areas involved in pain processing.

Chapter 7 describes the effect of deafferentation induced by spinal anesthesia on intrinsic brain connectivity measured by resting-state fMRI and on the pain perception of non-deafferented skin. Our aim was to investigate whether (1) pain perception above the level of the anesthetic was altered and (2) whether this co-

incided with changes in functional neuroimaging markers of cortical and thalamic networks in healthy volunteers.

References

1. Beecher HK. Pain in men wounded in battle. *Ann Surg* 1946; 123: 96-105
2. Beecher HK. The powerful placebo. *J Am Med Assoc* 1955; 159: 1602-6
3. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; 150: 971-9
4. Wall PD. The laminar organization of dorsal horn and effects of descending impulses. *J Physiol* 1967; 188: 403-23
5. Basbaum AI, Clanton CH, Fields HL. Opiate and stimulus-provided analgesia: functional anatomy of a medullospinal pathway. *Proc Natl Acad Sci* 1976; 73: 4685-8
6. Fields HL, Basbaum AI, Heinricher MM. Central nervous system mechanisms of pain modulation. In: McMahon S, Koltzenburg M. *Wall and Melzack's textbook of pain 5th edition* 2006: 125-142
7. Le Bars D, Dickenson AH, Besson J. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain* 1979; 6: 283-304
8. Le Bars D, Dickenson AH, Besson J. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain* 1979; 6: 305-327
9. Talbot JD, Duncan GH, Bushnell MC et al. Diffuse noxious inhibitory controls (DNICs): psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. *Pain* 1989; 30: 221-32
10. Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. *Pain* 2011; 152: 1469-77
11. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest* 2010; 120: 3779-87
12. Yarnitsky D, Arendt-Nielsen L, Bouhassira D et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010; 14: 339
13. Grill JD, Goghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol* 2002; 87: 2205-8