Evolution of endogenous analgesia

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Chapter 8

Summary & Conclusions

Summary

Endogenous pain modulation is a complex phenomenon involved in the perception of pain. It consists of top-down inhibitory and facilitatory pathways that originate at higher sites within the central nervous system and converge at dorsal horn neurons in the spinal cord, to modulate incoming afferent nociceptive information. Dysfunction of inhibitory pain pathways or a shift in the balance between pain facilitation and pain inhibition has been associated with the development of chronic pain. This thesis describes the effect of several central-acting drugs on descending control of pain in both healthy volunteers and chronic pain patients to further understand the underlying mechanism of endogenous pain control in health and disease.

In **chapter 2** the effect of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine on endogenous pain modulation was investigated in healthy volunteers. Ten healthy subjects (4 men/6 women) received an 1-hour placebo or S(+)-ketamine (40 mg/70 kg) infusion on two separate occasions in random order. Upon termination of the infusion the capacity to recruit descending pain inhibitory pathways was evaluated using two experimental or surrogate biomarkers for endogenous modulation of pain: conditioned pain modulation (CPM) and offset analgesia (OA). After placebo treatment significant inhibition of pain responses was present for CPM and OA. In contrast, after ketamine infusion no CPM response was observed, but rather a significant facilitatory pain response ($p < 0.01$); the OA response remained unchanged. These findings indicate that the balance between pain inhibition and pain facilitation was shifted by ketamine towards pain facilitation and suggest a modulatory involvement of the NMDA and/or other glutamatergic receptors at some level within the endogenous pain system. The absence of an effect of ketamine on OA indicates the presence of different mechanisms and neurotransmitter influences underlying OA and CPM and suggests that OA and CPM differ in their susceptibility for glutamatergic influences.

In contrast to CPM, the relatively new phenomenon offset analgesia had only been described in young healthy volunteers. In **chapter 3**, we explored OA in a large population consisting of several age categories and in ten chronic neuropathic pain patients. We defined OA by the reduction in electronic pain score upon the 1 °C decrease in noxious heat stimulus relative to the peak pain score. OA was present in healthy volunteers irrespective of age and sex (pain score decrease = 97 ± 1% (mean ± SEM), which suggests that OA is fully developed at the age of 6 years and does not undergo further maturation. In contrast, a reduced or absent offset analgesia response was observed in neuropathic pain patients (pain score decrease = 56 ± 9% *vs.* controls 98 ± 1%, $p < 0.001$). This indicates that chronic neuropathic pain patients are unable to modulate changes in pain stimulation with perseverance of pain perception where healthy subjects display signs of strong analgesia. Whether the altered OA responses contribute to the chronification of pain or are a consequence of the chronic pain process remains unknown

and requires further study. Intravenous treatment with ketamine, morphine and placebo had no effect on OA responses in patients despite sharp reductions in spontaneous pain scores, which suggests that the NMDA and μ-opioid receptors are less likely to be involved in OA mechanisms. Possibly, not central but peripheral sites may be involved in the altered offset analgesia responses in these patients.

Chapter 4 describes the effect of ketamine and morphine on CPM responses in chronic pain patients. CPM responses were obtained in 10 neuropathic pain patients (2 men/8 women), with peripheral neuropathy as defined by abnormal quantitative sensory testing. Patients were treated with S(+)-ketamine (0.57 mg/kg/h for 1 hour) and morphine (0.065 mg/kg/h for 1 hour) in a randomized, placebo-controlled double-blinded study. CPM was measured at baseline and 100 minutes after the start of treatment. Without treatment no CPM was detectable, which indicated that the descending pain inhibitory properties within this group of chronic pain patients were diminished. Treatment with ketamine, morphine and placebo produced significant CPM responses of respectively 40.2 ± 10.9%, 28.5 ± 7.0% and 22.1 ± 12.0% with no statistical difference in magnitude of CPM among treatments. However, the magnitude of the CPM responses correlated positively with the magnitude and duration of spontaneous pain relief observed after treatment. This suggests a role for CPM engagement of descending pain inhibition in analgesic efficacy of ketamine, morphine and placebo treatment in chronic neuropathic pain patients.

In **chapter 5** the effect of long-term treatment with the new analgesic tapentadol is described. Tapentadol is an analgesic agent for treatment of acute and chronic pain that activates the μ-opioid receptor combined with inhibition of neuronal noradrenaline reuptake. Both mechanisms are implicated in activation of descending inhibitory pain pathways. Twenty-four patients with diabetic polyneuropathy were randomized to receive daily treatment with tapentadol sustained-release (average daily dose 433 ± 31 mg) or placebo for 4 weeks. CPM and OA responses were measured before and on the last day of treatment. Prior to treatment none of the patients had significant CPM or OA responses. After 4 weeks of treatment, CPM was significantly activated by tapentadol slow-release (SR) and coincided with significant analgesic responses. CPM increased from 9.1 ± 5.4% (baseline) to 14.3 ± 7.2% after placebo treatment and 24.2 ± 7.7% after tapentadol SR treatment ($p < 0.001$ *vs.* placebo). Relief of spontaneous pain was also greater in patients treated with tapentadol than placebo ($p = 0.028$). Neither placebo nor tapentadol SR treatment had an effect on the magnitude of the OA responses ($p = 0.78$). These results show that patients with painful diabetic polyneuropathy who display absent CPM responses benefit from tapentadol, which induces pain relief coupled to (re)-activation of descending inhibitory pain pathways.

A relatively new approach in central nervous system drug research is resting-state fMRI (RS-fMRI), which measures intrinsic network interactions of the brain in

rest (*i.e.* not task-related). In **chapter 6** the effect of low-dose S(+)-ketamine on intrinsic brain connectivity was investigated. We aimed to identify brain regions involved in ketamine's pharmacodynamic profile with respect to intended (analgesia) and side effects (most importantly psychedelic effects) and areas involved in pain processing. Twelve healthy, male volunteers received a 2-hour intravenous S(+)-ketamine infusion (first hour 20 mg/70 kg, second hour 40 mg/70 kg). Before, during and after S(+)-ketamine administration resting-state brain connectivity was measured. Additionally, heat pain tests were performed in-between imaging sessions to determine ketamine-induced analgesia. Ketamine increased the connectivity in the cerebellum and visual cortex in relation to the medial visual network. A decrease in connectivity was observed in the auditory and somatosensory network in relation to regions responsible for pain sensing and the affective processing of pain, which included the amygdala, insula, and anterior cingulate cortex. Connectivity variations related to fluctuations in pain scores were observed in the anterior cingulate cortex, insula, orbitofrontal cortex and the brain stem, which are all regions involved in descending inhibition of pain. This study demonstrated that RS-fMRI is a useful and efficient method to assess drug effects on the brain. Low-dose ketamine induced connectivity changes in brain areas involved in motor function, psychedelic effects and pain processing. With respect to pain processing, ketamine's analgesic effect may arise from multiple pathways. We observed a decreased connectivity in regions of the pain matrix responsible for the perception of pain (pain sensing) and the affective processing of pain. Additionally, ketamine affected connectivity in brain areas involved in endogenous pain inhibition.

Descending (efferent) pain pathways are important for the normal perception of pain. However, little is known on the effect of afferent pain pathways on pain modulation. In **chapter 7**, the effect of spinal deafferentation on pain sensitivity was studied and linked to whole-brain functional connectivity as assessed by RS-fMRI. Deafferentation was induced by spinal or sham anesthesia (spinal: 15 mg bupivacaine injected at L3-4; sham: no puncture of the dura mater) in 12 male volunteers. Resting-state brain connectivity was determined in relation to 8 predefined and 7 thalamic resting-state networks and measured before, and 1 and 2 hours after spinal or sham injection in a cross-over study design. To measure the effect of deafferentation on pain sensitivity, responses to heat pain were measured at 15-minute intervals on non-deafferented skin and correlated to the RS-fMRI connectivity data. Spinal anesthesia altered functional brain connectivity within brain regions of the sensorimotor system and pain matrix in relation to somatosensory and thalamic resting-state networks. A significant enhancement of pain sensitivity on non-deafferented skin was observed after spinal anesthesia compared to sham (area-under-the-curve (mean ± SEM)): 190.4 ± 33.8 *versus* 13.7 ± 7.2; $p < 0.001$), which significantly correlated to functional connectivity changes observed within the thalamus in relation to the thalamo-prefrontal network, and in the anterior cingulate cortex and insula in relation to the thalamo-parietal network. This study demonstrated that deafferentation from spinal anesthesia was associated with rapid connectivity changes in the brain involving both cortical

and subcortical areas. These changes are best described as reorganization of neuronal interactions due to a rebalancing of excitatory and inhibitory factors that mediate adaptation and neuronal plasticity. Furthermore, spinal anesthesia enhanced pain sensitivity that was correlated to enhanced connectivity patterns of the thalamus, anterior cingulate cortex and insula, which are all areas associated with endogenous modulation of pain.

Comparison with the literature

In order to compare the results of this thesis to published data, a PubMed search was performed to identify studies evaluating the effect of central-acting drugs on CPM in healthy volunteers and chronic pain patients. From all relevant studies, on the condition that adequate quantitative data were presented, standardized effect sizes were calculated using the statistical program Comprehensive Meta

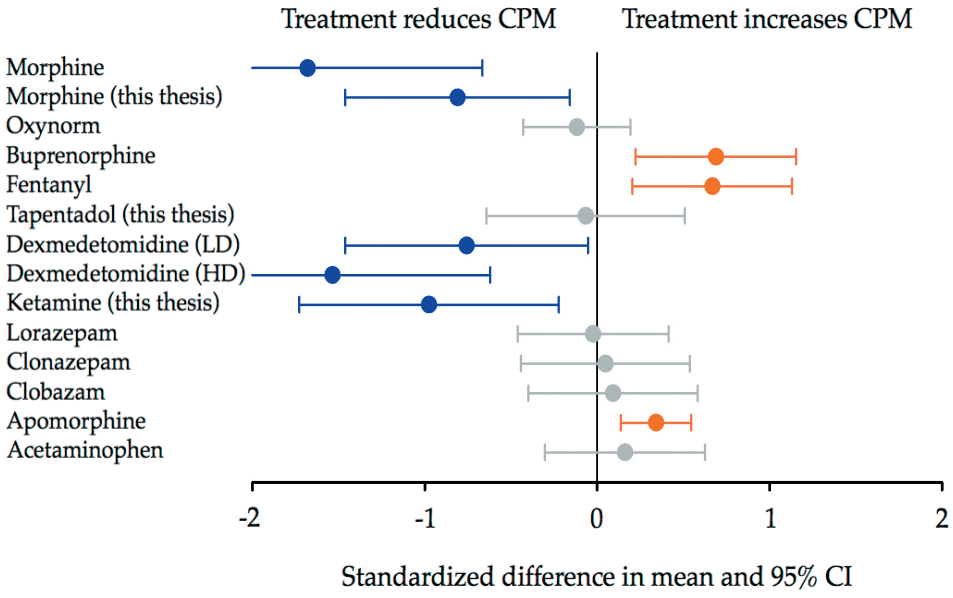

Figure 1. *Comparison of the literature on the effect of central-acting drugs on conditioned pain modulation (CPM) responses in healthy volunteers. Values are the standardized differences in mean ± 95% confidence interval (CI) calculated from CPM values relative to either placebo treatment or control (baseline or pretreatment) values. The orange symbols depict treatment that increased CPM, the blue symbols treatment that decreased CPM. The grey symbols depict treatment that caused CPM responses not different from control or placebo. The data collected from studies outside this thesis are from Le Bars et al.[1] (morphine); Suzan et al.[2] (oxycodon); Arendt-Nielsen et al.[3] (buprenorphine and fentanyl); Baba et al.[4] (dexmedetomidine); Kunz et al.[6] (lorazepam); Vuilleumier et al.[7] (clonazepam and clobazam); Treister et al.[8] (apomorphine) and Meeus et al.[5] (acetominophen). LD: low dose; HD: high dose.*

Analysis v2.2.064 (Biostat, Englewood, NJ, USA). The results for the healthy volunteers are given in figure 1. Apart from morphine, all studied drugs were tested only once. Intravenous morphine administration decreased CPM responses in both studies (this thesis and ref. 1). Single dose oxycodone and tapentadol, given orally on a single occasion, had no effect on CPM (this thesis and ref. 2). In contrast, buprenorphine and fentanyl, both administered by a continuous drug delivery transdermal patch formulation, did produce a significant increase in CPM.[3] CPM responses following treatment with non-opioid analgesics (single administration) such as ketamine and dexmedetomidine, are predominantly reduced with the exception of acetominophen.[4,5] With regard to non-analgesic central-acting drugs, no effect on CPM was observed for the single administration of GABA-ergic agonists.[6,7] The dopamine-agonist apomorphine did increase CPM responses in healthy volunteers.[8] These data indicate that drugs acting on the μ-, α_2- and NMDA-receptor influence CPM responses in healthy volunteers. However, large dissimilarities in the methods used to study CPM are present between these studies. Hence a significant part of the variability observed in study outcomes may be related to methodological issues.

The results for the chronic pain patients are given in figure 2. All studied drugs were tested only once. A significant decrease in CPM responses was observed in

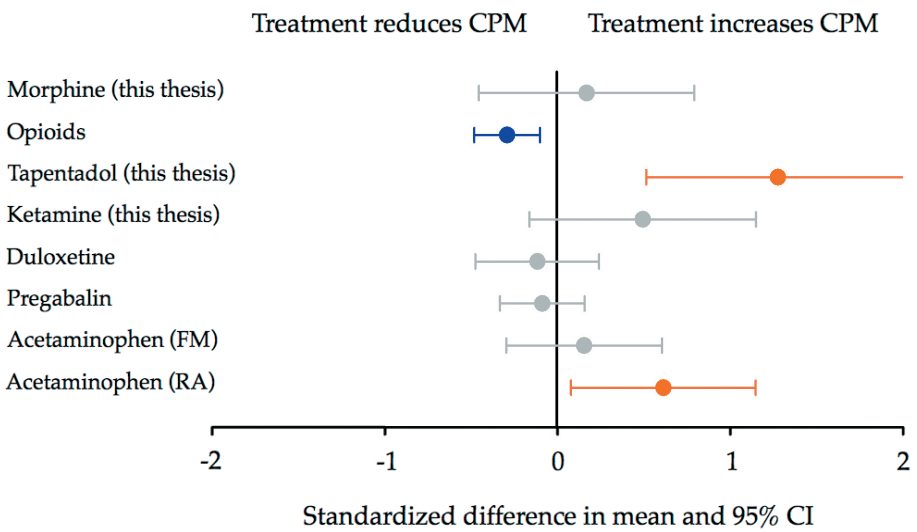

Figure 2. *Comparison of the literature on the effect of central acting drugs on conditioned pain modulation (CPM) responses in chronic pain patients. Values are the standardized differences in mean ± 95% confidence interval (CI) calculated from CPM values relative to either placebo treatment or control (baseline or pretreatment) values. The orange symbols depict treatment that increased CPM, the blue symbols treatment that decreased CPM. The grey symbols depict treatment that caused CPM responses not different from control or placebo. The data collected from studies outside this thesis are from Ram et al.[9] (opioids); Yarnitsky et al.[10] (duloxetine); Bouwense et al.[11] (pregabalin) and Meeus et al.[5] (acetominophen). FM: fibromyalgia; RA: rheumatoid arthritis.*

a group of chronic pain patients (either cancer or non-cancer related) who were treated with opioids compared to patients who were not on opioid treatment.[9] An increase in CPM response was observed in patients with chronic painful diabetic neuropathy after tapentadol treatment (this thesis) and in patients with rheumatoid arthritis after treatment with acetominophen (this effect was not observed in fibromyalgia patients).[5] And although no significant effect on CPM responses was observed after treatment with morphine, ketamine (this thesis), duloxetine and pregabalin,[10,11] a (linear) relationship was observed between the magnitude of increase in CPM and magnitude of pain relief induced by ketamine, morphine and tapentadol (this thesis). These data indicate that also in patients opioidergic and noradrenergic pathways influence CPM. The different responses between healthy volunteers and pain patients observed after treatment with morphine, tapentadol and ketamine may be related to central pathological alterations observed in pain patients (*i.e.* central sensitization and inflammation), and hence comparison of treatment effects between patients and volunteers should be done with caution. Again a large variability in study methods was present, which may have influenced the outcome of the meta-analysis.

Conclusions

From the data presented in this thesis several conclusions may be drawn:

1. In healthy volunteers, short-term ketamine treatment induces a shift in the balance between pain inhibition and pain facilitation towards pain facilitation (as measured by CPM responses). In contrast, in chronic neuropathic pain patients, in whom descending control of pain is dysfunctional, ketamine restores pain inhibitory pathways.

2. Short-term morphine treatment significantly restores CPM responses in chronic neuropathic pain patients who display dysfunctional descending inhibitory pain control prior to treatment.

3. Long-term (4-week) tapentadol treatment significantly enhances CPM responses compared to placebo in patients with chronic painful diabetic neuropathy.

4. Chronic neuropathic pain patients show an absent or diminished OA response compared to healthy volunteers. None of the central-acting drugs described in this thesis (ketamine, morphine and tapentadol) alters or restores OA responses in healthy volunteers or chronic pain patients. Whether this is because there is no central origin for OA or that other central receptors or neurotransmitter systems (which are not influenced by these drugs) are involved in this phenomenon remains unknow.

5. Resting-state fMRI is a valuable, reliable and efficient method to assess pharmacological effects on the brain.

6. Ketamine treatment and deafferentation by spinal anesthesia induce alterations in functional brain connectivity in cortical and subcortical areas. Furthermore, they both alter pain sensitivity, where ketamine induces analgesia and deafferentation induces hyperalgesia, which is correlated to alterations in functional brain connectivity in brain areas involved in descending control of pain.

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