Paresthesia free spinal cord stimulation in experimental chronic neuropathic pain

Appendix

Impact paragraph

Chronic neuropathic pain is a condition that severely affects patients' lives. Most people suffering from chronic pain experience some level of reduced functionality or disability and they often develop comorbidities such as sleep disturbances, anxiety or depression. Unsurprisingly, chronic neuropathic pain patients often report a reduced quality of life. Chronic neuropathic pain affects about 7-10% of the world population, and therefore it is a major burden for the healthcare system and economy as well.

Treatment of chronic neuropathic pain has proven to be difficult. Less than 50% of patients respond to pharmacological treatment and the occurrence of severe side effects limits their use. Spinal cord stimulation (SCS) is an important and effective advanced treatment option for those chronic neuropathic pain patients which are resistant to pharmacological treatment.

There are multiple variants of SCS that are currently available for use and treatment of chronic neuropathic pain patients. Conventional tonic stimulation was developed in the 1970s and has been the sole SCS paradigm used in the clinic until the development of burst SCS and high frequency SCS in 2010. Conventional tonic stimulation is programmed at intensities above the sensory threshold, which results in tingling sensations, also known as paresthesias, covering the painful area. Some patients not only dislike these sensations but overstimulation may result in uncomfortable paresthesias as well. From a scientific point of view, the presence of paresthesias with conventional tonic SCS does not allow to study outcomes based on double blinded, placebo-controlled design. The latter type of studies are important in unbiased determination of SCS effectiveness. Paresthesia free (PF)-SCS paradigms, such as burst SCS, HF SCS, but also more recently developed paradigms such as Fast Acting Sub-perception Therapy (FAST SCS), now allow for blinded placebo-controlled studies.

Although an effective advanced treatment option, SCS is not without limitations. SCS is effective in about 50% of patients and produces generally about 50% pain reduction. In addition, the effectivity of SCS treatment on pain relief in chronic neuropathic pain patients has been shown to reduce over the course of multiple years of treatment and sometimes even becomes inefficient. It is therefore of utmost importance to optimize these PF-SCS paradigms in order to provide maximal pain relief for patients.

An important tool in the optimization of SCS paradigms is the titration and subsequent selection of parameters that may result in an optimal pain relief. SCS parameters include stimulation intensity (i.e. amplitude of stimulation pulse), pulse width and rate (i.e. frequency or number of pulses per second) [1]. Furthermore, charge balancing needs to occur to prevent buildup of positive charge, which may induce tissue damage otherwise. Charge balancing can occur in an active or passive manner. Varying all these parameters may result in the improvement of the pain relieving effect of the SCS paradigm in chronic neuropathic pain patients. Preclinical studies can be a valuable tool when optimizing parameters as the use of crossover designs allow for a rapid evaluation of a range of parameters. All but one of the preclinical studies presented in this thesis induce neuropathic pain through partial sciatic nerve ligation, a validated model of chronic neuropathic pain [2, 3]. Pain is measured as mechanical hypersensitivity based on hind paw withdrawal sensitivity to von Frey filaments. Neuropathic pain is considered chronic in this model if mechanical hypersensitivity is present after two weeks, which, considering the rodent lifespan in relation to the human lifespan is consistent with the human definition of chronic of pain being present for more than three months. Chapters 4 and 5 were aimed to evaluate the behavioral effect of 90 Hz SCS with varying parameters in order to select the optimal parameter settings. 90 Hz SCS is a preclinical SCS paradigm modeled after FAST SCS settings.

FAST SCS is a recently developed SCS paradigm and is a type of tonic stimulation, programmed with active charge balance below the sensory threshold. Initial clinical evidence showed that FAST SCS induces significant reductions in pain scoring on the NRS, persisting up to 6 months, with onset of analgesia occurring within minutes of programming [4]. The studies presented in Chapter 4 and 5 show that there are differences in 90 Hz SCS efficacy on reducing mechanical hypersensitivity based on charge balance and intensity. Optimal parameter settings for 90 Hz SCS (active charge balance, sub-sensory intensity of 40% motor threshold (MT)) were in line with clinical programming of FAST SCS, providing a good animal model for further investigation of the underlying mechanisms of action. Furthermore, there has been much discussion in the SCS-field on possible differences between active and passive charge balance, specifically related to burst SCS. Chapter 4 provides valuable information regarding this matter, as for 90 Hz SCS a difference in stimulation-induced pain relief between active and pseudo-passive charge balance was shown. Future studies should aim to elucidate the underlying mechanisms that bring forth the behavioral difference.

The amount of electrical charge delivered by an SCS paradigm is dependent on the combination of the different stimulation parameters (i.e. pulse width, frequency and amplitude) [1]. In Chapter 5, 90 Hz SCS is applied at different intensities, resulting in different amounts of electrical charge that is delivered during SCS, described as mean charge per second (CPS). Results from Chapter 5 show that the comparable behavioral efficacy of 50 Hz SCS at an intensity of 67% MT and 90 Hz SCS at 40% MT was related to an equal amount of mean CPS. From this, it is suggested that the use of mean CPS as treatment dose in SCS provides a new angle on the approach of optimizing SCS treatment.

A good understanding of the mechanisms of actions underlying the effectivity of SCS therapy in chronic neuropathic pain is a crucial aspect needed for further optimization of SCS-induced pain relief. In this context, studies in this thesis specifically focus on the involvement and role of the descending serotonergic system from brain to spinal cord (see Chapters 2, 3 and 6). Serotonin (5-HT) is a neurotransmitter with a complex and multifaceted biological function. Serotonin is mainly produced in the gut and brain and is involved in many processes including cognition, learning and memory, pain and mood but also intestinal motility and vasoconstriction. Dysregulation in the serotonergic system may result in depression and anxiety and contributes to chronic pain. It is because of the widespread involvement of serotonin in human physiology that antidepressant drugs are also used to treat chronic neuropathic pain. Descending serotonergic projections originating from the rostral ventromedial medulla in the brainstem to the spinal cord are very important in the modulation of nociceptive transmission in the spinal dorsal horn (SDH) [5]. Although much is known about the role of the descending serotonergic projections on modulation of the nociceptive network in the SDH of adult rodents, a better understanding of the changes in serotonergic modulation throughout the development of neuropathic pain and how this may be affected by SCS is urgently needed. The review described in Chapter 2 provides a clear overview on this matter, providing a detailed explanation on the involvement of the serotonergic system in the SDH in the healthy adult rodent, the neuropathic adult rodent and upon receiving SCS. Furthermore, the review in Chapter 2 highlights present gaps in our knowledge and thereby provides direction for the design of future studies to increase understanding on the serotonergic mechanisms in neuropathic pain and SCS and the improvement of SCS-induced pain relief in chronic neuropathic pain.

The review in Chapter 2 specifically focusses on the involvement of the brainstem-spinal serotonergic projections as related to efficacy of conventional tonic SCS, as there is

no information available on the involvement of the serotonergic system on analgesia induced by PF-SCS paradigms. Experimental studies as described in Chapters 3 and 6 of this thesis aimed to analyze the role of serotonergic brainstem-spinal cord projections in burst SCS (Chapter 3) and in 90 Hz SCS (Chapter 6). These types of neuroanatomical (Chapter 3) and pharmacological (Chapter 6) studies create a wider understanding on the involvement of the descending serotonergic system in the analgesic efficacy of burst SCS and 90 Hz SCS and are very important to create a foundation for mechanism-based optimization of not only these, but also other PF-SCS paradigms. The information in this thesis regarding the mechanisms of 90 Hz SCS may contribute to the optimization clinical FAST SCS as well, due to the similarities between the two paradigms.

As reported by long-term follow-up studies [6, 7], efficacy of SCS on pain relief tends to reduce over-time, a process also referred to as treatment tolerance. Treatment tolerance is of course a major issue for patients, as it results in an increased pain experience over the years. Treatment tolerance has been linked to plasticity and neural adaptation to the long-term and constant triggering of the nociceptive network through SCS. Besides the scientific need for more insight into the neural adaptations upon long-term SCS and treatment tolerance, different approaches to SCS may be required to prevent or delay this phenomenon. A potential solution may be the use of time-dynamic stimulation. Although the presented data result from a small-scale, proof of concept experiment, the results are promising and provide a starting point for future studies into time-dynamic SCS. Further development of time-dynamic PF-SCS parameters will be of scientific importance as unraveling the mechanistic underpinnings can result in a better understanding of neuronal responses to dynamic stimulation and create new insights into treatment tolerance. With the development of this type of PF-SCS, patients may receive prolonged pain relief and treatment efficacy through the reduction of tolerance.

The preclinical evaluation of pain in animal experiments is difficult as pain is a highly emotional experience. Animals cannot simply communicate their levels of pain through questionnaires as is the common way of evaluating pain in clinical studies. Most preclinical studies on pain utilize reflex-based, evoked tests such as von Frey filaments for mechanical hypersensitivity, Hargreaves for thermal hypersensitivity or the acetone test for cold allodynia, among others. From a translational point of view these test provide very limited information about the pain experience in patients, as they do not allow for the evaluation of spontaneous pain or assessment of emotional-affective and cognitive-motivational components of pain. This may explain why the translation of preclinical study results to the clinic often fails. The study described in Chapter 7 of this thesis uses electroencephalography (EEG) to measure spontaneous pain. As EEG can be used in both animal and human subjects and the inclusion of this type of measurement of spontaneous pain will increase translationability of study results. Spontaneous pain can also be measured in rodents through behavioral tests such as the conditioned placed preference test. Inclusion of operant tests such as the mechanical-conflict avoidance system (MCAS) allows the assessment of cognitive-motivational components of pain. Preclinical studies on burst SCS have shown a differential modulation cognitive-motivational aspects of pain compared to tonic SCS, as measured through MCAS exit latency [8]. Clinically, burst SCS was also shown to improve cognitive components of pain, measured with the pain vigilance and awareness questionnaire, whereas tonic SCS did not [9]. This suggests a difference in involvement of higher brain areas between burst SCS (i.e. PF-SCS) and tonic SCS. As this may be relevant for other PF-SCS paradigms such FAST SCS, the inclusion of operant tests are of utmost importance in future preclinical studies on PF-SCS paradigms to create a full understanding

of treatment efficacy of all aspects of pain and increase translationability to the clinic. Clinical studies on FAST SCS should therefore also include questionnaires aimed at cognitive-emotional aspects of pain to fully characterize SCS treatment effect and incorporate the results in treatment optimization strategies to maximize pain relief in patients.

In a broader perspective, the results presented in this thesis provide a strong fundament for future studies into a mechanism based optimization of PF-SCS paradigms. The exploration of mechanisms involved in PF-SCS-induced pain relief increases the scientific understanding of these SCS paradigms and the parameter titration studies emphasize the possibility of optimizing pain relief through adequate parameter selection and mean CPS dose. Although major steps still need to be taken in optimizing pain relief in chronic neuropathic pain patients with use of SCS and in particular with PF-SCS paradigms, the preclinical studies presented in this thesis provide a scientific foundation on which larger clinical studies can be build. This then will not only improve the life of chronic neuropathic pain patients but also reduce the social and economic impact of chronic neuropathic pain.

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