Neuromodulation of the dorsal root ganglion in experimental chronic neuropathic pain

Appendix

Valorization

Chronic neuropathic pain affects approximately 8% of the total adult human population and comes with significant burden for both the patient and healthcare system [1]. Patients often experience reduced functionality, which, in many cases results in them being uncapable of working. Chronic neuropathic pain is typically characterized by a low health-related quality of life; compared to other major diseases such as cancer, type-2 diabetes, and cardiovascular diseases, the health-related quality of life of patients with chronic neuropathic pain is significantly lower [2]. Because of the high prevalence of chronic neuropathic pain and the low health-related quality of life patients suffer from, chronic neuropathic pain forms a serious burden on both the healthcare system as well as the economy.

The effectiveness of pharmacological treatment of chronic neuropathic pain is often very limited, with less than 50% of patients responding to therapy. Furthermore, pharmacological interventions are often accompanied by unacceptable side effects such as development of tolerance and addiction [3]. It is therefore that further optimization of chronic neuropathic pain treatment is needed and it is in this context that the present thesis focusses on the role and mechanisms of action of interventional neuromodulatory approaches.

Interventional neuromodulation techniques such as spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRGS) and pulsed radiofrequency (PRF) often provide a suitable therapy for refractory neuropathic pain patients [4-16]. Moreover, the side effects associated with these types of interventional treatments are typically less severe than those associated with many pharmacological treatment options [3]. However, despite the many advantages, these neuromodulation techniques do not come without limitations. A substantial group of patients treated with either SCS, DRGS or PRF still do not respond to treatment or experience a lack of treatment success over time. In this light it is of utmost importance to understand why, when and how chronic neuropathic pain patients do not respond to these treatments. A mechanism-based approach which allows understanding of the mechanisms of action of these neuromodulatory treatments might result in improved efficacy of these therapies.

SCS with conventional settings (Con-SCS) has been successfully used to treat chronic neuropathic pain for over 50 years. Over the last decade, several new stimulation waveforms and new stimulation targets (such as DRGS) have been introduced to the field of SCS in order to further improve stimulation efficacy, while simultaneously eliminating some of the limitations with Con-SCS. One of the most prominent examples of innovation within the parameter space of SCS is the paresthesia-free Burst paradigm [17]. While indeed evidence suggests that Burst-SCS can yield superior pain relief compared to Con-SCS [17-19], especially related to the cognitive-affective dimensions of the pain experience, Burst-SCS still lacks the anatomic specificity (ability to stimulate difficult-to-reach areas such as the extremities and the groin) and stability (stable paresthesia intensity regardless of body position) of DRGS. Based on this knowledge, summarized in *Chapter 2*, we set out to combine for the first time the advantage of a new stimulation paradigm with a new location of SCS in an animal model of painful diabetic peripheral neuropathy (PDPN) in *Chapter 3*: burst stimulation of the dorsal root ganglion. From these experiments we concluded that while the maximum amount of pain relief was comparable between Con-DRGS and Burst-DRGS, Burst-DRGS, but not Con-DRGS, showed a delayed wash-out effect, which might have serious implications for optimal stimulation delivery of Burst-DRGS as well as battery life of the IPG in clinical practice. In line with this, preclinical observations have been extended to the clinic, where further clinical studies have been performed on the efficacy of Burst ''microdosing'', a paradigm that relies on the introduction of stimulation-off phases inbetween stimulation-on phases. From this it was concluded that Burst-SCS microdosing is as effective as standard Burst-SCS, while having significantly lower battery consumption (and thus fewer battery replacements for the pain patient) [20]. Whether or not such a microdosing approach can also be successfully utilized for Burst-DRGS remains to be studied. Interestingly, with the publication of our first preclinical study on Burst-DRGS in PDPN, one clinical study has been published utilizing Burst-DRGS in neuropathic pain patients [21]. The authors found that at the end of the 18 months treatment period, 78% of patients preferred the Burst-DRGS protocol over the Con-DRGS protocol. Burst-DRGS is currently being assessed formally, however, in a RCT that is under way (ClinicalTrials.gov identifier: NCT03318250).

Previous studies have indicated that Burst-SCS can be further optimized by adjusting relevant stimulation parameters, such as amplitude, in order to modulate the amount of charge delivered to the nervous system [22]. In *Chapter 4*, we titrated the optimal stimulation amplitude for Burst-DRGS to approximately 52% of the motor threshold (MT), and found a nonlinear relation between Burst-DRGS amplitude and pain behavior outcome. Combined with the results of *Chapter 3*, these results allowed us to further optimize Burst-DRGS to give a form of stimulation that delivers maximum pain relief, while at the same time minimizing battery consumption. As the chronic pain patient is likely to benefit from such an optimized treatment, future clinical studies should aim to verify these findings.

Besides the titration of optimal stimulation parameters, another important aspect for optimizing DRGS therapy is understanding its underlying mechanism of action. From the field of SCS we know that the presence of the neurotransmitter GABA in the dorsal horn of the spinal cord plays an important role in its mode of action [23-27]. This even led to translation to the clinic, where baclofen, a $GABA_B$ receptor agonist was used to rescue initial nonresponders to SCS, and turn them into responders [28, 29]. Similarly, gaining more insight into the mechanisms of action underlying DRGS might lead to improved treatment of the chronic neuropathic pain patient. While it was recently shown that DRGS is not likely to rely on the release of GABA in the dorsal horn of the spinal cord [30], it is possible that local, GABAergic signaling in the DRG is involved [31]. In *Chapter 5*, we therefore tested the hypothesis that a second GABAergic gate is responsible for the pain relieving effect of DRGS. Based on our immunohistochemical findings, we found no evidence for such a GABAergic gate located in the DRG. Still, we consider the presentation of these data to be of great importance, as publishing bias (skewed towards positive findings) is an important problem that the academic community has to deal with. Based on this work, we can now look for alternative modes of action of DRGS to further improve DRGS therapy for the pain patient.

In the last part of the thesis (*Chapter 6*) the efficacy of a PRF treatment adjacent to the DRG on experimental chronic neuropathic pain is investigated and described. Fundamentally, PRF greatly differs from DRGS in the way it is delivered (once vs continuous

delivery of current), something that is also expressed in the differences between the duration and amount of pain relief obtained with these two therapies. We showed that treatment with PRF to the DRG significantly attenuated mechanical and thermal hypersensitivity, albeit to lesser extent than DRGS (*Chapter 3 and 4*), whereas no effect was observed on pain-related gait using the CatWalk system. With our study, previous findings [32] related to the pain relieving effect of PRF were confirmed, something which is important when establishing a reproducible and valid animal model for studying the effects end mechanisms of action of a given treatment. At the same time, our, and previous [33] data strongly suggests that CatWalk gait analysis does not allow to detect or analyze behavioral effects of interventional treatment approaches such as PRF and SCS in the chronic experimental PSNL model. Nevertheless, studying behavioral effects (short or long-lasting) is still an issue in the experimental pain field and may make the impact of pain relieving effects and the interpretation and translation of findings to the clinic very difficult. To date, reflex-based outcome measures such as mechanical hypersensitivity (e.g. Von Frey test) and thermal hypersensitivity (e.g. Hargreaves test) are considered to be the golden standard in experimental pain research. However, as these tests are rather subjective and rely on evoked nociception instead of spontaneous pain, they are not optimal. Future studies should therefore aim to include more operant-like tests that also take into account the affective-emotional and cognitive aspects of pain in order to improve the translational significance of preclinical observations.

From a practical point of view, the results presented in this academic thesis provide strong arguments for continuing experimental research on the efficacy and mechanisms of action of neuromodulation of the DRG in experimental chronic neuropathic pain. This should then be based on an orchestrated interplay between reproducible experimental animal studies and well-designed large, (preferably) non-industry initiated clinical trials. Given the fundamental differences in terms of efficacy and duration of pain relief between DRGS and PRF, they are very likely to depend on different mechanisms of action. By gaining more insight into these mechanisms of action, the efficacy of interventional pain treatments for the

chronic neuropathic pain patient might significantly increase, thereby reducing the societal and economic burden of chronic neuropathic pain as a disease.

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