Neonatal procedural pain

Impact Paragraph

In this section the scientific and societal impact of the research described in this thesis will be discussed.

Scientific impact of experimental neonatal pain research

Significant advances have been made in the understanding, recognition and management of neonatal pain over the last three decades. The scientific field of neonatal pain research has shifted from a general believe that human neonates did not consciously experience, remember, or respond to painful stimuli, to the present understanding that nociception and pain are already apparent in neonates from 20-24 weeks of gestation. Today, the importance and optimization of pain management for neonates is widely acknowledged. Effective management of pain in neonates is necessary to minimize acute physiological and behavioural distress, but also to improve the potential long-term and negative effects. However, at this stage many questions remain that cannot easily be answered in humans. In this context preclinical research has provided tremendous information regarding the development of the nociceptive system in neonates based on clinical relevant juvenile animal models [1]. Common painful procedures such as heel sticks in the neonatal intensive care unit (NICU) are mimicked by repetitive needle pricking as described in **Chapters 2, 4 and** 5 of this thesis. A growing body of evidence reports long-term consequences of painful experiences during a critical window of development, where changes in somatosensory and brain development, mood/anxiety, pain responses and cognitive functioning are observed [1,2]. So far, research has not yet focussed on alterations in descending inhibitory pathways that control the balance of excitation and inhibition at the level of the spinal dorsal horn, the most important level of central nociceptive and somatosensory processing [3]. Serotonergic projections originating in the rostral ventromedial medulla play an important role in this descending modulation of spinal nociception [4].

The studies described in this thesis aim to unravel the involvement of descending serotonergic projections from the brainstem rostral ventromedial medulla in the mechanisms underlying the long-term effects of neonatal procedural pain. In doing so, we provide a first read-out of injury-induced plasticity in supraspinal areas involved in processing of both pain and anxiety. In this thesis, we have provided clarity in the contradicting evidence for long-term effects of neonatal procedural pain on anxiety. In **Chapter 2** we point to a distinct profile of (state) anxiety affected by neonatal procedural pain when investigating these in separate and validated behavioural constructs in rodents. This may provide the foundation for future clinical studies to integrate tests measuring

different anxiety profiles in former NICU patients, an area that is hardly investigated in a structured manner.

Although descending modulation forms an important aspect of the nociceptive network there is an unmet scientific need for a better understanding of the descending serotonergic projections that regulate pain processing throughout postnatal development. The review in **Chapter 3** describes the postnatal development of such serotonergic projections, and highlights important developmental differences in anatomy and function at different developmental phases in rodents. This review contributes to the scientific field by providing an extensive overview of the anatomy and functionality of descending serotonergic projections throughout the life span, not only focussing on the adult system. The latter also demonstrates that the descending serotonergic projections show high plasticity in neonates, and excessive stimulation that intervenes with this normal development may result in long-lasting changes. Evidence for structural anatomical changes in this descending serotonergic system after painful stimulation in neonates is described in **Chapter 4.** The results point to a potential role of descending serotonergic projections in the modulation of injury-induced long-term effects. This is the first time that anatomical alterations in serotonin projections are described after pain in early life. This information can be placed in the context of other injury-induced changes in the nociceptive network in both a pre-clinical and clinical setting. Pain management may also be targeted to restore these anatomical alterations in descending serotonergic projections using the concept of pre-emptive analgesia targeted at the serotonergic system in future research. When doing so, the presence or absence as well as the functionality of specific serotonergic receptors should be taken into account using knowledge of the developing neonatal nociceptive system. This may provide new therapeutic venues for pain management in neonates and changes the focus of therapy from opioids presently considered a first choice drug following major tissue injury in the NICU.

Adequate pre-emptive pharmacological therapy to manage the acute pain associated with skin-breaking procedures in neonates may play an important role in preventing the long-term negative effects observed in both clinical and pre-clinical studies. Moreover, long-term effects of neonatal procedural pain are not limited to somatosensory processing, but also affect anxiety behaviour as described in **Chapter 2.** Going forward, greater emphasis should be placed on pain management that also mitigates these adverse effects of pain exposure such as the serotonergic system. The pharmacological studies in **Chapter 5** use developmentally identified serotonin receptor targets within the descending serotonergic system selected based on the review in **Chapter 3**. Studies like these

contribute to establishing the scientific foundation the clinical field needs to provide adequate analgesia in neonates, along with increased knowledge of neonatal pharmacodynamics and pharmacokinetic data.

Anticipated societal impact

Worldwide, one of every ten babies are born prematurely (<37 weeks of gestation). The increased survival rates after preterm birth present a public health concern and economic burden due to high costs of hospitalization and long term sequelae even in adulthood, especially in extreme low birthweight infants. While hospitalized in the neonatal intensive care unit (NICU) preterm babies undergo up to 14 painful procedures daily [5]. Using a clinically relevant rodent model that mimics common painful procedures in the NICU, as described in this thesis, can deepen our in-depth knowledge of the effect of interventions like repetitive neonatal procedural pain on the neurobiology and plasticity of the nociceptive system. The neurobiology of neonatal pain processing differs significantly from more mature infants, children, adolescents and adults. This thesis shows that within the descending serotonergic projections that regulate pain sensitivity, developmental differences in function occur and plasticity changes are observed after neonatal interventions such as repetitive procedural pain, depending on the developmental phase. Moreover, in contrast to underlying diseases as rationale for admission to the NICU that can usually not be prevented, the number of painful preventions can be decreased by an active attitude of treatment teams based on more knowledge on the neurobiology provided by this thesis.

Individual pain sensation is naturally variable and depends on subjective experiences. Descending modulatory systems have been associated with individual differences in pain perception and response to analgesic therapy. Moreover, impaired descending inhibition may contribute to individual risk factors of the development of chronic post-operative pain [6]. Early life adversity such as repetitive neonatal pain exposure may also increase the risk of the development of (chronic) pain syndromes in later life [7]. This thesis shows that descending serotonergic projections play a role in the mechanisms of neonatal pain-induced long-term consequences, including longer post-operative recovery after surgery in adulthood. Permanent alterations in descending serotonin signaling may contribute to impaired descending inhibition in later life leading to a higher risk of developing chronic postoperative pain. A better understanding of descending serotonergic modulation and its role in later-life pain perception contributes to identifying individuals most at risk for long-term effects after NICU admittance. For obvious reasons

other factors have to be taken into account, such as major operative procedures in selected infants, cumulative dose of analgesics, and whether opioids or other classes of drugs were used. Apart from structured follow up, quantitative sensory testing in ex-preterm neonates can be used to identify impaired descending inhibition as an essential tool for pre-operative risk assessment.

Inadequate pain management in neonates impairs neurodevelopmental outcomes (including sensory, cognitive, motor and affective behaviors) [2]. Despite increased knowledge of the developing pain system and a long list of non-pharmacological and pharmacological strategies, pain management remains suboptimal in the neonatal intensive care unit. Results from this thesis provide a new therapeutic venue targeted towards the descending serotonergic system. Using a mechanism-based approach the serotonergic system can be modulated in rodents to prevent neonatal injury-induced acute and long-term effects. Currently serotonin-mediated analgesia is not used in the NICU. At this stage, the findings presented in this thesis are still too preliminary to result in any clinically used pharmacological therapies for the NICU. The wide variability of patients regarding post conceptual and postnatal age with inherent differences in response to pain, the use of validated assessment instruments, evolving liver and kidney function, receptor density and maturation have to be taken into account to reach the next step of therapy. Certainly, one size fits all is an oversimplification of this complex problem. Nevertheless our preclinical studies do provide a foundation for serotonin-mediated therapies that may be effective in the management of procedural pain in the human neonates in the future.

References

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