From nociception to perception

IMPACT PARAGRAPH

Disorders of the gut brain interaction (DGBIs) are highly prevalent disorders, with an overall prevalence of 40% worldwide. Many DGBI, including irritable bowel syndrome (IBS) and functional dyspepsia (FD), are characterized by chronic visceral pain. Chronic visceral pain constitutes a substantial clinical challenge with largely unmet medical needs, as underlying mechanisms are incompletely understood. Factors of influence are related to cognition, affect and behaviour, including learning and expectations around pain, and comorbid mood and anxiety disorders. Chronic visceral pain is associated with high patient burden and decreased quality of life, and results in increased healthcare seeking behaviour. Similar to somatic chronic pain syndromes, the misuse of opioids is major problem. In the USA for example, this misuse has reached epidemic proportions. Importantly, opioids can result in a paradoxical effect in visceral pain, further escalating symptoms upon opioid continuation, which is referred to as narcotic bowel syndrome. New treatment strategies in chronic visceral pain are necessary to meet the needs of this large patient group, and to reduce healthcare resource utilization and associated costs.

In the first part of this thesis, we focus on molecular aspects of pain, in particular transient receptor potential (TRP) channels as promising targets for visceral pain management. Studies indicate sensitization and/or increased expression of TRP channels in IBS. Unfortunately, direct antagonism of these channels has shown to be associated with various side effects, mainly due to the involvement of TRP channels in a wide range of physiological functions (e.g. thermosensation and thermoregulation). The reversal of sensitization and overexpression could provide a better approach, as this does not alter physiological functions. More detailed insights in these processes is necessary to develop such therapies. We have therefore here reviewed TRP channel involvement in visceral pain in inflammatory and non-inflammatory conditions. It is unclear to what extent inflammation has a role in TRP channel regulation in chronic visceral pain in DGBIs. Other mechanisms will need to be explored in future studies. For example, we have shown that ageing results in decreased visceral sensitivity and decreased TRPV1 and TRPA1 expression. This natural analgesic process could provide new clues for TRP channel regulation, and therefore holds significant therapeutic potential in chronic visceral pain.

One of the major challenges in the development of new pain treatment strategies relates to the large heterogeneity of DGBI patients. Phenotyping, even in specific syndromes such as IBS and FD, is difficult. It is likely that underlying mechanisms in visceral hypersensitivity differs among patients, affecting treatment outcome. In the second part of this thesis, we investigated the overlap between DGBI and hypermobility spectrum disorder (HSD), a condition characterized by increased mobility of joints. IBS and FD are highly prevalent among HSD patients, and vice versa, we showed a high

prevalence of HSD in a cohort of IBS patients. However, we did not find differences in gastrointestinal symptomatology or comorbid affective disorders in HSD and non-HSD IBS patients, arguing against a separate clinical entity. We furthermore found no evidence for increased pain sensitivity during colonoscopy in HSD patients versus non-HSD. HSD patients with DGBI therefore do not seem to require an alternative management approach. Alternate identifiers will need to be explored to optimise DGBI patient phenotyping.

In the third part of this thesis, we have investigated the propagation and integration of visceral pain signals using a novel visceral pain model. The brainstem has a central role in the relay of visceral signals, which in particular includes the nucleus of the solitary tract (NTS), the principal relay station for visceral afferents. We demonstrated NTS activation following capsaicin infusion in the duodenum in healthy individuals. Moreover, the NTS was activated irrespective of the subjective pain response. The NTS, or projections from the NTS, appear to serve an important role in determining which signals are ultimately perceived as painful. It can be speculated that stimulation of the NTS, such as via transcutaneous vagus nerve stimulation (tVNS), might interfere with nociceptive signals, disrupting their propagation. As such, we have recently acquired ethical approval for a study combining our visceral pain model with tVNS (active versus sham stimulation during capsaicin infusion). This study will help to identify whether the NTS is indeed an attractive treatment target for chronic visceral pain, and thereby expand basic scientific evidence for existing treatment options, such as tVNS, deep breathing exercises and mindfulness.

Finally, the incorporation of detailed symptom registration methods in research could aid treatment development. In this thesis, we report on experience sampling method (ESM), also known as ecological momentary assessment, as an easy to use and highly informative symptom sampling method. Adding ESM aids patient stratification, as for example symptom patterns and triggers differ between patients. It will be particularly interesting to add ESM to neuroimaging studies, to investigate whether phenotype-based patient stratification reflects on brain activity patterns. Such combinations could then help identify patient subgroups, possibly aiding the discovery of specific underlying mechanisms of pain sensitivity, development of new treatments and finally the prediction of treatment outcome.