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Editorial overview: physiology of pain

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Lucy F Donaldson

Lucy Donaldson began her career as a dentist, training in Edinburgh, but realised the joys of neuroscience were more fulfilling that a life in saliva, when she intercalated a degree in neuroscience. There she developed an interest in pain, which translated into a PhD in which she spent time with many inspiring people in the Scottish nociception/pain field, such as Ainsley Iggo, Alan Brown, Arthur Duggan, at the University of Edinburgh. She has worked at UC Davis, and the Universities of Leicester and Bristol before moving to the University of Nottingham. She leads a research group focused on mechanisms of acute and chronic inflammatory pain, recently focusing on the contributions of alternative RNA splicing, vascular endothelial splice variants, and neuro-glial-vascular interactions in pain processing. She is also the University Associate Pro-Vice Chancellor for the Graduate School, and co-founder and equity holder in two companies focused on the development of novel inhibitors of alternative pre-mRNA RNA splicing for various indications, including pain. In her copious free time, she paints, practices yoga and tries vainly to keep the garden under control.

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When we were invited to co-edit this issue of *Current Opinion in Physiology* with a focus on nociception and pain, we aimed to build a 'go-to' physiology issue that would be of use to as many people as possible. We wanted to include undergraduate students who needed some approachable depth or detail on a specific topic, postgraduate researchers seeking a good grounding in the area, and more seasoned researchers in the field aiming to refresh or expand into a new area. Although the issue includes a plethora of wide-ranging, interesting and timely reviews in the ever-expanding area of nociception and pain physiology, it unfortunately cannot cover everything. We hope however that there will be something in this issue of interest to everyone.

Since we embarked on our research careers, the understanding of nociceptive and pain physiology has advanced enormously, alongside and certainly enabled by technological advances over the same time. We are amazed on a daily basis about how much more we now understand, and of course, how much is still very unclear. Thirty years ago, mechanisms of transduction and nociceptive neuronal modality specificity were unknown, nociceptive pathways were linear and consisted of a chain of three (!) neurons between the periphery and the cortex. We had relatively limited, often (and still) debated animal models in which to study the mechanisms of inflammatory and neuropathic pain, which were first distinct, then common, then different again. The possibility of an influence of sex on nociception and pain was never a consideration in research, nor in the clinic. Study of interactions between affective and nociceptive areas of the brain, sleep, diet, microbiome or the environment and pain were rare. That the immune system could modulate central nervous system activity, and that glia cells did anything other than support neurons and mop up potassium ions had never crossed anyone's mind. For a long time, it was held neonates did not feel any pain, and no-one had ever considered the impact of early neonatal and adolescent pain experience on the development of the nervous system or future pain experience. Of course, we now know that many of these beliefs were oversimplified, needed more nuanced interpretation, or were just incorrect. Articles in this issue cast a spotlight on advancements in many of these areas, aim to give both concise overviews and updates on recent findings in the area, and highlight important additional references for those wishing to delve deeper into individual areas.

Cheryl Stucky is the Marvin Wagner Endowed Chair at the Medical College of Wisconsin (MCW). She is also Director of the Neuroscience Doctoral Program and Director of the Pain Division of the Neuroscience Research Center at MCW. Cheryl grew up on a wheat farm in central Kansas, received her BA in Biology and Psychology from Bethel College in Newton, Kansas. She then earned her Ph.D. in Neuroscience at the University of Minnesota. After this, she moved to Germany to pursue postdoctoral research first at the University of Würzburg in Würzburg, Germany, and next at the Max Delbruck Center for Molecular Medicine in Berlin, Germany. She is currently the lead principal investigator on three NIH individual investigator grants from the National Institute of Neurological Disorders and Stroke. One of these is a recent Jacob Javits award for seven years of funding. Cheryl's lab studies the molecular, cellular and physiological mechanisms of sensation, particularly how we sense touch and pain. She is interested in how our skin cells communicate with sensory neurons to convey touch and cold, the causes of severe pain in sickle cell disease, migraine pain, and the causes of neuropathic and inflammatory pain. She loves training graduate students, postdoctoral fellows and technicians, and teaching them to write grants, papers and give talks. She also enjoys designing jewelry for more right brain activity.

As undergrads and postgrads, for us, the specifics of nociceptive-specific transduction and neuronal conduction were an enigma, although one that was just starting to be solved with advances in molecular cloning and sequencing. The cloning of TRPV1 was certainly a landmark in nociceptive transduction. The identification of the functions of multiple key molecules and channels in nociceptive transduction and transmission has led to breakthroughs in the characterisation of different groups of primary afferents at the molecular and functional levels. Despite major advances in our understanding of (arguably) the simplest aspect of the nociceptive system, primary afferents, their categorisation, functions and encoding of information is still an area of hot debate. Two articles in this issue address this in great depth, combining data from multiple studies taking different approaches, from the molecular to physiological study of over 1000 identified sensory afferent neurons. These articles aim to reconcile emerging contradictory data on peripheral nociceptors and peripheral modality coding.

An area in which some real advances in understanding have been made is that of the development of nociceptive systems and the impact of early exposure to pain. Four of our contributors address different aspects of this — from childhood chemotherapy and peripheral neuropathy, the effects of early exposure to pain, nociceptive processing and descending controls, to mood, pain and sleep in adolescents, bringing the coverage of this emerging area up to date. Input from the primary afferents is key to many of the central changes that occur as a consequence of the types of peripheral injury that can lead to chronic pain, and they continue to drive pain in many people. The CNS changes consequent to this peripheral input are also obviously fundamental to the initiation and maintenance of chronic pain. Many of the reviews in the issue concentrate, unsurprisingly, on the huge advances made in this area over the last thirty years. There have been incredible steps forward in our appreciation of the different classes and functions of spinal projection and interneurons, and in the functions of spinal and higher centres circuits, both inhibitory and facilitatory, in the processing of both pain and itch. We now better understand the common and distinct mechanisms underpinning multiple different pain states from inflammatory to skeletal and neuropathic pain. We are beginning to dissect mechanisms in the most intransigent of pain states, such as fibromyalgia, with the incredible tools advanced imaging technology is giving us. Of key importance is how predictive each of our findings in animal pain models will be to human pain. It is tremendously exciting that more mechanistic research with human DRGs, skin and human-derived IPSC cells are now being done by many labs , and these findings can be compared to those from animal models. We anticipate that important discoveries of similarities and differences between humans and our animal models lie just around the corner and this knowledge will advance the translatability of our discoveries that will change patients' lives. It is also truly inspiring to see major advances in open collaboration, assistance and information sharing, such as data base sharing, searchable website tools, human tissue sharing, and 'in kind' research partnerships between academic labs and pharmaceutical companies. Together, these significant advances will have huge impact on people living with such difficult, long-term painful conditions.

As a result of these leaps in our understanding in the last few decades, our undergraduate and postgraduate curricula now emphasise many things we would have previously dismissed as irrelevant to pain, such as neuronal remodelling/sprouting, the emerging importance of glia, central neuroimmune processes, our sex and genetics OR EPIGENETICS, co-morbidities such as anxiety and depression, and even our internal and external

environments. New technologies and models continue to help push the boundaries of understanding and translatability. We have come a long way over such a short time.

This special issue thus contains a diverse collection of reviews, spanning myriad aspects of pain physiology. As such we hope that we have succeeded in building an issue that will be a useful resource for our research community, as well as one that showcases exciting recent advances across pain physiology.

- New discoveries in migraine mechanisms and therapeutic targets 10.1016/j.cophys.2019.10.013.
- Mechanisms underlying non-malignant skeletal pain 10.1016/j.cophys.2019.10.003.
- Spinal cord projection neurons: a superficial, and also deep, analysis 10.1016/j.cophys.2019.10.002.
- Pain Bugs: Gut Microbiota and Pain Disorders 10.1016/j.cophys.2019.10.001.
- The Changing Role of Descending Control of Spinal Nociception Over Postnatal Development 10.1016/j.cophys.2019.08.003.
- ADVANCES IN ASSESSMENT OF PAIN BEHAVIORS AND MECHANISMS OF POSTOPERATIVE PAIN MODELS 10.1016/j.cophys.2019.07.002.
- Analgesia for non-mammalian vertebrates. 10.1016/j.cophys.2019.07.001.
- Chronic non-inflammatory muscle pain: central and peripheral mediators 10.1016/j.cophys.2019.06.006.
- Descending pain modulation: Influence and impact 10.1016/j.cophys.2019.06.004.
- Chronic Pain and Childhood Cancer Survivorship 10.1016/j.cophys.2019.06.002.
- Inflammatory pain neural plasticity 10.1016/j.cophys.2019.06.001.
- Recent advances toward understanding the mysteries of the acute to chronic pain transition 10.1016/j.cophys.2019.05.015.
- Rewards, perils and pitfalls of untangling spinal pain circuits 10.1016/j.cophys.2019.04.015.
- Somatosensation a la mode: plasticity and polymodality in sensory neurons 10.1016/j.cophys.2019.04.014
- The Interrelationship between Sleep and Chronic Pain in Adolescents 10.1016/j.cophys.2019.04.012.
- Early life pain â€ "effects in the adult 10.1016/j.cophys.2019.04.011.
- Supraspinal neuroimmune crosstalk in chronic pain states 10.1016/j.cophys.2019.03.008.
- Sex differences and mechanisms of muscle pain 10.1016/j.cophys.2019.03.006
- Nociceptor subtypes and their incidence in rat lumbar dorsal root ganglion (DRG): focusing on polymodal nociceptors, Aβ-nociceptors, Aβ-moderate pressure receptors and their receptive field depths 10.1016/j.cophys.2019.10.005.

Finally, we gratefully acknowledge all the hard work of the contributors and reviewers, and the editorial team at *Current Opinion in Physiology*. In particular, we thank Kathleen Sluka for the additional contribution of the cover image for this issue. We deliberated over several of Kathleen's amazing images (www.kathleenslukaart.com) before deciding that 'Pain Brain' was the best to represent this issue.