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EDITORIAL
Neurotrophin and endocannabinoid interactions in the neurobiology of pain

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Pain, broadly defined as an unpleasant sensory and emotional experience varying in severity as a consequence of disease or actual or potential tissue damage (Geber *et al.*, 2009), is by far the most common debilitating condition for which patients seek medical treatment. The cumulative incidence of acute and chronic pain is estimated to be in excess of ~500 million cases per year worldwide (Turk *et al.*, 2011). Patients with chronic pain represent ~25% of the adult population with further increases forecast as our population ages. Despite the general incidence of pain, and the loss of work performance and reduced quality of life of affected individuals, treatment options are surprisingly limited. The medical treatment of a large percentage of patients is considered unsatisfactory, due to side-effects outweighing therapeutic benefits and/or progressive reduction in drug efficacy upon chronic use (Breivik *et al.*, 2006). Therefore, intense research is directed towards the development of efficacious treatment options.

The neuronal pathways transmitting nociceptive information to the brain to evoke evasive motor commands and emotional responses are hierarchically organized. The essential blueprint of ascending pathways includes the encoding of sensory stimuli by polymodal peripheral nociceptors, which are sensory neurons specialized to only respond to some stimuli of noxious intensity. The central synapse of these first-order neurons terminates on second-order neurons in the dorsal horn of the spinal cord, whose axons form ascending pathways towards the brain stem, midbrain and thalamus. Here, third-order neurons relay sensory information to higher CNS areas, including the cerebral cortex. Despite this ordered layout, pain pathways emerge as a string of complex information-encoding units, with many local neurons and neuromodulatory signalling systems (e.g., endocannabinoids at spinal nociceptor synapses; Kato *et al.*, 2012) to refine and gate signal transduction. Therefore, decoding the molecular organization and plasticity of the pain system will be of major therapeutic significance.

This Special Issue entitled *Neurotrophin and Endocannabinoid Interactions in the Neurobiology of Pain* is a compilation of 16 reviews and original research articles. This mix of reviews and primary research articles reinforces the emergence of focal points of broad scientific interest, and suggests innovative strategies for medical intervention, which promise increased and long-lasting benefits whilst considering the effective reduction of side-effects. The contributions of some of the leading research groups working on endocannabinoids, neurotrophins and their molecular interactions in this Special Issue are naturally exciting, and are hoped to serve as guideposts for the broader Neuroscience community for years to come.

We start by dissecting pathogenic mechanisms underscoring nociceptive and neuropathic mechanisms of chronic pain, with specific emphasis on skeletal pain (Mantyh, 2014) and osteoarthritis pain (that is, associated with degenerative joint disease; La Porta *et al.*, 2014), and by discussing the role of major genetic variations (Capsoni, 2014; Di Lorenzo *et al.*, 2014; Indo, 2014). Next, contributions are aimed at disentangling novel nodes of pain-related signalling in neurons; in particular, they address with outstanding precision and attention to novel facets of information the specific contributions of both endocannabinoids and neurotrophins, more specifically nerve growth factor (NGF) and its receptors, at successive levels of hierarchically organized pain pathways (Horváth *et al.*, 2014; Hu *et al.*, 2014; Keimpema *et al.*, 2014).

Of critical importance are the signalling systems that contribute to both neuropathic and inflammatory (that is, focal immune response at the site of injury) components of pain (La Porta *et al.*, 2014). As such, NGF and its receptor system(s) have emerged as key regulators of both processes. Tissue injury leads to excess NGF production and release by infiltrating immune cells (e.g. macrophages), which triggers the rapid sensitization of nociceptors, reducing the threshold for pain sensation (allodynia) and increasing the pain intensity experienced (hyperalgesia; Devesa & Ferrer-Montiel, 2014). Human genetic evidence validates NGF as a molecular target as mutations in both the *NTRK1* and *NGF* genes (encoding the TrkA receptor and NGF, respectively) cause congenital forms of insensitivity to pain in humans (Capsoni, 2014; Indo, 2014). The therapeutic relevance of an anti-NGF therapy for pain is highlighted by the analgesic potency of anti-NGF monoclonal antibodies in experimental models of cancer, osteoarthritis and neuropathic pain, as well as in clinical trials, in which long-lasting and remarkable (45–62%) pain reduction has been reported (Seidel & Lane, 2012). For this reason, the clinical development of humanized or human anti-NGF (Lane *et al.*, 2010; Covaceuszach *et al.*, 2012) or anti-TrkA (Ugolini *et al.*, 2007) antibodies is currently being pursued as a novel class of pain drugs based on antagonism of the NGF system (Hefti *et al.*, 2006; Pezet & McMahon, 2006). However, the potential liabilities of targeting the pleiotropic NGF system for pain (Cattaneo, 2010), as well as the observed adverse events in anti-NGF clinical trials (McKelvey *et al.*, 2013), call for more research into the mechanisms of how the neurotrophin system modulates pain responses and how

it interacts with other signalling systems, among which endocannabinoid signalling is of primary importance. Thus, a critical aim of this Special Issue is to present and discuss the available understanding of key molecular mechanisms.

The most common approach to the study of neurotrophin functions is the analysis of the effects of mature neurotrophins (Keimpema *et al.*, 2014), yet the identification of secreted pro-forms of neurotrophins, particularly proNGF, and the fact that proNGF engages a sortilin-$p75^{NTR}$ complex (alternative to TrkA-mediated signalling), suggests an unexpected diversification of (patho-)physiological functions. Here, Lewin & Nykjaer (2014) present a compelling case that this alternative receptor system has independent functions in inflammatory and neuropathic pain.

The endocannabinoids, a family of small signal lipids, act as agonists at G protein-coupled CB1 and CB2 cannabinoid receptors (CB_1R/CB_2R) and likely GPR55. Moreover, arachidonoyl ethanolamine (anandamide), a major endocannabinoid in the nervous system, activates transient receptor potential vanilloid subfamily type 1 (TRPV1) channels (Devesa & Ferrer-Montiel, 2014). Notably, NGF signalling can directly modulate TRPV1 channel functions and increase its membrane surface availability (Zhang *et al.*, 2005). Mounting evidence supports the idea that NGF also regulates endocannabinoid bioavailability and signalling by the coordinated control of mRNA expression and protein stability for degrading enzymes and the CB_1R (Keimpema *et al.*, 2013). Therefore, our collection of scientific reports on neurotrophin–endocannabinoid interactions opens with Keimpema *et al.* (2014) setting forth the hypothesis that the overlap between the cellular functions and subcellular positioning of neurotrophin and endocannabinoid signalling systems denotes coordinated functions, particularly at the level of orchestrating effector cascades conferring signal competence and cell type-specific responses. Whilst molecular data on neurotrophin–endocannabinoid interactions are predominantly available from developing neuronal systems, a case is made for similar molecular interactions to exist in the adult, including under pathological conditions.

Next, Schwaller & Fitzgerald (2014) outline the concept that developmental modifications to nociceptive pathways, which can range from erroneous network wiring ('direct hit') to maladaptive synaptic neurotransmission (that is, reduced adaptation and pain manifestation in response to subthreshold stimuli; 'second-hit hypothesis'), exert life-long adverse effects by not only increasing pain focally but also spreading over more distal parts of the body. The authors discuss the involvement of nerve sprouting, neuronal sensitization and neuroimmune priming underscoring increased pain, and changes to stress responses during later life. Endocannabinoid signalling is proposed as an appealing target for future investigations, particularly as these contribute to the assembly of neuronal networks during infant development (Keimpema *et al.*, 2014) and protect against cell death brought about by neonatal sciatic nerve injury (Perez *et al.*, 2013).

In the adult, molecular components of endocannabinoid metabolism, as well as CB_1R and TRPV1, are expressed at many levels in neuronal pathways (dorsal root ganglia, spinal dorsal horn, periaqueductal gray, hippocampus, neocortex) transducing nociceptive information (Hohmann & Suplita, 2006; Horváth *et al.*, 2014; Hu *et al.*, 2014). Exogenous administration of endocannabinoids (2-arachidonoylglycerol is shown here; Rea *et al.*, 2014) and phytocannabinoids (Hu *et al.*, 2014) suppress noxious stimulus-evoked neuronal activity in nociceptive neurons in the spinal cord, periaqueductal gray, thalamus and hippocampus in a cannabinoid receptor-dependent fashion (for review see Hohmann & Suplita, 2006). Moreover, 'on-demand' endocannabinoid production is driven by G protein-coupled receptor (GPCR) signalling through Gq inducing a phospholipase C-*sn*-1-diacylglycerol lipase cascade (Hu *et al.*, 2014). Metabotropic glutamate receptors (mGluRs) are prime candidates for inducing endocannabinoid production. Here, Palazzo *et al.* (2014) describe the synaptic localization, cell type- and area-specificity of mGluRs, and discuss the potential use of subtype-selective mGluR ligands for pain relief. In addition, Ji & Neugebauer (2014) demonstrate that CB_1R and mGluR coactivation is beneficial, with CB_1R agonists gating mGluR5 function. In view of the above evidence, it is not unexpected that genetic disruption or pharmacological blockade of endocannabinoid degradation and CB_1R and CB_2R agonists can be exploited to reduce nociception (Hu *et al.*, 2014).

In contrast, TRPV1, TRPA1 and TRPM8 (the latter ones also known as thermoTRPs; Devesa & Ferrer-Montiel, 2014) contribute to generating painful signals. Thus, the co-expression of CB_1Rs and TRPV1 channels and the sensitivity of their crosstalk to NGF (Evans *et al.*, 2007) at, e.g., primary sensory neurons, adds additional levels of complexity to the design of efficacious therapeutic strategies because unwanted TRPV1 activation by endogenous anandamide upon inhibitioning its degradation can outweigh CB_1R-induced analgesia (Sousa-Valente *et al.*, 2014).

Presynaptic CB_1Rs are generally considered the primary receptor system transducing endocannabinoid effects in the nervous system. Recently, however, functional CB_2Rs have been characterized in the brainstem (Van Sickle *et al.*, 2005), glial CB_1Rs have been associated with impaired synaptic neurotransmission (Han *et al.*, 2012), and increased CB_2R expression on infiltrating microglia at lesion sites has been shown to partake in chronic neuroinflammation. The mind-provoking review by Luongo *et al.* (2014) discusses how microglia–astroglia–neuron signalling and metabolic axes via CB_2R and non-cannabinoid receptor-mediated mechanisms shape endocannabinoid signalling in pain states, and emphasize that the glial niche can provide radically new opportunities for pain therapy.

We hope this Special Issue appropriately reflects contemporary advances blending relevant knowledge at the molecular, cellular and systems neurobiology levels, and from specialist technologies to novel, clinically-relevant avenues of the pharmacotherapy of pain. Furthermore, we expect this collage of papers to be a first step in bringing together two mechanistically-related research fields, which have so far been largely studied in isolation. These studies unite in a striking 'take-home message': while neurotrophins and TRP channels orchestrate painful signals, endocannabinoids primarily protect against pain; and an exploitable pharmacological niche exists to cross-modulate these signalling systems for improved therapeutic benefit. We are confident that each contribution in this Special Issue is an exemplary reference which, on its own merit, will have great value not only in attracting cross-disciplinary endeavors but also in sparking the interest of neurobiologists for investigating further the complex hierarchical organization of pain circuits and the precise orchestration of their function. This, ultimately, will take us closer to the development and safe clinical use of powerful, and probably personalized, medications to alleviate pain.

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