**Molecular basis for novel analgesic interventions**

**CHRONIC PAIN IS AN IMPORTANT PROBLEM REMAINING AN UNMET NEED BECAUSE EXISTING ANALGESIC TREATMENT IS OFTEN INEFFECTIVE ESPECIALLY WHEN ASSOCIATED WITH DAMAGED NEURONS. CHRONIC HYPERSENSITIVE PAIN IS MAINTAINED BY MOLECULAR CHANGES WITHIN THE NERVOUS SYSTEM THAT DO NOT APPEAR TO OCCUR AFTER A BRIEF PAINFUL EVENT. OUR AIM IS TO CLARIFY SUCH ALTERATIONS TO HELP IDENTIFY BETTER ANALGESICS.**

In addressing crucial factors responsible for central sensitisation we have focused on the enhanced excitatory events. Two varieties of receptor for glutamate (an important excitatory transmitter released from sensory neurones) are clearly implicated; NMDA and AMPA receptors. NMDA receptors are a core component of synaptic plasticity in the central nervous system and crucially contribute to chronic pain.

Using mutant mice with a domain deletion in the synaptic linker protein, PSD-95, in experiments involving pharmacological, biochemical and in vivo assessments of sensory responsiveness together with electrophysiological measurements, we revealed that NMDA receptors and their interacting proteins play an essential role in neuropathic pain. This could point the way to designing new analgesics for particular types of chronic pain.

**THE PROBLEM OF CHRONIC PAIN**

Chronic pain is a serious problem in many disorders and often has dramatically adverse effects on quality of life. Approximately a third of the population experience chronic pain at some point and about 8% suffer from neuropathic pain, which is brought about following nerve damage and is particularly problematic because it is not consistently alleviated by current analgesics. This even includes morphine, which is not reliably effective at tolerable doses.

Chronic neuropathic pain arises from diabetes, trauma, surgery, cancer and certain viral infections, such as shingles. This is a major unmet need that demands a concerted research effort to best develop new and effective treatments.

**CENTRAL SENSITISATION**

Central sensitisation is a complex phenomenon that brings about chronic hypersensitivity to both painful and innocuous stimuli so that both provide the perception of pain. There are changes in the neurotransmitters expressed in sensory nerves and in areas of the central nervous system such as the spinal cord where these are released. Persistent neuronal activity is important in this condition, encouraged by enhanced excitatory processes and diminished inhibition.

**Figure 1:** Lanes numbered 1 and 2 reveal increased association of CaM kinase II (an important signalling protein involved in synaptic plasticity) with the spinal NMDA receptor ipsilateral to nerve injury. This is prevented in mice expressing a mutated form of the linker protein, PSD-95 (lanes 3 and 4), which correspondingly fail to develop hypersensitivity.

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Further, we used mutant mice with a single amino acid substitution in a distinct domain of PSD-95 to show that recruitment of an unpredicted lipid kinase to the spinal NMDA receptor complex plays a key role in inflammatory sensitisation. Additionally, we have identified that AMPA receptors and their interactions with docking proteins are crucial for chronic pain. Alternative subtypes of NMDA and AMPA receptor subunits may play distinct roles due to partnering with different interacting proteins. In recent work we have been investigating effects of early life stress and other adverse events on these and other biomarkers of central sensitisation with the aim of improving animal welfare and potentially finding new analgesic strategies. We have identified new processes underlying hyper-responsiveness at different levels of the nervous system using biochemical and proteomic strategies and identified some of the signalling mediators responsible.

NEW INSIGHTS INTO RELIEF OF CHRONIC PAIN

Understanding such protein:protein interactions that crucially underlie sensitisation gives a strong way forward by defining peptide research tools that inhibit these events. In the longer term this should lead to the development of pharmaceutical molecules that can specifically disrupt the interface necessary for chronic pain.

Recently, in collaboration with Dr Rory Mitchell (Centre for Integrative Physiology) we discovered that the TRPM8 ion channel, which is present in nerves innervating the skin and can be activated by either cooling or by selective chemical activators, achieves a completely new form of analgesia for neuropathic and other chronic pain states. It appears that TRPM8 neurons act at a central site to gate out the inputs from other major classes of nociceptive (pain-signalling) sensory neurons.

It has also been possible to identify that inhibitory glutamate receptors of Group II/III act as one crucial downstream mediator in TRPM8 suppression of nociceptive transmission. This form of analgesia appears to be quite separate from those involving endogenous opioid receptors that can be accessed by morphine. It therefore represents a quite novel drug target that is expected to lead to new efficacious analgesics with few side effects.

Current work involves research into the precise biological basis and regulation of TRPM8 action within sensory nerves and their gating actions within the central nervous system. In addition we are running an active translational drug discovery programme for the development of mechanistically novel analgesics.

This overall research strategy not only leads to new insights into fundamental biological processes but also drives a path towards real clinical benefit in both human and veterinary applications.

Selected references:

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