N example being that there is little evidence

n summary, Nav1. 7, Nav1. 8 and Nav1. 9 channels are involved in modality-specific pain pathways via various mechanisms (see Fig. 2). Nav1. 8 and Nav1. 9 channels play an important role in noxious cold-specific pain pathways, as they appear to be resistant to slow inactivation at low temperatures and remain active when channels of other afferents are inactivated by noxious cold.

On the other hand, it is proposed that Nav1. 7 channels are essential for the amplification of noxious heat-specific transducer currents, the release of substance P and wind-up of responses at the dorsal horn of the spinal cord. Nav1. 9 were seen to be important in noxious thermal and mechanical hypersensitivity in inflammatory pain, potentially via a mechanism that involved their axonal transport to nerve terminals of DRG neurons. Gain-of-function mutations in Nav1. 7 channels are important clinically as they are associated with conditions of burning pain, such as inherited erythromelalgia, whereas, recently, an activity-enhancing missense mutation in Nav1.

9 channels was associated with cold-aggravated pain (Leipold et al., 2015). Finally, both Nav1. 7 and Nav1. 8 channels in DRG nociceptors that co-express them can contribute to thermal hyperalgesia. Despite all that has been suggested, some considerations ought not to be ignored.

For example, global Nav1. 8 knockout in mice ablates withdrawal responses to noxious cold stimuli, but not to chemically-induced, e. g. acetone, noxious cooling (Minett et al., 2012), highlighting the importance of the experimental protocol used to model cold or thermal pain. Research findings in rodent

models of pain should be translated to human physiology with a great deal of caution.

Whereas mouse DRG tissues highly express Nav1. 8 channels (45% of total Nav expression) in comparison to Nav1. 7 channels (18%), human DRG tissues express more Nav1. 7 channels (50%) and less Nav1. 8 channels (12%) (Chang et al., 2017). Although TTXs and TTXr currents are relatively similar in rat and human DRG neurons, there are also important species differences, a notable example being that there is little evidence that the inactivation of TTXr currents is use-dependent in human DRG neurons (Zhang et al.

, 2017). Furthermore, whereas Nav1. 7 channels likely play a major role in noxious heat-specific somatic pain pathways, they may not be important in visceral pain pathways, given that vast deletion of Nav1. 7 channels from colonic sensory neurons in mice did not alter pain reflexes to intracolonic application of capsaisin or mustard oil, or induction of cystitis (Hockley et al.

, 2017). Like noxious cold-specific pain pathways, visceral pain pathways may implicate TTXr voltage-gated Na+ channels (Laird et al., 2002; Saito et al., 2008; Hockley et al., 2014).

However, unlike noxious cold-specific pain pathways, knockout of Nav1. 8 or Nav1. 9 in rodents has been shown to affect the senitization, but not the detection, of visceral pain (Qi, Zhou, Xu, 2011). This may be because the majority of visceral mucosal mechanosensory are chemosensitive (Sengupta, 2009), responding to inflammatory mediators, e. g. nerve growth factor (NGF), prostaglandin E2 (PGE2) that act to sensitize voltage-gated

Na+ channels by various signalling transduction mechanisms, e. g. protein kinase A (PKA), protein kinase C (Qi, Zhou, Xu, 2011).

The TTXr voltage-gated Na+ channels could be involved in hypersensitivity in a manner similar to the one described earlier for thermal hyperalgesia. These considerations may have important implications in the development of effective analgesics. Any differences between human and rodent DRG neurons in the expression of voltage-gated Na+ channels or in their TTXr and TTXs currents can be accompanied by species differences in the pharmacological properties of voltage-gated Na+ channels in nociceptor neurons. For example, it has been reported that TTXs currents in human DRG neurons are resistant to the Nav1. 7-selective blocker Pro-Tx II and that the Nav1. 7-selective small molecule inhibitor PF-05 089 771 blocks both TTXs and TTXr currents in human nociceptors (Zhang et al.

, 2017). In addition, whereas the TTXr blocker A-803 467, which potently blocks human Nav1. 8 channels (IC50 = 8 nM), can significantly limit acute visceral nociceptive responses (Jarvis et al., 2007), selective pharmacological blockade of Nav1. 7 channels in the viscera is unlikely to be sufficient in targeting chronic visceral pain (Hockley et al., 2017).

Nevertheless, future studies could identify markers for mechanisms related to the activation of modality-specific pain pathways, in the hopes of delivering more promising treatments for human pain (Emery et al., 2016).