Genes and the dynamics of pain control

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Summary

There are well-documented sex differences in the prevalence of various painful disorders. To comprehend the mechanisms underlying these differences requires an understanding of the molecular organisation and systems biology that are responsible for the pain experience. The pain system evolved to secure the survival of the animal under a variety of environmental constraints and needed to be flexible enough to compete against other behavioural needs and homeostatic demands. From the periphery to the cortex, mechanisms exist to facilitate or inhibit nociceptive signalling and it is this inherent plasticity that is thought to be perturbed in chronic pain states. There is limited evidence to suggest that polymorphisms or mutations in certain genes and gender can influence the pain experience but it seems likely that epigenetics and the influence of past experience are responsible for a substantial part of the variation between sexes and between individuals.

KEY WORDS: descending control, local translation, MeCP2, pain, sensitisation.

Introduction

The relationship between pain and injury is complex and dependent on a large number of variables including genetic make-up, previous experience and the emotional state of the individual (1,2). To explain this variability at a neurobiological level has proved challenging but research, primarily on animals, has provided some insights into mechanisms both at the molecular and systems level. Acute pain refers, usually, to the initial response of the animal or human subject to noxious thermal, mechanical or chemical stimulation. Following injury, there is almost always an increased sensitivity to noxious or innocuous stimulation of the injured, inflamed tissues. This increased sensitivity usually resolves with healing of the wound or regeneration of a damaged nerve but in some cases may persist for more than six months and is referred to as a chronic pain state. Chronic pain states can be extremely difficult to manage clinically and research aimed at identifying new analgesic targets has been a priority for many pharmaceutical companies, although in recent years little has been achieved. For example, neuropathic pain, a chronic pain state which can follow peripheral nerve injury, affects 2.4% of the British population rising to 8% with increasing age and has remained difficult to treat effectively with only around one in three patients experiencing adequate pain relief (3). Sex seems to be an important variable in the development of some chronic pain states. For example, female patients have higher rates of fibromyalgia and causalgia while male patients experience greater pain levels following brachial plexus avulsion and tend to be more likely to develop post herpetic neuralgia (4).

To understand the neurobiological networks subverted to generate chronic pain states has proved difficult. Emphasis has been placed on a molecular and systems analysis of the peripheral and central neurons that transmit pain signals. It was hoped that investigating pain signalling in animal models of chronic pain would lead to a more informed understanding of what goes wrong in those unfortunate individuals who develop a chronic pain state following, for example, routine surgery, infection or after minor injury. However, this approach has met with limited success, in part, because of the lack of good animal models. The majority of rats or mice in which the peripheral nerve is manipulated will show changes in pain sensitivity whereas in humans the development of a chronic pain state is only seen in a small percentage of patients. This has led to an increased awareness of the importance of the central nervous system in the generation of pain states and shifted attention away from the primary afferent nociceptor and spinal cord. More attention is now being focused on any previous trauma the patient may have suffered, the genetic predisposition, gender, cognitive processing and the ongoing events in the subject's life.

Peripheral control of nociceptive sensitivity

Primary afferent neurons still attract considerable research interest particularly as many express unique patterns of sodium channel receptors and neuropeptides. Nevertheless, given the recent explosion of knowledge of peripheral pharmacology and the cloning of large numbers of genes specifically expressed by nociceptors, it is at first sight surprising that new treatments have not been developed. Targeted knockout or disruption of identified genes has suggested that particular nociceptor specific transcripts may well be involved in

maintaining abnormally high levels of nociceptive sensitivity following either inflammation or nerve injury but specific drugs that mimic these molecular interventions have yet to be successfully developed (5).

Primary afferents fall into two broad categories: myelinated A-fibres that signal noxious or innocuous stimuli and unmyelinated C-fibres that in the rat are the vast majority of sensory fibres and largely nociceptors. A-nociceptors mediate 'first' pain, perceived as rapid and sharp, and C-fibres signal 'second' pain, delayed, diffuse and dull (6). Inflammation or injury provokes the release of a variety of cytokines and growth factors that increase the sensitivity of some nociceptors to noxious thermal stimulation. A critical role in this process of primary sensitisation is played by the capsaicin-sensitive TRPV1 receptor that acts as a focus for many signalling pathways within the axon terminal of the majority of C-fibres (7). Primary sensitisation thus acts at the periphery to amplify the response to noxious stimulation. C-fibres can be divided into two groups (8-10). While all C-fibres express TRPV1 receptors and release the neurotransmitter glutamate, approximately 50% of fibres also express the trkA receptor (which binds nerve growth factor, NGF) and synthesise and release neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP) (10,11). This subset of C-fibres releases peptides peripherally to aid inflammation and healing through plasma extravasation and vasodilatation and centrally activating dorsal horn projection neurons that convey pain-related information to the brain. Blocking NGF (produced by inflamed tissue) access to the trkA receptor is proving to be one of the most effective ways of blocking inflammatory pain (11), while CGRP receptor antagonists are showing efficacy in the control of migraine (12). The second group of C-fibres does not contain peptides, is unresponsive to NGF and does not have an identified peripheral role in inflammation. However, these fibres express Ret receptors that bind glial cell derived neurotrophic factor (GDNF) and express the ectonucleotidase prostatic acid phosphatase (PAP) previously known as fluoride-resistant acid phosphatase (FRAP) (13). This enzyme has recently been shown to break down adenosine triphosphate (ATP), producing adenosine that binds to the A1 receptor and reduces nociception. GDNF given intrathecally has also been shown to have a potent role in reducing neuropathic pain symptoms (14) in rats possibly by driving the breakdown of ATP by PAP within the dorsal horn and generating anti-nociception. This illustrates an important point that is met with at all stages of pain processing, namely that mechanisms exist for both increasing and decreasing pain sensitivity. One hypothesis is that maintained facilitation or reduced inhibition of pain signalling may generate persistent pain states in both animals and humans.

The heightened response to mechanical stimulation following injury involves different mechanisms. Primary sensitisation may result in some amplification of noxious mechanical stimulation but the available evidence suggests that central sensitisation is the major amplifier of mechanical responses. Central sensitisation is an increase in the excitability of dorsal horn neurons and is usually the result of a strong C-fibre input from the periphery. In essence, therefore, a peripheral injury results in both peripheral and central sensitisation. This has important consequences for nociceptive A-fibres especially those that do not express TRPV1. A-nociceptors are not thought to sensitise peripherally following inflammation or injury. However they do form synapses on superficial dorsal horn neurons that have been sensitised by the C-fibre barrage. The result is thus amplification of the A-fibre response but only post-synaptically when it reaches the dorsal horn. The behavioural correlate of this is known as secondary hyperalgesia and represents an increased mechanical sensitivity largely around the site of injury. Of crucial importance is the fact that it is a capsaicin-insensitive A-nociceptor pathway that supports increased mechanical sensitivity – a common hallmark of neuropathic pain conditions in humans (15). Also increased descending facilitation from the brainstem is thought to be essential for both secondary hyperalgesia and increased mechanical sensitivity in neuropathic pain models. Recent research has, however, uncovered a novel mechanism for regulating A-nociceptor sensitivity in the periphery (16). We were able to show that mTOR (mammalian target of rapamycin) and the related machinery for mRNA translation is present in this subpopulation of capsaicin-insensitive A-nociceptive primary afferent sensory fibres in the rat skin and demonstrated that the response to noxious mechanical and thermal stimulation is regulated by ongoing mTOR-mediated local protein synthesis. Local protein synthesis in dendrites and axons is known to play a critical role in the modulation of long-term synaptic plasticity, axon regeneration in the peripheral nervous system and axon guidance during development. Indeed, it has been argued that adjustments to local conditions at the axon terminal or region of axonal trauma would be greatly enhanced by local protein synthesis, particularly in primary afferent sensory fibres where the cell body, the established site of protein synthesis, can be located at a considerable distance from the axon terminals in cutaneous and other tissues. mTOR, together with its binding partner raptor (17), controls translation via phosphorylation of both i) the eukaryotic initiation factor 4E (eIF4E)-binding protein 1/2 (4E-BP1/2) and ii) p70S6 kinase (S6K) which activates a number of downstream targets involved in translation. mTOR signalling can be inhibited by rapamycin thus preventing the phosphorylation of both S6K and 4E-BP1/2 (18,19). We therefore proposed the novel hypothesis that ongoing local translation of mRNA maintains the sensitivity of a subset of A-nociceptors and offers a therapeutic target for the control of pain states.

A major step in the functional analysis of local translation in subsets of sensory fibres was the observation that the rapamycin-sensitive A-fibres were a distinct functional group of fibres that (as described above) in man and rodents support secondary hyperalgesia. Secondary hyperalgesia is characterised by increased sensitivity, particularly to punctate mechanical stimuli, in the undamaged skin that surrounds the site of injury. We confirmed behaviourally that secondary hyperalgesia was substantially attenuated by local injection of rapamycin into the hind paw. Our findings throw new light on the control of A-fibre sensitivity. Previously, A-fibres had not been thought to possess the inherent plasticity of C-fibres and modulation of A-fibre sensitivity was assumed to be wholly contingent upon central sensitisation established by activation of C-fibres. In other words, the excitability of central dorsal horn neurons increases

following a C-fibre barrage and the response to subsequent A-fibre inputs is amplified by these sensitised neurons. The data presented here imply that, even in the absence of C-fibre activation, local translation of mRNA regulates the sensitivity of some A-fibres and therefore modulation of mTOR signalling can influence the response of these fibres. Local translation may maintain A-fibre sensitivity through modulation of either the transduction process or excitability of the primary afferent terminal, but at present the mechanism is unclear. In our experiments A-fibre nociceptor sensitivity was not seen to change for 2-3h after rapamycin administration, implying that regulation of A-fibre excitability by rapamycin was a relatively slow process. We hypothesised that local protein synthesis was continuously replenishing proteins essential for the full response of the fibre to noxious stimulation. In the presence of rapamycin, the inhibition of mTOR signalling prevents the replenishment of the stores of these key proteins. From our results, 2 to 3h was required for a significant degradation of these pools of proteins and loss of A-fibre sensitivity.

How might this finding be significant clinically? mTOR is known to play a crucial role in the signalling pathway that regulates cell growth in response to a variety of external stressors and cues including nutrients and growth factors, hypoxia, DNA damage and osmotic stress, and it seems likely that peripheral changes in the physiological state of the body, for example during illness, are reflected in modulation of A-fibre sensitivity. For example, pinprick hyperalgesia is attenuated in diabetic patients, both in those with painful neuropathy and those without symptoms (20,21). This may be related to the decreased levels in diabetes of insulin and insulin-like growth factor 1 (IGF1), which are both powerful activators of the mTOR pathway and which could act on the insulin-like growth factor receptor that is expressed on small and medium sized dorsal root ganglia neurons (21).

Central processing: the dorsal horn and central sensitisation

Central sensitisation describes the state of increased excitability of dorsal horn neurons after injury. This increased excitability in dorsal horn neurons is driven by glutamate released following high threshold stimulation of primary afferent C-fibres and maintained by a series of molecular changes generated largely by depolarisation of the neuronal membrane and subsequent influx of calcium ions through glutamatergic NMDA receptors (22-24). AMPA glutamate receptor subunits are rapidly recruited to the neuronal membrane from cytoplasmic stores (25), transcription factors are activated and a large number of immediate-early transcription factors are rapidly transcribed and translated. There are also contributions from descending controls and intersegmental spinal pathways. Peripheral injury always results in rapid molecular changes in dorsal horn neurons. Activity-dependent changes in neurons of the rat superficial dorsal horn are crucial for the induction and maintenance of neuropathic and inflammatory pain states (1, 26-31). Many years ago we demonstrated that the transcription factors c-fos and zif268 could be rapidly generated following noxious stimulation of the periphery and manipulation of levels of these genes can regulate pain sensitivity.

To identify other molecular mechanisms underlying sensitisation of superficial dorsal horn neurons, we recently undertook a genome-wide microarray profiling of dorsal horn gene transcripts at various times after induction of peripheral inflammation (30). We identified a small number of highly up-regulated transcripts including serum and glucocorticoid-inducible kinase (*SGK1*) a gene known to be important in experience-dependent plasticity in the hippocampus, sulfotransferase family 1A, phenol-preferring, member 1 (*SULT1A*) (32,33) and FK 506 binding protein 5 (*FKBP5*), a glucocorticoid receptor-regulating co-chaperone of hsp-90.

Remarkably, this pattern of gene expression was virtually identical to that seen after deletion of the methyl-CpG-binding protein 2 (*MeCP2*) gene regulator in mice (34, 35). A decrease in expression of *SIN3A*, a co-repressor in the MeCP2 silencing complex, was also detected following inflammation. As MeCP2 phosphorylation had been reported to dissociate the MeCP2 protein from target gene promoters and de-repress gene transcription (35), we then analysed MeCP2 phosphorylation after noxious stimulation. We were able to show that MeCP2, a transcriptional regulator involved in chromatin remodelling and RNA splicing, was an important component of the molecular cascade that accompanied the setting up of the pain state. Furthermore, knocking down *SGK1*, one of the MeCP2-regulated transcripts, delayed the onset of an inflammatory pain state. Previous work had established that mutations in MeCP2 (located on the X chromosome) lead to the progressive 'neurodevelopmental' disorder Rett syndrome in humans although a mechanistic understanding of this disease is far from clear (36). However, there is some evidence that children with Rett disease do have higher pain thresholds (S. Géranton, personal communication). Our results therefore brought together two apparently disparate areas of research: the molecular pathology of a severe neurological disorder and the neurobiology of pain.

The differential contribution of ascending pain pathways

Pain information is conveyed by primary afferent nerve C- and A-fibres that terminate predominantly within the superficial laminae I-II and lamina V of the dorsal horn and reaches the brain through projection neurons located in laminae I and V(1). Lamina I projection neurons express the SP preferring receptor (NK1) (37,38) and support long-term potentiation (LTP) (38), a form of long-term synaptic plasticity associated with learning and memory. Noxious stimulation induces the rapid activation of transcription factors such as MeCP2 and the transcription of c-fos and zif268 alongside many other genes in specific temporal patterns (30,31). Applying slow and fast heat ramps to the skin to activate either C-fibres or the capsaicin-insensitive A-nociceptors respectively indicated that A-fibre nociceptors activated neurons primarily within the most superficial laminae (I-II) of the dorsal horn whereas C-fibre activation caused a more widespread activation of neurons throughout the dorsal horn (39). Lamina I projection neurons terminate within the autonomic motor column in the thoracic spinal cord and

within the brainstem. Terminations have been found within the parabrachial area, an autonomic integrating zone that projects to the limbic forebrain and hypothalamus, the posterior and lateral thalamus which innervates the somatosensory and insula cortex (areas which together comprise the 'primary nociceptive' cortex), the medial thalamus innervating the prefrontal and anterior cingulate cortex (the 'nociceptive motor cortex') (ACC) and finally the periaqueductal grey (PAG) (40,41). This distribution is remarkable from two points of view. First, lamina I sends nociceptive information to areas of the brain concerned with most aspects of the pain experience including discriminative, emotional (affective) and cognitive dimensions. Second, all of these brain areas send descending projections that converge upon areas of the brainstem. The brainstem orchestrates the complex interplay of descending facilitatory and inhibitory influences that reach the dorsal horn of the spinal cord and modulate nociceptive traffic (1). In comparison, the other major ascending pathway, from lamina V projection neurons, terminates largely within the reticular formation and motor centres of the brainstem and forebrain and seems to be positioned to play a major role in arousal and planning the rapid motor response to noxious stimulation (40). Lamina V projection neurons respond to both noxious and non-noxious stimulation and do not express the NK1 receptor. In a series of experiments, lamina I neurons were destroyed by intrathecal application of a saporin-SP complex (42). This complex was specifically internalised by NK1-expressing neurons leading to their death within weeks. Acute pain thresholds were found to be normal but all experimentally induced pain and inflammatory or neuropathic sensitivity was blunted. It was also found that destruction of lamina I neurons after establishing a neuropathic pain state in rats reversed the increased pain sensitivity suggesting possible clinical applications for the procedure. Given that acute pain thresholds were normal, what was the role of lamina I projection neurons in setting up pain states? The answer seems to be that lamina I neurons alert different regions of the forebrain and brainstem to injury. These brain regions then compute a response in the light of ongoing environmental contingencies and that includes setting the sensitivity of dorsal horn neurons through descending controls. The role of descending controls in establishing increased mechanical sensitivity has indeed been established by selective lesioning of descending pathways.

Descending control of spinal sensitivity

Recent studies have emphasised the influence of descending pathways on nociceptive signals passing through the dorsal horn (43,44). These descending influences originate from various parts of the brainstem including the rostroventral medulla (RVM), PAG and pontine noradrenergic cell groups. The PAG is very much at the crossroads of projections from the amygdala, prefrontal cortex and hypothalamus and projects to the RVM. Stimulation of the RVM can produce both facilitatory and inhibitory influences on dorsal horn processing, again reflecting the general point that the decision to restrict nociceptive information entering the system is closely tied to 'other competing behavioural needs and homeostatic demands' (45).

Stimulation of the ACC generates hyperalgesia and acts through projections to the RVM while, in contrast, fear conditioning, which requires amygdala function, generates almost complete analgesia when rats are re-exposed to the conditioning chamber (46). The complexity of the cortical contribution is, however, illustrated by a series of experiments that showed that the ACC is not required for registering the intensity of painful stimulation but does contribute to forming the association between noxious stimulation and the arena in which the stimulus was given (47). Nevertheless, it seems likely that both secondary hyperalgesia and the increased mechanical sensitivity seen in animal models of neuropathic pain are dependent upon descending facilitation from the RVM. It has been repeatedly shown that ablation or inactivation of descending pathways from the brainstem alleviates pain states (43,48,49). This suggests that the maintenance of chronic pain states requires the cooperation of descending pathways and that inappropriate activation of brain systems that modulate nociception is in some way contributing to the pathology.

Projections from the RVM are neurochemically heterogeneous. However, one subset of serotonergic (5HT) RVM neurons (generally thought of as 'neutral cells') has been implicated in descending facilitation. Other subpopulations contain the inhibitory neurotransmitter GABA that, together with noradrenergic inputs to the dorsal horn, exerts a substantial inhibitory influence on nociception. We were able to show that lamina I-NK1 positive pathways are important in supporting the electrophysiological enhancement of the activity of lamina V neurons following inflammation and suggested that activation of brainstem descending pathways to the spinal cord was impaired after disruption of the lamina I projection system. Extensive activation of RVM neurons following hind paw injection of formalin was detected using c-fos immunohistochemistry. Many of these neurons co-stained for 5HT. Ablation of the lamina I-NK1 positive pathway resulted in reduced activation of RVM including neurons that contained 5HT (50). This suggested that serotonergic pathways had been activated by noxious stimulation of the periphery and that serotonin may have been providing the excitatory drive to the dorsal horn, facilitating nociception. A similar conclusion has been reached following direct ablation of a subpopulation of RVM neurons using saporin conjugated to the mu-opioid receptor agonist dermorphin or following injection of local anaesthetic (51). A proportion of the neurons ablated were thought to be 'on' cells and to give rise to descending facilitatory drive. This resulted in an attenuation of neuropathic pain behaviours although normal nociceptive responses were intact. Finally, it was possible to replicate the effects of lamina I-NK1 positive lesions with 5HT receptor antagonists both behaviourally and electrophysiologically and to ameliorate pain states by selectively depleting 5HT locally within the lumbar spinal cord. Although there are multiple 5HT receptors expressed both by dorsal horn neurons and primary afferent fibres, the 5HT3 receptor was found to be a major candidate for the mediation of descending facilitation (50,52,53). 5HT is excitatory at the 5HT3 receptor, a ligand gated ion channel localised to both subsets of dorsal horn neurons and small diameter primary afferent fibres (54-56). Previous work has suggested that this may include a population of A delta primary afferent nocicep-

tors and perhaps the capsaicin-insensitive A-nociceptors that form such an important component of the pathway generating secondary mechanical hyperalgesia (15). Application of the 5HT3 receptor antagonist ondansetron directly to the spinal cord replicated many of the effects of lamina I-NK1 neuron ablation (53).

To summarise, descending controls make an essential contribution to the final experience of pain. Descending facilitation of nociceptive processing is mediated, in part, by descending 5HT pathways from the RVM, triggered by activity in the lamina I-NK1 positive projection pathway but modulated by higher brain centres. Finally, activity in both ascending and descending pathways appears to be essential for the maintenance of chronic pain states (42,43).

Gender, genetics and pain

Against this complex physiological and molecular background it might now be worth asking how genetics and gender might impact on the pain experience. At one end of the spectrum there are mutations in the alpha subunit of the sodium channel gene *Nav 1.7* that result in a complete inability to feel pain or an indifference to pain in humans (57,58), interestingly a result not duplicated in knockout mice (5). Mutations in other Nav1.1 sodium channels and voltage-gated calcium channels have been associated with familial forms of migraine (59). Children (largely girls) with Rett syndrome and a deletion of the *MeCP2* gene are reported to have increased pain thresholds and appear less concerned about injury. One outstanding example of genetic and sex difference in pain processing is generated by inheritance of the non-functional variant of the melanocortin 1 receptor (*MC1R*) gene, which produces red hair and fair skin. As the 'first strong evidence for a gene-by-sex interaction in pain genetics' (59), Mogil and co-workers (60) demonstrated that red-headed women, but not men experienced enhanced kappa-opioid sensitivity. More subtle polymorphisms in genes such as the serotonin transporter (*SLC6A4*), catechol-O-methyltransferase (*COMT*) and GTP cyclohydrolase (*GCH1*) impact on pain sensation and importantly on the painful consequences of injury (59,61,62). All of these genes regulate some aspect of monoamine function. As has been described above, both serotonin and noradrenaline have important roles in setting pain sensitivity and in the development of persistent pain states. The met/met polymorphism commonly present in low functioning COMT (which metabolises catecholamines) is thought to lead to chronic overactivity of the dopaminergic system and therefore a reduced activation of mu-opioid function coupled with higher affective and sensory pain ratings following intramuscular injections of hypertonic saline (61,63).

But it seems likely that all differences in the pain experience will not simply be explained on a genetic basis. Fibromyalgia, a disease more commonly seen in women, may be a case in point. Once considered a stress-related disease, recent brain imaging and other studies have suggested that a disturbance in dopamine function may contribute to the symptoms of the illness and reflect a 'top-down' failure of processing (63). (That is pain derived from aberrant patterns of brain activity rather than peripheral injury). Dopamine release has long been associated with reward processing (64,65) and there is evidence to indicate that increased dopamine release results in analgesia probably by increasing the release of endogenous opiates as well as by activation of descending pathways (61). This relationship between pain and pleasure has been commented on previously. For example, many brain sites that support self-stimulation also produce analgesia (66-68) and most drugs of abuse are also analgesics (69). In healthy individuals dopamine release in response to painful muscle stimulation is correlated with the amount of perceived pain but this correlation breaks down in fibromyalgia patients suggesting a disturbance in dopamine function. This could of course be the result of a polymorphism in a gene related to monoamine function and several have been suggested but there may also be a case for examining epigenetics (changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence). There is evidence that early experience can influence later gene expression that may predispose to depression (70). In another recent study a constellation of traits in the adult rat is induced by the mothering style to which the rat was exposed as a pup (71). Mothering characterised by high levels of licking and grooming generates two interacting pathways in the pup. In the first, increased serotonin tone in the hippocampus leads to increased expression of the transcription factor zif268. In the second, the first exon of the glucocorticoid receptor gene in the hippocampus is demethylated, and the histones surrounding it are acetylated. This results is a glucocorticoid receptor gene that is permanently more available for transcriptional activation by zif268. This produces higher numbers of glucocorticoid receptors in the hippocampus of the rat as an adult. The paper essentially describes an influence of maternal behaviour on the young which influences the development of the stress axis in the offspring and which, importantly, is reversible. Epigenetic influences on pain experience have yet to be explored but early experience, including previous injury, also contributes to the development of pain chronicity (72).

Concluding remarks

In this brief overview of the neurobiology of pain I have emphasised the potential for choices that are available to the nervous system in the context of ongoing events in the life of the individual, their past history and their genetic make-up. Analgesia or enhanced nociception can be generated by activation of descending controls under the direction of forebrain motivational, cognitive or affective systems. Injury requires a period of escape from further damage and a subsequent period of recuperation. Escape or attack behaviours are thought to be accompanied by a temporary period of 'stress-induced analgesia' as, for example, recorded in Beecher's accounts of the Normandy landings when severely injured soldiers rarely took significant amounts of analgesics (73). More generally the survival value of an intrinsically generated analgesia would allow the animal to escape or attack without significant distraction from the pain of an injury inflicted by a predator. In contrast, the period of convalescence following injury is accompanied by heightened sensitivity at the site of damage that is essential to pre-

vent further injury. However, it is also likely that within this intricate adaptive network lies the potential for the development of persistent and chronic pain states.

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