Pain in the brain: are hormones to blame?

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Pain is a multi-dimensional process involving the physical, emotional and perceptual integration of noxious information. The physical component is relayed via the spinal cord to several brain areas to initiate the detection of pain. The emotional aspect is encoded by the limbic system and encapsulates the relationship between pain and mood. Within the limbic system, the hypothalamus undertakes a diversity of separate and interrelated functions. Dysfunction of the hypothalamo-pituitary–adrenal axis has been implicated in a variety of chronic pain conditions and might also be associated with increased risk of developing mood disorders. Experimental and clinical evidence also exists to implicate the effects of other hormonal modulators in the manifestation of chronic pain. Specific targeting of hormonal cascade and effector mechanisms could provide an alternative strategy for the treatment of various chronic pain conditions.

Several chronic PAIN (see Glossary) conditions are resistant to currently available ANALGESICS, and conservative estimates suggest that one in ten adults suffer from chronic pain at some point in their lives. For such patients, disruption of normal life is almost inevitable. This can take the form of reduced mobility, loss of employment or disruption of family relationships. Deleterious secondary consequences include increased risk of developing psychiatric illness, particularly depression [1,2]. For society, the economic burden is substantial. Current estimates suggest that, in terms of both lost productivity and treatment, the cost to society in the USA alone surpasses US$100 billion annually (http://www.painfoundation.org/page.asp?file = page_fastfacts.htm). But what is chronic pain and what role do hormonal systems play in its development and maintenance?

The trials of chronic pain

What is chronic pain?

Nociceptive pain is the reflex physiological response to NOXIOUS or potentially tissue-damaging stimulation, which acts as an early warning system, telling the body to take evasive action. The longer lasting pain associated with, for example, a sprained joint has a limited inflammatory response, and serves to protect the injury from further trauma, enabling any damage to be repaired. In spite of their intrinsic unpleasantness, these are examples of beneficial pain. However, there is a more insidious type of pain that persists beyond its biological usefulness, often described as NEUROPATHIC PAIN. This is typified by damage to the nervous system and is associated with disease states as diverse as diabetes, multiple sclerosis, post-herpetic neuralgia, cancer and AIDS [3]. Conversely, the joint and muscle tenderness associated with pain disorders such as fibromyalgia or back pain, or the diffuse pain associated with visceral pain disorders, such as irritable bowel syndrome, serve no obvious biological purpose, and yet do not necessarily involve damage to the nervous system. This leaves us with the ubiquitous term of chronic pain. The clinical diagnostic requirement that this pain be present for a period of at least two to three months indicates that long-term maladaptive changes must occur in the sensory processing of pain.

The initiation and maintenance of chronic pain

Peripheral sensory neurones act as the interface that enables both low (non-noxious touch) and high (noxious stimuli) threshold sensory information to be relayed from the periphery to central neurones within the spinal cord [4,5]. Normally, these respective functions are mediated by large diameter myelinated Aβ-fibres and by small unmyelinated C-fibres. For noxious stimuli, this is achieved via activation of peripheral receptor complexes called NOCICEPTORS, which are located on the terminal endings of C-fibres. These adapt to mild pain-causing stimuli, but stronger stimuli release several factors from the damaged tissue that act to sensitize the nociceptor to subsequent stimuli (Box 1). In turn, sensory neurones terminate within spatially distinct regions of the dorsal horn of the spinal cord. Here, at the first synapse in the pain pathway, functional connections are made with dorsal horn neurones, which also have an array of stimulus-encoding abilities [6]. These can range from being exclusively non-noxious to exclusively noxious. A physiological consequence of peripheral sensory neurone hyperexcitability is that it can set into motion transient changes in the way that pain is processed centrally within dorsal horn neurones [4]. However, in the continued presence of injury-induced signals, this modulation recruits activation of intracellular signalling cascades and long-term changes in nociceptive transmission (Fig. 1) [4].

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Glossary (Ref. [56] and see also http://www.iasp-pain.org/pubsopen.html)

Allodynia: Pain resulting from a stimulus that does not normally provoke pain.
Analgesics: Drugs removing the sensation of pain from stimuli that would normally be painful.
Hyperalgesia: An increased response to a stimulus that is normally painful.
Neurogenic pain: Initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral or central nervous system.
Neuropathic pain: Initiated or caused by a primary lesion or dysfunction in the nervous system.
Nociceptor: A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged.
Noxious stimulus: A stimulus that is damaging to normal tissues.
Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

A link between chronic pain and mood disorders?

Several brain areas involved in the fast defensive processing of nociceptive pain are also involved in the longer term cognitive appraisal of pain (Box 2). Variables, such as attentional state, emotional context and expectation of pain, have all been shown to alter both pain perception and forebrain pain transmission in humans [7]. Thus, in addition to the sensation of pain, pain is associated with moment-to-moment unpleasantness, comprising emotional feelings that pertain to the present or short-term future, such as distress or fear. For the patient suffering from chronic pain, this aspect of the pain response is probably associated with negative feelings, depressed mood and increased risk of developing psychiatric illnesses, such as depression. Indeed, there is growing evidence to suggest that >50% of patients suffering from chronic pain also express clinically diagnosable symptoms of depression [8],

Box 1. Processing of pain by peripheral sensory neurones

The normal reflex processing of pain begins with activation of nociceptive transducer receptor/ion channel complexes located on sensory neurone nerve terminals, which generate depolarizing currents in response to noxious stimuli. Transducer ion channel proteins, such as VR1, vanilloid receptor 1 and acid-sensing ion channel subtypes, are selectively expressed within subsets of sensory neurones to encode noxious information, which might range from chemical to thermal to mechanical in its diversity (Fig. I) [a,b]. Tissue damage at the site of injury releases ATP and H^+ from damaged cells, which act directly upon their cognate receptors/complexes to reduce the membrane threshold required for depolarization to occur and facilitate action potential propagation from the nociceptor terminal to the spinal cord [a].

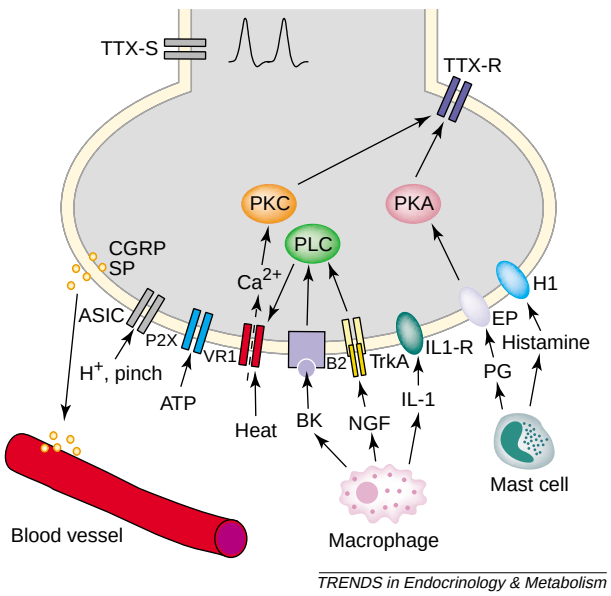

Fig. I. Injury-induced peripheral sensitization. Some of the stimuli and molecules that contribute to sensitization of sensory neurones after injury. Abbreviations: ASIC, acid-sensing ion channel; B2, bradykinin receptor; BK, bradykinin; CGRP, calcitonin gene-related peptide; EP, prostanoid receptor; H1, histamine receptor; IL-1, interleukin 1; IL-1R, interleukin 1 receptor; NGF, nerve growth factor; PG, prostaglandin; PKA protein kinase A; PKC, protein kinase C; PLC, phospholipase C; P2X, purine receptor; SP, substance P; TTX-R, tetrodotoxin-resistant Na? channel; TTX-S, tetrodotoxin-sensitive Na? channel; VR1, vanilloid receptor 1; TrkA, tyrosine kinase receptor A.

Injury also results in the release of neurotransmitters, primarily substance P and calcitonin gene-related peptide, from activated nociceptor terminals to initiate the process of neurogenic inflammation. This induces vasodilation of blood vessels and plasma extravasation (leakage of proteins and fluid from postcapillary venules) and might serve a protective function by diluting or removing tissue-injurious factors [c]. Neurogenic inflammation also results in the activation of immune cells, and this in turn contributes to the manifestation of chronic pain [d]. Inflammatory molecules including bradykinin, cytokines and growth factors released from macrophages, in addition to prostaglandins, cytokines and histamine released from mast cells, can have indirect sensitizing actions on sensory neurone terminals.

The parallel activation by their cascade pathways of intracellular lipases and kinases can remove constraining inhibitory influences on VR1 function (phospholipase C) [e] and induce phosphorylation-dependent modulation of nociceptor-specific ionic currents (protein kinase A and protein kinase C) [a]. One of these is a nociceptor-specific voltage-dependent Na^+ current (TTX-R) which is resistant to block by the puffer-fish toxin tetrodotoxin. Inflammation-mediated phosphorylation of the TTX-R nociceptor-specific Na^+ channel acts to reduce the threshold required for its activation and increases action potential propagation from damaged tissue – regarded as one of the key events underpinning sensory neurone excitability [f]. Nerve growth factor released by immune cells can be retrogradely transported to sensory neurone cell bodies to induce the transcription of proinflammatory molecules. Eventually, the sustained activation of nociceptor complexes manifests as a progressive increase in the response of the system, a process referred to as peripheral sensitization.

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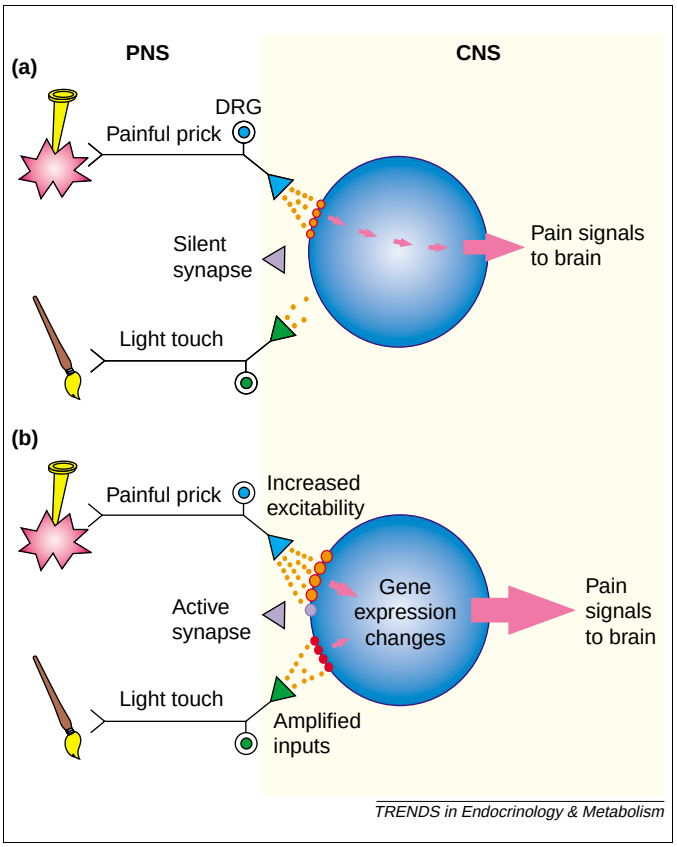

Fig. 1. Amplification of peripheral nociceptive transmission by central sensitizing events within the spinal dorsal horn. (a) Under normal conditions, low-frequency activation of nociceptors by mild noxious stimuli, such as a pin-prick, results in fast AMPA/kainate EPSPs. This signals the original onset, duration and intensity of the stimulus for wide dynamic range neurones within the dorsal horn and subsequently within the brain. Activation of non-noxious mechanoreceptors by a brush stimulus also results in fast AMPA/kainate excitatory postsynaptic potentials but at a level insufficient to initiate depolarizing responses in the postsynaptic cell. (b) After injury, the same low-threshold noxious stimulus is correlated with persistent noxious input to the dorsal horn [4], as a consequence of peripheral sensitizing processes (Box 1), or as a result of spontaneous ectopic discharges arising from neuromatous tissue formed at the site of injury. The sustained noxious stimulation produces slow EPSPs, with the resultant cumulative depolarization recruiting spinal NMDA receptors and increasing release of peptide modulators, such as substance P, to induce a 'wind-up' of action-potential discharge. The amplification of responses might be restricted to the activated synapse or spread to adjacent 'silent' synapses to recruit AMPA receptors. Because most excitatory input to pain pathway neurones is subthreshold, an increase in gain can result in central sensitization (i.e. the recruitment of these presynaptic inputs to the postsynaptic output of the neurones, causing them to fire in response to normally ineffective stimuli). Injury-induced changes in the peptide content of nociceptive sensory neurones also contributes to this process [4]. The parallel induction in the transcriptional regulation of other gene products, such as the opioid peptide dynorphin (which has bimodal effects on pain sensitivity as opposed to enkephalin and endorphin opioid peptides) within the dorsal horn, also contributes to long-term changes in neuronal function [57]. Abbreviations: AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CNS, central nervous system; DRG, dorsal root ganglion; EPSP, excitatory postsynaptic potential; NMDA, *N*-methyl D-aspartic acid; PNS, peripheral nervous system.

and that psychiatric illness might in fact arise as a consequence of chronic pain [1,2].

The current and often inadequate treatment of numerous chronic pain disorders also supports the concept that chronic pain might be associated with inappropriate functioning of several key brain areas that regulate mood. Neuropathic pain is relatively resistant to standard therapeutic treatment with opiates [9]. Recently, anticonvulsant drugs typified by lamotrigine and gabapentin have demonstrated reasonable efficacy [10]. Arguably, the most successful class of drugs used for the treatment of neuropathic pain is also used in the treatment of mood disorders. Antidepressants, such as amitriptyline, are particularly well suited for the treatment of neuropathic pain, although patient compliance and side-effect issues have had a negative impact on their use [11]. Inflammatory disorders, such as rheumatoid arthritis, are treated routinely with nonsteroidal anti-inflammatory drugs and cyclooxgenase inhibitors, but these have little impact on mood status [12]. Consequently, expert opinion agrees that better all-round treatment of chronic pain is required, and the identification of novel targets is a key method of achieving this. Recently, the neuroendocrine hypothalamus has been the focus of intense interest in the aetiology of mood disorders. However, much less is known about its potential involvement in chronic pain. Can an understanding of neuroendocrine dysfunction in chronic pain or in conjunction with comorbid mood disorder provide us with a basis to identify novel analgesic targets?

The HPA axis as a prime suspect in chronic pain

Normally, the stress response is geared to precipitate a complex series of adaptive responses that leads to alterations in autonomic, neuroendocrine and behavioural function [13]. Activation of the sympathoadrenal and hypothalamo-pituitary–adrenal (HPA) axes results in elevated plasma levels of catecholamines and glucocorticoids [14]. These act in concert to mediate central changes, which include enhanced arousal, appraisal and cognitive performance. Within the periphery, their changes are related to modulation of cardiovascular and immune function [14].

The magnitude and pattern of the HPA stress response is driven by the intensity, type and subjective context of the stressor [13,15]. In general, stressors (including acute noxious stimuli) can stimulate the hypothalamus to release corticotropin releasing hormone (CRH) and vasopressin, which in turn promote secretion of adrenocorticotrophin (ACTH) from the pituitary. ACTH then acts on the adrenal gland to enhance synthesis and release of glucocorticoids [13]. Glucocorticoids have major anti-inflammatory effects owing in part to suppression of cytokine activity. They are also potently catabolic. To limit the possibility of tissue destruction, the HPA axis is subject to negative feedback control at all levels. Chronic stress, however, provides the HPA axis with a difficult challenge: to maintain sensitivity to novel incoming stressors when the system is already chronically stimulated. To do this, either it increases the central drive on hormone production and release, or it becomes resistant to the effects of the circulating glucocorticoids [16]. The result is manifest as either hyper- or hypofunction of the axis. In either scenario, appropriate negative feedback within the axis is lost [17].

The importance of glucocorticoid-mediated negative feedback can be seen experimentally in different rat strains. Inflammation-induced tissue damage is associated with sensory neurone sensitization and eventual expression of pain behaviours (Box 1). In addition, the generation of proinflammatory cytokines, such as tumour necrosis factor α and interleukin 1, can result in direct or

Box 2. The cognitive appraisal of pain and relationship to mood

Nociceptive pathways ascending primarily from lamina I and laminae IV–V of the spinal cord dorsal horn project via brainstem nuclei to distinct regions of the thalamus, including the ventral posterior and medial nuclei [a], (Fig. II). These thalamic connections activate the somatosensory cortices (S1 and S2) to result in the fast discrimination of the pain response in terms of its location, intensity and duration.

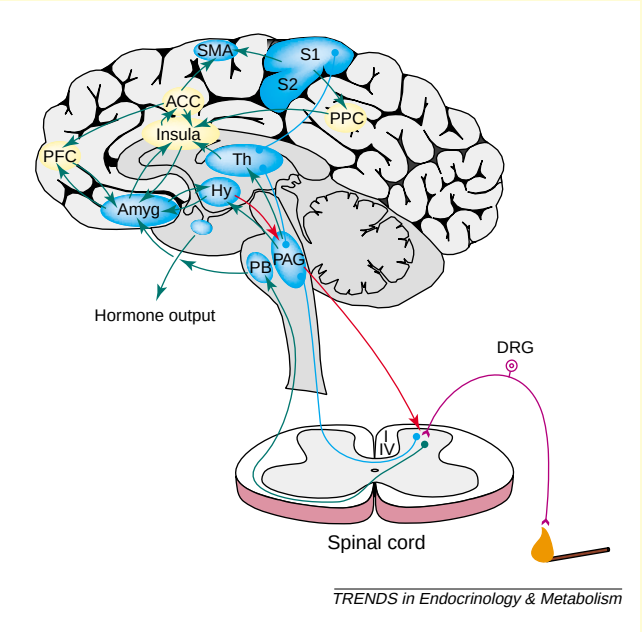

Fig. I. Supraspinal processing of pain. Reciprocal connections between the spinal cord and brain influence the multifactorial nature of pain. Blue structures are involved in the 'fast' processing of pain. Yellow structures are involved in the 'slower' cognitive processing of pain. Green arrows represent excitatory connections and red arrows represent inhibitory connections. Abbreviations: ACC, anterior cingulate cortex; Amyg, amygdala; DRG, dorsal root ganglion; Hy, hypothalamus; Insula, insular cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; PFC, prefrontal cortex; PPC, posterior parietal cortex; S1/S2, somatosensory cortex; SMA, supplementary motor area; Th, thalamus.

Cells within the hypothalamus and amygdala also receive nociceptive projections from the spinal cord to mediate the neuroendocrine aspect of the fast pain response [b]. Reciprocal connections with brainstem catecholamine cell groups – the parabrachial nucleus and the periaqueductal grey – are important for integration of nociceptive activity with the homeostatic processes that are subserved by the brainstem. Activation of descending brainstem serotonergic and noradrenergic relay pathways in turn modulates nociceptive transmission at the level of the spinal dorsal horn by reducing excitatory neurotransmitter release (glutamate, substance P) from nociceptive sensory neurone terminals [c,d]. This helps to act as a 'brake' on nociceptive signalling to supraspinal structures to allow for maximal neural encoding of afferent information. These responses occur somewhat automatically and involve a minimum amount of cognition.

A slower, adaptive response to pain results from activation of somatosensory cortices and subsequent activation of brain structures involved in perceptual and cognitive aspects of pain processing [e]. Posterior parietal cortical areas that integrate somatosensory input from S1 and S2 with other contextual inputs (visual and auditory stimuli) and with prefrontal cortical-associated learning and memory converge on the same limbic structures that receive direct input from pain pathways [f]. Convergence at the level of the insular and anterior cingulate cortices is consistent with a mechanism where the sensory and cognitive features of pain are integrated with attentional and basic emotional processing mechanisms [g]. This component of the pain response reinforces the desire to terminate, reduce or escape its presence. Neuroimaging studies have revealed multiple abnormalities of regional cerebral blood flow and glucose metabolism in these same limbic and prefrontal cortical structures in mood disorders [h].

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indirect activation of the HPA axis [14]. Early work by Chrousos and colleagues demonstrated that Lewis rats are more susceptible to inflammatory autoimmune disease than are histocompatible F344 Fischer rats [18], and the former were shown to have a blunted HPA axis response to stress. The inappropriate glucocorticoid response failed to control inflammation, because administration of the synthetic glucocorticoid dexamethasone was shown to decrease the severity of disease. Subsequent work has suggested that increased stimulatory actions of hypothalamic vasopressin on the HPA axis might be part of the adaptive response to such HPA axis hypoactivity [19]. Lewis rats also have higher plasma levels of vasopressin, where proinflammatory interactions might further contribute to disease pathology and, ultimately, to pain behaviour [19]. Work by Harbuz and others supports several of these findings. Using a rat model of polyarthritis, they have reported decreased expression of mRNA encoding CRH within parvocellular neurones of the paraventricular nucleus and attenuated CRH secretion into the portal system [20,21]. By contrast, hypothalamic vasopressin content and expression of mRNA encoding vasopressin is increased.

Similar HPA axis dysfunction can occur in several chronic pain conditions in humans [14,22,23]. Fibromyalgia is a rheumatological disorder characterized by widespread muscle pain [17]. Multiple studies suggest that a hypoactive stress system characterized by reduced plasma cortisol levels is both a core symptom and mediator of susceptibility to fibromyalgia [14,24]. Similar findings have been reported for rheumatoid arthritis and low back pain [25]. Others have indicated that raised cortisol levels might be responsible for the observed HPA axis dysfunction in fibromyalgia and rheumatoid arthritis [26,27].

There is less direct evidence to implicate HPA axis dysfunction in visceral pain disorders or in chronic pain associated with nerve injury. However, CRH antagonists reduce stress-induced gastric ulceration in rats via peripheral and central sites of action, indicating disturbance of HPA axis function [28], and pain of apparent neuropathic origin might also involve focal nerve inflammation [29]. Lewis rats also appear to be more susceptible to developing neuropathic pain behaviours than other strains under certain circumstances [30].

Both hypercortisolaemia and hypocortisolaemia might be associated with the development of mood disorders. Melancholic subtypes of depression are most often associated with hypercortisolaemia, whereas the atypical subtype of depression is associated with hypocortisolaemia (as seen in fibromyalgia) [16]. Many of these stress-induced changes can be reversed by antidepressant treatment with consequent improvement of mood status [31]. Antidepressants have also been shown to interact with components of the nociceptive pathway to attenuate pain behaviour. It would seem reasonable to assume that this might be mediated in part via modulation of cognitive processes involved in the long-term appraisal of pain. This raises the possibility that it might in fact be the restoration of normal HPA function that is associated with reduced pain sensitivity.

Sex as a mitigating factor in chronic pain

Perhaps the most readily appreciated contribution of hormones to pain behaviour is that of the sex steroids, estrogen, progesterone and testosterone. Rheumatoid arthritis, irritable bowel syndrome, fibromyalgia and tension-type headache are more prevalent in females, and experimentally induced pain is generally associated with greater pain sensitivity in female than in male subjects [32]. Numerous studies have attempted to correlate pain behaviours with fluctuating levels of estrogen and progesterone throughout the menstrual cycle [33]. The diverse range of nociceptive stimuli used to induce reflex pain behaviours in a variety of tissues probably accounts for the inconsistent results that were obtained, although overall, Fillingham and Ness have suggested that pain sensitivity peaks when plasma levels of estrogen are high [33].

Surprisingly little is known about the influence of sex steroids on the development and maintenance of chronic pain in animal models. Estrogen receptors are located throughout the nociceptive axis, including the brainstem, spinal dorsal horn and dorsal root ganglia [34,35]. In a rat model of partial nerve injury, intact female rats were twice as likely to develop ALLODYNIA to mechanical hindpaw stimulation than were either male or ovariectomized female rats [36,37]. Similarly, the severity of experimental arthritis is greater in female than in male rats [38]. Levine and colleagues have suggested that this might be caused, in part, by estrogen actions on the adrenal medulla reducing protective effects of neurogenic plasma extravasation [38]. By contrast, short-term estrogen replacement in ovariectomized rats has been shown to upregulate neurotrophin tyrosine kinase receptor A levels in axotomized dorsal root ganglion cells [35], an effect that would be expected to be associated with a decrease in pain behaviours. These apparently contradictory effects of estrogen on nociceptive transmission highlight the complex nature of hormone actions on behaviour.

Nevertheless, there are clear gender differences in susceptibility, disease progression and pain threshold to pain-related diseases in both animals and humans. There is also evidence to support the existence of gender differences in pain perception. Keogh and Herdenfeldt have used the cold pressor task (the subject's hand is placed into an ice water bath) to show that, when females are asked to concentrate on the emotional feelings and responses evoked by the cold water, they report an increase in pain experiences as compared with males [39]. Although the hormonal status of the female participants in this study was not documented, the ability of sex steroids to modulate changes in general behaviour, especially mood [40], suggests that sex steroids probably play an integral part in the emotional aspects of chronic pain disorders.

The growth hormone–IGF axis

The pulsatile secretion of growth hormone (GH) from the anterior pituitary is controlled by the reciprocal actions of GH-releasing hormone and somatostatin, in addition to interactions with other neuronal networks, including the HPA axis. Many of the effects of GH are mediated by the actions of insulin-like growth factor I (IGF-I), which is synthesized and released from the liver [41]. In the adult, there is a progressive decline in GH secretion, and deficiency of GH in senescence has been associated with deleterious changes in both body composition and brain function, including increased risk of developing psychological symptoms, such as depression. Several clinical features of fibromyalgia are similar to those described for adult GH deficiency syndrome, including muscle weakness and fatigue. Fibromyalgia patients have been reported to have lower nocturnal and 24-h mean levels of GH, in addition to reduced stimulation-induced secretion of GH and low levels of IGF-I [42]. Rheumatoid arthritis patients have also been reported to have decreased nocturnal GH secretion, but only when very high inflammatory activities were present [26]. GH replacement in fibromyalgia patients with low levels of IGF-I has been shown to provide a significant improvement in symptomatology [27]. It has been proposed that impaired GH secretion could disturb normal muscle homeostasis and as a result induce muscular pain [26]. The relevance of this to other chronic pain conditions remains to be determined.

Nevertheless, a role for IGF-I in lowering the pain threshold in diabetic neuropathy is worth considering. Intrathecal administration of IGF-I has been shown to elevate the nociceptive threshold in normal rats [43], an effect that is acutely attenuated in streptozotocin-treated diabetic rats, an animal model of diabetic neuropathy. This last effect might be overcome by increasing the dose of IGF-I administered, because chronic systemic administration of IGF-I in the same model has been shown to halt the progression of HYPERALGESIA and partially diminish the impairment in sensory nerve regeneration [44].

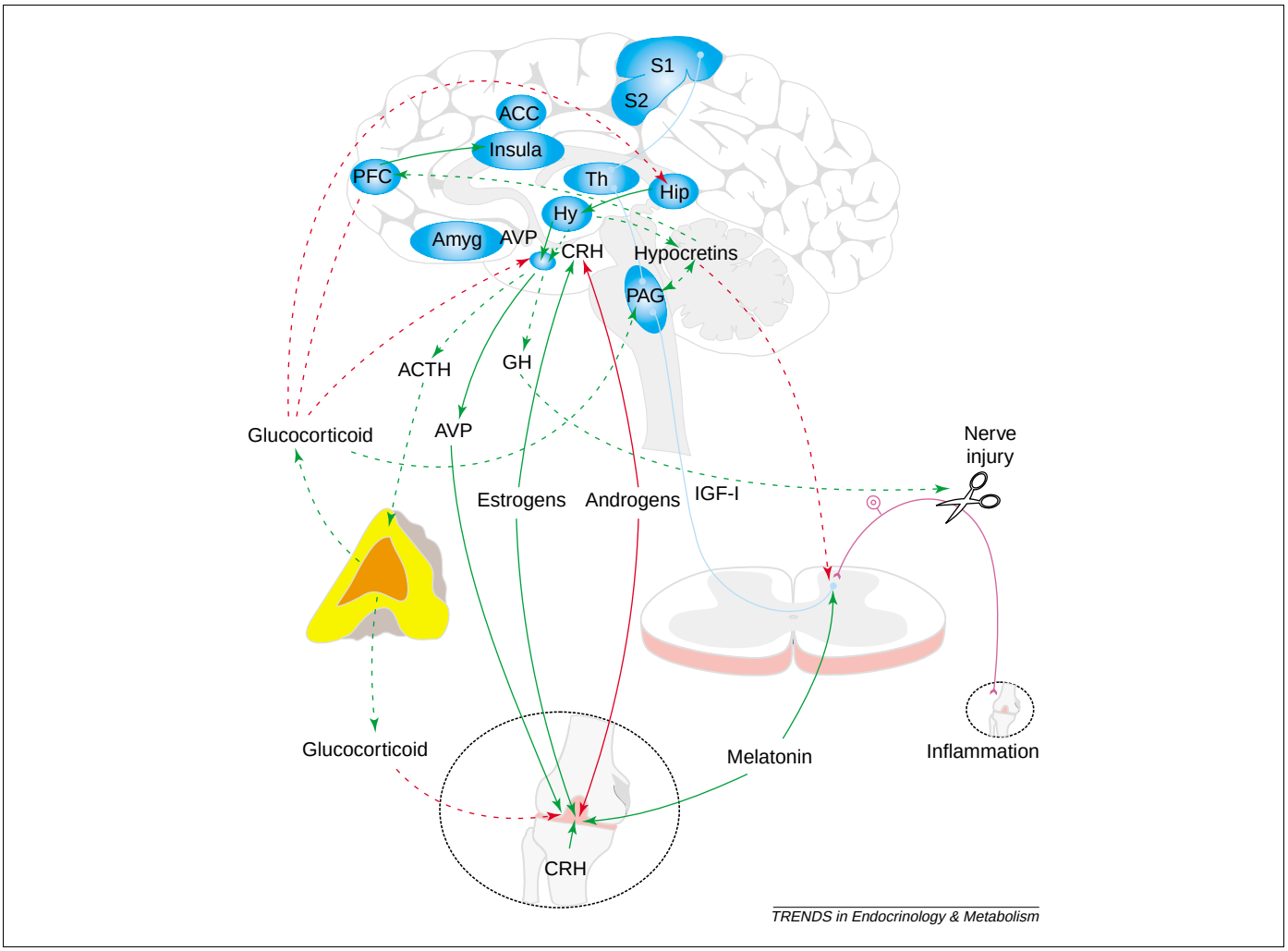

Fig. 2. Hormones can act at all levels of the pain pathway to affect nociceptive transmission. Various hormones and known modulators of hormone function participate in the development and maintenance, or arise as a consequence of, chronic pain. HPA axis dysfunction and other hormonal and/or modulator adaptations to tissue injury might induce depressed mood and enhanced perception of pain. Green and red arrows indicate stimulatory and inhibitory effects on nociceptive transmission, respectively. Solid lines indicate presumed functions that result from tissue injury (e.g. inflammation and nerve injury). Dashed lines indicate presumed loss of pre-injury function. Abbreviations: ACC, anterior cingulate cortex; ACTH, adrenocorticotrophin; Amyg, amygdala; AVP, vasopressin; CRH, corticotropin releasing hormone; DRG, dorsal root ganglion; GH, growth hormone; Hip, hippocampus; HPA, hypothalamo-pituitary–adrenal; Hy, hypothalamus; IGF-I, insulin-like growth factor I; Insula, insular cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; PFC, prefrontal cortex; S1/S2 somatosensory cortex; Th, thalamus.

Other hormonal mediators/modulators of hormone function as accessories to chronic pain

Melatonin

Melatonin has been shown to have profound analgesic effects in behavioural nociceptive tests in both rats and mice [45]. Melatonin-induced antinociception appears to be mediated via specific interaction with melatonin receptors [45], although there are probably also effects on other signalling systems, such as modulation of *N*-methyl D-aspartic acid (NMDA) receptor function [46]. Recent reports describing modulation of lipopolysaccharide-induced hyperalgesia by melatonin suggest that another mechanism of action could be via inhibition of the sensitizing actions of proinflammatory cytokines on nociceptive sensory neurones [47]. A large body of evidence also implicates melatonin in the modulation of mood [48]. In view of the widespread use of drugs that modulate serotonergic neurotransmission in the treatment of psychiatric illness and chronic pain, it is worth noting that 5-hydroxytryptamine receptor agonists appear to increase circulating melatonin levels in the rat [49]. This presumably affects mood and pain perception. A potential role for melatonin in chronic pain in human patients has also been proposed. In patients suffering from functional abdominal pain syndromes, melatonin rhythms have been shown to be of lower amplitude as compared with controls [50]. Low concentrations of serum melatonin have also been reported in patients suffering from either idiopathic pain (pain of undefined origin) or NEUROGENIC PAIN syndromes [51], and in patients suffering from cluster headache [52]. At present, it is unclear if these changes in melatonin are causally related to pain, or are secondary to the sleep disturbance common in chronic pain disorders.

Hypocretins

The hypothalamic peptides hypocretin 1 and 2 (also known as orexin-A and orexin-B) are synthesized in cells within the lateral hypothalamus, which project to numerous regions within the central nervous system to regulate behaviours associated with arousal [53]. Noradrenergic neurones in the locus caeruleus and serotonergic neurones in the dorsal raphe of the brainstem can stimulate cortical

arousal and are activated by local administration of hypocretins [53]. These regions also project to prefrontal cortical areas to modulate attentional state and participate in mood regulation.

Recent studies have shown that hypocretins can also affect nociceptive transmission. Hypocretin 2 increases the frequency of both spontaneous excitatory postsynaptic potentials and inhibitory postsynaptic potentials within superficial dorsal horn neurones, and as a result might be capable of modulating nociception via multiple mechanisms of action [54]. Another study has shown that hypocretin 1 administration in mice attenuates nociceptive responses to thermal and inflammatory stimulation. The selective hypocretin 1 receptor antagonist SB-334867 blocked these pain behaviours and was shown to be prohyperalgesic during inflammatory pain. Thus, some form of tonic descending hypocretin inhibitory system from the hypothalamus to the spinal cord appears to be activated in the setting of tissue injury [55]. Whether disturbance of hypocretin signalling and function contributes to chronic pain via modulation of brain areas involved in arousal and regulation of emotional processing remains to be determined.

Can hormonal pathways be targeted in the treatment of chronic pain? A verdict

Inflammatory and neuropathic pain conditions arise as a result of long-term maladaptive changes in sensory processing within peripheral and central pain pathways. Increasing evidence suggests that disturbances in HPA axis and gonadal steroid function might be causally linked with arthritic disorders, such as rheumatoid arthritis and fibromyalgia. To date, their potential involvement in neuropathic pain conditions has yet to be robustly demonstrated. However, a more clearly defined role for HPA axis hormones, and to a lesser extent gonadal steroids and hypocretins, in the modulation of attention and mood status suggests that the regulation of hormone function might be differentially disturbed in all chronic pain disorders, regardless of aetiology (Fig. 2). The lack of successful treatment of chronic pain with currently available analgesics continues to represent a major problem for health specialists. The selective targeting of hormone function to help restore mood imbalance, modulate spinal nociceptive transmission and aid functional recovery of damaged sensory neurones represents an alternative strategy for the future treatment of chronic pain disorders.

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