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Review Article

Chronic Pain, Chronic Stress and Depression: Coincidence or Consequence?

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Abstract

Chronic pain and depressive illness are debilitating disease states that are variably resistant to currently available therapeutic agents. Animal models of chronic pain are associated with activation of the hypothalamo-pituitary-adrenal (HPA) axis, upon which chronic pain acts as an inescapable stressor. Inescapable stress is also associated with 'depressive-like' symptoms in experimental animals. Based on reports of the comorbidity between chronic pain and depressive illness in human patients, it is possible that these disease states are linked, via chronic stress-induced HPA dysfunction. Here, we discuss the possible involvement of the HPA axis in the aetiology of both chronic pain and clinical depression, and suggest a strategy for the development of novel pharmacotherapies.

Few of us will escape without some experience of prolonged pain during our lifetimes. For some people however, pain becomes a chronic, intractable state that interferes with their normal functioning. In the United Kingdom alone, approximately 1 in 10 adults suffer from clinically diagnosed chronic pain, such as that associated with cancer, back problems, neuropathies, neuralgia and arthritic disorders (http://www.halcyon.com/iasp). Of these, 80% receive temporary pain relief with prescribed analgesics such as morphine, nonsteroidal anti-inflammatory drugs and anticonvulsants. Unfortunately, such therapies can bring long-term complications, and their limited extended efficacy leaves a significant number of people untreated and in constant pain. Pain such as this constitutes chronic, largely inescapable stress, and a substantial proportion of patients with chronic pain also present with frank symptoms of depression. In addition, clinical reports indicate that depressed patients who do not suffer from chronic pain, exhibit alterations in their perception of pain and in their threshold and tolerance to pain. Are these coincidental phenomena, or is there a unifying link which implicates the development of one disease process in the other? In the laboratory, chronic inescapable stress is associated with 'depressive-like' symptoms in experimental animals. The present review draws together evidence from experimental and clinical studies to consider the mechanisms subserving chronic stress, chronic pain and depression.

Depression

Depression is not a single disease; the term is used loosely to describe a plethora of illnesses that have some core symptoms in common. For this review, the term depression will be used to signify Major Depressive Disorder (1). The first drug to be associated with antidepressant effects, ipraniazid, targets monoamine pathways in the brain via inhibition of monoamine oxidase. The discovery that neurotransmission within these pathways was compromised in depression led to the 'biogenic amine theory' of depression (2), that has driven most of the basic experimental, pharmaceutical, and clinical science of depression for the past five decades. All antidepressant drugs currently on the market target monoaminergic pathways in the brain, by mechanisms of action that range from blockade of axonal monoamine oxidase enzymes to inhibition of dendritic and presynaptic neurotransmitter transporters.

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Their common final effect is to enhance monoaminergic neurotransmission. However, monoaminergics are effective in only 60–70% of depressed patients, their onset of therapeutic effect is slow, and they provide poor protection from disease relapse following cessation of therapy (2). In addition, they appear to be less effective in depressed patients who suffer particularly severe symptoms and who consequently often require more interventive therapy. As our understanding of the complexity of depression has improved, so has our appreciation that a biochemical deficit in a single neurotransmitter pathway is unlikely to be causative. Genetic, biochemical, socio-economic, psychological, environmental, and life-experience factors all play a role. However, the biggest risk factor is chronic stress, defined as 'an excess of negative events in the 6 months prior to the onset of depression' (3).

HPA axis and stress

A stressor can be defined as any stimulus that threatens normal homeostatic mechanisms. Stressors can include events such as sudden changes in body temperature or blood pressure, prolonged reduction in food intake, illness, infection and pain. In addition, there are stressors in the most commonly understood sense – fear, worry, bereavement or unemployment. The body's first defence against homeostatic challenge is the sympathetic 'fight or flight' response. The neuroendocrine HPA stress axis has traditionally been considered to be a slower, back-up defence to stress. However, as well as providing the energy substrates that support the sympathetic responses, the HPA stress axis is responsible for both the cognitive appraisal of the stressful situation, as well as the behavioural and endocrine adaptation to stress (4). The normal functioning of the HPA axis in response to stress (Fig. 1) has been the subject of several recent review articles (4–6).

HPA axis in chronic stress and depression

For both experimental animals and humans, survival during chronic stress requires not only that increased secretion of corticosteroid hormones be maintained in the face of negative-feedback control, but also that an additional corticosteroid response can be mounted to an incoming stressor when required. Such requirements dictate adaptive responses at all levels of the HPA axis (7). However, continued and prolonged stress may disturb the HPA axis to such an extent that the negative feedback mechanisms are disrupted; the adaptive responses of the HPA axis may then become maladaptive. Table 1 summarizes some of the most consistent changes in HPA axis function seen during chronic stress in experimental animals. There are some striking parallels between these changes and those seen in clinical depression. The combined general effect of these changes for both experimental animals and patients is enhanced central drive on the axis, elevated basal glucocorticoid concentrations, altered circadian rhythmicity of ACTH release, sluggish cessation of stress responses (implying reduced negative feedback control), and adrenal hypertrophy.

For experimental animals, the pattern of HPA mal/adaptation depends both upon the nature of the chronic stressor, and upon the period and mode of stress application. Repeated homotypic stressors such as restraint, foot shock and intraperitoneal injections of hypertonic saline, are associated with consistent elevations of vasopressin mRNA expression in the parvocellular paraventricular nucleus. CRH mRNA expression appears to be elevated only in those stress paradigms that are associated with conserved HPA responses

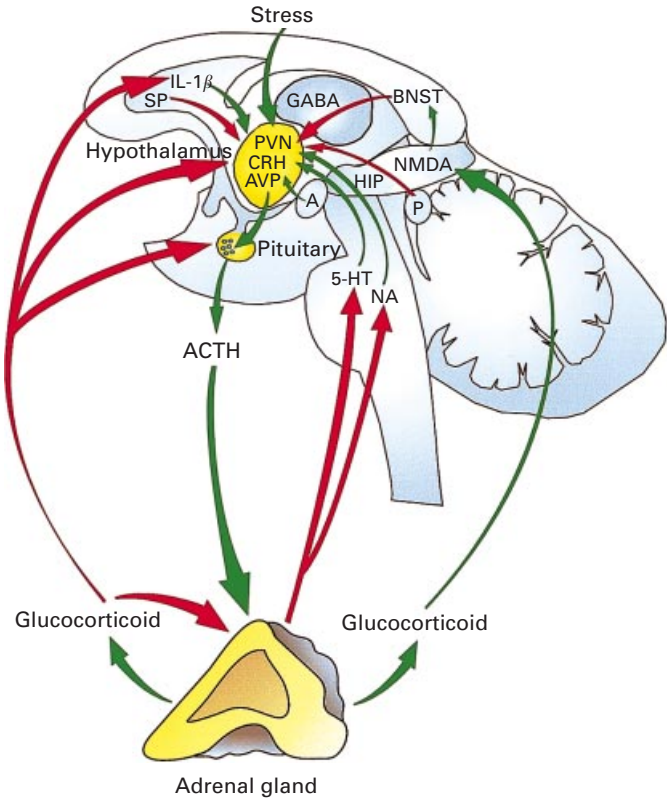

FIG. 1. Schematic representation of HPA axis modulation in response to stress. Stimulatory pathways to the HPA axis (yellow) are shown in green, and inhibitory pathways shown in red. Stressors of multiple origins activate neurones within the parvocellular division of the paraventricular nucleus that contain either CRH, arginine vasopressin (AVP), or both. These peptides are then released into the hypophyseal portal system and transported to the anterior pituitary gland. CRH acts at anterior pituitary corticotropes as a secretagogue in synergy with the weaker secretagogue vasopressin to release adrenocorticotrophic hormone (ACTH) into the systemic circulation. ACTH acts upon specialized receptors in the zona fasciculata of the adrenal cortex to initiate synthesis and release of the glucocorticoid hormones cortisol (in humans and some other mammals) or corticosterone (in rats and some other rodents). Glucocorticoids, acting primarily at the glucocorticoid receptor (GR), exert a negative feedback influence at the pituitary to prevent further ACTH release, at the paraventricular nucleus to prevent further CRH and vasopressin release, and at the adrenal cortex to prevent further glucocorticoid release. Additional negative feedback may be provided via both GR and the high affinity mineralocorticoid receptor acting within the hippocampus (HIP) to modulate glutamate (NMDA)-stimulated activity of inhibitory GABAergic neurones within the bed nucleus of the stria terminalis (BNST). The HPA axis may also be regulated by additional stimulatory inputs from brainstem serotonergic (5-HT) and noradrenergic (NA) neurones, from the amygdala (A), and by the inflammatory cytokine interleukin-1β (IL-1β); all of which are in turn subject to negative glucocorticoid feedback. Additional postulated inhibitory inputs are provided by the pineal gland (P) and the neurokinin substance P (SP).

TABLE 1. Comparison of a number of key changes in HPA axis function during chronic stress in experimental animals and clinical depression in humans. Note the parallels between the two states. A number of listed references are review articles. Abbreviations: ↑, elevation; ↓, reduction; CRH, corticotrophin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; GR, glucocorticoid receptor (Type II); MR, mineralocorticoid receptor (Type 1); mRNA, messenger ribonucleic acid; N/R, not reported.

Chronic stress	Clinical depression
↑CRH/CRH mRNA (14, 15)	↑CRH/CRH mRNA (30, 31)
↓CRH receptor affinity/number (16, 17)	↓CRH receptor affinity/number (31, 32)
↑AVP/AVP mRNA (5, 14–16, 18)	↑AVP/AVP mRNA (33)
↑CSF levels of CRH/AVP (19)	↑CSF levels of CRH/AVP (34)
↑Co-expression of CRH/AVP (14, 20, 21)	↑Co-expression of CRH/AVP (33)
↓GR/MR number/function (20, 22, 23)	↓GR/MR number/function (35, 36)
Altered plasma ACTH concentrations/circadian rhythmicity (8, 18)	Altered plasma ACTH concentrations/circadian rhythmicity (37, 38)
Adrenal supersensitivity to ACTH (22, 24)	Adrenal supersensitivity to ACTH (37)
↑Corticosterone (21)	↑Cortisol (31, 36, 39)
↓Negative feedback (7, 25)	↓Negative feedback (12, 13, 25, 37, 39)
Adrenal hypertrophy (22, 24)	Adrenal hypertrophy (40)
Pituitary hypertrophy (N/R)	Pituitary hypertrophy (41)
Exaggerated corticosterone response to stress (26, 27)	Exaggerated cortisol response to stress (42, 43)
Cognitive deficit/behavioural disturbance (26, 28, 29)	Cognitive deficit/mood disturbance (28, 29, 42)

to repeated activation, such as osmotic loading/dehydration or hypertonic saline injection (8). Some stress paradigms (e.g. adjuvant-induced arthritis) that continuously activate the HPA axis are actually associated with *reductions* in central CRH drive, but concomitant increases in vasopressin drive on the pituitary (9–11). The pattern of ACTH release in chronic stress also depends upon the stressor, such that ACTH secretion may be maintained or reduced (8).

Similarly, the HPA profile in clinical depression may vary. Approximately 50% of patients with major depressive disorder exhibit elevated cortisol secretion throughout the normal 24 h circadian cycle. The remainder may be eucortisolaemic, or may even have lowered baseline cortisol secretion (12, 13). Such data reflect the fact that depression is not a single disease, and that its symptomatology is variable in a heterogeneous patient population. However, most depressed patients exhibit dysfunction of HPA axis regulation, whether this be a reduction in negative feedback control of the axis, or altered central drive on the pituitary (Table 1). Normalization of the dysfunctional HPA axis has been shown to precede successful antidepressant treatment of depression (36, 37), and this has been attributed to an up-regulation of brain glucocorticoid receptor expression, restoration of appropriate negative feedback, and subsequent dampening of enhanced central drive (13, 44, 45). Such findings parallel those in experimental models of chronic stress-induced depressive-like behaviour, where chronic antidepressant treatment has been shown to up-regulate glucocorticoid receptor expression, normalize the HPA axis, and resolve behavioural symptoms (12).

Increasing evidence suggests that the HPA axis may be an appropriate target for the development of a new generation of antidepressant drugs. Trimipramine, a compound devoid of the serotonin (5-HT) and noradrenergic-enhancing properties of classical antidepressants, but which decreases HPA activity, has been found to be a clinically effective antidepressant (37). Tianeptine, a tricyclic compound that enhances 5-HT uptake (as opposed to classical antidepressants) but reduces HPA activity, has shown some antidepressant activity in preliminary clinical studies (46). Cortisol synthesis inhibitors such as metyrapone, aminoglutethimide and ketaconozole, which rapidly reduce circulating cortisol concentrations have proved to be effective antidepressants in monoamine-resistant, severely depressed patients, and the nonselective glucocorticoid receptor antagonist RU-486 has also been shown to ameliorate depressive symptoms (47). Preliminary clinical trials suggest that CRH receptor antagonists may also have therapeutic benefit in depression (48). Even the classic monoaminergic antidepressants are now known to evoke changes in the HPA axis. Although most antidepressants stimulate the HPA axis when given acutely, when given chronically they reduce CSF concentrations of CRH, desensitize CRH receptors, up-regulate brain glucocorticoid and mineralocorticoid receptor expression, suppress plasma ACTH and cortisol release, and normalize negative feedback control (as tested, for example, by the dexamethasone suppression test) (12).

Thus, while many different mechanisms may be involved in the therapeutic effect of antidepressants, all seem to involve a normalization of the dysfunctional HPA axis preceding the onset of therapeutic effect. Of particular interest is that many currently available antidepressants are also endowed with analgesic properties. In experimental animals it has been reported that acute stress is analgesic (49). Such findings provide the simple framework on which to explore the links between pain, stress and mood.

Chronic pain

The pain response appears to have evolved towards a level of complexity that is related to the cognitive capacity of the organism. The realization of pain is a multidimensional process involving physical, emotional and perceptual integration. The primary function of pain is to protect the organism from a potentially tissue-damaging stimulus via activation of spinal reflex withdrawal mechanisms. Longer-lasting pain,

such as that which follows damage to tissue, in association with an ankle sprain for example, is usually correlated with hyperalgesia (an increase in the pain elicited by a noxious stimulus and felt as a sharp, burning sensation) and allodynia ('other' pain evoked by a normally innocuous stimulus) (50), and serves to protect the injury from further trauma whilst allowing the damage to be repaired. A more insidious type of pain is that which persists beyond its biological usefulness and compromises the quality of life for the individual. In the context of this review, it is this type of chronic pain that often coexists with depressive illness.

Sensory neurones and chronic pain

There are three categories of sensory neurones, defined by their roles in the transduction of sensory information at the primary afferent terminal before its encoding and transmission to the spinal cord. The first type is myelinated: fast conducting and transduces low-intensity signals such as innocuous, mechanical stimulation of the skin (Aβ fibres; Fig. 2). The second type is unmyelinated: slow conducting and responds to high intensity activation by noxious heat, mechanical and chemical stimuli (C fibres); these are also referred to as nocispecific sensory neurones (nociceptors). The third type of sensory neurone has an intermediate conduction velocity, is myelinated, and also responds to high intensity activation (Aδ fibres). Under *normal* circumstances, only C and Aδ fibres transmit nociceptive information, but recent research utilizing knock-out and transgenic models in combination with physiological, pharmacological and biochemical analyses, has implicated all three types of sensory neurone in chronic pain disorders (50).

Nociceptors themselves belong within two classes, based in part on phenotype (peptide- and non peptide-containing), and in part on their responsiveness to neurotrophic factors (Fig. 2). Their afferents terminate within spatially distinct regions (laminae I–VI) of the superficial dorsal horn. A large number of the neurones within the dorsal horn that are targeted by the peptide population relay nociceptive information to higher brain centres such as the brainstem and thalamus, whilst the nonpeptide population appears to target interneurones within the superficial dorsal horn. Within the dorsal horn, three basic types of neurone have been classified by their response to nociceptive input (Fig. 2). Silent nociceptive-specific neurones are activated exclusively by noxious stimuli mediated by C and Aδ fibres, and have limited stimulus-encoding ability. Multireceptive neurones can produce a dynamic response over a broad stimulus range, from innocuous to noxious stimuli. The third class of neurone is non-nociceptive. Maladaptive neuroplastic events within these three types of neurone as a consequence of pathological damage to their input pathways, are key to the genesis and maintenance of chronic pain (51). As part of a relay conduit of nociceptive information, are they also implicated in HPA axis disturbance and possibly even depressive illness?

Peripheral pain

To perceive a nociceptive signal such as that incurred during an inflammatory response, it must first be detected at the

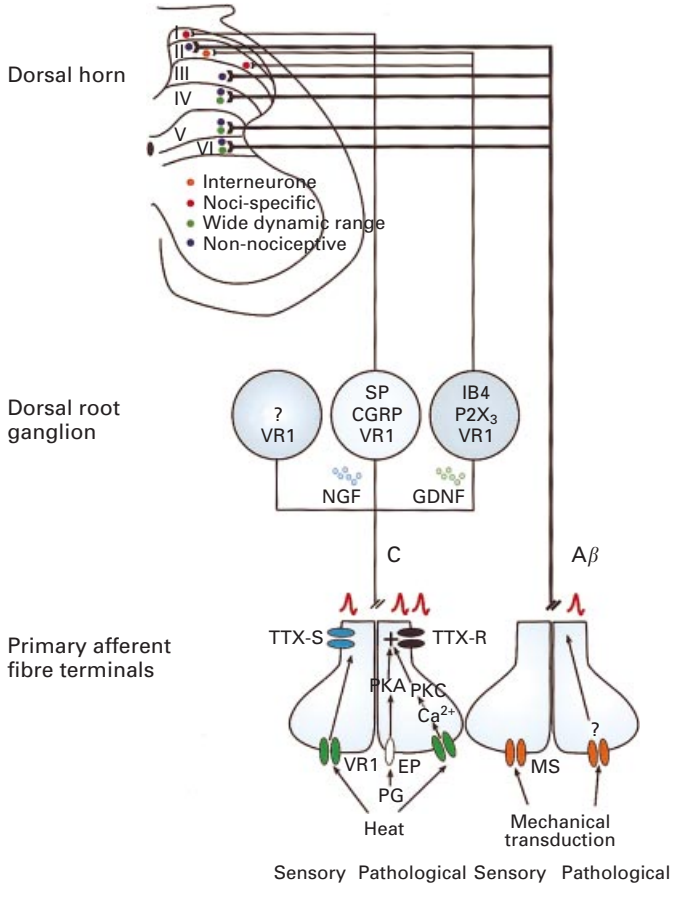

FIG. 2. Organization of peripheral sensory input to the dorsal horn of the spinal cord. Under normal circumstances, C-fibres are activated in response to nociceptive stimulation (via VR1) and action potentials propagated from the nerve terminal via TTX-S Na^+ channels. In contrast Aβ fibres are activated in response to non-nociceptive stimulation via interaction with MS complexes and synapse with non-nociceptive neurones in the dorsal horn. Nocispecific sensory neurones can be subdivided into at least two types based primarily on their peptide content and responsiveness to neurotrophins. The peptide-containing (SP/CGRP) class of nociceptor is NGF-responsive and project directly to laminae I and II of the superficial dorsal horn to synapse with nocispecific neurones, whose axons ascend to supraspinal structures. The nonpeptide (IB4/$P2X^3$) class of nociceptor is GDNF-responsive and may terminate on interneurones within lamina II which are partially responsible for mediating pathological consequences of inflammatory pain and nerve-injury. A third VR1-positive population of DRG cells fails to stain for either SP or IB4. Injury-induced pathological changes within C fibres result in the recruitment of sensitizing agents (PG, VR1), which induce phosphorylation-dependent changes in TTX-R Na^+ channels and increased action potential discharge. Injury-induced pathological changes within Aβ fibres are associated, with their inappropriate synapsing, with wide dynamic range neurones in the dorsal horn, which are then capable of transmitting nociceptive information to supraspinal structures in response to normally non-noxious stimuli. Changes within the terminals of Aβ fibres after injury are largely unknown at the present time. Abbreviations: CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; EP, prostaglandin receptor; GDNF, glial-derived neurotrophic factor; IB4, cell surface isolectin; MS, mechano-sensitive ion channel; PK, protein kinase; $P2X^3$, purinergic receptor subtype 3; NGF; nerve growth factor; SP, substance P; TTX, tetrodotoxin; VR1; vanniloid receptor 1.

nociceptor nerve terminal by specific receptor/ion channel complexes (Fig. 2). Although nociceptors can adapt to mild algogenic (e.g. pain-causing) stimuli, stronger stimuli release a number of factors from the damaged tissue that act to sensitize the nociceptor to subsequent stimuli. The primary function of this sensitizing response is tissue protection and ultimately, tissue repair.

The vast array of mediators involved in the sensitization of primary afferent fibres can be broadly defined as having either peripheral or central actions on nociceptive sensory neurones (Table 2). Peripheral sensitization may involve direct activation of the nociceptor terminal via ligand-gated ion channel interactions, or indirect activation by inflammatory mediators such as cytokines, growth factors and prostaglandins, which act to reduce the transduction threshold of the terminal membrane. These initial events induce parallel activation of intracellular kinases such as protein kinase A or protein kinase C (51, 59). Many of the key mediators of peripheral pain have also been implicated, in modulation of the HPA axis (Table 2). At the primary afferent terminal, sensitization appears to involve other distinct mechanistic entities, including phosphorylation-dependent modulation of nociceptor-specific ionic currents. One of these is a nociceptor-specific voltage-dependent Na^+ current called SNS (sensory neurone specific) (89). Sensory neurones express two principal types of Na^+ current; a fast TTX-sensitive current and a slow TTX-resistant current (90). Inflammatory-mediated phosphorylation of the TTX-resistant SNS Na^+ channel reduces the threshold for its activation and is one of the key components underpinning nociceptor sensitization (52).

Central pain

Although primarily peripheral in its aetiology, chronic pain has a centrally mediated component which is induced by long-term changes in primary afferent fibre projections to the dorsal horn (65). Peripheral nerve injury generally produces phenotypic changes in sensory neurones opposite to those that occur in response to inflammation. Nerve damage, by contrast to inflammation, is associated with decreased protein levels of substance P, CGRP, VR1 and SNS Na^+ channels, and much of the injury-induced remodelling of primary afferent fibre input occurs at the first synapse in the nociceptive relay circuit.

A plethora of mechanisms responsible for C-fibre-induced, activity-dependent synaptic plasticity in the spinal dorsal horn have been suggested. In general, these can be classed as those which are either NMDA receptor-dependent or NMDA-independent, and studies have compared the processes involved in dorsal horn neurone 'central sensitization' with processes underlying long-term potentiation in the hippocampus (91). Within the dorsal horn, mild noxious stimulation results in fast glutamate-mediated excitatory postsynaptic

TABLE 2. Comparison of a number of the key mediators thought to be involved in the induction and maintenance of inflammatory and neuropathic pain states and in regulation of both the HPA and nociceptive axes. A number of listed references are review articles. Note the lack of known mediators common to HPA axis dysfunction and neuropathic pain. Abbreviations: CGRP, calcitonin gene-related peptide; P2X, purinoreceptor 2X; PACAP, pituitary adenyl cyclase activating protein; POMC, proopiomelanocortin; TNF-α, tumour necrosis factor alpha; VIP, vasoactive intestinal polypeptide.

Peripheral mediators Primary afferent fibres	Central mediators Spinal dorsal horn	HPA
Inflammatory pain		
Ion channels, acid-sensing ion channel, P2X (52, 53), VR1 (54)	Ion channels (53) VR1 (54)	CRH (75), vasopressin (8)
Substance P, bradykinin, 5-HT, CGRP, nerve growth factor, opioids, histamine, prostaglandins (55)	Substance P/NMDA (51) Thr/Ser kinases (51)	Glucocorticoid receptors, mineralocorticoid receptors (76) Interleukin-1, TNF-α (77)
CRH (56), vasopressin (57)	Protein kinase C (58), TNF-α (66)	Substance P (78), neuropeptide Y (79)
Glucocorticoid receptors (58) protein kinase A (59)	Cyclooxygenase (67)	POMC, 5-HT/noradrenaline (12)
Oestrogen/testosterone (60)	VIP, PACAP (68) Vasopressin (69)	GABA, NMDA (80) Nitric oxide (81), VIP, PACAP (82) Brain derived neurotrophic factor (83), oxytocin (84) Neurotensin (85), prostaglandins (86) Cholecystokinin (87) Oestrogen, progesterone (88)
Neuropathic pain		
Ion channels (53, 61)	Ion channels (53)	
Brain derived neurotrophic factor (62)	Brain derived neurotrophic factor (71)	
TNF-α, interleukin-1β (64)	TNF-α, interleukin-1β (70)	
Bradykinin (64)	Substance P, NMDA, AMPA/kainate (51)	
Substance P, CGRP, VIP, somatostatin, galanin, cholecystokinin, nitric oxide synthase, neuropeptide Y (65)	Nitric oxide, protein kinase C (59) Noradrenaline/neuropeptide Y (72) Dynorphin, neurotensin (73) VIP, PACAP (68) GABA (74)	

potentials (EPSPs), which signal the original onset, duration and intensity of the stimulus. Sustained noxious stimulation produces slow EPSPs, and the resultant cumulative depolarization recruits spinal NMDA receptors to 'wind-up' action potential discharge. Further enhancement of NMDA channel gating occurs via convergent signalling cascades from metabotropic glutamate receptors and receptor tyrosine kinases. These increase cytosolic Ca^{2+} functioning with subsequent phosphorylation of the membrane bound NMDA receptor, and it appears that phosphorylation-specific changes are also important for the expression and maintenance of central sensitization (51).

Rewiring of central nociceptive circuits

Sensory neurones are exquisitely sensitive to neurotrophic factors both in terms of making appropriate connections within the periphery and spinal cord during development, and in the regulation of their designated phenotype. Uptake of neurotrophins from neuronal target tissues into primary afferent fibres by high-affinity tyrosine kinase receptors is followed by retrograde transport to cell bodies in the dorsal root ganglia (DRG). The dynamics of neurotrophin actions on activated nociceptive sensory neurones depend on the mode by which they are activated. Inflammatory pain increases the retrograde transport of nerve growth factor (NGF) to the DRG to initiate transcriptional changes that lead to altered production of neuropeptides, ion channels and receptors (Table 2). After peripheral nerve injury however, the target-supplied retrograde transport of neurotrophins can be lost. In this situation, complex alterations in transcription can occur, as observed when exogenous NGF administration to the proximal stump of the sciatic nerve after axotomy partially rescues TTX-resistant Na^+ channel function in DRG neurones (61).

After injury, a dynamic process of cellular degeneration and regeneration is initiated within neurones of the dorsal horn (92). Aβ fibres from laminae III and IV sprout to innervate inappropriate targets within the superficial dorsal horn (particularly the outer zone of lamina II), and this appears to be associated with the trophic actions of brain derived neurotrophic factor (93), which is up-regulated in this area after injury (62). These targets are inappropriate for Aβ fibre innervation in that they have been programmed to deal specifically with nociceptive processing (Fig. 2). This reorientation of Aβ fibres is further compounded by their phenotypic switch to a pronociceptive role (similar to that of C-fibres) as opposed to their role in non-nociceptive sensory transmission. These morphological changes within the spinal cord may persist long after the precipitating injury has healed, and contribute to ongoing perception of pain, and as a result, continued activation of the HPA axis. Glucocorticoid receptor mRNA is expressed in the superficial laminae of the dorsal horn, and glucocorticoid receptor and Fos immunoreactivity colocalize in subpopulations of cells within this area in response to nociceptive stimulation (94). Although this suggests that glucocorticoids may also be involved in the central rewiring observed after injury, chronic glucocorticoid infusion has no effect on either substance P or neurokinin receptor immunoreactivities within the dorsal horn after nerve injury, indicating that effects of glucocorticoids on nociceptive transmission may be mediated at other sites such as the brainstem (95).

Supraspinal sites of pain modulation

Pain also incorporates a significant emotional component. Pain is defined by the International Association for the Study of Pain as, 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (96). So, how are pain-related events of initial peripheral origin transduced into mood-modulating sequelae? After integration in the dorsal horn, nociceptive information is relayed via sensory pathways to higher brain centres that are generally located contralaterally (50). The ascending pathways of primary importance to central nociceptive processing can be segregated into those that involve direct (spinothalamic, spinohypothalamic and spinobulbar tracts), and indirect (spinocervical tract and postsynaptic dorsal column) projections (see 97).

Of the direct projections, spinothalamic cells originate primarily from lamina I and laminae IV–V of the dorsal horn to project to distinct regions of the thalamus including the ventral posterior and medial nuclei. Specific thalamic nuclei appear to be involved in the processing and transferral of nociceptive information to the cortex in rats and monkeys (98), and thalamic neurones responding to low threshold mechanical stimulation and high threshold noxious stimulation have been identified in each species (97). Some spinohypothalmic cells also respond to noxious stimulation, and whilst the potential role of these cells in the autonomic and neuroendocrine aspects of the pain response appears obvious (99), their terminations have not been clearly defined using either electrophysiological or anterograde labelling techniques. Spinobulbar nociceptive projections are important for integration of nociceptive activity with the homeostatic processes subserved by the brainstem. Ascending spinobulbar terminations occur in the catecholamine cell groups, the parabrachial nucleus, and the periaqueductal grey (PAG), and may contribute to processes which descend to the spinal dorsal horn to modulate nociceptive transmission.

From the thalamus, nociceptive information is relayed principally to the somatosensory (S1 and S2) cortex. Imaging studies of the forebrain have revealed that noxious stimulation also activates neurones in the insular and anterior cingulate cortical areas, in addition to areas of the limbic system including the amygdala, hippocampus, and hypothalamus (100, 101). These ascending pain pathways and their supraspinal targets contribute towards two distinct, yet related, aspects of pain: (i) the *sensory-discriminative* aspect which involves the perception and detection of a noxious stimulus in terms of its intensity, location and duration, and (ii) the *affective-cognitive* aspect which encapsulates the relationship between pain and mood, including pain memories, individual coping strategies, and the overall rationalization of the pain response. Although particular pathways and regions may have a predominant contribution to either aspect of the pain response, it is believed to be the overall activity in

these areas that ultimately forms the basis of the conscious experience of pain.

Electrical stimulation of the midbrain periaqueductal grey (PAG) modulates nociceptive transmission at the level of the spinal dorsal horn (102) via descending serotonergic and noradrenergic relay pathways that originate in the rostral ventromedial medulla (RVM) and the dorsolateral pontine tegmentum of the brainstem. Normally, activation of these pathways reduces neurotransmitter release (e.g. glutamate, substance P) from nociceptive primary afferent fibre terminals, and helps to act as a 'brake' on nociceptive signalling to supraspinal structures (100, 103) to allow for maximal neural encoding of afferent information. However, this may be overly simplistic, in view of recent research, which suggests that descending facilitatory pathways also affect ascending nociceptive transmission, acting to promote neuronal sensitization within the spinal dorsal horn (104). In addition, the electrical activity of monoaminergic neurones in these areas can be modulated directly by glucocorticoids (105), and glucocorticoid receptor immunoreactivity has been shown to increase within the RVM of rats after chronic antidepressant treatment (106). Ultimately, brainstem nuclei responsive to glucocorticoids are capable of integrating inputs from limbic structures involved in the expression of emotional behaviour and regulation of HPA axis stress responses, with ascending nociceptive input from the dorsal horn. Dysfunction of the complex circuitry that connects the brainstem with the thalamus, limbic and somatosensory cortices may occur in response to chronic painful stimuli (107), and may provide a basis for HPA axis involvement in the comorbidity of chronic pain and depression.

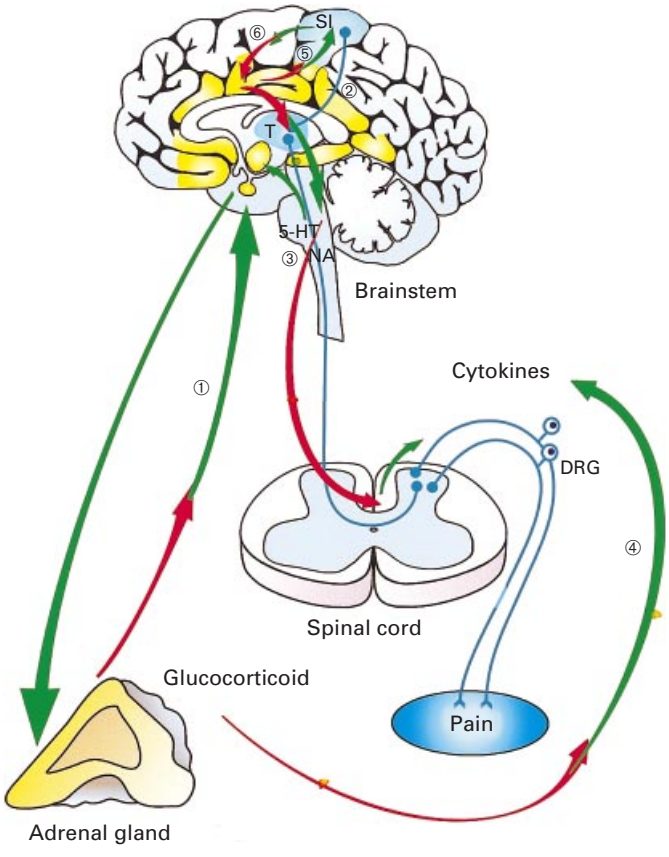

FIG. 3. Schematic representation of the nociceptive and HPA axis interactions that may underlie comorbidity of chronic pain and depression. Central to the coincidence or consequence hypothesis is the concept that the chronic stress evoked by chronic pain leads to loss of negative glucocorticoid feedback on the HPA axis, resulting in a positive drive on the axis and down-regulation of the glucocorticoid receptor within the brain and periphery (1). Inflammation and nerve injury stimulate noci-responsive neurones within the dorsal horn of the spinal cord, and the relay of nociceptive information ascends to the brainstem to be gated within the thalamus prior to its cognitive appraisal within the somatosensory cortex (2). Monoaminergic neurones in the brainstem normally descend to the spinal cord to act as a 'brake' on nociceptive transmission. During chronic pain, loss of monoaminergic tone in response to glucocorticoid-induced monoamine depletion may lead to reduced descending inhibitory impulses to the spinal cord to effect an enhancement of pain sensation (3). Loss of glucocorticoid inhibition of pro-inflammatory cytokines leads to proliferation of peripheral inflammatory events, contributing to pain sensitization (4). Although acute stress is analgesic, implying an inhibitory circuitry between the limbic and somatosensory cortices, chronic stress evoked by chronic pain may lead to down-regulation of glucocorticoid-mediated activity of this inhibitory connection, leading to enhanced pain perception (5). Similarly, although acute pain is mood enhancing via both sympathetic and glucocorticoid routes (implying an excitatory reciprocal link between the somatosensory and limbic cortices), chronic pain-induced down-regulation of glucocorticoid-modulation of this link may lead to depressed mood (6). Abbreviations: DRG, dorsal root ganglion; 5HT, 5-hydroxytryptamine; NA, noradrenaline; SI, somatosensory cortex; T, thalamus.

HPA axis and chronic pain

Central to the argument that the HPA stress axis and chronic pain may share common aetiologies, are clinical and experimental data suggesting three major areas of overlap: (i) both the neuroendocrine and the immune systems play an important role in the adaptation of an organism to stress, (ii) the HPA axis can be activated by a wide variety of stressors including nociceptive stimuli used in animal models of tonic and phasic pain (108), and (iii) various components of the HPA hormone cascade have been implicated in the pain response (Fig. 3). Many studies suggest that the HPA axis is involved in some of the commonest types of chronic pain (109).

Fibromyalgia, for example, is a non-arthritic rheumatological syndrome in which patients display reduced pain tolerance, multiple painful tender points, widespread pain, sleep disturbance, fatigue, and distress (110). Its prevalence is estimated to be 2% of the adult population. Studies with fibromyalgic patients have implicated dysfunctional HPA responsivity in the disease, as evidenced by inappropriate prolongation of stress responses, increased plasma release of ACTH in response to stress, reduced cortisol secretion, glucocorticoid feedback resistance, and reduced hypothalamic CRH content (111). Reduced hypothalamic CRH content and function is a finding supported by studies in which fibromyalgic patients showed significantly reduced and delayed ACTH release in response to the powerful CRH-releasing stimulus, interleukin-6 (IL-6) (112). These patients also exhibited exaggerated noradrenaline release and sympathetic activation in response to IL-6, suggesting that

fibromyalgic patients may suffer from a primary disorder of the neuroendocrine stress system (112).

The basis for HPA dysfunction in fibromyalgia is unknown, but clinical studies suggest that chronic pain-induced dysfunction of the HPA axis may be involved in reduced sensitivity of glucocorticoid receptors to glucocorticoid negative feedback (111). Current therapy for fibromyalgia includes local analgesics, corticosteroids, and antidepressant treatment (110). It has been hypothesized that there is a direct relationship between basal and dynamic function of the HPA axis and clinical manifestation of fibromyalgia (113). Chronic low back pain shares some of the same symptomatologies as fibromyalgia, and it has been estimated that the HPA dysfunction in this disease state lies somewhere between that of normal controls and fibromyalgia patients in severity (111). Depressive illness is estimated to be comorbid in the majority of chronic back pain sufferers (114).

Another common chronic pain state is rheumatoid arthritis. Genetic components contribute to the development of rheumatoid arthritis and other autoimmune diseases, but multiple lines of evidence suggest that there is also an association between these diseases and dysfunction of the HPA axis. It now seems that the complex interplay between the nervous system and the immune system plays a role in the development of some autoimmune diseases, and the HPA axis is an important link between the CNS and the immune system. Key here is the fact that the HPA axis is continuously stimulated rather than intermittently stimulated in rheumatoid arthritis, and this may partially explain why the profile of HPA dysfunction in this disease state is different from that in fibromyalgia or chronic back pain (9).

Much of our knowledge of HPA axis function in rheumatoid arthritis has been gained through experimental studies of adjuvant-induced inflammatory arthritis. The changes within the HPA axis that accompany progression of adjuvant-induced arthritis are similar to those that follow chronic repeated stress, in that consistently elevated basal secretion of ACTH and corticosterone, as well as loss of circadian rhythmicity, indicate that normal glucocorticoid feedback has been lost (10, 11). However, in contrast to some paradigms of repeated chronic stress, adjuvant-induced arthritis is not associated with elevated hypothalamic content or release of CRH – in fact, CRH mRNA expression and CRH concentrations within the portal system are decreased. Conversely, hypothalamic vasopressin content and vasopressin mRNA expression in the parvocellular neurones of the paraventricular nucleus are elevated (11). These data suggest that vasopressin assumes the role of the major driving force on HPA axis function in conditions where the axis is constantly challenged. Since CRH is the only known factor that is capable of stimulating POMC mRNA and transcription within the anterior pituitary, these data indicate that during sustained chronic immune disease, permissive levels of CRH only may be required to allow vasopressin to positively drive the axis forward (11). In this context, it is of interest that recent clinical data report up-regulation of vasopressin release in patients suffering from rheumatoid arthritis (115).

Although numerous factors play a role in the aetiology of rheumatoid arthritis (116), a consistent finding is that patients are incapable of mounting an additional cortisol response to a variety of acute stressors, and that circadian cortisol rhythmicity is lost (116, 117). Given the powerful effects of cortisol to suppress inflammatory events and immune function, such data have been interpreted to indicate that HPA dysfunction may contribute to the failure of the immune system to be adequately controlled. Loss of circadian cortisol rhythmicity may compromise normal immune function even further, since natural killer cells, cytokines, and lymphocytes are all subject to a circadian control that closely parallels that of the glucocorticoids (118). There are many reports of depressive symptomatology in patients with rheumatoid arthritis; some studies suggest that over 50% of these patients experience significant depressive symptoms, and there are often overlaps between depression and anxiety among individuals with chronic arthritis pain (117, 119). In general therefore, clinical data suggest that HPA axis dysfunction rather than hyperactivity *per se,* may be a common underlying factor in chronic pain and depression comorbidity.

Chronic pain and depression

A number of recent studies have attempted to provide a more precise working definition of pain by integrating the sensory qualities of the pain response with its affective aspects (120). This is especially relevant in the context of pain and depression comorbidity, since it is in such patient groups that the defining aspects of pain stray most commonly from those used by scientists investigating pain processing using animal models.

It has been estimated that over 50% of patients suffering from chronic pain also express clinically diagnosable symptoms of depression (121). However, chronic pain, like depression, is not a single disease. In medical terms, it has a definition that spans a broad spectrum of pathophysiological and psychological aetiologies. In general, it can be categorized into four classes based on its origins: (i) undiagnosed medical or surgical disease, (ii) psychiatric disorder, (iii) neurologic lesion (e.g. multiple sclerosis), or (iv) somatic lesion (cancer, back pain, headache, HIV, rheumatoid arthritis). Treatment of chronic pain presents a difficult challenge, since it may require a multidisciplinary approach including pharmacotherapy, cognitive therapy, psychotherapy and neurosurgery.

Given the diverse origins of chronic pain, controversy surrounds the relationship it bears to the depression with which it is often coexpressed. Five major hypotheses have been proposed: (i) the 'antecedent hypothesis', in which depression precedes the development of chronic pain, (ii) the 'consequence hypothesis', in which depression is a consequence of the chronic pain, (iii) the 'scar hypothesis', in which episodes of depression occurring before the onset of chronic pain predispose the patient to a depressive episode after the onset of pain, (iv) the 'cognitive mediation' hypothesis, in which psychological factors such as poor coping strategies are considered to mediate the reciprocal interactions between chronic pain and depression, and (v) the 'independent hypothesis', in which depression and chronic pain are

considered to share some common pathogenetic mechanisms but remain distinct diseases without causal interaction (122).

There is little doubt that clinical depression has a strong influence on a patient's subjective perception of chronic pain (123). Patients suffering from depression are more likely to score their pain as severe than those without depression, even if there is no obvious medical basis for the difference in pain intensity (124). This has led to the idea that depression is associated with a lowering of the pain threshold, which could arguably be described as behavioural allodynia, and reconciled with the 'antecedent hypothesis'. However the patient populations studied are generally mixed, and pain of any of the four major aetiological classes may be represented. A recent meta-analysis, controlled on several levels to address each of the five current hypotheses of coexpression of depression and chronic pain, confirmed that depression was more common in chronic pain patients than in healthy controls, and indicated that depression was a *consequence* of the presence of chronic pain, not a predisposing factor (121). Thus, it would appear that there is more support for the consequence hypothesis for chronic pain and depression comorbidity.

Several clinical studies have suggested that pharmacotherapies used to treat depression may also be effective analgesics in chronic pain sufferers (125, 126). Detailed meta-analyses of multiple antidepressant trial studies indicate that antidepressants are associated with pain relief that is over 74% more effective than placebo alone in chronic pain patients (127). There are, however, difficulties in studying the effects of antidepressants on chronic pain. The issue of organic *vs* unexplained psychogenic or somatiform pain has to be resolved, as patients suffering from affective disorders are more likely to develop idiopathic chronic pain than those who are not (123). To address this, a recent study utilizing only nondepressed patients suffering from chronic neuropathic pain of nerve injury, degeneration, or postherpetic neuralgic origins, demonstrated 50% pain relief in response to antidepressants (125). Meta-analyses designed to control for 'masked depression', have also demonstrated that antidepressants act in chronic pain patients through an analgesic effect rather than through an effect to improve undiagnosed depression (127). Although the analgesic effect of antidepressants is to some extent independent of their antidepressant properties, clinical studies have shown that tricyclic antidepressants have greater analgesic potency than serotonin-selective drugs, probably reflecting differential effects on serotonergic pathways (126). Evidently, not all drugs with antidepressant profiles will provide adequate pain relief in the clinical situation.

Regardless of the credibility of the above hypotheses, the importance of accurate diagnosis and reporting of chronic pain should not be underestimated. If chronic pain is excluded as a diagnostic tool for depression, the apparent prevalence of depression in a given patient population may be reduced. However, the clinical consequence of ignoring patients' complaints of chronic pain may be their failure to receive appropriate (if indeed any) treatment for their depression (124).

Molecular targets common to HPA axis modulation and chronic pain

Thus, classical pain targets may prove useful in the generation of novel antidepressants and, conversely, new HPA-targeted antidepressants may be effective analgesics in the treatment of chronic pain. The final section of this review highlights a few of the molecular targets postulated to modulate HPA axis stress responses and examines evidence that they may also be implicated in chronic pain processes.

CRH and vasopressin

Aside from its role as the major central secretagogue of the HPA axis, CRH appears to induce analgesia by both peripheral and central actions (56, 128). The peripheral analgesic actions appear to be related to the local inflammatory response, acting at CRH receptors on immune cells to evoke the release of opioid peptides, which in turn inhibit the activity of primary afferent neurones (129, 130). Although central analgesic effects of CRH are less well established (130), Lariviere and Melzack have suggested that CRH in a narrow dose range can have antinociceptive actions within the central nervous system (56). Analgesic actions of CRH seem to argue against the involvement of a hyperactive HPA axis in the genesis of chronic pain, but as discussed above, many clinical cases of chronic pain are associated with a reduction in central CRH expression and release. Moreover most studies have assessed pain responses during phasic pain tests such as the tail flick and hot plate tests (56). Such models of pain may have limited inflammatory components, and exclusively investigate acute pain.

A subpopulation of parvocellular vasopressin neurones project to the spinal cord, where they are believed to affect autonomic and nociceptive processing (131). In rodent models of tonic pain, dose-dependent analgesia is observed after systemic administration of vasopressin (69). However, increased plasma concentrations of vasopressin have been reported in patients suffering from chronic pain (130), and iontophoresis of vasopressin to the capsaicin-treated forearms of human subjects appears to contribute to thermal hyperalgesia by both vascular and unidentified nonvascular modes of action (57). No studies to date have addressed the potential pro/antinociceptive role of central vasopressin. It is possible that vasopressin of parvocellular origin and systemic vasopressin of magnocellular origin have differential effects on both pain processing and pain-induced HPA axis function.

Cytokines

The potential for inflammatory elements to play a role in HPA axis regulation, independent of underlying immunological events, is a relatively new concept, and has gained support following the reported development of depression in cancer patients receiving therapy with cytokines such as interferon (http://www.reutershealth.com/eline/open/1998031303). Much of the experimental evidence for HPA–cytokine interactions pertains to the pro-inflammatory pleiotropic cytokine, interleukin 1β (IL-1β). Central injection of IL-1β (in rodents)

has behavioural effects that mimic many symptoms of depressive illness, including suppression of food intake, depression of locomotor activity, reduction in social exploration, altered spatial perception, decreased attention and memory deficits, hyperalgesia, and increased slow-wave sleep (132, 133).

IL-1β may also interact with the HPA axis in a less direct manner. Peripheral administration of the cytokine activates subsets of neurones within the nucleus tractus solitarii, raphe, locus coeruleus, and DVC that express CRH, and this activation can be prevented by abdominal vagotomy (134). As brainstem monoamine systems are activated by stress and are compromised in clinical depression, and as central IL-1β stimulates the release of serotonin from the hypothalamus and increases the turnover of brain monoamines (135), it is possible that IL-1β may modulate the behavioural and physiological sequelae of psychiatric disease. In this context, elevated IL-1β concentrations in unmedicated depressed in-patients have been shown to 'normalize' after 4 weeks of treatment with the antidepressant clomipramine (136).

Glucocorticoids suppress cytokines such as IL-1β by interfering with their transcription, translation, mRNA stability, and secretion. Loss of glucocorticoid-mediated feedback in depression may therefore account for enhanced cytokine activity in the disease. Glucocorticoids may also enhance the expression of IL-1β receptors both peripherally and centrally (137), leading to sensitization to the central effects of the cytokine, and IL-1β is reported to attenuate the activation of glucocorticoid receptors in the brain by interfering with receptor dimerization and genomic signalling (138). These data suggest that IL-1β may play a role in HPA dysfunction during depression, whether the immune system is challenged or not.

Cytokines such as IL-1β, tumour necrosis factor alpha (TNF-α), IL-6 and leukaemia inhibitory factor (LIF), also affect sensory neurone nociceptive transmission by peripheral and central modes of action (50). Hyperalgesia after peripheral inflammation is associated with local release of TNF-α, which in turn induces IL-1β and NGF mRNA expression in nociceptive primary afferent fibres (66, 139). However, pain of apparent neuropathic origin may also involve a focal nerve inflammation (140), and increased mRNA expression of IL-6, LIF and their receptors (IL-6Rα, LIFRβ, gp130) in injured peripheral nerves has been reported (141). Thus, neuroimmune factors that are involved in the induction and maintenance of the joint inflammatory process in rheumatoid arthritis and in the systemic manifestations of the disease (142), may be involved in hyperalgesia and allodynia. IL-6, IL-1β and LIF may also induce allodynia and hyperalgesia via actions within the dorsal horn, as measured by glial activation and increased gene expression of each cytokine after peripheral nerve injury (70, 143). Similar changes in glial cell activation and expression of IL-1β mRNA within the spinal cord occur after inflammation induced by formalin or zymosan (144), which suggests that the hyperalgesia observed in conjunction with inflammatory and neuropathic pain may have a common cytokine-dependent mechanism of action. These actions may account for the analgesic effects of antidepressants in patients suffering from chronic inflammatory pain. Antidepressants such as fluoxetine and amitriptyline have been shown to inhibit pro-inflammatory cytokines produced by connective tissue cells within the affected joints of patients suffering from rheumatoid arthritis (145).

Monoamines

The role of brain noradrenaline and serotonin in depression is well substantiated, but the evidence suggesting a link between monoamines and the HPA axis is often neglected. Data indicate that the main effect of noradrenaline is a facilitatory one, mediated via α_1-adrenergic receptors (12). The noradrenergic innervation of the parvocellular paraventricular nucleus arises mainly from the A2 cell group of the brainstem, and travels via the ventral noradrenergic bundle (VNAB) to impinge on CRH cells (99). Electrical stimulation of the VNAB elevates plasma corticosterone secretion and the release of CRH into the hypophyseal portal blood (146). Stress-induced ACTH and corticosterone release is attenuated after lesion of noradrenergic fibres in the VNAB or paraventricular nucleus with 6-hydroxydopamine (147). Noradrenaline depletion also blocks the transmission of impulses from the ventral subiculum of the hippocampus to the hypothalamus (148); these glutamatergic neurones synapse with GABA neurones in the bed nucleus of the stria terminalis (BNST), tempting speculation that reduced noradrenergic tone during depressive illness may result in enhanced activity in the paraventricular nucleus via loss of inhibitory GABA tone (80, 149) (Fig. 1). An additional network for HPA activation may be subserved by the amygdala, which receives a dense noradrenergic input from the locus coeruleus, and which innervates the paraventricular nucleus (99). Lesion of the amygdala ameliorates stress-induced HPA hormone release to a variety of stressors (6). The role of serotonin (5-HT) in the regulation of the HPA axis has also been reported to be predominantly stimulatory. Drugs that enhance 5-HT outflow such as fenfluramine, and those that inhibit 5-HT uptake, such as the selective serotonin reuptake inhibitors, enhance HPA activity (150). The paraventricular nucleus receives serotonergic input from the midbrain raphe nuclei via the medial forebrain bundle. Again, depletion of 5-HT within the raphe or the paraventricular nucleus with the neurotoxin 5,7-dihydroxytryptamine causes depletion of hypothalamic 5-HT and blocks stimulated corticosterone release (151). High concentrations of corticosterone have been associated with down-regulation of the postsynaptic 5-HT_{1A} receptor (152), one consequence of which may be anxiogenic behaviour, as is often seen in depressive illness.

The primary effects of monoamines on nociceptive transmission in the spinal cord are, as discussed, largely mediated by descending brainstem pathways (100). The administration of amine uptake blockers or monoamine oxidase inhibitors increases the nociceptive response threshold and decreases spontaneous pain behaviour in animal models of inflammatory and neuropathic pain (153). These effects are mediated largely by actions of noradrenaline at α_2 adrenoceptors and serotonin at 5-HT_{1A} receptors in the brainstem

(pre) and spinal cord (postsynaptic) (100, 153). However, monoamines can also function as pro-nociceptive molecules at primary afferent fibres (50, 55). Under normal conditions, the sympathetic nervous system has minimal interplay with primary afferent pain fibres. After injury, sympathetic innervation of the DRG, which is normally limited to the control of blood supply, can extend into the DRG to form basket-like structures around cell bodies (154). Increased expression and sensitivity of α-adrenergic receptors occurs at both injured and intact primary afferent fibres as a result of decreased vascular tone after injury (155, 156). Thus, noradrenaline released by stimulation of sympathetic terminals can enhance the relay of nociceptive transmission to the spinal dorsal horn. Although sympathetic mechanisms can contribute to neuropathic pain, they are not necessarily causal. In view of the potentially contrasting roles of peripheral and central actions of noradrenaline on nociceptive transmission, this discrimination may prove important for the effective therapeutic treatment of chronic pain and depression comorbidity.

Substance P

The acute actions of substance P on the HPA axis are predominantly inhibitory, whereas NK_2 and NK_3 agonists appear to be stimulatory (78). However, studies of chronic substance P effects are less widely reported. Some studies suggest that substance P directly stimulates the adrenal cortex to release glucocorticoids, indirectly stimulates the adrenal medulla to release catecholamines, and that the substance P-stimulated adrenal medullary chromaffin cells may in turn exert a paracrine control on adrenocortical cells (85). Further, activation of central substance P pathways occurs in response to acute stress and noxious pain stimuli (157), and repeated administration of antidepressants causes a down-regulation of substance P biosynthesis in various brain areas in the rat (158). The potential antidepressant role of substance P antagonists is currently under investigation (159).

The co-operation of substance P- and NMDA-associated events in the development and maintenance of inflammatory mediated central sensitization suggests that pharmacological intervention of substance P-mediated transmission within the spinal dorsal horn might be an effective way of providing pain relief. However, selective cytotoxic targeting and destruction of NK_1 receptor-expressing cells in the spinal dorsal horn has a more pronounced effect on pain transmission than observed in transgenic mice in which the NK_1 receptor gene has been disrupted. This suggests that the transmission neurones themselves, rather than substance P neurotrafficking, may play a more important role in pain signalling (160). NK_1 receptor knockout mice exhibit decreased anxiety-related behaviours, possibly as a result of desensitization of brainstem $5HT_{1A}$ autoreceptors (161). Since activation of these receptors would be expected to inhibit ascending nociceptive transmission from the dorsal horn (103), the use of specific substance P antagonists for the combined treatment of chronic pain and depression should not be overlooked, despite the acute inhibitory effects of substance P on HPA axis activity.

Chronic pain, chronic stress and depression – a working hypothesis

Common sites of action for the above targets are supraspinal structures, including the brainstem nuclei, the limbic, and the somatosensory cortices (Fig. 3). We propose that high levels of glucocorticoid induced by acute stress may initially result in enhanced firing of midbrain serotonergic raphe neurones, via actions of substance P, CRH, or glucocorticoids. As stress becomes more chronic, this may lead to depletion of central serotonin, up-regulation of the brainstem presynaptic $5\text{-}HT_{1A}$ receptor, and glucocorticoid-induced down-regulation of the postsynaptic hippocampal $5\text{-}HT_{1A}$ receptor. Such events could lead to symptoms of depression and anxiety. Depletion of central serotonin might also lead to an increase in ascending nociceptive transmission, associated with either peripheral inflammation or neuropathic injury, as activation of dorsal horn-projecting serotonergic RVM neurones generally attenuates ascending nociceptive transmission (102). Similar pathological mechanisms could also account for a decrease in brainstem and spinal cord noradrenaline levels, leading to an increase in nociceptive transmission (162). Down-regulation of, and loss of, negative feedback at glucocorticoid receptors in areas such as the limbic system might also have deleterious consequences for the cognitive appraisal of the pain response. Thus, pain threshold may be lowered in patients suffering from depressive illness to such an extent that it manifests as part of the pathology of the depression. Similarly, as acute pain activates the HPA axis via ascending spinal pathways, it is feasible that chronic pain might induce a profound disturbance of HPA axis function. The analgesic potential of some classes of antidepressant drugs suggests that at least some of the mechanisms involved will be similar to those just discussed. Thus, depressive symptoms may manifest in chronic pain patients as a consequence of indirect, long-term nociceptive activation of the HPA axis.

This 'Coincidence or Consequence' hypothesis highlights the comorbidity of chronic pain and depressive illness, and implicates chronic stress-induced HPA dysfunction as a potential common link uniting the two disease states. Ultimately, a better understanding of this link might provide relief for, and enhance the coping strategies available to, the many patients currently suffering from chronic pain and depressive illness.

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