Minireview

Stress-Induced Pain: A Target for the Development of Novel Therapeutics

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ABSTRACT

Although current therapeutics provide relief from acute pain, drugs used for treatment of chronic pain are typically less efficacious and limited by adverse side effects, including tolerance, addiction, and gastrointestinal upset. Thus, there is a significant need for novel therapies for the treatment of chronic pain. In concert with chronic pain, persistent stress facilitates pain perception and sensitizes pain pathways, leading to a feed-forward cycle promoting chronic

pain disorders. Stress exacerbation of chronic pain suggests that centrally acting drugs targeting the pain- and stress-responsive brain regions represent a valid target for the development of novel therapeutics. This review provides an overview of how stress modulates spinal and central pain pathways, identifies key neurotransmitters and receptors within these pathways, and highlights their potential as novel targets for therapeutics to treat chronic pain.

Introduction

Acute pain is a critically important sensation that is required for survival. By signaling actual or potential tissue injury, acute pain is a protective sensation with sufficient unpleasant qualities to motivate a change in behavior to both prevent further injury and promote healing of the affected area. In contrast, chronic pain is a pathologic state that no longer serves as a protective mechanism and is harmful to the organism. A recent Institute of Medicine report (Institute of Medicine, 2011) estimates that >100 million adults over the age of 18 years experience chronic pain, which is defined as pain persisting for >6 months after the resolution of or in absence of an injury. In this review, we briefly discuss the

current therapies for treating chronic pain. This is followed by an overview of pain pathways, the potential mechanisms leading to chronic pain, and the site of action within the pain matrix of the currently available therapeutics. Although there is a well known interaction between stress and chronic pain, this relationship requires further investigation. The focus of the review is to link nociception to the stress axis and highlight the nonclassic targets for pain therapeutics that lie within this axis.

Current Therapies for Treating Chronic Pain

Opioidergic drugs are a primary choice for the management of patients experiencing pain (Inturrisi and Lipman, 2010; Trescot, 2013). Examples of drugs in this class include morphine, oxycodone, and fentanyl. These compounds can produce significant pain relief through a direct effect on pain pathways; however, the use of these drugs is limited by side effects, including nausea, constipation, and respiratory depression, as

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ABBREVIATIONS: ACTH, adrenocorticotrophic hormone; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; AM215, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP5, 2-amino-5-phosphonopentanoic acid; CB, cannabinoid receptor; CeA, central nucleus of the amygdala; CNS, central nervous system; CORT, corticosterone/cortisol; CPP, conditioned place preference; CRF, corticotropin-releasing factor; CRF₁, CRF receptor type 1; CRF₂, CRF receptor type 2; DRG, dorsal root ganglion; E-52862, 4-[2-[5-methyl-1-(naphthalen-2-yl)-1*H*-pyrazol-3-yloxy]ethyl]morpholine; GAT, GABA reuptake transporter; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; JWH015, (2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenylmethanone; mGluR, metabotropic glutamate receptor; MIFE, mifepristone; MK-801, (5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohept-5,10-imine maleate; MR, mineralocorticoid receptor; NMDA, *N*-methyl-D-aspartate; NNC05-2090, 1-[3-(9*H*-carbazol-9-yl)propyl]-4-(2-methoxyphenyl)-4-piperidinol hydrochloride; LSP4-2022, (2*S*)-2-amino-4-[[[4-(carboxymethoxy)phenyl](hydroxymethyl)(hydroxy)phosphoryl]butanoic acid; PACAP, pituitary adenylate cyclase-activating polypeptide; PAC₁, PACAP receptor type 1; PAG, periaqueductal gray; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; RVM, rostral ventromedial medulla; SNAP5114, 1-[2-[tris(4-methoxyphenyl)methoxy]ethyl]-(*S*)-3-piperidinecarboxylic acid; SNL, spinal nerve ligation; SPIRO, spironolactone; URB597, cyclohexylcarbamic acid 3'-[(aminocarbonyl)-[1,1'-biphenyl]-3-yl] ester.

well as the potential for tolerance and dependence with chronic use. Nonsteroidal anti-inflammatory drugs are another therapeutic option for pain management (Buvanendran and Lipman, 2010; Buvanendran, 2013). Broadly, this class of compounds includes diverse agents, such as ibuprofen, naproxen sodium, celecoxib, and meloxicam. Pain relief is achieved indirectly by suppressing cyclooxygenase activity to prevent prostaglandin formation in response to injury. Although there is little evidence of tolerance with this class of compounds, careful dosage titration is essential to avoid gastric ulcers and detrimental effects on renal function. Acetaminophen (alone or in combination with an opiate) can be administered as an alternative therapy but has potential to damage the liver. Other options for chronic pain management include compounds that target inhibitory neurotransmission, including gabapentin and pregabalin, which target calcium channels; and clonazepam and carbamazepine, which target GABA type A receptors (Eisenberg and Peterson, 2010; Nicholson, 2013). There is a spectrum of side effects associated with these compounds; the most common include sedation, dizziness, dry mouth, edema, and the potential for withdrawal symptoms if discontinued. Other drugs used specifically for neuropathic pain disorders include clonidine and tizanidine, which are α_2 -adrenergic receptor agonists; and duloxetine and milnacipran, which are examples of serotonin-norepinephrine reuptake inhibitors (Eisenberg and Peterson, 2010; Jackson and Argoff, 2010; Murinson, 2013). Common side effects with both classes of compounds include dizziness, sedation, dry mouth, and nausea, and severe hypotension is a common side effect of α_2 agonists.

Pain Pathways

Pain neurotransmission is complex and occurs at multiple levels (Fig. 1), which have been recently described in excellent reviews (Almeida et al., 2004; Wilder-Smith, 2011). Briefly, peripheral nociceptors are found throughout the body, including the skin, skeletal muscle, visceral organs, and joints. Nociceptors have free nerve endings that respond to various stimuli, including temperature, pH, stretch, and/or other algescic chemicals, based on differential expression of neurotransmitter receptors (Fig. 1A). The cell bodies for these nerve fibers are in the dorsal root ganglion (DRG) adjacent to the vertebral column. The nociceptors are bipolar cells that send processes into the dorsal spinal cord somatotopically in the case of somatic sensation and dichotomously in the case of visceral sensation. Additionally, there are small populations of nociceptors that innervate both somatic structures and visceral organs. The second level of pain neurotransmission occurs at the level of the spinal cord (Fig. 1B). Somatic and visceral nociceptors terminate primarily in the superficial lamina of the dorsal horn of the spinal cord on two classes of neurons: interneurons and second-order neurons. Interneurons communicate between spinal lamina to activate withdrawal reflexes. Second-order neurons receive pain signals that cross the midline and ascend via multiple tracts, including the spinothalamic tract, the spinoparabrachial tract, and/or the spinoreticular tract. The third and highest level of control occurs supraspinally within the central pain matrix (Fig. 1C), where the behavioral, cognitive, and emotional components of the noxious stimulus are integrated. The thalamus relays the ascending nociceptive signals to the somatosensory cortex for localization. Direct synaptic connections from the

spinoparabrachial and spinoreticular pathways activate limbic structures, such as the amygdala and insula, to apply an emotional response to the stimulus. The remainder of the central pain matrix [prefrontal cortex (PFC), cingulate, and parietal cortex] is engaged to determine the magnitude (low, moderate, or intense) and quality (sharp, dull, stabbing, burning, etc.) of the final pain signal. A series of descending pathways (Fig. 1D) are then invoked, including motor cortex and brain stem areas, such as the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), that participate in the descending modulation of the pain signals.

Mechanisms of Chronic Pain. Chronic pain can be maintained at three sites within pain pathways (Fornasari, 2012). The first location is peripheral sensitization of the nociceptive afferent terminals. The nociceptors become sensitized due to the release of inflammatory mediators, such as cytokines, prostaglandins, histamine, proteases, or pH, at the site of an acute injury (Arroyo-Novoa et al., 2009; Widgerow and Kalaria, 2012). Additionally, in response to immune stimulation or tissue damage, the afferent fibers can release neurotransmitters, such as substance P, calcitonin gene-related peptide, and/or nitric oxide, that further sensitize nociceptive afferents. The mechanism(s) leading to prolonged sensitization of the nociceptor is the result of long-lasting changes in gene expression that affect the number and type of receptors expressed to alter receptor properties that change the excitability of the neuron (Woolf and Salter, 2000). Because neuronal sensitization is the result of activation of G protein-coupled receptors (prostaglandin receptor, tyrosine receptor kinase A, neurokinin receptor type 1, protease-activated receptors, etc.) and subsequent signaling through second-messenger systems (protein kinase A and protein kinase C), these receptors and the second-messenger systems represent likely targets for therapies to treat chronic pain (Reichling and Levine, 2009). The initial nociceptive signal is produced through activation of ion channels (sodium, calcium, and potassium), producing the action potentials that are transmitted to the central nervous system (CNS). Experimental evidence has demonstrated that the excitability and expression of these ion channels are modified by the second-messenger systems that participate in the generation of chronic pain signaling (Schaible et al., 2011; Stemkowski and Smith, 2012). The second site that can participate in chronic pain sensitization lies in the dorsal horn of the spinal cord. Within the superficial lamina, the primary nociceptive afferent releases glutamate onto the second-order neuron, causing initial activation of sodium-permeable α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors followed by activation of sodium- and calcium-permeable *N*-methyl-D-aspartate (NMDA) receptors. In addition to the glutamatergic signaling, the primary nociceptive afferent releases algescic mediators, such as substance P, which cause activation of G protein-coupled receptors, which subsequently activate second-messenger signaling that results in changes to the properties of the receptors present in the dendritic structure of the second-order neuron (Woolf and Salter, 2000). As the second-order neuron is chronically activated by the primary nociceptor, a phenotypic switch can occur in the dendrites leading to increased expression of a calcium-permeable variant of the AMPA receptor, which results in increased excitability of the second-order neuron (Tao, 2012). A parallel mechanism leading to hypersensitivity within the dorsal horn of the spinal cord is primary nociceptive afferent modulation of inhibitory interneurons. Release of neurotransmitters

Fig. 1. Pain signaling pathways and site of action for current therapeutics. (A) Within the skin or viscera, nociceptive neurons, with cell bodies in the DRG, are activated by a noxious stimulus. The nociceptive signal is then transmitted to the superficial lamina of the dorsal horn of the spinal cord. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the release of prostaglandins at the site of injury to decrease nociceptive signaling. (B) Within the spinal cord, nociceptive afferents synapse on second-order neurons and interneurons. The second-order neurons cross the midline and ascend to the brain. Opioids, calcium channel blockers, and GABAergic drugs change pre- and postsynaptic properties on the primary afferents, the second-order neurons, or the interneurons to interrupt nociceptive signals. (C) The nociceptive signal activates the central pain matrix by being relayed through the thalamus (THAL) to the somatosensory cortex (SOM) for localization, while parallel pain pathways synapse within the amygdala (AMYG) and insula (INS) for emotional context. The nociceptive information is then processed by the PFC, cingulate (CING), and parietal cortex (PAR) to produce the final pain perception. (D) Descending inhibition of the nociceptive signal occurs from neurons within the PAG and the RVM that send axons down the dorsal column (dashed line) of the spinal cord to release analgesic mediators within the dorsal horn. Opioids, GABAergics, α_2 antagonists, or serotonin-norepinephrine reuptake inhibitors (SNRIs) change neurotransmission at multiple central sites to decrease pain perception. Modified public domain images (commons.wikimedia.org) of the coronal brain and shadow are from user Mikael Häggström, while the sagittal brain image is from user Nickbyrd.

from the primary nociceptive afferent activates presynaptic receptors on the inhibitory interneuron, leading to its hyperpolarization and a decrease in the release of GABA and/or glycine onto the second-order neuron (Zeilhofer et al., 2012; Braz et al., 2014). Thus, the combined influence of an increased signal generated by excitatory stimuli and a loss of inhibitory signaling can lead to a persistent hyperexcitable state in the second-order neuron, resulting in chronic nociceptive signaling. The final proposed mechanism that can induce chronic pain is supraspinal hypersensitivity, in which the balance of activity between the different brain nuclei that respond to pain signaling (the central pain matrix) is disturbed in response to a sensitizing event (Jaggi and Singh, 2011). Tertiary neurons within the thalamus, raphe, or parabrachial nucleus may undergo similar remodeling of receptor expression as occurred in the dorsal horn, which promotes hyperexcitability within the pain matrix by increasing the sensory signals reaching secondary cortical and limbic structures. Alternatively, remodeling of the integration nuclei can make the perception of the noxious stimulus more unpleasant, producing an enhanced negative emotional response (Staud, 2012). Imaging studies have demonstrated that in patients with chronic pain, there is increased activation of brain regions that integrate pain signals and produce negative-affect, such as the amygdala and insula, along with decreased activity in pain-inhibitory/positive-affect-producing nuclei, such as the

PFC and cingulate (Wilder-Smith, 2011; Saab, 2012). Another consequence of the altered signaling within the pain matrix is a disruption of the descending dorsal column inhibitory pathway through modulation of activity in the PAG and RVM (Ossipov et al., 2000; Heinricher et al., 2009).

Stress Modulation of Central Pathways in Chronic Pain

Evidence suggests that stress and negative emotions have profound effects on nociception (Scarinci et al., 1994; Lampe et al., 2003; Maizels et al., 2012; Racine et al., 2012). The stress response is divided into two complementary systems: the sympathomedullary axis and the hypothalamic-pituitary-adrenal (HPA) axis. The sympathomedullary axis releases epinephrine in response to sympathetic nervous system stimulation of the adrenal medulla to allow the organism to fight or flee from a threat, whereas the HPA axis stimulates the adrenal cortex to release cortisol (or corticosterone in rodents) (CORT) to mobilize glucose reserves to replenish the energy expended in the initial response. The HPA axis is initiated by stress when the paraventricular nucleus of the hypothalamus (PVN) secretes corticotropin-releasing factor (CRF) into the hypophyseal portal circulation. CRF then binds to its type 1 receptor (CRF₁) in the anterior pituitary, leading to synthesis of pro-opiomelanocortin,

which is cleaved within the pituitary to produce adrenocorticotrophic hormone (ACTH), which is released into general circulation. ACTH receptors in the adrenal cortex then bind the circulating ACTH to stimulate production of CORT, which is bound to a carrier (cortisol-binding globulin) before being released at target organs throughout the body. For its role in the HPA axis, CORT initiates feedback inhibition through binding to the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) (Sapolsky et al., 1983; Reul and de Kloet, 1985) at multiple sites, including the hippocampus, PVN, and anterior pituitary (Herman and Cullinan, 1997). In contrast, CORT binding at the amygdala promotes CRF expression and facilitation of the stress axis (Schulkin et al., 1998; Shepard et al., 2000). Thus, the amygdala is a key nucleus that can integrate both stress and pain signaling (Myers and Greenwood-Van Meerveld, 2010, 2012). Chronic stress promotes an increase in dendritic arborization and axonal connections in amygdaloid neurons, while simultaneously pruning dendrites and axon connections within the hippocampus and PFC (Woolley et al., 1990; Vyas et al., 2002; Mitra and Sapolsky, 2008; Radley et al., 2013). The result of the neuronal remodeling is increased prostress/pronociceptive activity from the amygdala concurrent with decreased antistress/antinociceptive activity from the hippocampus and PFC, leading to chronic facilitation of both the HPA axis and pain. Finally, three brain stem regions responsible for modulation of descending inhibitory pain signals are also modulated by both pain and stress. The PAG receives excitatory signaling from the PFC and inhibitory signaling from the amygdala (da Costa Gomez and Behbehani, 1995; Price, 1999). The RVM receives not only direct nociceptive information from the spinoreticular pathway but also integrated pain and stress signals from the amygdala and PAG. The locus coeruleus and amygdala form a circuit that can potentiate both endocrine and autonomic stress responses (Reyes et al., 2011). Thus, novel therapeutics that selectively target neurotransmitters or receptors within the central stress and pain circuits should be able to reverse chronic pain and/or stress disorders through restoration of the facilitatory and inhibitory balance.

Receptors in Stress Pathways That Modulate Nociception

A multitude of neurotransmitters interact within the stress axis and pain pathways, and while an exhaustive description of each is beyond the scope of this review, we refer the reader to several excellent reviews (Mora et al., 2012; Asan et al., 2013; Reichling et al., 2013; Timmermans et al., 2013; Grace et al., 2014). The focus of the following section of this review is to highlight potential targets within the overlapping stress and pain neurocircuits that may lead to novel approaches to treat chronic pain.

GRs and MRs. GR and MR are in the 3-ketosteroid nuclear receptor superfamily (Lu et al., 2006; Alexander et al., 2013b), functioning as cytoplasmic transcription factors that slowly adapt cellular physiology over hours, days, or weeks (McKenna and O'Malley, 2005). There is also evidence for "fast" actions (seconds or minutes) of GR and MR due to membrane-bound versions of the receptors (Haller et al., 2008; Evanson et al., 2010; Prager et al., 2010; Hammes and Levin, 2011). In contrast to widespread GR expression, MR expression is restricted to specific brain nuclei important for both HPA and pain regulation, such as the hippocampus,

PVN, and amygdala (Lu et al., 2006); studies suggest that both the cytoplasmic and membrane versions are present in those nuclei (Johnson et al., 2005; Karst et al., 2005; Evanson et al., 2010; Prager et al., 2010). Thus, the balanced activation between the "slow" transcriptional and "fast" membrane GR and MR effects produces the appropriate response to an acute stressor. However, chronic stress disrupts the balance between the two responses, which may potentiate chronic pain disorders due to the overlap between the limbic and pain neurocircuitry (Johnson and Greenwood-Van Meerveld, 2012).

The effects of GR and MR agonists and antagonists in common neuropathic pain models of injury to peripheral nerves (chronic constriction nerve injury or spared nerve injury) or injury to spinal nerve roots [chronic compression of the lumbar DRG, spinal nerve ligation (SNL), or DRG inflammation with zymosan] have been studied. Common to all the neuropathic pain models is a decrease in withdrawal threshold to mechanical or thermal stimulation, which is enhanced after exposure to stress. Studies using GR antagonists, such as mifepristone (MIFE), demonstrated that intrathecal administration could increase both mechanical and thermal withdrawal thresholds in the injured limb (Wang et al., 2004; Takasaki et al., 2005; Gu et al., 2007). Those results were also replicated with intrathecal administration of antisense oligodeoxynucleotides selective for GR (Wang et al., 2004; Dina et al., 2008). Conversely, administration of a GR agonist, dexamethasone or triamcinolone, mimicked stress-induced exacerbation of withdrawal threshold (Wang et al., 2004; Gu et al., 2007). Similarly, intrathecal dosing of an MR antagonist, spironolactone (SPIRO) or eplerenone, also reversed the allodynic responses (Gu et al., 2011; Dong et al., 2012). Additional studies have provided evidence for antinociceptive mechanisms that involve NMDA and possibly opiate receptor modulation by GR (Wang et al., 2005; Dong et al., 2006; Alexander et al., 2009) and modulation of spinal microglia activity by MR (Sun et al., 2012). In addition to the spinal site of action, targeting GR or MR within the central nucleus of the amygdala (CeA) with agonists (CORT/dexamethasone or aldosterone) or antagonists (MIFE/SPIRO) can also induce or inhibit somatic allodynia and colonic hypersensitivity to colorectal distension (Myers et al., 2007; Myers and Greenwood-Van Meerveld, 2007, 2010). There is also evidence for the involvement of GR and MR in the development of pain-like behaviors induced by a repeated stress. Systemic MIFE administration reversed colonic hypersensitivity to colorectal distension in response to either a repeated water avoidance stress or subcutaneous CORT injections, with a potential mechanism of altering cannabinoid receptor (CB) type 1 and transient receptor potential cation channel V1 receptors in the dorsal horn of the spinal cord (Hong et al., 2011). In a similar fashion, MIFE or SPIRO administered to the CeA also prevented repeated water avoidance stress-induced pain-like behaviors (Myers and Greenwood-Van Meerveld, 2012). Thus, there is sufficient preclinical evidence of an interaction between stress hormones and experimentally evoked pain behaviors to suggest that novel, centrally acting GR or MR antagonists might provide significant relief for some chronic pain conditions.

CRF Receptors. CRF is a 41-amino-acid peptide produced by the key nuclei within the pain-stress brain circuitry, such as the PVN and CeA (Gallagher et al., 2008). CRF activates two G protein-coupled receptors, CRF₁ and CRF₂, with CRF₁ having an ~10-fold-higher binding affinity than CRF₂ (Alexander et al., 2011, 2013a). Both receptors signal through Gs activation

of adenylate cyclase and increases in cAMP, but they produce opposite behavioral effects: CRF₁ facilitates and CRF₂ inhibits stress and nociceptive responses in rodent behavioral models (Ji and Neugebauer, 2007, 2008; Yarushkina et al., 2009; Tran et al., 2014). In patients with chronic pain, CRF concentration within the cerebrospinal fluid correlated with pain rating (McLean et al., 2006) and a selective CRF₁ antagonist decreased enhanced amygdala activity and emotional ratings (Hubbard et al., 2011), suggesting that CRF is a valid target for therapeutic intervention in some chronic pain conditions. However, clinical evidence to date has produced mixed effects on pain relief in this therapeutic class (Sagami et al., 2004; Sweetser et al., 2009).

Pituitary Adenylate Cyclase-Activating Polypeptide Receptors. Pituitary adenylate cyclase-activating polypeptide (PACAP) is a 27- or 38-amino-acid polypeptide expressed within the brain and peripheral tissues that binds to one high-affinity receptor, PACAP receptor type 1 (PAC₁), and two lower-affinity receptors, vasoactive intestinal peptide receptors type 1 and 2, which are expressed throughout the brain and spinal cord (Harmar et al., 2012). PACAP regulates CRF expression and the HPA axis in models of acute and chronic stress and has been implicated in the pathophysiology of post-traumatic stress disorder, schizophrenia, and migraine (Mustafa, 2013; Shen et al., 2013; Edvinsson, 2014). A recent study demonstrated that PACAP infusion into the CeA could induce anxiety-like behavior and lower thermal withdrawal thresholds in healthy animals (Missig et al., 2014). PACAP also modulates inflammatory, neuropathic, and visceral pain-like behaviors based on results in experimental models (Bon et al., 1998; Ohsawa et al., 2002; Shimizu et al., 2004). Evidence suggests that the modulation of nociception by PACAP involves activation of PAC₁, since most of the behaviors could be inhibited by a selective antagonist, PACAP₆₋₃₈, through an interaction with dynorphin release within the spinal cord (Davis-Taber et al., 2008; Liu et al., 2011). Thus, PAC₁ regulates not only the stress response but also some pain-like behaviors, making it a prime target to treat stress-associated chronic pain. Unfortunately, there is currently a shortage of selective antagonists or agonists, indicating that more research into novel therapeutics for this receptor may be a worthwhile approach.

Glutamate Receptors. Glutamate is the primary excitatory neurotransmitter within pain pathways and the stress axis, with its receptors (AMPA and NMDA) expressed throughout the CNS. Selective antagonists, applied into discrete brain or spinal regions, are antinociceptive in animal models of neuropathic pain. Specifically, MK-801 [(5*S*,10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine maleate], an NMDA antagonist, decreased mechanical allodynia and reduced microglia activation in a model of SNL (Kim and Jeong, 2013), while both MK-801 and AP5 (2-amino-5-phosphonopentanoic acid) reversed mechanical allodynia induced by vincristine in a model of chemotherapy-induced neuropathic pain (Ji et al., 2013). When applied to stress-responsive brain regions, ionotropic glutamate receptor antagonists inhibit the HPA axis. However, due to a lack of receptor specificity, this class of compounds shows marked sedation at doses that are antinociceptive. There are also three classes of metabotropic glutamate receptors (mGluRs) (Julio-Pieper et al., 2011) that are emerging targets for novel therapeutics based on the availability of novel selective agonists and antagonists. Although specific classes of mGluRs are expressed in different nuclei, both the amygdala

and PAG express all three classes of mGluR (Swanson et al., 2005; Palazzo et al., 2014b). Thus, these receptors are in key anatomic locations to modulate both stress and pain responses. While two complementary reviews explore the potential of this pharmaceutical class (Palazzo et al., 2014a,b), there is also some additional evidence for antinociception from animal models. Specifically, LSP4-2022 [(2*S*)-2-amino-4-([(4-(carboxymethoxy)phenyl)(hydroxy)methyl)(hydroxy)phosphoryl]butanoic acid], a novel mGluR4 agonist, dose-dependently inhibited mechanical allodynia caused by carrageenan inflammation, with complementary results produced with mGluR4 antisense oligodeoxynucleotides and in mGlu4 knockout mice (Vilar et al., 2013). However, opposing results were found with selective mGluR5 antagonists, with which thermal allodynia was inhibited and mechanical allodynia was enhanced in the SNL model of neuropathic pain (Zhou et al., 2013). Activation of mGluR5 within the CeA via microinjection of selective agonists was also found to induce both somatic and visceral pain-like behaviors, effects blocked with selective antagonists (Kolber et al., 2010; Crock et al., 2012). Based on the expression of mGluRs within the amygdala and PAG, there will likely be an interaction between the stress and pain circuitries, making this receptor class a prime target for novel, subclass-specific therapeutics.

Endocannabinoid Receptors. The endocannabinoid receptors, CB₁ and CB₂, are G protein-coupled, with anandamide (AEA) and 2-arachidonoylglycerol (2-AG) as endogenous ligands (Pertwee et al., 2010). CB₁ receptors are located in CNS areas that can modulate pain perception, whereas CB₂ receptors are predominantly peripheral, with central expression in some chronic pain models (Luongo et al., 2014). Additionally, there is strong evidence that endocannabinoids are expressed within stress-responsive brain areas (PVN, amygdala, PFC, and hippocampus) and participate in both inhibition of the HPA axis as well as acute stress-induced analgesia (Gorzalka et al., 2008; Butler and Finn, 2009; Hill and McEwen, 2010). A combined model of chronic pain from plantar formalin injection with fear conditioning demonstrated that the CB₁ antagonist rimonabant was able to restore the ability of 2-AG, injected into the ventral hippocampus, to prevent fear behaviors, but did not demonstrate a direct role for pain modulation (Rea et al., 2014a). However, in the Wistar-Kyoto rat, which is genetically predisposed to increased stress responsiveness and exaggerated pain-like behaviors, formalin-induced hyperalgesia was increased and associated with decreased expression of AEA and 2-AG within the RVM (Rea et al., 2014b). The role of the RVM was confirmed by microinjection of AM215 [*N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide], a CB₁ antagonist/inverse agonist, which exacerbated the hyperalgesic response, while URB597 [cyclohexylcarbamic acid 3'-(aminocarbonyl)-[1,1'-biphenyl]-3-yl ester], a fatty acid amine hydrolase inhibitor that prevents degradation of AEA and 2-AG, inhibited the hyperalgesic response (Rea et al., 2014b). A novel CB₁ peptide agonist, VD-hemopressin, produced antinociception to tail flick in mice following either spinal or supraspinal administration; however, there were some behavioral indications of tolerance and dependence with repeated dosing (Han et al., 2014). The selective CB₂ agonist JWH015 [(2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenylmethanone] demonstrated a role for the receptor in the regulation of opioid-induced hyperalgesia, via the stabilization of glia and a reduction in proinflammatory markers (Sun et al., 2014).

Thus, endocannabinoids are present in central stress and pain circuitries, and future therapeutics that selectively target those systems should likely alleviate chronic pain without producing unwanted psychotropic effects.

GABA Transporters. GABA_A receptors are ionotropic chloride channels that were initially characterized by their sensitivity to the antagonist bicuculline (Barnard et al., 1998; Olsen and Sieghart, 2008). In contrast, GABA_B receptors are metabotropic G protein receptors that are resistant to bicuculline and sensitive to baclofen, a selective agonist (Bowery et al., 2002). Both GABA_A and GABA_B are expressed throughout the pain- and stress-responsive areas of the brain as well as within the dorsal horn of the spinal cord. The roles of these receptors in the regulation of stress and nociception have been reviewed previously (Enna and Bowery, 2004; Goudet et al., 2009; Munro et al., 2013; Gunn et al., 2014). Another level of regulation of GABA signaling occurs with the GABA reuptake transporters (GATs), of which four have been identified (GAT1–4). Studies of mice that overexpress GAT1 demonstrated increased pain-like behavior, and conversely, GAT1 knockout mice showed decreased pain-like behaviors to mechanical and thermal stimulation (Hu et al., 2003; Xu et al., 2008). Additionally, GAT1 knockout mice exhibit lower basal levels of anxiety-like and depressive-like behaviors as well as a lower basal plasma CORT (Liu et al., 2007), findings that were replicated with chronic dosing of the GAT1 inhibitor tiagabine (Thoeringer et al., 2010). Recent studies testing a GAT3 inhibitor, SNAP5114 (1-[2-*tris* (4-methoxyphenyl)methoxyethyl]-(*S*)-3-piperidinecarboxylic acid), found antinociception in response to mechanical and thermal stimuli via an interaction with both GABA_A and GABA_B receptors (Kataoka et al., 2013). However, SNAP5114 did not change withdrawal thresholds in a mouse SNL model, whereas NNC05-2090 (1-[3-(9*H*-carbazol-9-yl)propyl]-4-(2-methoxyphenyl)-4-piperidinol hydrochloride), a betaine/GAT1 inhibitor, demonstrated efficacy (Jinzenji et al., 2014). Thus, drugs targeting GATs can produce antinociception and reduce the response of the stress axis, suggesting that this class of compounds may be effective in patients with chronic pain.

Sigma-1 Receptors. Sigma receptors are a class of novel receptor chaperones that interact with a multitude of receptor classes including G protein-coupled and ionic channels (Guitart et al., 2004). In its role as a molecular chaperone, the sigma receptor modulates downstream signaling pathways within neurons to change overall excitability (such as through the inositol triphosphate pathway) or gene transcription (via cAMP response element-binding protein and c-Fos). The sigma receptor's ability to act as a chaperone can be modulated by agonists and antagonists that change the binding properties of the molecule. Sigma receptors are distributed throughout the CNS and are expressed in brain regions that modulate stress and pain perception, including the PFC, hippocampus, hypothalamus, PAG, locus coeruleus, and RVM, and are colocalized in neurons that express NMDA, GABA, and opioid receptors (Bouchard and Quirion, 1997; Hayashi et al., 2011; Zamanillo et al., 2013). In support of previous reports of antinociceptive effects, recent studies have shown that the selective sigma-1 receptor antagonist E-52862 (4-[2-[5-methyl-1-(naphthalen-2-yl)-1*H*-pyrazol-3-yloxy]ethyl]morpholine) inhibits chronic pain induced by inflammation (intraplantar formalin, carrageenan, or complete Freund's adjuvant) at the level of the dorsal horn and with efficacy similar to that of ibuprofen and celecoxib (Gris et al., 2014; Vidal-Torres et al., 2014). Thus, data suggest that

further development of novel, selective, centrally active sigma-1 receptor antagonists is a valid approach for the treatment of both chronic pain as well as behavioral disorders, such as depression, that are influenced by the stress axis.

Evaluation of Pain Behaviors in Experimental Models

Many rodent models of nociception evaluate the efficacy of therapeutics through changes in acute, evoked responses that are applied in healthy animals, knockout models, as well as inflammatory and neuropathic pain models. In the case of somatic pain, typical assays include von Frey probes and the Randal-Selitto test for mechanical stimuli, Hargreaves and hot/cold-plate tests for thermal stimuli, as well as tail-flick and grip strength tests. Visceral pain is typically measured as a contractile response to hollow organ distension (stomach, colon, uterus, and bladder). In these tests, the ability of the novel therapeutic to produce analgesia is measured as a decrease in the evoked nociceptive response. However, although these are widely used and validated assays for testing analgesic effects, there are limitations that must be considered; these include the requirement that the experimenter manipulate the animal to induce the nociceptive behavior and the possibility that the acute response may not sufficiently model chronic pain to accurately predict the efficacy of a novel drug. In an attempt to avoid these limitations, operant tests have been developed that allow the animal to perform behaviors that indicate whether it is experiencing spontaneous pain. One such test is conditioned place preference (CPP), which takes advantage of the rodent's ability to associate pain relief with an area of the testing apparatus, thereby removing the limitation of the acute manipulation by the experimenter to evaluate pain behavior. CPP has been used to demonstrate ongoing pain in multiple models, to test the efficacy of potential therapeutics, and to determine neural mechanisms of chronic pain and pain relief (reviewed by Navratilova et al., 2013). Additionally, CPP has been used in addiction research to demonstrate spontaneous drug-seeking behaviors, and different stress paradigms (i.e., acute/repeated, mild/intense) modifies both the development of the addiction and the reinstatement of behaviors following drug withdrawal (Smith et al., 2012; Vaughn et al., 2012; Mei and Li, 2013). Although the interaction between stress and pain has not been extensively studied with CPP, use of both acute, evoked responses and chronic, spontaneous behavior provides additional validation of analgesic efficacy when developing novel therapeutics.

Conclusions and Implications for Future Therapies

The treatment of chronic pain represents a significant unmet therapeutic need. In this review, we have attempted to highlight for the reader the common central mechanisms that facilitate both stress and nociception. Further, we have provided evidence from the literature that suggests that novel therapeutic approaches for chronic pain relief might be discovered by targeting the common pathways between stress and chronic pain. An important key message is the need for more research focusing on potential synergistic mechanisms between the overlapping stress and pain neurocircuits, which

will produce therapeutic targets with increased efficacy and fewer unwanted side effects.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Johnson, Greenwood-Van Meerveld.

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