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Neural mechanisms of pain and alcohol dependence☆

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Abstract

An association between chronic pain conditions and alcohol dependence has been revealed in numerous studies with episodes of alcohol abuse antedating chronic pain in some people and alcohol dependence emerging after the onset of chronic pain in others. Alcohol dependence and chronic pain share common neural circuits giving rise to the possibility that chronic pain states could significantly affect alcohol use patterns and that alcohol dependence could influence pain sensitivity. The reward and emotional pathways that regulate drug/alcohol addiction also mediate chronic pain. For example, pain-evoked activation of brain learning and brain reward circuitry may modulate cortical processing of pain and central sensitization mediated by mesocorticolimbic circuitry. Imbalance and reorganization of amygdala–mPFC interactions may not only be important for persistent pain, but also for disorders characterized by the abnormal persistence of emotional-affective states such as drug and alcohol addiction. Further studies are necessary to understand how these neural circuits are regulated in comorbid conditions of alcoholism and chronic pain. In addition, long term alcohol use could induce pain symptoms and may exacerbate chronic pain arising from other sources. While prior studies have established a role of neuroendocrine stress axis mediators in alcohol abuse and neurotoxic effects, these studies have not explored the distinction between the individual impact of alcohol and stress hormones. Future studies should explore the mechanisms mediating the contribution of alcohol and stress axis hormones on pain, an important question in our understanding of the neurobiology of alcohol abuse and chronic pain.

Keywords

Chronic pain; Drug addiction; Alcohol; Reward; Emotion

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1. Introduction

Each year, an estimated 116 million Americans suffer from persistent pain arising from a variety of sources. Alcohol dependence and chronic pain share common neural circuits giving rise to the possibility that chronic pain states could significantly affect alcohol use patterns and alcohol dependence could influence pain sensitivity (Egli et al., 2012). In addition, long term alcohol use could induce pain symptoms and may exacerbate chronic pain arising from other sources. The National Institute of Alcohol Abuse and Alcoholism organized a satellite symposium that highlighted central and peripheral mechanisms involved in pain transmission and in the development of alcohol and drug dependence. Of interest is whether these circuits are affected by chronic alcohol exposure, stressors and other insults to mutually influence the development of alcohol dependence as well as pain-related problems. The symposium also highlighted how alcohol use and stress influence the development of neuropathic pain. This symposium summary presents evidence that brain circuits implicated in key aspects of addiction, namely central reward circuits involving nucleus accumbens (NAc), medial prefrontal cortex (mPFC) networks and emotion circuits composed of the amygdala and the mPFC, also play an important role in pain states and pathology. The role of stress pathways in regulating central and peripheral mechanisms of chronic pain and alcohol dependence is also discussed. Recognizing possible common mechanisms of pain pathology and alcohol dependence will promote research to help better understand interrelationships between these two debilitating conditions and expand treatment approaches.

1.1. Mesocortico-limbic reward circuitry in transition from acute to chronic pain: implications for alcohol dependence

1.1.1. Cortical mechanisms of pain—Studies of the mesocorticolimbic circuitry regarding value and motivated behavior provide detailed descriptions of the reorganization of the components of this circuitry in addiction. Only recently has evidence emerged regarding the mechanistic reorganization of this same circuitry with pain chronification. The earliest hint that cortical representation for pain is distinct between acute and chronic pain states was a brief report of fMRI activity in complex regional pain syndrome patients before and after sympathetic blocks (Apkarian et al., 2001a). The study concluded that in such subjects, chronic pain engages prefrontal/limbic networks more extensively than in acute pain-states. During the same time period, the other approach to study brain properties in chronic pain was MR spectroscopy, with which one could interrogate specific metabolite concentrations in different brain regions. These studies provided the first evidence that brain circuitry and anatomy may also be distorted with chronic pain (Grachev et al., 2000, 2001, 2002), given that the relative concentration of a number of brain metabolites were decreased in specific brain regions. The latter observations led to the use of the new technology, which was just becoming available, of quantifying brain gray matter density and comparing it between patients and healthy subjects. Thus in 2004, it was reported that brain regional gray matter density is decreased in chronic back pain patients (Apkarian et al., 2004). Since this initial work, further studies have now established that brain anatomy and function are distinct between chronic pain conditions. As shown anatomically, this reorganization can be

viewed as a unique signature for each clinical chronic pain condition (Baliki et al., 2011). Regarding the study of the brain functional properties in chronic pain, the tools with which directly interrogate the brain for the pain that a given subject experiences and the time variability of such ratings were used to identify related brain activity (Apkarian et al., 2001b). The first proper demonstration of brain activity in chronic back pain patients showed that activity for the perceived clinical condition engaged medial prefrontal cortex (mPFC) and was dissociated from regions involved in acute pain perception (Baliki et al., 2006). The result suggests again that prefrontal/limbic circuitry is preferentially involved in perception of chronic pain, and in this case, ongoing chronic back pain. Subsequent studies further reinforced the notion that the mPFC engaged in chronic pain is part of the prefrontal circuitry being identified for cocaine and other types of addictive drug use (Kalivas et al., 2005; Koob and Volkow, 2010; Goldstein and Volkow, 2011).

A separate line of thought linked the observations of the involvement of mPFC in chronic pain to mechanisms of memory extinction. Studies by Quirk and colleagues identified single neurons in this same region that are specifically involved in fear memory extinction (Quirk et al., 2000; Milad and Quirk, 2002; Santini et al., 2004). Similarly, studies of the application of D-cycloserine (DCS) in enhancing fear memory extinction (Walker et al., 2002; Ledgerwood et al., 2003; Parnas et al., 2005) suggested that chronic pain may also be conceptualized as an inability to extinguish the aversive pain memory by sheer persistence of the condition. Based on this idea, it was demonstrated that DCS, given orally or directly into the mPFC, indeed reduces many of the signs of neuropathic pain in rodent models (Millecamps et al., 2007). These findings established the basis for a viable therapy for chronic pain based on the results of human brain imaging studies, by using a therapy approach that exclusively seems to manipulate the prefrontal cortical/limbic circuitry. The application of the approach in humans remains to be demonstrated.

1.1.2. NAc-mPFC connections and pain perception—The discovery that brain reward circuitry, mainly the involvement of the nucleus accumbens (NAc), was involved in chronic pain occurred serendipitously in a study examining differences in brain activation to acute thermal pain in individuals with chronic pain and healthy subjects (Baliki et al., 2010). In this study, no group differences were found in the psychophysical results and brain activity measures in response to the stimulus and to its perception. However, brain activity contrast between the groups identified bilateral NAc activity, as a region not correlated to the stimulus or the perception, but significantly more active in the patient group. Further analysis of the BOLD signal in the NAc revealed the existence of transient activity in the NAc that signaled the impending pain—a salience signal—and the cessation of the stimulus as the impending reward value of analgesia. Importantly, the reward value BOLD signal was completely reversed in the chronic pain patients, as if they were disappointed with the stimulus cessation. This notion was confirmed by showing that, during the thermal stimulus, back pain patients experienced a simultaneous decrease of their own ongoing back pain, and thus these patients actually enjoyed the thermal pain only if their attention was directed to their own pain. In this study, for the first time, the link between mPFC activity and NAc valuation responses was established. This link was based on the fact that in healthy subjects NAc activity showed functional connectivity (shared information by synchronous activity)

with the insula. In contrast, in the pain patients the strength of the NAc functional connectivity with the mPFC was directly proportional to the amount of back pain each subject reported at the time of the study. The study, therefore, demonstrates that, for chronic pain patients, the value of acute painful stimuli is determined in relation to their chronic pain. The extent, to which these results can be generalized across types of chronic pain, across valuation of aversive inputs, and also for rewarding inputs, remains to be studied. However, the study provides the first direct evidence of the interaction of brain valuation circuitry with acute and chronic pain. Furthermore, it suggests that the mesocorticolimbic circuitry is influenced and, in turn, is likely influenced by chronic pain conditions, implying that addiction circuitry is linked with chronic pain.

Recent efforts to identify brain reorganization with pain chronification (Baliki et al., 2012) extends the above results by demonstrating that brain gray matter density decreases only in subjects for which the initial acute/sub-acute back pain persists over the next year. This density loss correlates with concomitant functional connectivity changes, and both anatomical and functional changes correlate with the subjects' pain trajectories. Thus, the study reveals that the interlinked anatomical and functional reorganization of the cortex can be viewed as the mechanism of transforming the brain from an acute to a chronic pain condition. Moreover, the strength of functional connectivity between the mPFC and NAc at the time of entry into the study accurately predicted who would transition to chronic pain and who would recover from the condition one year later. Importantly, this strength remained invariant over the longitudinal study period (over 4 measurements in about 12 weeks, 3, 6, and 12 months from onset of acute/sub-acute back pain). Therefore, it was concluded that the extent of information shared between the mPFC and the NAc was a causal factor facilitating pain chronification, implying that the extent of hyperexcitability of the mesocorticolimbic circuitry is predetermined and thus was the driving force for the cortical reorganization leading to chronic pain.

1.1.3. NAc-mPFC connections in addiction and pain—The dysregulation of the NAc-mPFC reward circuitry during drug addiction is well established in animal models and human addiction (Kalivas and Volkow, 2005). Recent evidences suggest that this circuitry is also involved in the transition of pain from acute to chronic state. One key observation during the transition from occasional drug use to drug addiction is the strengthening of functional connectivity between mPFC and NAc and higher glutamatergic transmission. Similar observation of increased mPFC–NAc connectivity in chronic pain patients suggests overlapping neural mechanisms in drug addiction and chronic pain. n fact, animal studies have shown that ongoing chronic pain following surgery produces conditioned place preference for relief reward and activates the mesolimbic dopaminergic circuit implicated in positive reinforcement (Navratilova et al., 2012). Further studies are needed to establish the specific involvement of brain learning and reward circuitry as a method to predict progression to drug addiction or chronic pain. A previous review specifically outlined the dopamine and glutamate neurotransmission interaction between the prefrontal cortex and the NAc as summarized in the title “Unmanageable motivation in addiction: a pathology in prefrontal–accumbens glutamate transmission” (Kalivas et al., 2005). Perhaps, along the

same lines, chronic pain can be formulated as: “Unmanageable persistence of pain: a pathology critically involving prefrontal–accumbens interaction.”

1.2. Pain-related amygdala plasticity

A distinguishing characteristic of alcohol dependence is the emergence of negative affect when intake is reduced or discontinued. This has been attributed to neuroadaptive changes in the extended amygdala resulting from chronic alcohol intoxication and withdrawal. Similarly, chronic pain has a strong emotional-affective component and is significantly associated with anxiety and depression (Carleton et al., 2009; Vlaeyen and Linton, 2012). Pain also produces cognitive deficits such as impaired attention, information processing, memory, executive and general cognitive functioning (Hart et al., 2000; Moriarty et al., 2011). Here, the novel concept of imbalance in the interaction between two brain areas, the amygdala and the medial prefrontal cortex (mPFC), is proposed as an important pain mechanism. In this model, abnormally increased activity in the amygdala, a brain center for emotions, accounts for emotional-affective aspects of pain and impairs mPFC-dependent cognitive functions such as decision-making and control of emotional processing.

The mPFC serves executive functions such as decision-making, which are essential for selecting appropriate and inhibiting inappropriate actions. Dysfunction of the medial prefrontal cortex (mPFC) has been identified as a key neurobiological correlate of behavioral disinhibition, inflexibility and perseverance, which are key characteristics of neuropsychiatric disorders such as drug addiction, obsessive–compulsive disorder, and schizophrenia. The amygdala, an almond-shaped cluster of several anatomically and functionally distinct nuclei (Pape and Pare, 2010; Sah et al., 2003), plays a key role in emotions and affective states and disorders (Pape and Pare, 2010; Phelps and Ledoux, 2005). Current concepts of top–down cognitive control of emotions agree on the critical role of intact interactions between the mPFC and the amygdala (Ochsner and Gross, 2005; Dalley et al., 2011). The infralimbic region of the mPFC inhibits amygdala output to “extinguish” aversive behavior. Increased mPFC activity correlates with successful control (extinction) of negative emotions and decreased activity with cognitive control deficits in models of extinction and behavioral disinhibition.

An important element of the pain-related amygdala circuitry is the central nucleus (CeA), which serves major amygdala output functions to generate emotional-affective behaviors and modulate nocifensive responses (Neugebauer et al., 2004, 2009). The laterocapsular division of the CeA (CeLC) has been termed the “nociceptive amygdala” because it receives nociceptive-specific information from the spinal cord and brainstem (parabrachial area) and most CeLC neurons respond exclusively or preferentially to noxious stimuli (Gauriau and Bernard, 2004; Neugebauer et al., 2004, 2009). The CeA also receives highly processed affect-related information from the lateral–basolateral amygdala (LA–BLA) network through an indirect multimodal pathway via posterior thalamus (Neugebauer et al., 2004, 2009). The BLA exerts not only excitatory but also inhibitory influences on the CeA through a cluster of GABAergic interneurons in the intercalated cell mass (Ren et al., 2011; Ren and Neugebauer, 2010). Interposed between the input (LA–BLA) and output (CeA) regions of

the amygdala these so-called ITC cells are generally believed to serve gating functions and play an important role in fear extinction (Amano et al., 2010; Pape and Pare, 2010).

Neuroplasticity in the amygdala network has emerged as an important contributor to emotional-affective aspects of pain (Neugebauer et al., 2004, 2009). Synaptic plasticity of presumed parabrachial input to the CeLC is well documented in models of arthritic pain (Bird et al., 2005; Han et al., 2005; Neugebauer et al., 2003), formalin-induced pain (Adedoyin et al., 2010), visceral pain (Han and Neugebauer 2004) and chronic neuropathic pain (Ikeda et al., 2007). Pain-related plasticity of excitatory transmission has also been observed at the LA–BLA (Ji et al., 2010) and BLA-CeLC synapses (Fu et al., 2008; Neugebauer et al., 2003; Ren et al., 2011; Ren and Neugebauer, 2010). In addition to glutamatergic inputs, inhibitory transmission involving GABAergic ITC neurons (see previous paragraph) modulates processing in the CeA. ITC-mediated inhibitory control of the CeA is impaired in an arthritis pain model (Ren et al., 2011; Ren and Neugebauer, 2010). Pain-related synaptic plasticity in the amygdala network is associated with increased responsiveness and output of CeLC neurons (Han et al., 2005; Ji and Neugebauer, 2007; Li and Neugebauer, 2004; Neugebauer and Li, 2003). Projection neurons in the lateral regions of the CeA, including CeLC neurons interconnected with the substantia innominata, form connections with the brainstem and forebrain areas involved in the expression of aversive behaviors and pain modulation such as the periaqueductal gray (Bourgeais et al., 2001; Neugebauer et al., 2004).

Preclinical (for reviews see Neugebauer et al., 2004, 2009) and clinical (reviewed in Simons et al., 2012) studies established a close correlation between amygdala activity and pain. Amygdala activity correlates positively with pain behaviors in animals. Increasing activity in the amygdala can elicit or enhance pain responses even in the absence of tissue injury (Bourbia et al., 2010; Han et al., 2010; Li et al., 2011; Myers and Greenwood-Van, 2010). This is important because it may serve as the neurobiological basis for the exacerbation or precipitation of pain in primarily non-pain conditions such as anxiety, depression and addictive states. Conversely, deactivation of the amygdala can inhibit pain in animal models of inflammatory and neuropathic pain (Ansah et al., 2010; Fu et al., 2008; Han et al., 2005; Han and Neugebauer, 2005; Hebert et al., 1999; Ji et al., 2010; Martin et al., 2011). Outcome measures of the emotional-affective dimension of pain in these studies included vocalizations, escape/avoidance and anxiety-like behavior. Clinical studies (reviewed in Simons et al., 2012) found amygdala activation by experimental pain induced in healthy subjects with laser (evoked potentials in CeA; Liu et al., 2010), electrical, thermode and mechanical stimulation and vascular/gastric distension, and by clinical pain in patients with osteoarthritis (Kulkarni et al., 2007), irritable bowel syndrome (Tillisch et al., 2010), postherpetic neuralgia (Apkarian et al., 2011), dental pain, somatoform pain and fibromyalgia.

An important player in pain-related amygdala plasticity and behavior is the corticotropin releasing factor (CRF). The latero-capsular region of the CeA represents the major site of extrahypothalamic CRF expression (Gray, 1993; Rouwette et al., 2012). CRF-containing neurons are innervated by calcitonin gene-related peptide (CGRP) terminals of neurons in the lateral parabrachial area as part of the spinoparabrachio-amygdaloid pain pathway

(Neugebauer et al., 2004, 2009). CRF neurons projecting to the forebrain and brainstem (Gray, 1993) can be glutamatergic or GABAergic hence activating or inhibiting descending behavioral control systems. CRF in the CeA produces proand anti-nociceptive effects through CRF1 and CRF2 receptors, respectively (Ji and Neugebauer, 2008). CRF mRNA expression in the CeA is increased in models of visceral (Greenwood-Van Meerveld et al., 2006) and neuropathic (Rouwette et al., 2012) pain. Pharmacological blockade of CRF1 receptors attenuated pain-related facilitation of synaptic transmission in CeLC (Fu et al., 2008) and BLA neurons (Ji et al., 2010) and inhibited central sensitization and output of CeLC neurons (Ji and Neugebauer, 2007). Blockade of CRF1 receptors in the CeA (Fu et al., 2008; Ji et al., 2007) or BLA (Ji et al., 2010) also inhibited pain- and anxiety-like behaviors in a model of arthritic pain. Thus, the amygdala CRF system plays an important role in pain and serves as a useful tool to modulate neuronal activity and amygdala dependent behaviors. As discussed below, intra-CeA infusion of a CRF1 receptor antagonist reduced alcohol self-administration in alcohol-dependent animals suggesting that the amygdala CRF system may serve as a nexus between alcohol dependence and chronic pain.

Amygdala neuroplasticity also impairs mPFC function and cognitive processes such as decision making (Ji et al., 2010). Both mPFC (Pais-Vieira et al., 2007; Vertes, 2006) and amygdala (Bechara et al., 2003; Seymour and Dolan, 2008) contribute to emotion-driven value-based decision-making, which has been shown to be impaired in patients with chronic back pain or complex regional pain syndrome (Apkarian et al., 2004), migraine headache (Mongini et al., 2005) and fibromyalgia (Verdejo-Garcia et al., 2009) using the Iowa Gambling Task. Pain patients perseverate in making disadvantageous choices. Animals with arthritic pain show similar decision-making deficits in the food reward-based Rodent Gambling Task because of their inability to switch strategies (Ji et al., 2010; Pais-Vieira et al., 2009).

Pain-related amygdala plasticity drives excessive activation of cortical inhibitory networks (Ji et al., 2010; Sun and Neugebauer, 2011), resulting in the relative dominance of inhibitory over excitatory influences on mPFC pyramidal cells so that the mPFC goes off-line. As a consequence mPFC-dependent cognitive functions such as decision-making are impaired in pain (Apkarian et al., 2011; Ji et al., 2010; Moriarty et al., 2011; Sun and Neugebauer, 2011). Another consequence of mPFC deactivation would be the loss of cortical control of pain-related processing in subcortical limbic areas including the amygdala. Projections of the infralimbic region of the mPFC to the amygdala preferentially target inhibitory ITC cells and are believed to play an important role in the extinction of negative emotions such as fear by engaging feed forward inhibition of amygdala output from the CeA (Peters et al., 2009; Sierra-Mercado et al., 2011; Sotres-Bayon and Quirk, 2010).

1.3. Neuropathic pain produced by interaction of stress and ethanol

While the previous two sections described the role of central cognitive circuits in regulating addiction and chronic pain, this section discusses the peripheral mechanisms shared by chronic pain alcohol abuse. Although alcohol withdrawal-induced hyperalgesia has been extensively studied, the direct effects of alcohol on sensory neurons have not been investigated. Moreover, the effects of the activation of the HPA axis on alcohol-induced and

withdrawal-induced hyperalgesia are not clear. Small-fiber painful peripheral neuropathy is a devastating complication of alcohol abuse (Zambelis et al., 2005; Koike et al., 2003). While there is evidence that complications of alcohol abuse, including painful peripheral neuropathy, are due, at least in part, to activation of neuroendocrine stress axes (Adinoff et al., 2005; Walter et al., 2006; Dina et al., 2008), it has been difficult to parse out the individual contributions of alcohol and the stress axis mediators (i.e., catecholamines and glucocorticoids) to the pain reported in patients with alcoholic neuropathy. Dysesthetic states, including diverse pain syndromes are common during withdrawal from chronic ethanol consumption in humans, adding an important component to the morbidity associated with alcohol abuse (Egli et al., 2012). Consistent with a peripheral neuropathic component, in early stages of alcohol withdrawal the patient complains of severe pain in the extremities (Brain and Walton, 1993). Recent evidence shows that abnormalities in small-diameter nociceptive primary afferent nerve fibers play an important role in ethanol- and ethanol-withdrawal induced pain (Dina et al., 2000). Studies of the effects of chronic ethanol consumption on the peripheral nervous system are numerous (Dina et al., 2000; Diamond and Messing, 1994; McLane, 1987). Despite these efforts, past studies have focused on neuropathic decrease of function rather than neuropathic hyperactivity that causes far more common and debilitating symptoms of pain. The degree to which ethanol-induced peripheral neuropathy is a direct neurotoxic effect of ethanol on sensory neurons (Claus et al., 1985) has been controversial. Besides the alcohol withdrawal-induced hyperalgesia, the possibility that ethanol-induced pain involves its direct action on nociceptive nerve fibers, which induces hyperexcitability in primary afferent nociceptors, needs to be considered.

Most people who abuse alcohol do it intermittently, for example as binge drinkers (who work during the day or can only drink on weekends), producing episodes of dysesthetic withdrawal symptoms including pain. Even for those individuals who consume alcohol on a more continuous basis, their pain is initiated or greatly exacerbated when their consumption is interrupted. These considerations led to the development of a model of neuropathic pain induced by ethanol consumption and withdrawal (Dina et al., 2000, 2006). Rats were fed a standard liquid diet containing ethanol. Each withdrawal cycle consisted of 4 days continuously on the ethanol diet followed by 3 days on an equi-caloric ethanol-free diet. The major findings in this model were: 1) Rats maintained on a continuous diet containing 6.5% ethanol progressively develop hyperalgesia over a course of 2–3 months (Dina et al., 2000); 2) Withdrawal of ethanol from the diet precipitates the much more rapid development of hyperalgesia, maximal over a period of approximately 3 days (Dina et al., 2006); 3) A second cycle of ethanol feeding and withdrawal causes an increase in the hyperalgesia (Dina et al., 2006); 4) A third cycle of withdrawal produces a qualitatively different pain condition, characterized by markedly prolonged (chronic) mechanical hyperalgesia. Plasma levels of epinephrine are significantly greater after 3 (but not after 1) cycles of ethanol withdrawal; and, 5) Antagonizing either the hypothalamic–pituitary–adrenal (HPA) axis (by glucocorticoid receptor antagonist or oligodeoxynucleotide anti-sense to glucocorticoid receptor) or the sympathoadrenal axis (by adrenal medullectomy or intrathecal oligodeoxynucleotide antisense to β_2-adrenergic receptor) on nociceptors can both prevent and reverse ethanol-induced hyperalgesia.

Chronic alcohol abuse produces a sustained increase in HPA and sympathoadrenal release of glucocorticoids and catecholamines (Kiefer et al., 2006; Walter et al., 2006) that is exacerbated by withdrawal from ethanol (Kiefer et al., 2006; Walter et al., 2006). Increased activity in the sympathetic nervous system has been implicated in some forms of neuropathic pain (Singh et al., 2003), and receptors for these stress hormones are expressed by sensory neurons (Bowles et al., 2003; Hucho et al., 2006). Therefore, it has been considered important to evaluate the role of neuroendocrine stress axes and their principal effector hormones, catecholamines and glucocorticoids, in ethanol-induced neuropathic pain.

To determine if the mediators of both stress axes – sympathoadrenal and HPA – contribute to the hyperalgesia induced by the combined exposure to topical alcohol and sound stress, and whether the action of the stress hormones are at their receptors on the primary afferent nociceptor, rats were administered, intrathecally, oligodeoxynucleotide antisense to either β_2-adrenergic receptor or glucocorticoid receptor mRNA. Compared to rats treated with oligodeoxynucleotide mismatch to the β_2-adrenergic receptor or glucocorticoid receptor mRNA, the anti-sense to either receptor markedly attenuated the hyperalgesia induced by alcohol followed by sound stress. In addition, the co-administration of oligodeoxynucleotide antisense to both receptor mRNAs completely eliminated the development of mechanical hyperalgesia. Since adrenal medullectomy prevents painful peripheral neuropathy induced by oral alcohol consumption (Dina et al., 2008), it was also determined if the source of the catecholamines involved in the contribution of sound stress to alcohol-induced hyperalgesia is the adrenal medulla. In this experiment the hypothesis was tested that adrenal medullectomy would also prevent the effect of sound stress in rats that had been treated with topical alcohol. It was found that adrenal medullectomy markedly reduced the hyperalgesia induced by sound stress in rats pretreated with alcohol, topically. Moreover, adrenal medullectomy also prevented the hyperalgesia induced by the topical application of alcohol in rats previously submitted to sound stress.

It is well established that stress exacerbates several of the effects of alcohol (Liu and Weiss, 2002), including those on the peripheral nervous system (Dina et al., 2008). In studies of a model of alcohol-induced painful peripheral neuropathy it has previously been shown that adrenal medullectomy can completely prevent as well as reverse mechanical hyperalgesia produced by binge drinking (Dina et al., 2008). This finding has been interpreted to suggest that stress hormones are permissive for a neurotoxic effect of alcohol on the peripheral nervous system, one that can produce a painful peripheral neuropathy. Recent experiments have further tested this suggestion by administering alcohol in the absence of unpredictable sound stress, a form of psychological stress that alone does not affect nociceptive threshold (Khasar et al., 2009), and the two together. As suggested, while the isolated exposure to either topical alcohol or stress alone had no effect on nociceptive threshold, their combined administration produced robust mechanical hyperalgesia. Importantly, this study provides evidence for the independent effects of alcohol and neuroendocrine stress axis mediators to produce painful peripheral neuropathy, a more direct test than the previous observation that adrenal medullectomy eliminates painful peripheral neuropathy induced in a model of binge drinking of alcohol (Dina et al., 2008).

Recent findings also provide evidence that the mechanism of action of the stress axis hormones is at their G-protein coupled receptors, the β_2-adrenergic receptor for catecholamines such as epinephrine, and the glucocorticoid receptor for glucocorticoids such as cortisol and corticosterone (Bowles et al., 2003; Hucho et al., 2006), located on the peripheral terminals of primary afferent nociceptors. While the mechanism by which alcohol contributes to painful peripheral neuropathy remains to be established, ethanol has been shown to have several effects on neuronal function (Diamond and Messing, 1994). Among these are effects mediated by protein kinase C (PKC), in particular the calcium-independent, novel isoform, PKCε (Pandey, 1996; Gerstin et al., 1998; Dina et al., 2000). Importantly, in this regard, it has been shown that the mechanical hyperalgesia observed in alcohol-induced painful peripheral neuropathy, in the rat, is mediated by PKCε (Dina et al., 2000, 2006). Given the recent development of a model in which alcohol is applied to the peripheral nervous system in such a way as to exclude actions in the central nervous system, it should be possible to determine if PKCε mediates the alcohol and/or stress hormone contribution to alcohol-induced painful peripheral neuropathy.

Two established cellular effects of alcohol that might contribute to the interaction between alcohol and stress hormones to produce painful neuropathy are: (1) enhancing oxidative stress (Rouach et al., 1997; Chen et al., 2010) and other mitochondrial functions that interact with mitochondrial bioenergetics (Ramachandran et al., 2001; Raval et al., 2007; Jaatinen and Rintala, 2008), and (2) neuroplastic changes in peripheral nervous system, produced by binge alcohol consumption (Weise et al., 1985; Dina et al., 2000, 2006), which can create a catecholaminergic phenotype in nociceptors that could, in turn, provide a positive feedback loop contributing to alcohol-induced painful peripheral neuropathy (Dina et al., 2008). Additional studies will be required to elucidate whether these effects of alcohol on neuronal function, primarily established on central nervous system neurons, or as yet to be described effects of alcohol, mediate the interaction between stress hormones and alcohol to produce painful peripheral neuropathy. One issue could be that a sub-neuropathic exposure to alcohol and stress hormones might have been used in these studies. It is likely that the combination should reach a threshold level to produce painful peripheral neuropathy. However, while some forms of stress (e.g., water avoidance stress) can alone produce a decrease in nociceptive threshold (Green et al., 2011), other stressors such as the sound stress used in these studies is not effective (Khasar et al., 2009). Similarly, longer topical exposures to alcohol, alone, also have no effect on the nociceptive threshold. Thus, it is suggested that alcohol exposure requires additional, independent, exposure to stress hormones released from the neuroendocrine stress axes, to produce alcoholic painful peripheral neuropathy.

An alternative approach going forward would be to attempt to induce alcoholic painful peripheral neuropathy in vitro, by the addition of alcohol and stress axis hormones to cultures of dorsal root ganglion neurons. While in vitro studies of the effect of alcohol (Mameli et al., 2005; McCool, 2011), and neuroendocrine stress axis hormones (Hu et al., 2010; Chen et al., 2010; Daftary et al., 2009; Duvarci and Pare, 2007) on neuronal function have been performed, their combined effect on neuronal function remains to be established. Also, these previous studies have been performed mainly on neurons derived from the CNS. And, while, the combined local administration of alcohol to the peripheral nervous system, with and without stress axis hormones, may provide a model system to study the

independent effects of stress and alcohol, a considerable number of parametric studies will be required to establish an in vitro model of the combined effects of alcohol, catecholamines and glucocorticoids on nociceptor function.

1.4. Neural circuits of pain and alcohol dependence: an allostatic view

Like chronic pain, alcoholism (or alcohol dependence) is a chronic relapsing disorder characterized by a persistent compulsion to seek and drink alcohol. It is also often detrimental to the pursuit of more conventional rewards (e.g., career, family, and social functioning). Alcoholism is also typically accompanied by the emergence of negative emotional states that constitute a motivational withdrawal syndrome when access to drinking is disrupted (Gilpin and Koob, 2008). Importantly, the limited, recreational use of alcohol seen in the majority of the population is clinically distinct from the escalated drinking, loss of control, and emergence of compulsive alcohol-seeking behaviors that characterize dependence. These latter symptoms are hypothesized to be driven by negative reinforcement mechanisms that may promote excessive drug-seeking behavior, even as tolerance to the positive rewarding effects of alcohol persists as a consequence of within- and between-circuit neuroadaptations (Edwards and Koob, 2010). In humans, the development of peripheral neuropathic pain following a history of excessive drinking may represent one crucial marker of dependence that is clinically distinct from alcohol abuse (Diamond and Messing, 1994). Reduced nociceptive thresholds also gradually emerge in animal models of excessive (but not limited) alcohol exposure (Dina et al., 2000), and this hypersensitivity is alleviated by blocking stress-associated signaling through glucocorticoid or corticotropin-releasing factor (CRF) receptors (Dina et al., 2008; Edwards et al., 2012). Given that chronic pain is well known to both cause emotional distress and engender a tonic negative emotional state (King et al., 2009), hyperalgesia associated with persistent pain states or excessive drinking itself may constitute a condition intimately associated with the transition to alcoholism by facilitating negative reinforcement processes. In concert with chronic pain-induced sensitization of nociceptive circuitry along the neuraxis (Woolf, 1983), a functional gain in anti-reward, negative reinforcement mechanisms associated with a recruitment of stress factors (Koob and Le Moal, 2008) may modify the central processing of nociceptive stimuli, ultimately producing aberrant plasticity that links pain and various affective disorders associated with the compulsive seeking of pain relief.

Neural systems respond to events such as alcohol intoxication, stress, and injury by selecting responses that promote physiological stability in the face of an altered set point (allostasis). When these events are frequent or severe (as with chronic excessive alcohol use), these stabilizing responses become dysregulated allostatic state (Koob and Le Moal, 2001), resulting in neuroadaptations (allostatic load) that engender enduring pathology. Within this framework, alcohol triggers an initial rewarding and analgesic response (acute intoxication) followed by an opposing dysphoric and hyperalgesic state (acute withdrawal). Repeated episodes of alcohol intoxication and withdrawal alter brain stress circuitry, including CRF signaling, and are postulated to engender a persistent negative affective state, including hypersensitivity to pain (hyperalgesia) and emotional distress termed *hyperkatifeia* (Shurman et al., 2010). Such conditions may drive excessive alcohol consumption in an effort to restore the organism to a more natural hedonic/emotional state (Koob, 2008). In this

sense, it has been suggested that alcoholism might be considered a type of chronic emotional pain syndrome (Egli et al., 2012).

At the anatomical level, the nociceptive CeA represents a potential node that links chronic pain and motivationally relevant negative affect associated with alcohol dependence. Neuroadaptations in this region are associated with the advanced progression of disease in animal models of both alcohol dependence and pain. Specifically, intra-CeA infusion of a CRF receptor antagonist reduces excessive levels of alcohol drinking in dependent animals without altering limited alcohol self-administration in nondependent animals (Funk et al., 2006). In a similar fashion, rodents that undergo arthritis induction display enhanced CeA excitability that is reduced by CRF1 receptor antagonism (Ji and Neugebauer, 2007). Moreover, magnified anxiety-like behavior following either alcohol withdrawal or arthritis induction (Ji et al., 2007) is attenuated following intra-CeA CRF1 receptor antagonism. Thus, targeting dysregulated brain stress signaling, with a focus on CRF systems (Logrip et al., 2011) may represent a valuable therapeutic avenue for severing the destructive intersection of chronic pain, affective disorders, and alcoholism.

2. Conclusions

The objective of this review is to evaluate the current status of the neural circuits of chronic pain and addiction pathways and the impact of alcohol use on chronic pain as presented in the symposium. Two major themes emerged from the symposium. The reward and emotional pathways mediate chronic pain and drug addiction and the interaction between stress hormones and alcohol use influence neuropathic pain. Several evidences were presented indicating the close relationship between neural circuits of reward and emotion with chronic pain. For example, pain-evoked activation of brain learning and reward circuitry may modulate cortical processing of pain and central sensitization mediated by mesocorticolimbic circuitry. In addition, the amygdala neuroplasticity and enhanced amygdala output is associated with altered cognitive processing in the mPFC in chronic pain. Imbalance and reorganization of amygdala–mPFC interactions may not only be important for persistent pain, but also for disorders characterized by the abnormal persistence of emotional-affective states such as drug and alcohol addiction. However, future studies are necessary to understand how these neural circuits are regulated in comorbid conditions of alcoholism and chronic pain. While prior studies have established a role of neuroendocrine stress axis mediators in alcohol abuse and neurotoxic effects, these studies have not explored the distinction between the individual impact of alcohol and stress hormones. Recent experimental approaches have allowed examining the impact of alcohol and stress independently. Future studies should explore the mechanisms mediating the contribution of alcohol and stress axis hormones to pain, an important question in our understanding of the neurobiology of alcohol dependence and chronic pain.

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