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Neurobiological aspects of pain in the context of alcohol use disorder

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Abstract

Alcohol is an effective and widely utilized analgesic. However, the chronic use of alcohol can actually facilitate nociceptive sensitivity over time, a condition known as hyperalgesia. Excessive and uncontrollable alcohol drinking is also a hallmark feature of alcohol use disorder (AUD). Both AUD and chronic pain are typically accompanied by negative affective states that may underlie reinforcement mechanisms contributing to AUD maintenance or progression. Frequent utilization of alcohol to relieve pain in individuals suffering from AUD or other chronic pain conditions may thus represent a powerful negative reinforcement construct. This chapter will describe ties between alcohol-mediated pain relief and potential exacerbation of AUD. We describe neurobiological systems engaged in alcohol analgesia as well as systems recruited in the development and maintenance of AUD and hyperalgesia. Although few effective therapies exist for either chronic pain or AUD, the common interaction of these conditions will likely lead the way for promising new discoveries of more effective and even simultaneous treatment of AUD and co-morbid hyperalgesia. An abundance of neurobiological findings from multiple laboratories has implicated a potentiation of central amygdala (CeA) signaling in both pain and AUD, and these data also suggest that attenuation of stress-related systems (including corticotropin-releasing factor, vasopressin, and glucocorticoid receptor activity) would be particularly effective and comprehensive therapeutic strategies targeting the critical intersection of somatic and motivational mechanisms driving AUD, including alcohol-induced hyperalgesia.

1. Alcohol use disorder and chronic pain

1.1 Pain as a central symptom of AUD

Alcohol use disorder (AUD, ranging from mild to severe) is characterized by an escalation of alcohol drinking and gradual emergence of negative affective symptoms (e.g., depression, anxiety) over time (Edwards & Koob, 2010). Such negative emotional states may promote escalated drinking as well as relapse during attempted abstinence periods. Consequently, AUD typically represents a chronic psychiatric condition requiring close management over the patient's lifespan (Koob & Volkow, 2010). AUD affects roughly 10–13% of the

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population in the United States at any given time, and up to one-third of adults in the United States will meet criteria for AUD in their lifetime (Grant et al., 2017). In addition to the negative affective symptoms described above, both clinical and preclinical evidence demonstrates that nociceptive hypersensitivity emerges alongside chronic or excessive alcohol exposure (Dina et al., 2000; Edwards, Guerrero, et al., 2012; Edwards, Vendruscolo, et al., 2012; Edwards, Vendruscolo, Gilpin, Wojnar, & Witkiewitz, 2020; Fu et al., 2015; Gatch & Lal, 1999; Jochum, Boettger, Burkhardt, Juckel, & Bar, 2010). Facilitation of pain by alcohol is evident in that the nocifensive response to painful (noxious) stimuli is enhanced (termed hyperalgesia) and also in that innocuous stimuli (normally non-painful) become noxious (termed allodynia). Consequently, pain represents a negative subjective experience that can have a powerful influence on reward and reinforcement mechanisms, possibly facilitating the transition to substance use disorders in vulnerable individuals (McGinn & Edwards, 2016).

1.2 The negative affective dimension of chronic pain

Chronic pain affects approximately 20% of adults worldwide (Goldberg & McGee, 2011), a number that will likely increase over the next several decades given the aging global population. In the United States alone, over 50 million individuals report chronic pain at a cost of over $600 billion in healthcare expenses and lost productivity (Dahlhamer et al., 2018). While these numbers appear to eclipse the impact of other chronic diseases such as heart disease and cancer, the devastating impact of chronic pain is related more to its effects on morbidity (compared to mortality), especially with regard to the potentiation of negative affect in association with unrelieved pain. Negative affective mood states (anxiety, sadness, anger, and irritability) are considered highly aversive psychodynamic constructs that are distinguishing features of anxiety and depression (Watson & Tellegen, 1985). In general, negative affective disorders represents an umbrella term encompassing a number of mood disorders, including neuroticism, major depressive disorder, general anxiety disorder, and panic disorder.

Chronic pain and negative affective disorders have an alarming rate of comorbidity, likely because of the bidirectional relationship between the two (Elman, Borsook, & Volkow, 2013). Indeed, patients with chronic pain and high negative affect report higher pain severity and pain interference compared to patients with only one of the two disorders (Arnow et al., 2006; Naliboff, Chang, Munakata, & Mayer, 2000). In both children and adults, multiple types of pain disorders are associated with increased likelihood of a positive diagnosis for negative affective disorders, with higher pain ratings elevating the likelihood of affective disorder diagnoses (Campo et al., 2004; Means-Christensen, Roy-Byrne, Sherbourne, Craske, & Stein, 2008). It is important to note that the prevalence of comorbid chronic pain and negative affect varies depending on the type of negative affective disorder. For example, 35–85% of chronic pain patients experience comorbid depression, while 16–60% experience comorbid anxiety disorders (Bair, Robinson, Katon, & Kroenke, 2003; Fishbain, Cutler, Rosomoff, & Rosomoff, 1998; Fishbain, Goldberg, Meagher, Steele, & Rosomoff, 1986; Lee et al., 2018; McWilliams, Cox, & Enns, 2003; Williams et al., 2003).

1.3 Chronic pain and depression

Because chronic pain has a higher incidence of comorbidity with depression than anxiety, and because depression is a major global health burden (Liu et al., 2019), much of the research into the relationship between chronic pain and negative affect has revolved around depressive disorders. Clinical studies have investigated the development of depression across a number of different chronic pain conditions (Bair et al., 2003), including low back pain (France, Houpt, Skott, Krishnan, & Varia, 1986), orofacial pain (Cox et al., 2016; Feinmann, 1983), and pelvic pain (Magni, Salmi, de Leo, & Ceola, 1984; Siqueira-Campos, Da Luz, de Deus, Martinez, & Conde, 2019). Additionally, both clinical (Aguera-Ortiz, Failde, Mico, Cervilla, & Lopez-Ibor, 2011; Lee et al., 2009; von Knorring, Perris, Eisemann, Eriksson, & Perris, 1983) and preclinical (Goncalves et al., 2008; Kontinen, Kauppila, Paananen, Pertovaara, & Kalso, 1999; Schwartz et al., 2014) studies have found that chronic pain precedes and induces symptoms of depression in a variety of chronic pain conditions and models.

1.4 Chronic pain and anxiety

Although most of the research on chronic pain and negative affect has traditionally revolved around depression, there has been a rapid growth in research regarding comorbid chronic pain and anxiety disorders (Asmundson & Katz, 2009). While clinical reports of comorbid chronic pain and anxiety are highly variable across populations, chronic pain-induced anxiety-like behavior is readily observed in both neuropathic and non-neuropathic animal models of pain (Bahaaddini, Khatamsaz, Esmaeili-Mahani, Abbasnejad, & Raoof, 2016; Dimitrov, Tsuda, Cameron, & Usdin, 2014; Ji, Fu, Ruppert, & Neugebauer, 2007; Matsuzawa-Yanagida et al., 2008; Narita et al., 2006). Additionally, chronic pain can generate pain-related anxiety in humans, in which the patient experiences fear and anxiety in the anticipation of experiencing future pain (McCracken & Dhingra, 2002; McCracken, Zayfert, & Gross, 1992).

1.5 Does hyperalgesia and associated negative affect facilitate AUD severity?

An emerging question is whether and how the negative experience of chronic, unrelieved pain contributes to the maintenance of AUD. Hyperalgesia may drive both continuous alcohol drinking and relapse propensity as a powerful negative reinforcement mechanism based on the strong affective valence associated with persistent and unrelieved nociceptive hypersensitivity (Egli, Koob, & Edwards, 2012; Zale, Maisto, & Ditre, 2015). Within this context, negative reinforcement would occur whenever the perceived or real effects of alcohol drinking reduce hyperalgesia symptoms. At the basic science level, evidence for this relationship comes from a recent study where hyperalgesia symptoms in alcohol-dependent animals were attenuated by alcohol self-administration (Roltsch Hellard, Impastato, & Gilpin, 2017). At the clinical level, pain prospectively predicts AUD development (McDermott, Joyner, Hakes, Okey, & Cougle, 2018) and relapse propensity (Witkiewitz et al., 2015). A host of neurobiological and psychosocial mechanisms are shared between chronic pain and alcohol reinforcement (Ditre, Zale, & LaRowe, 2019; LeBlanc, McGinn, Itoga, & Edwards, 2015). As described within this chapter, the dysregulation of such systems may become central in the progression of AUD, while targeting these aberrant

processes may represent valuable therapeutic strategies for the treatment of pain in the context of AUD.

2. Analgesic actions of alcohol

2.1 History of alcohol as an analgesic

For centuries, people have consumed alcohol for its analgesic properties, dating as far back as ancient Egypt and Greece (Crocq, 2007; McGovern, Mirzoian, & Hall, 2009). The medicinal properties of alcohol were so numerous that 14th and 15th century European physicians referred to alcohol as “aqua vitae,” or “water of life,” reporting that alcohol “eases the pain in the teeth,…[and] in the breasts when swollen” (Roueche, 1963). Many 19th and 20th century physicians prescribed and administered oral or intravenous alcohol prior to medical procedures due to its analgesic and anesthetic properties (Brown & Cutter, 1977; Chapman & William, 1951; Crocq, 2007; Hanson, 1995). In the 1930s and 1940s, scientists began investigating the analgesic effects of alcohol in the laboratory setting. Indeed, various studies have found that alcohol dampens pain in a variety of pain tests in both humans and animals. Orally consumed alcohol decreases both mechanical and thermal pain sensitivity in both humans and rodents (Gatch, 2009; Gatch & Lal, 1999; Mullin & Luckhardt, 1934; Wolff, Hardy, & Goodell, 1942; Woodrow & Eltherington, 1988). Although there is conflicting evidence regarding the analgesic efficacy of intravenous (i.v.) ethanol in rodents (Bukusoglu, Thalhammer, & Krieger, 1993), in humans i.v. alcohol has been shown to produce analgesia comparable to i.v. morphine (Saddler, James, & Harington, 1985) as well as anti-nociceptive effects against pain due to electrical stimulation (Perrino et al., 2008; Ralevski et al., 2010) and capsaicin-induced hyperalgesia (Arout et al., 2016).

2.2 Alcohol analgesia in the context of AUD

Seventy-nine percent of high-risk drinkers and 61% of individuals suffering from alcohol dependence consume alcohol to treat pain, compared to only 38% of heavy drinkers and 35% of unhealthy drinkers (Alford et al., 2016). There is a strong mutual relationship between pain and alcohol in which alcohol affects nociceptive sensitivity and pain motivates alcohol consumption (Beasley, Macfarlane, & Macfarlane, 2016; Zale et al., 2015). This shared symptomatology can often make co-morbid directionalities difficult to assess (Macfarlane & Beasley, 2015). We will next discuss these interactions, beginning with a discussion of the analgesic effects of alcohol based on drinking history and on chronic pain status.

Early studies investigating the analgesic effects of alcohol in people with alcoholism found that whiskey dose-dependently reduces and abolishes reported pain in alcoholics but has no analgesic effects in non-alcoholics, regardless of dose (Cutter, Maloof, Kurtz, & Jones, 1976). Later studies found that alcohol reduces pain ratings in heavy social drinkers but increases pain ratings in people who regularly consume alcohol in a home setting, suggesting that the analgesic effects of alcohol may vary based on drinking history and pattern of drinking (Brown & Cutter, 1977). From a motivational perspective, alcohol is frequently self-administered for both its stress-reducing and analgesic effects (Egli et al., 2012; Thompson, Oram, Correll, Tsermentseli, & Stubbs, 2017). Self-reports of alcohol use

specifically for pain management are common (e.g., Riley & King, 2009). Problem drinkers at risk for AUD not only report more severe pain symptoms compared to non-drinkers, but also report a higher incidence of using alcohol to manage their pain (Brennan, Schutte, & Moos, 2005).

As people with AUD experience a higher incidence of pain (Brennan, Schutte, SooHoo, & Moos, 2011; Zale et al., 2015) and appear to be more sensitive to the analgesic effects of alcohol, it is not surprising that pain severity and experience affects AUD treatment outcomes. Increases in both pain interference and intensity significantly increase the risk for relapse both during and after AUD treatment, and, more specifically, pain significantly predicts heavy drinking lapses both during and after AUD treatment (Witkiewitz et al., 2015). Likewise, decreases in physical pain from the start of AUD treatment are correlated with a decreased likelihood of relapse (Jakubczyk et al., 2016). Additionally, persistent pain is associated with increased heavy alcohol use 24 months following detoxification (Larson et al., 2007).

Chronic pain also affects the analgesic efficacy of alcohol. Adults with chronic pain, regardless of age, drink alcohol more heavily than the general population (Ditre et al., 2019), and 25% of people with chronic pain report using alcohol to manage their pain symptoms (Riley & King, 2009). Although one study found that a higher percentage of younger participants self-medicated their chronic pain with alcohol compared to older participants (Riley & King, 2009), alcohol consumption is self-reported as one of the most effective pain-relief methods in elderly persons who require assistance with activities of daily living (Jakobsson, Rahm Hallberg, & Westergren, 2004). Both human and animal studies have found that chronic pain is associated with and may drive increased alcohol consumption (Butler et al., 2017; Lawton & Simpson, 2009; Yu, Hwa, Makhijani, Besheer, & Kash, 2019).

Genetic vulnerability for high alcohol drinking may also play a role in the analgesic effects of alcohol. One study found that men with a high familial-genetic risk for alcoholism report higher pain ratings and experience greater reduction of pain in response to alcohol compared to men with no familial-genetic risk for alcoholism (Stewart, Finn, & Pihl, 1995). However, more recent studies have found that the analgesic effects of alcohol do not differ based on family history (Perrino et al., 2008; Ralevski et al., 2010). Rodents selectively bred for alcohol preference display decreased thermal pain thresholds in examinations of either spinal or supraspinal nociceptive behaviors (Kampov-Polevoy et al., 1996; Kimpel, Brown, & Froehlich, 2003). Several genes have been proposed to link alcohol dependence and pain, including the catechol-*O*-methyl-transferase (COMT) and mu opioid receptor 1 (OPRM1) genes (Egli et al., 2012).

2.3 Neurobiological mechanisms of alcohol analgesia

Despite the surplus of evidence that alcohol produces analgesia, the spinal and supraspinal neurobiological mechanisms behind this phenomenon are drastically understudied (Thompson et al., 2017). Three current hypotheses for this mechanism of action are discussed here, but it is important to note that alcohol likely produces analgesia via

interactions between all of the mechanisms described below, as well as through other undiscovered mechanisms.

2.3.1 Opioid receptor systems—As the endogenous opioid neuropeptide system is integral to the production of analgesia, many scientists have examined the hypothesis that alcohol produces its analgesic effects by interacting with opioid receptor pharmacology. Interestingly, mice with high activity (HA) opioid systems display significantly greater ethanol-induced analgesia compared to controls, while their low activity (LA) counterparts display significantly less ethanol-induced analgesia (Mogil et al., 1993). However, other studies have produced mixed results. Depending on the dose of alcohol, pain model, pain test, and experimental species, the non-selective opioid receptor antagonist naloxone has been shown to both prevent and not affect alcohol-induced analgesia (Boada, Feria, & Sanz, 1981; Campbell, Taylor, & Tizabi, 2006, 2007; Cutter & O'Farrell, 1987; Jorgensen & Hole, 1981; Saddler et al., 1985). The specific opioid receptors responsible for the analgesic effects of alcohol are yet to be definitively determined. Genetic and pharmacological manipulation has implicated the delta-opioid receptor in the differences seen between the aforementioned HA and LA mice (Poznanski et al., 2017; Sacharczuk et al., 2014). However, a recent study found that the selective delta-opioid receptor antagonist naltrindole did not affect ethanol-induced anti-nociception (Neddenriep et al., 2019). This same study found that both high doses of naltrexone and the selective kappa-opioid receptor antagonist nor-BNI prevented ethanol-induced anti-nociception in a mouse model of chronic neuropathic pain, suggesting that the analgesic effects of alcohol are also mediated through both mu- and kappa-opioid receptors (Neddenriep et al., 2019). Complementary to their role in analgesia, it is important to note that all three opioid receptor systems represent targets for treating hyperalgesia in the context of substance use disorders (Delery & Edwards, 2020).

2.3.2 GABAergic and glutamatergic signaling—Alcohol is a positive allosteric modulator of the $GABA_A$ receptor, and GABAergic signaling likely plays a major role in the analgesic effects of drinking (Davies, 2003). The benzodiazepine antagonist flumazenil abolishes the anti-nociceptive effects of alcohol in thermal pain tests in rodents (Gatch, 1999), suggesting that GABA receptors are involved in mediating alcohol-induced analgesia. Additional studies are warranted to determine the contributions of regional (both spinal and supraspinal) activation of GABAergic neurons and interneurons in regulating pain sensitivity. Interestingly, infusion of ethanol directly into the medial prefrontal cortex of rats increases mechanical pain sensitivity by activating $GABA_A$ receptors there (Geng et al., 2016). In addition to the $GABA_A$ receptor, alcohol-induced analgesia may also be mediated via interactions with the *N*-methyl-D-aspartate (NMDA) glutamate receptor. The NMDA receptor antagonist MK-801 decreases anti-nociception produced by alcohol, and systemic administration of both MK-801 and naloxone completely abolishes alcohol-induced anti-nociception in mice, suggesting that the analgesic effects of alcohol are mediated by both NMDA and opioid receptors (Mogil et al., 1993).

2.3.3 GIRK2 potassium channels—The G protein-coupled inwardly rectifying potassium 2 (GIRK2) channels play a major role in substance-induced analgesia and have also been implicated in alcohol-induced analgesia (Bodhinathan & Slesinger, 2014; Ikeda et

al., 2002; Lewohl et al., 1999). Ethanol directly interacts with and opens GIRK2 channels (Kobayashi et al., 1999). Mice with a mutated GIRK2 channel display reduced ethanol analgesia (Kobayashi et al., 1999), while the analgesic effects of ethanol are fully abolished in GIRK2 knockout mice (Blednov, Stoffel, Alva, & Harris, 2003).

2.3.4 Additional systems and considerations—Additional research is needed to examine the contribution of other neurobiological systems to alcohol analgesia. In addition to opioid signaling, it is likely that another endogenous analgesic system, the endocannabinoid system, may be intimately involved. Endocannabinoids regulate not only pain sensitivity (Woodhams, Chapman, Finn, Hohmann, & Neugebauer, 2017), but also act as a buffer of stress and negative affect (Hillard, 2014; Morena, Patel, Bains, & Hill, 2016; Tasker et al., 2015). Extensive research has also implicated endocannabinoid signaling in alcohol reward and reinforcement (Kirson, Oleata, Parsons, Ciccocioppo, & Roberto, 2018; Serrano et al., 2018; Varodayan et al., 2016).

Another consideration for future research is whether and how tolerance to alcohol analgesia develops over time across a range of disease contexts. Damaj and colleagues (Neddenriep et al., 2019) recently demonstrated that the analgesic efficacy of repeated alcohol diminished over time in an animal model of chronic neuropathic pain. Such findings presage a possible rationale for escalation of drinking in individuals using alcohol to manage pain, possibly also driving AUD. Further research is needed to determine the neuroanatomical and molecular sites of action for alcohol analgesia. It will also be important to understand which analgesic systems or mechanisms become compromised with chronic alcohol use, as supporting these systems may represent a beneficial pharmacological strategy for targeting alcohol-associated hyperalgesia. Such treatments may also support additional strategies described in the next section, which correspond to known neuroadaptations shared between excessive alcohol use and chronic pain conditions that underlie hyperalgesia.

3. Medication strategies for treating pain in the context of AUD

3.1 Shared neuroadaptations between chronic pain, negative affect, and AUD

AUD has been hypothesized to stem from functional alterations in the neurobiological substrates of supraspinal pain processing (Egli et al., 2012), including a key contribution from the nociceptive central amygdala (CeA; Neugebauer, 2015). Importantly, the sensitization of pain-driven negative affect (Ji et al., 2007) is also thought to be mediated by the CeA and to closely interact with similar neuronal mechanisms related to the development of AUD (Edwards et al., 2020). Both alcohol dependence and persistent pain produce multiple neurophysiological adaptations within the CeA (e.g., Carrasquillo & Gereau, 2008; Gilpin, Herman, & Roberto, 2015; Ji & Neugebauer, 2009; Roberto et al., 2010; Zhang et al., 2014). The CeA receives functionally distinct projections from the pontine parabrachial area (PB, nociceptive coding) and basolateral amygdala (BLA, sensory-affective coding) that are sensitized in the context of chronic pain (Ikeda, Takahashi, Inoue, & Kato, 2007; Neugebauer, Li, Bird, Bhave, & Gereau, 2003). Chronic pain-induced activation of the CeA is accompanied by dysregulation of amygdala-driven prefrontal cortex function and resultant cognitive deficits (Ji & Neugebauer, 2011; Ji et

al., 2010; Sun & Neugebauer, 2011). Importantly, executive system dysfunction is thought to play a central role in the heavily compromised decision-making that accompanies the transition from recreational drug use to substance use disorder (George & Koob, 2010), which may contribute to alcohol misuse in individuals suffering from chronic pain. Alcohol withdrawal produces hyperalgesia that is mediated by altered activity of CeA projections to the periaqueductal gray (PAG), a region that is critically involved in descending pain modulation (Avegno et al., 2018).

Elucidation of chronic alcohol-induced neuroadaptations within brain stress and nociceptive systems may provide valuable insights into potential mechanisms underlying the transition to AUD in vulnerable individuals. In these regions, elements of brain stress signaling, such as the corticotropin-releasing factor (CRF), vasopressin, and glucocorticoid receptor (GR) systems, are recruited (Edwards, Little, Richardson, & Vendruscolo, 2015; Koob & Le Moal, 2008) during the transition to dependence, as described below.

3.2 Corticotropin-releasing factor receptor systems

As a key mediator of the heightened negative affective response that manifests during alcohol withdrawal, the functional potentiation of CRF signaling is evident in the establishment and progression of AUD-related behaviors (including escalated alcohol drinking) observed in preclinical animal models (Edwards & Koob, 2010; Funk, Zorrilla, Lee, Rice, & Koob, 2007; Roberto et al., 2010; Schreiber & Gilpin, 2018). CRF is a neuropeptide synthesized by the paraventricular nucleus (PVN) of the hypothalamus where it initiates the hypothalamic-pituitary-adrenal (HPA) axis response to stress. CRF stimulates synthesis of adrenocorticotropic hormone (ACTH) in the anterior pituitary, which then facilitates the secretion of glucocorticoids from the adrenal gland to mediate adaptive stress responses and restore homeostasis. High concentrations of CRF are also present in basal forebrain and brainstem areas (Swanson, Sawchenko, Rivier, & Vale, 1983), where the neuropeptide regulates autonomic and behavioral responses to stress. Importantly, extra-hypothalamic CRF1 receptors (CRF1Rs) are widely expressed throughout the brain, and activation of these receptors potentiates central stress responsiveness. However, activation of complementary CRF2 receptors mediates a contrasting (but not necessarily opposing) effect on anxiety-like behavior (Zhao et al., 2007) and CeA plasticity (Varodayan et al., 2017).

Chronic pain produces a number of physiological changes throughout the body, including increases in CRF levels in the CeA (Rouwette et al., 2012). Complementary to this neuroadaptation, the anti-hyperalgesic effects of CRF1R antagonists (administered either systemically or in some cases intra-CeA) have been demonstrated in both mice and rats across a variety of pain models, including neuropathic pain, inflammatory pain, and visceral pain (e.g., Hummel et al., 2010; Ji & Neugebauer, 2007; Nijsen, Ongenae, Meulemans, & Coulie, 2005; Schwetz et al., 2004). CRF would indeed appear to play a key role in processing an array of pain modalities (e.g., mechanical, thermal, visceral), suggesting that its role is not modality-specific but may generalize to all classes of pain. Importantly, CRF1R antagonists do not alter baseline measures of various nociception-related indices (e.g., mechanical or thermal paw withdrawal thresholds, audible or ultrasonic vocalizations) in non-injured animals, indicating the absence of a direct analgesic effect (e.g., Baiamonte

et al., 2014; Cohen et al., 2015; Fu & Neugebauer, 2008; Roltsch et al., 2014). In comparison, CRF infusion into the CeA produces hyperalgesia in otherwise naïve animals (Itoga et al., 2016). CRF also directly alters the electrophysiological properties of CeA neurons to drive pain sensitization. For example, rodents in a state of arthritic inflammatory pain (Neugebauer, Han, Adwanikar, Fu, & Ji, 2007) exhibit enhanced CeA excitability that is attenuated by CRF1R antagonism (Ji et al., 2007). The authors also found that the normally inhibitory role of CRF2R signaling in this region was lost in the arthritis model, further demonstrating the complementary roles of CRF1 vs CRF2 receptors in neurophysiology, including pain signaling (Ji & Neugebauer, 2008). Interestingly, arthritis increases anxiety-like behavior and this effect is attenuated by either systemic or intra-CeA CRF1R antagonism (Ji et al., 2007), suggesting that CRF signaling drives the intersection of pain and negative affect within the CeA (Egli et al., 2012; Neugebauer, Li, Bird, & Han, 2004). Stress- and alcohol-related factors other than pain also produce an enhancement of CRF activity in the CeA (Gilpin, 2012; Roberto et al., 2010), and it was also demonstrated that non-pain-related activation of CRF1R signaling in the CeA augments nociceptive sensitivity (Ji, Fu, Adwanikar, & Neugebauer, 2013).

3.3 Vasopressin receptor systems

Several emerging lines of evidence have implicated the neuropeptide vasopressin in the pathophysiology of stress- and emotion-related behaviors, often in a sexually dimorphic fashion (Bisagno & Cadet, 2014). In addition to the well-characterized role of hypothalamic vasopressin acting in conjunction with CRF to stimulate the HPA axis (Lolait, Stewart, Jessop, Young, & O'Carroll, 2007), vasopressin-synthesizing neurons are also localized in the bed nucleus of the stria terminalis (BNST) and medial amygdala (De Vries & Buijs, 1983), project extensively throughout the limbic system (Veinante & Freund-Mercier, 1997), and play a significant role in regulating various complex behaviors, including aggression and social affiliation. Vasopressin signaling within the brain is thought to underlie various aspects of emotional processing (Caldwell, Lee, Macbeth, & Young, 2008), and early studies established a specific role for central vasopressin in aversive learning and memory mechanisms (Koob & Bloom, 1982). More recently, the generation of small molecule, receptor subtype-selective antagonists has greatly advanced the characterization of the complex behavior regulated by V1b receptors (V1bR), which are thought to play a role in generalized negative affective-like behaviors, as demonstrated by the anxiolytic-like, antidepressant-like, and anti-hyperalgesic-like effects of the small molecule V1bR antagonist SSR149415 (Bradesi, Martinez, Lao, Larsson, & Mayer, 2009; Griebel et al., 2002). Studies utilizing regional microinjections of SSR149415 have established a particular role for negative affective-like V1bR signaling in the amygdala, as SSR149415 reduces both anxiety-and depression-like behavior (Salome, Stemmelin, Cohen, & Griebel, 2006). Vasopressin gene (*Avp*) expression levels are higher in the CeA of male Sardinian alcohol-preferring (sP) relative to alcohol-non-preferring (sNP) rats. Interestingly, the excessive drinking of sP rats reduces elevated *Avp* levels, while systemic SSR149415 administration is effective in reducing drinking in this population (Zhou et al., 2011). Independent lines of preclinical evidence strongly point to a role for vasopressin/V1bR signaling in the transition to alcohol dependence (Edwards, Guerrero, et al., 2012; Zhou & Kreek, 2014).

Given the literature suggesting that V1bR antagonists have substantial efficacy in reducing negative affective-like profiles and the fact that vasopressin and its central receptors (V1bR and V1aR) are highly expressed in extended amygdala and cortical areas (Stemmelin, Lukovic, Salome, & Griebel, 2005; Tribollet, Raufaste, Maffrand, & Serradeil-Le Gal, 1999), vasopressin systems could play a central role in the increased alcohol intake and hyperalgesia associated with dependence. These effects may occur via the ability of vasopressin to activate the HPA axis (Volpi, Rabadan-Diehl, & Aguilera, 2004) and/or via direct central (i.e., extra-hypothalamic) actions. Interestingly, the effects of V1bR blockade on excessive alcohol self-administration (Edwards, Guerrero, et al., 2012) closely resemble inhibition of the CRF1 receptor system on this behavior (Richardson et al., 2008), and CRF1R antagonism has already been demonstrated to alleviate symptoms of mechanical hyperalgesia in alcohol-dependent rats (Edwards, Vendruscolo, et al., 2012). Accordingly, either in addition to or in cooperation with CRF, vasopressin V1bR activity may represent another mechanism whereby negative reinforcement mechanisms regulate alcohol dependence-related symptomatology. Perhaps most importantly, recent evidence has emerged for the safety and clinical efficacy of V1bR antagonists to reduce HPA axis activation and increase abstinence in alcohol-dependent patients (Katz, Liu, Locke, Dutta, & Tracy, 2016; Ryan et al., 2017; ClinicalTrials.gov Identifier NCT01613014).

In comparison to V1bRs, V1aRs are expressed at even higher levels in the brain (Tribollet et al., 1999), and are important for mediating social behavior. Systemic and brain administration of the V1aR antagonist SR49059 improves neurological and neurobehavioral outcomes in animal models of traumatic brain injury (TBI; Krieg, Sonanini, Plesnila, & Trabold, 2015; Manaenko et al., 2011; Marmarou et al., 2014). Interestingly, pain-related affective responses are enhanced via vasopressin signaling through V1a receptors in the CeA (Cragg, Ji, & Neugebauer, 2016), an effect that is blocked via intra-CeA administration of SR49059. These findings make V1aR antagonism a promising therapeutic strategy for both TBI and pain (which are themselves highly comorbid), although the contribution of this receptor system to excessive drinking or hyperalgesia in the context of alcohol dependence has remained unexplored.

3.4 Glucocorticoid receptor system

Both alcohol and alcohol withdrawal elevate systemic glucocorticoid levels due to activation of the endocrine HPA axis (Rivier, 2014). In addition to profound dysregulation of HPA axis activity (Richardson, Lee, O'Dell, Koob, & Rivier, 2008), alcohol-dependent animals exhibit a functional increase in central brain GR signaling, a key mediator of stress responsiveness (Edwards et al., 2015). Importantly, GR antagonism via mifepristone reduces escalated drinking in both preclinical animal models and early clinical trials (Vendruscolo et al., 2015; ClinicalTrials.gov Identifier NCT01548417). As a potential biochemical correlate of sensitized central GR signaling that may underlie these promising clinical directions, previous work describes increases in GR phosphorylation in the CeA of alcohol-dependent animals (Vendruscolo et al., 2015). At the molecular level, the transcriptional activity of GR is directly controlled via phosphorylation at serine 232 (Adzic et al., 2009), and two key downstream targets of GR transcriptional activity are *Crh* and *Crhr1* (Yao & Denver, 2007). Importantly, systemic administration of either the GR antagonist mifepristone (Dina et al.,

2008) or a CRF1R antagonist (Edwards, Vendruscolo, et al., 2012) alleviates hyperalgesia in binge drinking and alcohol-dependent animals (respectively). It is also important to note that in contrast to the classic GR-mediated negative feedback regulation of CRF at the level of the HPA axis, GR activity actually facilitates CRF gene expression in certain central brain regions (Edwards et al., 2015) including the CeA (Makino, Gold, & Schulkin, 1994). Differential expression and activity of steroid receptor coactivator-1 (SRC-1) isoforms between the PVN and CeA may account for this dichotomy (Lachize et al., 2009). As described above, intra-CeA administration of CRF1R antagonists is effective in alleviating hyperalgesia in both pain and drug dependence models (McGinn & Edwards, 2016). Unfortunately, evidence for the clinical efficacy of CRF1 receptor antagonists to reduce excessive drinking has been slow to develop, with some early failures in clinical trials (e.g., Kwako et al., 2015). However, development of novel antagonists with different brain pharmacokinetics and/or a more precise selection of specific treatment populations (e.g., those suffering from co-morbid hyperalgesia) may unmask the true utility of this medication class (Spierling & Zorrilla, 2017). In addition to the CRF system, alternative stress-regulated targets either independent from or even transcriptionally regulated by GR, as in the case of V1aR (Watters, Swank, Wilkinson, & Dorsa, 1996) and V1bR (Aguilera & Rabadan-Diehl, 2000), would appear to offer a very promising path forward for treating severe AUD and associated pain conditions.

4. Summary

Pain represents a uniquely subjective experience that may exert a powerful influence on reinforcement processes, possibly facilitating the transition to substance use disorders (Miller & Gold, 2007; Shurman, Koob, & Gutstein, 2010), including AUD (Edwards et al., 2020). Recent insights into the mechanisms that mediate the analgesic efficacy and abuse-related properties of alcohol have provided a basis for a conceptualization of the neurobiological intersection of pain and AUD. The analgesic effects of alcohol have been known anecdotally for centuries and have been scientifically investigated for almost 100 years. Drinking history, alcohol dependence, chronic pain status, and genetic risk for AUD all affect the analgesic efficacy of alcohol (Edwards et al., 2020). The mechanisms behind alcohol-induced analgesia are understudied, but the primary mechanisms proposed include the endogenous opioid system, GABA/NMDA signaling, and GIRK2 channel activity. It is likely that alcohol interacts with each of these systems to produce its analgesic effects, while future studies are needed to understand the possible role of other endogenous analgesia systems, such as the endocannabinoid system.

Neurophysiological processes that counter the anxiolytic and analgesic properties of alcohol may drive AUD progression through the generation of hyperalgesia and closely associated negative affective states. In turn, given that chronic pain itself often produces emotional distress, alcohol-related hyperalgesia may be closely associated with the transition to AUD via facilitation of negative reinforcement mechanisms. Strong evidence suggests that the neural substrates associated with addiction may overlap with substrates of emotional aspects of pain processing in brain regions where ascending nociceptive circuitry terminates (Egli et al., 2012). Specifically, the affective component of pain is strongly regulated by the CeA (Neugebauer, 2015). Numerous preclinical models have demonstrated a functional role for

the CeA in regulating persistent hyperalgesia associated with a range of neurological and psychiatric conditions ranging from arthritis (Ji et al., 2007) to opioid dependence (McNally & Akil, 2002). This neurocircuitry may promote crosstalk among a variety of psychiatric disorders and account for the high degree of comorbidity between affective disorders, AUD and chronic pain (Edwards et al., 2020). Medications such as CRF1 receptor antagonists, vasopressin receptor antagonists, and GR antagonists that act on these shared systems would likely be effective in treating a range of affective pain-related conditions, including AUD (Fig. 1). Moreover, dependence on other abused drugs commonly taken with alcohol (e.g., nicotine) is associated with a CRF1R-dependent hyperalgesia (Baiamonte et al., 2014; Cohen et al., 2015; Edwards, Vendruscolo, et al., 2012). As a result, patients with a history of alcohol or other substance use disorders may be susceptible to the activation of a common set of nociceptive factors that could drive relapse and abuse of any or all of these substances. Thus, we and others have hypothesized that CeA neuroadaptations facilitate pain-driven motivated behaviors that underlie dependence-induced hyperalgesia and excessive drinking. It is our hope that the functional integration of pain- and addiction-related research objectives across the National Institutes of Health will promote further collaboration among addiction and pain neuroscientists, leading to broader and more integrative therapeutic strategies for these devastating conditions.

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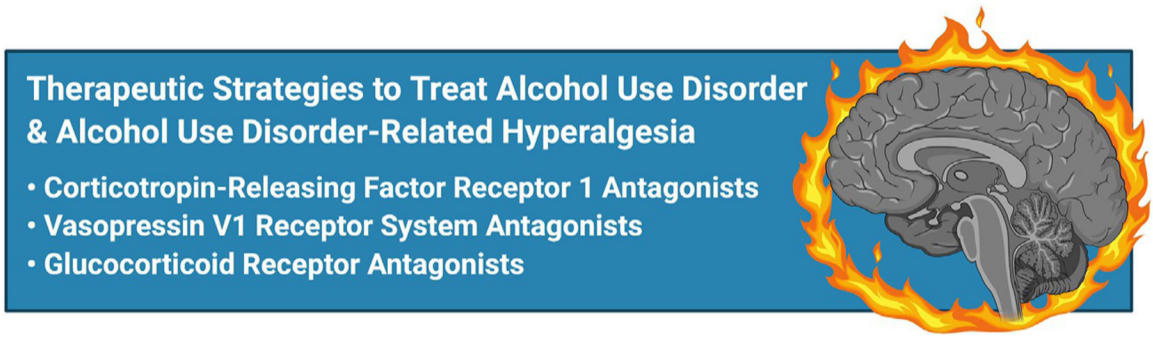

Fig. 1.

There is an urgent need to understand the neurobiological mechanisms of pain and AUD, as well as a continuing need for preclinical medication development targeted to novel systems to treat these devastating conditions. As hyperalgesia represents a form of chronic stress and negative affect, we expect that this condition plays a critical role in negative reinforcement mechanisms underlying excessive drinking in the context of AUD. Following from this conceptualization, the interrogation of brain stress systems would likely represent a prolific avenue for medication development. Neurobiological changes across both hypothalamic and extra-hypothalamic stress systems (including changes in CRF, vasopressin, and GR signaling) have been observed in preclinical AUD animal models, with the central amygdala (CeA) playing a critical role in mediating the interaction of pain and negative affective-related behaviors expected to contribute to AUD.