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The affective dimension of pain as a risk factor for drug and alcohol addiction

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ABSTRACT

Addiction, or substance use disorder (SUD), is a devastating psychiatric disease composed of multiple elemental features. As a biobehavioral disorder, escalation of drug and/or alcohol intake is both a cause and consequence of molecular neuroadaptations in central brain reinforcement circuitry. Multiple mesolimbic areas mediate a host of negative affective and motivational symptoms that appear to be central to the addiction process. Brain stress- and reinforcement-related regions such as the central amygdala (CeA), prefrontal cortex (PFC), and nucleus accumbens (NAc) also serve as central processors of ascending nociceptive input. We hypothesize that a sensitization of brain mechanisms underlying the processing of persistent and maladaptive pain contributes to a composite negative affective state to drive the enduring, relapsing nature of addiction, particularly in the case of alcohol and opioid use disorder. At the neurochemical level, pain activates central stress-related neuropeptide signaling, including the dynorphin and corticotropin-releasing factor (CRF) systems, and by this process may facilitate negative affect and escalated drug and alcohol use over time. Importantly, the widespread prevalence of unresolved pain and associated affective dysregulation in clinical populations highlights the need for more effective analgesic medications with reduced potential for tolerance and dependence. The burgeoning epidemic of prescription opioid abuse also demands a closer investigation into the neurobiological mechanisms of how pain treatment could potentially represent a significant risk factor for addiction in vulnerable populations. Finally, the continuing convergence of sensory and affective neuroscience fields is expected to generate insight into the critical balance between pain relief and addiction liability, as well as provide more effective therapeutic strategies for chronic pain and addiction.

Introduction

Drug and alcohol addiction, also termed substance use disorders (SUDs; DSM-5, 2013) represent devastating diseases (Leshner, 1997). The interaction of abused substances with brain circuitry has long been a focus of intense research generously supported by national governments, private foundations, and individuals. A lack of truly effective treatments for addiction has driven neuroscientists to generate an abundance of data related to drug-induced neuroadaptations as well as innovative conceptualizations of the transition from recreational drug use to addicted states. This transition is considered driven by a combination of tolerance and sensitization processes within specific neural circuitry following repeated or excessive drug exposure (Koob & Le Moal, 1997). For example, tolerance to the rewarding or otherwise intake-limiting effects of drugs coincides with a sensitization of incentive motivational processes to drive the pursuit and use of abused substances (Self, 1998). Consequently, individuals suffering from addiction will often report a phenomenon termed “chasing the dragon” where the seemingly maximal hedonic value of the initial drug experience is sought after but never recapitulated with subsequent use. Importantly, drug and alcohol exposure is also postulated to activate brain anti-reward systems that are considered vital for the adaptive process of reward homeostasis under normal conditions (Koob & Le Moal, 2008). However, repeated or heavy drug use potentiates negative affective conditions (e.g., anxiety, dysphoria) over time, representing a cumulative allostatic load challenging homeostasis and ultimately driving excessive intake and continued relapse via negative reinforcement mechanisms (Edwards & Koob, 2013). Historical investigations focused on negative motivational processes have delineated

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specific neuroanatomical and neurochemical substrates that promote a variety of addiction-related behaviors (Edwards & Koob, 2010). More recently, conceptualizations of opioid (Shurman, Koob, & Gutstein, 2010) and alcohol (Egli, Koob, & Edwards, 2012) addiction as chronic pain disorders have emerged, highlighting the negative affective dimension of pain as a central component to facilitate and maintain these devastating conditions. Valuable insights into the biobehavioral mechanisms that determine the analgesic efficacy and abuse-related properties of drugs and alcohol have provided a foundation for future investigations into the neurobiological intersection of pain and addiction.

Pain in clinical populations: risk for affective disorder and addiction

Chronic pain is a leading cause of long-term disability and affects over 100 million Americans (Institute of Medicine, 2011), more than diabetes, heart disease, and cancer combined. Treatment options largely rely on prescription analgesic drugs, primarily opioid-based, with incomplete success. Health care professionals must also balance the vital need to administer opioid analgesics with the risk for diversion, misuse, and addiction (Fields, 2011; Volkow & McLellan, 2011). It is important to note that addiction to prescription opioids in the context of proper analgesic use is rare (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff, 2008) although addiction liability is increased in individuals with a history of illicit alcohol or drug misuse. Additionally, chronic pain patients can still exhibit substantial craving for prescription opioids even in the absence of addiction, with affective state playing an important role in this relationship (Wasan et al., 2012). Finally, in addition to prior drug abuse, a history of mood disorder may place individuals at risk for prescription opioid misuse (Wasan et al., 2007).

Unfortunately, chronic pain is intimately associated with the manifestation of affective disorders such as major depression and generalized anxiety disorder (Demyttenaere et al., 2007; Elman, Borsook, & Volkow, 2013; Yalcin & Barrot, 2014). Increasing recognition of this troubling relationship has led some to label this interaction as the depression-pain syndrome (Chopra & Arora, 2014; Lindsay & Wyckoff, 1981), with the incidence of depression among chronic pain patients found to range from 30 to 85%, depending on the study setting (Bair, Robinson, Katon, & Kroenke, 2003; Dworkin & Gitlin, 1991; Maletic & Raison, 2009; Ruoff, 1996). Furthermore, depressed patients report more pain symptoms than the general population, with an average of 65% of patients experiencing one or more pain complaints (Bair et al., 2003). Another crucial dimension of this relationship is the extent of pain and depression severity, with reciprocal correlations increasing as the severity of either condition grows (Currie & Wang, 2004; Gerrits et al., 2012; Haley, Turner, & Romano, 1985; McWilliams, Cox, & Enns, 2003). While there does not appear to be differences in the overall incidence of chronic pain or depression based on age or sex, men and women differ in the relationships among depression, general activity, and chronic pain. For example, in female patients, depression most closely relates to their self-reported pain severity, whereas depression correlates more closely to decreased activity levels in males (Haley et al., 1985). Such distinctions warrant more preclinical investigation into sex differences that moderate nociceptive signaling (Mogil & Bailey, 2010) and pain-induced affective dysregulation. This is particularly important given the considerable differences in analgesic responsiveness between men and women (Loyd & Murphy, 2014).

Although the most common manifestation of chronic pain-related affective disorder is depression, anxiety and fear are also commonly experienced and may result in even greater psychiatric morbidity (Dersh, Polatin, & Gatchel, 2002). In a population-based study, the prevalence of anxiety disorders was 35% in persons with chronic pain compared with 17% in a healthy control population (McWilliams et al., 2003). The associations between chronic pain and anxiety disorders (e.g., panic disorder, agoraphobia, and PTSD) also appear to be even stronger than associations between pain and depression. Contrary to pain-related depression, most anxiety disorders are present prior to the onset of pain, and such anxiety-prone patients may develop significant distress and functional disability as the result of pain-related fear and catastrophizing (Dersh et al., 2002; Knaster, Karlsson, Estlander, & Kalso, 2012).

Pathologies associated with intermittent pain episodes are also linked with devastating and costly affective complications. For example, patients suffering from sickle cell disease (SCD), a condition characterized by severe acute pain crises on top of chronic somatic and neuropathic pain beginning in childhood and persisting throughout life, tend to have elevated rates of depression and anxiety disorders (Cepeda, Yang, Price, & Shah, 1997; Hasan, Hashmi, Alhassen, Lawson, & Castro, 2003; Levenson et al., 2008). Affective dysregulation in SCD patients is similar to other medical conditions associated with chronic pain (Bennett, 1994; Ericsson et al., 2002; Kato, Sullivan, Evengård, & Pedersen, 2006; Widmer & Cadoret, 1978), and these patients subsequently have longer lengths of hospitalization for treatment of pain (Myrvik, Burks, Hoffman, Dasgupta, & Panepinto, 2013) as well as higher overall health care usage and medical costs as compared to similar patients without psychiatric diagnoses. Data from the Pain in Sickle Cell Epidemiology Study (PiSCES) indicated that approximately one-third of SCD patients surveyed met criteria for alcohol abuse (Levenson et al., 2007). Interestingly, alcohol abusers reported greater pain relief from opioids compared to those who did not use alcohol.

In the absence of physician awareness and vigilance, chronic pain-associated affective disorders may remain unrecognized or misdiagnosed and subsequently may be inappropriately or inadequately treated. Although somatic symptoms of pain are a common marker of depression that are often initially addressed with a primary care physician, studies suggest that depressed patients presenting with pain symptoms are unlikely to receive an accurate diagnosis (Bridges & Goldberg, 1985; Kirmayer, Robbins, Dworkind, & Yaffe, 1993). Misdiagnosis of pain-related affective disorders carries significant implications for acute and long-term management and treatment outcomes. For example, patients with depressive symptoms who also report pain are often treated with opioid analgesics rather than antidepressants (Doan & Wadden, 1989), potentially increasing the risk of opioid addiction without adequately treating the underlying issue. Alternatively, patients who receive concomitant treatment for both pain and depression, either through antidepressant medications or psychotherapy, have better outcomes compared to those treated for pain alone (Teh, Zaslavsky, Reynolds, & Cleary, 2010), displaying an alleviation of depression as well as decreased pain symptoms (Kroenke et al., 2009).

Pain, affective dysregulation, and addiction in preclinical animal models

Given the overwhelming evidence connecting chronic pain and emotional disruption in humans, nociceptive physiology is now routinely investigated beyond the sensory dimension at the preclinical level (Yalcin, Barthas, & Barrot, 2014). Unresolved pain can be considered a form of chronic, inescapable stress (Blackburn-Munro & Blackburn-Munro, 2001), and a significant effort has been put forth to understand the underlying neurobiological mechanisms that represent the link between persistent pain states