9

β-Endorphin and Alcoholism

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1. Introduction

Extensive research over several decades indicates a strong relationship between alcohol use disorders and anxiety. Stress and anxiety are implicated in both the initiation of alcohol consumption and the maintenance of heavy drinking (Kushner et al., 1990; Pohorecky, 1981). For instance, anxiety disorders reliably precede the onset of alcoholism (Hettema et al., 2003) and over 35% of patients diagnosed with generalized anxiety disorder have engaged in self-medication with alcohol, defined as "drinking more than usual" in response to a stressor (Bolton et al., 2006). Stressors have also been linked to relapse in abstinent adults (Adinoff et al., 2005; Brown et al., 1995). Moreover, there is strong support suggesting that stress and alcohol abuse co-present so frequently as a result of common genetic factors in stress response systems. Genetically inherited variations in the hypothalamic-pituitary-adrenal (HPA) axis have been implicated in vulnerability to initial alcohol abuse, sustained alcohol addiction, and relapse (Crabbe et al., 2006; Kreek & Koob, 1998; Shaham et al., 2003). This paper will discuss the putative contribution of b-endorphin to the negatively reinforcing effects of alcohol.

2. The hypothalamo-pituitary-adrenocortical axis and β-endorphin

Although a thorough understanding of this nebulous concept is lacking, stress has been operationally defined as activation of the hypothalamo-pituitary-adrenocortical (HPA) axis in response to both physical and psychological stressors (for example, Pacak and Palkovits, 2001; Uhart and Wand 2009). The stress response is coordinated by neuronal activation of the paraventricular nucleus in the hypothalamus leading to the release of corticotrophin-releasing hormone (CRH) into the hypothalamic-hypophyseal portal. CRH reaches receptors on the anterior pituitary and initiates the synthesis of ACTH from its precursor, proopiomelanocortin (POMC). ACTH is released into the bloodstream where it influences the adrenal glands, initiating production and release of cortisol into the blood (corticosterone in rodents). Cortisol plays a fundamental role in the systemic reaction that characterizes physiological stress, though high levels of cortisol act in a negative feedback loop, inhibiting further CRH and ACTH synthesis in the brain.

Like stress, alcohol also leads to CRH release from the hypothalamus, initiating activation of this system (Hsu et al., 1998; see Gianoulakis, 2009; Uhart & Wand, 2009 for reviews). Indeed, the physiological effects of alcohol are in part mediated by the HPA axis and dependent upon neuronal activation of the paraventricular nucleus, and the subsequent release of CRH, ACTH and, eventually, adrenal activation (Lee et al., 2004).

Related to these endocrine changes, endogenous opioids are also synthesized and released in response to both the experience of stress and alcohol consumption (Keith et al, 1986; Sarkar & Minami, 1990; Schedlowski et al, 1995; Thiagarajan, 1989). Opioids are primarily known for their analgesic properties, but they are highly implicated in the physiological rewarding effects of alcohol and other drugs of abuse (Wei & Loh, 1976; Van Ree, 1979; Zalewska-Kaszubska et al., 2006; see Crabbe et al., 2006 for review) as well as a wide array of other behavioral states. One class of endogenous opioids is the endorphins. The primary endorphin is β-endorphin, which is both analgesic and addictive in human and animal studies (Janssen & Arntz, 2011; Wie & Loh, 1976), and contributes to the rewarding and reinforcing properties of alcohol (Grahame 1998; Grisel et al, 1999; Williams et al, 2007).

3. β-endorphin and alcohol

POMC is the precursor to all endorphins, including β-endorphin, which is synthesized in both the hypothalamus and the anterior pituitary. Endorphin producing neurons are located primarily in the arcuate nucleus of the hypothalamus, and project to other areas of the hypothalamus (supraoptic nucleus, paraventricular nucleus, and lateral hypothalamus) as well as to the amygdala, ventral tegmental area (VTA), periaqueductal gray, and bed nucleus of the stria terminalis (King & Hentges, 2011; McGinty & Bloom, 1983). Thus, β-endorphin is well situated to influence reward, stress and pain (see Kreek & Koob, 1998 for review). Moreover, EtOH-initiated dopamine release in the nucleus accumbens (NAC; de Waele & Gianoulakis, 1993; Koob & Le Moal, 1997) is thought to involve endorphin, which hyperpolarizes GABAergic neurons, and thereby disinhibits dopaminergic firing in the VTA (Johnson & North, 1992). Thus, the effects of acute alcohol administration on β-endorphin in the hypothalamus (Gianoulakis, 1990; Sakar et al. 2007) contribute to the positive reinforcing effects of alcohol. Additionally, acute administration of alcohol initiates synthesis and release of β-endorphin into the bloodstream (de Waele & Gianoulakis, 1993; Keith et al., 1986).

The relationship between β-endorphin and alcohol suggests at least two fundamental ways by which this peptide may be contributing to alcoholism. The first may underlie the heritable liability to develop an alcohol use disorder while the second comes into play as β-endorphin synthesis is down-regulated following chronic exposure.

4. β-endorphin and acute alcohol exposure

Individual variation in β-endorphin levels, as determined by heritable factors, predisposes individual differences in reinforcing properties of alcohol. Low β-endorphin may mediate enhanced reward either through more salient negative reinforcement or positive reinforcement from the drug. For example, the 'opioid deficiency hypothesis' builds on the

fact that individuals predisposed to alcoholism have low basal levels of β-endorphin and suggests that alcohol administration will ameliorate this deficiency (see Gianoulakis et al., 2006; Herz, 1997, 1998; Zalewska-Kaszubska & Czarnecka, 2004 for reviews).

Gianoulakis et al. (1996) examined the possibility that high risk individuals (as identified by familial history) will have increased sensitivity to EtOH-induced release of endogenous opioids, thus mediating the apparent enhanced reward those at high risk for alcoholism presumably experience with EtOH consumption. Subjects were between twenty and thirty years old and were categorized as either high risk (HR) or low risk (LR) based upon known family history of alcoholism. The results showed an EtOH-dose dependent increase in plasma β-endorphin levels in HR subjects, but not in LR subjects. This finding supports the notion that augmented sensitivity of β-endorphin release to EtOH could increase sensitivity to the positive rewards of EtOH.

Animal studies provided further support for the idea that increased sensitivity to an EtOH-mediated rise in β-endorphin might facilitate acquisition of alcohol drinking. We (Grisel et al. 1999) demonstrated that mice with low levels of β-endorphin self-administer more EtOH than either wild type (C57BL/6J) controls or mice that entirely lack the capacity for β-endorphin production. In these studies we used either homozygous or heterozygous B6.129S2-*Pomc*^{tm1Low}/J mice, commercially available from Jackson Laboratories, in Bar Harbor, ME. The mice with low β-endorphin self-administered more EtOH and exhibited higher alcohol preference than controls, regardless of EtOH dose, while those without any capacity to synthesize the peptide consistently drank the least. This experiment suggests two hypotheses. One is that those with low levels of β-endorphin are more inclined to drink. The other, that β-endorphin contributes to the rewarding effects of EtOH.

In animals, pharmaceutical agents that increase plasma β-endorphin levels have been most effective in attenuating self-administration of EtOH. Treatment of Warsaw High and Low Alcohol Preferring rats with the opioid antagonist naltrexone, stopped the plasma β-endorphin increase after EtOH administration in low-preference rats, and normalized β-endorphin plasma levels in high-preferring rats so that before and after alcohol exposure plasma levels were similar. These results indicate the clinical effectiveness of naltrexone in treatment of alcoholism may in part be due to both normalization of plasma β-endorphin levels and an attenuation of alcohol-rewarding properties (Zalewska-Kaszubska et al., 2006). In the same strains of rats, β-endorphin levels and EtOH intake were examined following treatment with acamprosate, which is approved for relapse prevention in withdrawing alcoholics. Chronic administration of acamprosate decreased voluntary intake of EtOH and increased plasma β-endorphin levels in high-preferring rats. Chronic administration of acamprosate also increased β-endorphin levels in rats in withdrawal from free EtOH access, suggesting that the clinical efficacy of this novel pharmacotherapy may be mediated by opioid effects.

The specific influence of β-endorphin on negatively reinforcing effects of EtOH has been examined in animals. Negative reinforcement occurs as alcohol alleviates an aversive state or condition. We (Grisel et al., 2008) looked at anxious behavior as a function of basal levels of β-endorphin. These studies utilized the Light-Dark Box and Elevated Plus Maze to evaluate anxious behavior in wild-type C57BL/6J (WT), heterozygous (HT) and β-endorphin deficient mice (B6.129S2-*Pomc*^{tm1Low}/J). In these assays, anxious behavior is

inversely related to time spent in the open or light areas of the assay apparatuses. In naïve subjects, the amount of time spent in the open arms of the Plus Maze or Light-Dark Box was inversely correlated with the amount of basal β-endorphin. These findings are consistent with the suggestion that β-endorphin release produces a calming and relaxing effect and thus lower levels of β-endorphin result in less regulation of HPA axis stress response (Gianoulakis, 1998; Sarkar et al., 2007). It follows that those with low basal β-endorphin levels, and therefore exaggerated stress responses, would be more inclined to self medicate with drugs of abuse, specifically anxiolytics such as EtOH (Zalewska-Kaszubska and Czarnecka, 2004).

Similar experiments were also conducted following acute exposure to EtOH (Grisel et al., 2008). Here, despite more anxious behavior at baseline, β-endorphin-deficient mice exhibited an exaggerated anxiolytic response after EtOH administration in both the plus maze and light-dark box in comparison to controls. These data may help explain the clinical relationship between this peptide and the propensity for alcoholism by suggesting that individuals with chronic β-endorphin deficiency have an increased sensitivity to the rewarding properties of EtOH, at least in part, because it alleviates their anxiety.

5. Interaction between β-endorphin and sex in acute EtOH exposure

Recent studies suggest that sex differences may play a moderating role in acute EtOH sensitivity differences. It is widely appreciated that females have lower incidence of alcoholism than males (Hunt and Zakhari, 1995), and these differences are theorized to manifest differences in coping response between sexes (Hettema et al., 2003). A burgeoning body of research supports the contention that females are more sensitive to stress than males (see Kleim et al., 2010; Maestripieri et al., 2010; Paris et al., 2010; Pratchett et al., 2010 for recent reviews of the human literature and Bangasser et al., 2010; Mogil et al., 1997; and Palanza 2001 for some basic research findings). For example, females, whose use and abuse of alcohol are increasing dramatically, also appear to be more sensitive to stress-induced changes in EtOH sensitivity (see Greenfield et al., 2010; Hudson & Stamp, 2010; Przybycien-Szymanska et al., 2010; Sartor et al., 2010).

Sex differences in stress sensitivity appear to result, at least in part, from differences in hypothalamic-pituitary-adrenal (HPA) functioning mediated by an interaction between gonadal hormones and β-endorphin (Hudson and Stamp, 2010). In β-endorphin deficient animals, stress response to EtOH becomes increasingly more hormone dependent (Barfield et al., 2010). In addition to main effects of both sex and β-endorphin on measures of stress-induced behavior, the effect of EtOH was most profound in females deficient in endorphin. This triple interaction between peptide, sex and EtOH sensitivity on stress response was evident in females during their sexually-receptive phase, but not at other times in their estrous cycle.

These data suggest a biologic mechanism for sexually-dimorphic coping responses to stress that is β-endorphin dependent. Unfortunately, there is a paucity of basic biomedical research on sex differences (Beery and Zucker, 2010) but these data suggest the need for future studies to examine the role the estrous cycle plays in the interaction between stress response and alcohol to further understand differences between males and females.

6. β-endorphin and chronic alcohol use

Though genetics certainly contribute to the liability toward alcohol use disorders, excessive drinking in virtually anyone will lead to neural adaptations that underlie dependence, and β-endorphin is also implicated in those changes. The hedonic dysregulation model suggests that a decrease in opioid peptide function (along with other adaptations) following chronic alcohol consumption results in dysregulation of opioid-mediated reward transmission. This blunted reward circuitry is expressed phenotypically as a negative affect that exacerbates the potency of negative reinforcement following drug administration or adds increased salience to relapse related cues (Koob 2008).

Indeed, empirical studies in humans have provided an extensive body of evidence supporting opioid dysregulation following chronic alcohol abuse. Chronic alcoholic patients exhibit decreased synthesis and release of β-endorphin as measured by plasma levels (Aguirre et al., 1990; see Zalewska-Kaszubska & Czarnecka, 2004 for review), and HPA axis dysregulation is a primary characteristic of withdrawal (Adinoff et al., 2005). Furthermore, the functional response of the mu-opioid receptor (which has a high affinity for β-endorphin) is impaired after chronic exposure to EtOH (He & Whistler, 2011). It is thus likely that overactivity of the HPA is at least partly a result of low β-endorphin and that this change contributes to chronically higher basal levels of anxiety and stress during withdrawal (Aguirre et al., 1990; Aguirre et al., 1995 Wand, 2001).

Investigations of recovering alcoholics have shown that levels of plasma β-endorphin are inversely correlated with self-rated measures of anxiety during the withdrawal period (Kiefer et al., 2002). Augmented negative reinforcement following alcohol consumption for subjects with low β-endorphin is likely because of its role in inhibiting CRH secretion. High levels of cortisol act as negative feedback for HPA axis stress response, (Buckingham, 1986) implicating β-endorphin in both behavioral allostasis and endocrine allostasis. Thus, it is likely that an alcohol-induced reduction of increased basal anxiety levels is a strong negative reinforcing factor in the maintenance of chronic alcohol dependence (Goldowitz et al., 2006; Kiefer et al., 2002).

Further support for the dysregulation models comes from Aguirre et al. (1995) who examined the possibility of classifying individuals as alcoholics or non-alcoholics based on plasma β-endorphin levels. They were able to identify alcoholics and non-alcoholics over 70% of the time by this measure alone. Even more impressively, they found a negative predictive value of 93.55% such that for every 100 people found to have normal plasma β-endorphin levels, 93 would actually be non-alcoholics. The results of this study supported a previous finding that low β-endorphin levels are significantly more common in clinical cases of alcoholics (Aguirre et al., 1990).

Plasma β-endorphin levels are involved in the withdrawal process. Kiefer et al. (2006) characterized alcoholics in recovery as either high preference or low preference based on individual average EtOH intake before detoxification. Basal β-endorphin levels of high preference individuals were found to be lower in comparison with low preference subjects. Treatment with acamprosate resulted in a significant increase in β-endorphin in high preference subjects but not in low preference subjects. Because acamprosate administration decreases withdrawal symptoms and increases abstinence, the increased β-endorphin levels in only high preference implicates β-endorphin deficiency as a key aspect in EtOH

withdrawal. In addition to acamprosate's efficacy in treating alcoholism, it has recently been shown to reduce anxiety (Schwartz et al., 2010).

7. Conclusion

In conclusion, a growing body of research suggests that sub-optimal levels of β-endorphin result in compromised allostasis of the HPA axis, and that the consequent enhanced sensitivity to stressors facilitates high drinking. Sex differences may play a moderating role in the interaction between stress sensitivity, β-endorphin levels and EtOH. In general, individuals with deficient β-endorphin levels are likely to find EtOH more rewarding from both exaggerated positive and negative reinforcement. Chronic EtOH consumption leads to alterations in β-endorphin activity, and these changes are responsible in part for feelings of anxiety during withdrawal and relapse. Thus, especially in stressful situations, alcohol is likely to serve as an alternative coping mechanism with particular potency for those with labile β-endorphin and therefore predisposed to enhanced sensitivity to its anxiolytic effects.

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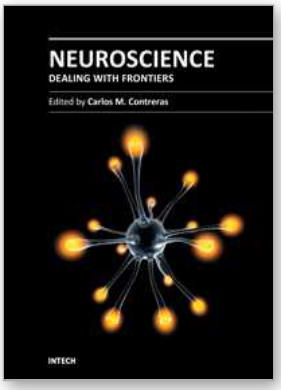

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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