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Corticotropin-releasing factor (CRF) and neuropeptide Y (NPY): Effects on inhibitory transmission in central amygdala, and anxiety- & alcohol-related behaviors

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ABSTRACT

The central amygdala (CeA) is uniquely situated to function as an interface between stress- and addiction-related processes. This brain region has long been attributed an important role in aversive (e.g., fear) conditioning, as well as the negative emotional states that define alcohol dependence and withdrawal. The CeA is the major output region of the amygdala and receives complex inputs from other amygdaloid nuclei as well as regions that integrate sensory information from the external environment (e.g., thalamus, cortex). The CeA is functionally and anatomically divided into lateral and medial subdivisions that themselves are interconnected and populated by inhibitory interneurons and projections neurons. Neuropeptides are highly expressed in the CeA, particularly in the lateral subdivision, and the role of many of these peptides in regulating anxiety- and alcohol-related behaviors has been localized to the CeA. This review focuses on two of these peptides, corticotropin-releasing factor (CRF) and neuropeptide Y (NPY), that exhibit a high degree of neuroanatomical overlap (e.g., in CeA) and largely opposite behavioral profiles (e.g., in regulating anxiety- and alcohol-related behavior). CRF and NPY systems in the CeA appear to be recruited and/or up-regulated during the transition to alcohol dependence. These and other neuropeptides may converge on GABA synapses in CeA to control projection neurons and downstream effector regions, thereby translating negative affective states into anxiety-like behavior and excessive alcohol consumption.

The central amygdala

Negative emotion circuitry

The extended amygdala is a conceptual macrostructure (Heimer & Alheid, 1991) that plays a prominent role in both fear and anxiety behaviors (Davis, Walker, Miles, & Grillon, 2010). Two major components of the extended amygdala are the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST; see the review by Kash, 2012, in this issue). These two regions exhibit a high degree of interconnectivity and play central roles in generating negative emotional responses (i.e., fear and anxiety) to environmental stimuli. The lateral amygdaloid complex (i.e., lateral and basolateral amygdala) receives significant sensory input from thalamus as well as dense cortical inputs (McDonald, 1998; Turner & Herkenham, 1991), sends prominent glutamatergic projections to CeA and BNST (Dong, Petrovich, & Swanson, 2001; Krettek & Price, 1978; Pitkänen et al., 1995), and is integral in both fear conditioning (Phelps & LeDoux, 2005) and fear extinction (Quirk & Mueller, 2008) processes. The CeA is composed mostly of GABAergic projection neurons and interneurons (Sun & Cassell, 1993; Veinante & Freund-Mercier, 1998), and has been divided into two subdivisions, the lateral and medial CeA, based on the connectivity and functionality of these subregions. The lateral division of the CeA projects to the BNST (Krettek & Price, 1978; Weller & Smith, 1982), and reciprocal connections between CeA and BNST contain neuropeptide co-transmitters, for example, the CeA is a major source of corticotropin-releasing factor (CRF) in the BNST (Sakanaka, Shibasaki, & Lederis, 1986). At a finer level, the lateral division of the CeA sends inhibitory projections to the medial division of the CeA, although there is not complete understanding of how emotional processing maps onto complex intra-amygdala connections (Ehrlich et al., 2009; Pape & Pare, 2010). The medial division of the CeA is the major output region of the amygdala and sends inhibitory projections to various effector regions (e.g., hypothalamus, periaqueductal gray, locus coeruleus, nucleus of the solitary tract, pedunculopontine tegmental nucleus; Pitkänen, 2000). Therefore, the amygdala receives strong inputs about the external

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environment and projects lateromedially to convert sensory information into appropriate behavioral and physiological responses.

The central amygdala and excessive alcohol drinking

Chronic alcohol consumption over long periods of time is defined by a transition from low/moderate to high levels of alcohol consumption. This transition is defined neuronally by down-regulation of dopamine signaling in the mesocorticolimbic reward system, hyperactivity of glutamate signaling, and dysregulation of brain stress systems (Koob & Volkow, 2010). Chronic alcohol effects on brain stress systems can refer to either alcohol-induced changes in neuroendocrine function (i.e., hypothalamic–pituitary–adrenal axis; Clarke et al., 2008; Kiefer & Wiedemann, 2004) or the recruitment of extra-hypothalamic (e.g., amygdalar) brain stress systems. This review will discuss the pivotal role of the CeA in mediating excessive alcohol consumption and other alcohol-related behaviors, as well as the important role of the CeA in regulating the negative emotional states often observed in excessive alcohol drinking phenotypes. In particular, genetic and environmental influences (e.g., alcohol withdrawal) may produce dysregulation of CeA (and extended amygdala circuitry at large) that resembles plasticity seen in those regions following exposure to fear- and anxiety-inducing environmental stimuli.

Central amygdala neuropeptides and alcohol

Neuropeptides in the extended amygdala have been attributed a prominent role in the negative affect produced by addiction to drugs, including alcohol (Koob, 2008). More specifically, these peptides have been conceptually divided into pro-stress peptides and anti-stress peptides that respectively promote and rescue negative affective disturbances during drug abstinence following heavy drug use. Many pro- and anti-stress peptides are highly expressed in the CeA and manipulation of those systems produces profound effects on affective-like and alcohol-related behaviors, effects that are often revealed or augmented in animals that exhibit excessive alcohol drinking phenotypes. Pro-stress peptides include CRF, dynorphin, hypocretin/orexin, and vasopressin, whereas anti-stress peptides include neuropeptide Y (NPY) and nociceptin. It is becoming increasingly evident that these peptides modulate synaptic transmission in the extended amygdala, and that this modulation is significantly altered in animals with a history of chronic high-dose alcohol exposure, presumably contributing to the negative emotional state observed in the absence of alcohol in those animals.

This review will focus on the roles of CRF and NPY in excessive alcohol drinking and related behavioral dysregulation, as well as modulation by these peptides of inhibitory transmission in the CeA. It is interesting that CRF and NPY show a high degree of neuroanatomical overlap and largely opposite behavioral profiles. For example, CRF promotes increases in anxiety-like behavior (Koob & Thatcher-Britton, 1985), increases in arousal (Koob et al., 1984), and decreases in feeding (Levine, Rogers, Kneip, Grace, & Morley, 1983), whereas NPY promotes decreases in anxiety-like behavior (Heilig et al., 1993), decreases in arousal (Heilig & Murison, 1987), and increases in feeding (Stanley & Leibowitz, 1984). As discussed below, alcohol-related behaviors exhibit heightened sensitivity to manipulation of brain CRF and NPY systems in individuals that are either alcohol-dependent, genetically vulnerable to consume high quantities of alcohol drinking, repeatedly cycled through periods of alcohol withdrawal, or innately. Of particular relevance to this review, the effects of CRF and NPY on anxiety-like and alcohol-related behaviors have been localized to the amygdala and neighboring regions, and are likely attributable to their modulation of synaptic transmission in those regions, which is altered following chronic alcohol exposure. It should be noted here that just as the lateral and medial divisions of the CeA differ in afferent inputs and efferent projections (for review of amygdala anatomical organization, see Pitkänen, 2000), they also differ in terms of their neuropeptide content, in that the lateral portion of the CeA contains a much higher density of neuropeptides (e.g., CRF; Cassell, Freedman, & Shi, 1999; Cassell, Gray, & Kiss, 1986; Shimada et al., 1989; Veening et al., 1984) than the medial CeA.

Rat models of alcohol dependence

Animal models of alcoholism aim to mimic specific components of the human addiction phenotype rather than the disorder as a whole. Much of the data discussed in this review comes from studies that utilize chronic high-dose alcohol exposure in the form of either alcohol vapor inhalation or alcohol liquid-diet to produce alcohol dependence in rats. These models have been utilized to produce the excessive alcohol-seeking and -drinking behaviors characteristic of humans that abuse and/or are dependent on alcohol, and allow examination of the neural dysregulation that mediates these behavioral changes. Throughout this review, *acute* alcohol exposure refers to in vitro application of ethanol to the slice preparation, whereas *chronic* alcohol exposure refers to long-term (at least several weeks) in vivo alcohol exposure. Furthermore, the chronic alcohol exposure protocols described here reliably produce somatic and motivational signs of alcohol dependence (Gilpin et al., 2009), therefore, the terms *chronic alcohol exposure* and *dependence* will be used interchangeably in this review.

Chronic intermittent alcohol vapor inhalation is a dependence induction procedure that allows for precise experimenter control of the dose, duration, and pattern of alcohol exposure (Rogers, Wiener, & Bloom, 1979), and stable blood-alcohol levels can be maintained for long periods of time in the presence of normal ingestive behaviors and weight gain (Roberts, Heyser, Cole, Griffin, & Koob, 2000). A second procedure used to produce alcohol dependence in rats makes an alcohol liquid-diet available to animals where diet is the sole source of available nutrition. This procedure allows animals to ingest large quantities via the natural route of administration, but there is substantial individual variability in the dose, duration, and pattern of alcohol exposure and resultant blood-alcohol levels (BALs) across animals. Both of these procedures produce alcohol tolerance and physical dependence on alcohol (Abu-Murad & Thurman, 1980; Gilpin et al., 2009; Lieber & DeCarli, 1982). Upon termination of alcohol vapor exposure, rats can be tested for a multitude of acute withdrawal- and protracted abstinence-related behaviors (Roberts, Cole, & Koob, 1996; Rogers et al., 1979; Valdez, Zorrilla, Roberts, & Koob, 2003; Zhao, Weiss, & Zorrilla, 2007). Behavioral data will be discussed from experiments that utilized both of these procedures, as well as electrophysiological data collected from brain slices of rats following chronic exposure to alcohol vapor. More specifically, the data reviewed below focus on neurotransmission in the CeA as it is relevant to the withdrawal/negative affect phase of the alcohol addiction cycle (Koob, 2003).

CRF and alcohol in central amygdala

CRF & anxiety- and alcohol-related behaviors

Amygdalar CRF & anxiety-related behavior

CRF is a 41-amino acid peptide that plays a central role in arousal as well as the hormonal, sympathetic, and behavioral responses to stress. CRF and its receptors are abundantly expressed in CeA, BNST, and BLA (De Souza et al., 1984; Sakanaka et al., 1986), and