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The Central Amygdala as an Integrative Hub for Anxiety and Alcohol Use Disorders

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Abstract

The central amygdala (CeA) plays a central role in physiological and behavioral responses to fearful stimuli, stressful stimuli, and drug-related stimuli. The CeA receives dense inputs from cortical regions, is the major output region of the amygdala, is primarily GABAergic (inhibitory), and expresses high levels of pro- and anti-stress peptides. The CeA is also a constituent region of a conceptual macrostructure called the extended amygdala that is recruited during the transition to alcohol dependence. In this review, we discuss neurotransmission in the CeA as a potential integrative hub between anxiety disorders and Alcohol Use Disorder (AUD), which are commonly co-occurring in humans. Human imaging work and multi-disciplinary work in animals collectively suggest that CeA structure and function are altered in individuals with anxiety disorders and AUD, the end result of which may be disinhibition of downstream “effector” regions that regulate anxiety- and alcohol-related behaviors.

INTRODUCTION

Anxiety disorders and Alcohol Use Disorders (AUD) are highly co-morbid in humans. Anxiety disorders often precipitate alcohol abuse, and high anxiety is a hallmark symptom of alcohol dependence that manifests during withdrawal. Many anxiety disorders are marked by hyperactivity and/or hyperreactivity of the amygdala (1), as supported by neuroimaging data, although functional MRI and PET do not yet possess the resolution to reliably differentiate amygdaloid nuclei.

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In healthy humans, amygdala activity is increased during fear conditioning (2, 3). Humans with post-traumatic stress disorder (PTSD) exhibit higher amygdala activity at rest (4), and hyper-reactivity of the amygdala to trauma-related stimuli (5) is predictive of symptom severity in PTSD patients (6, 7). Higher levels of amygdala activation are seen in generalized anxiety disorder (8, but see 9), social phobia (10), specific phobia (11, but see 12), and panic disorder (13, but see 14).

Alcohol withdrawal is defined by lasting increases in anxiety (15) that contribute to relapse (16, 17). Withdrawal-induced anxiety is attributable to recruitment of both neuroendocrine and extra-hypothalamic stress systems in humans and animals (18, 19). Alcohol-dependent humans exhibit reduced amygdala volume, which predicts alcohol craving and relapse (20, 21). Moderate-to-heavy non-dependent drinkers exhibit reduced amygdala activation during a risk-taking task (22). Individuals with a family history of alcohol dependence exhibit reduced amygdala volume (23) and reduced amygdala activation in response to fearful faces (24). PTSD patients that abuse alcohol exhibit altered amygdala blood flow relative to normal controls (4). In a cue-reactivity fMRI task, alcohol cues activate amygdala, striatum, and cortical regions (25, 26). Amygdala abnormalities may result in disinhibition of downstream brain regions that regulate physiology and behavior, as detailed below.

THE CENTRAL AMYGDALA (CeA)

The CeA functions as an integrative hub that converts emotionally-relevant sensory information about the external and internal environment into behavioral and physiological responses. The CeA is part of the extended amygdala (EA), a collection of limbic forebrain structures (including the lateral division of the bed nucleus of stria terminalis [BNST], and nucleus accumbens [NAc] shell [27]) that exhibit similar cytoarchitecture, overlapping afferents and efferents, and strong inter-connectivity (28, 29). The EA mediates negative affective states associated with stress and AUD (30, 31), and is densely populated by pro- and anti-stress neuropeptides (32). Here, we discuss CeA dysregulation in anxiety disorders and AUD, and the contribution of CeA peptides to these pathologies, with emphasis on the pro-stress peptide corticotropin-releasing factor (CRF) and the anti-stress peptide neuropeptide Y (NPY).

AMYGDALA CIRCUITRY

The amygdala is a collection of nuclei, including the lateral amygdala (LA), the basolateral amygdala (BLA), and the CeA, which contains lateral (CeA_L) and medial (CeA_M) subdivisions (Figure 1A). The amygdala exhibits a lateromedial flow of information from the LA/BLA to and through the intercalated cells (ITC), and into the CeA, which sends out information through amygdala efferents (33). The LA receives multi-sensory information from thalamus (34, 35), integrated sensory information from cortex (36), and noxious stimulus information from brainstem regions (37). The CeA also receives noxious stimuli information from brainstem regions (38, 39). Glutamatergic neurons in LA synapse onto glutamatergic BLA neurons, and onto GABAergic medial ITC cells (40) that separate BLA from CeA (41, 42). The LA/BLA sends dense glutamatergic projections to CeA, with the LA projecting only to CeA_L, and the BLA projecting to both CeA_L and CeA_M (28, 43, 44).

Projections out of BLA also synapse onto ITC GABA cells that in turn synapse on CeA neurons (45).

The CeA_L and CeA_M receive GABAergic afferents from other structures (46), contain local GABA interneurons and GABAergic projection neurons (47, 48) that may inhibit each other via axon collaterals (49; Figure 1B). The CeA_L projects to CeA_M, with no reciprocal projection from CeA_M to CeA_L (50). The CeA_M is the major output nucleus of the amygdala and projects to regions that produce behavioral and physiological responses to emotionally relevant events (49, 50, 51), but recent data suggest the CeA_L also sends GABAergic projections to behavioral and physiological effector regions (52).

Amygdala microcircuitry is critical for emotional processing, especially for interpretation of emotionally relevant stimuli or the attachment of emotional relevance to otherwise neutral stimuli (i.e., learning). Amygdala microcircuitry receives and integrates complex multi-modal information to produce behavioral responses. Amygdala dysfunction is implicated in both anxiety disorders (53) and substance abuse (30).

CeA AS A HUB FOR ANXIETY AND ALCOHOL CIRCUITS

Origins of Amygdala Afferents

Afferents from thalamus and cortex synapse in LA and ITC, which each project to CeA (Figure 1A). Medial prefrontal cortical (mPFC) inputs to amygdala have well-defined contributions to pathological behavioral states in humans and animals. Medial PFC pyramidal neurons send excitatory projections to the amygdala and are controlled by a complex network of GABA interneurons (54, 55). Human and animal studies suggest that alcohol and stress affect mPFC function and mPFC-amygdala functional connectivity.

The CeA integrates cortical/sensory inputs with innervation from “downstream” brainstem regions (50) including: 1) the ventral tegmental area (VTA), important for reward and synthesis of forebrain dopamine; 2) the locus coeruleus (LC) and nucleus of solitary tract (NTS), important for stress response, autonomic function and synthesis of brain norepinephrine; and 3) the periaqueductal gray (PAG), critical for pain processing. The CeA also receives input from the BNST (56), important for anxiety regulation, and is sensitized by glucocorticoid feedback following hypothalamic-pituitary adrenal (HPA) axis activation (57, 58), in contrast to glucocorticoid-mediated negative feedback in the PVN.

Effector Regions Targeted by CeA Efferents

The CeA integrates cortical, brainstem, and intra-amygdala afferents to coordinate behavioral and physiological responses via projections to downstream “effector” regions (Figure 1A). The target of specific CeA_M projections determines the behavioral consequences of changes in amygdala activity, but evidence also exists for a subpopulation of CeA_L neurons (i.e., oxytocin receptor-expressing neurons) with terminals in CeA_M and ventral forebrain that dictate whether fear coping behaviors are passive (e.g., freezing) or active (e.g., exploratory/risk assessment) (59). Whether CeA_M projection neurons exhibit mutually exclusive or overlapping targets and activation profiles is not fully understood. Basal amygdala projection neurons display anatomical and functional specificity in fear

expression versus extinction conditions (60), raising the possibility that CeA_M populations are likewise differentially activated by specific stimulus conditions.

Periaqueductal Gray (PAG)—The PAG is important for descending behavioral and physiological responses to fearful and painful stimuli (61). The CeA_M sends dense and organized GABAergic projections to PAG (62) that co-localize CRF and substance P (63) and gate the anti-nociceptive pain response mediated by opioids in PAG (64, 65). The amygdala and PAG are each activated by unconditioned aversive stimuli, and this response is dampened by signals predictive of those stimuli (66).

Lateral Hypothalamus (LHA)—The LHA mediates autonomic responses to fearful stimuli (61), and houses dopamine (DA) fibers that project from VTA to forebrain and mediate brain reward function (67). The CeA sends dense GABAergic projections to the LHA (28, 68). Electrical kindling of the CeA increases the sensitivity of LHA to drug-induced facilitation of brain reward function (69), whereas CeA lesion reduces DA activity in LHA (70).

Paraventricular Hypothalamus (PVN)—The PVN regulates the neuroendocrine stress response via CRF projections to the pituitary that promote ACTH and cortisol/corticosterone production and release. The CeA_M, but not the CeA_L, sends monosynaptic (71) and disynaptic (72) projections to the PVN, which may function as a relay station to brainstem nuclei (73). Electrical CeA stimulation activates the HPA stress axis (74), and the CeA mediates pro-inflammatory cytokine-induced activation of the HPA axis (75).

Locus Coeruleus (LC)—The LC produces norepinephrine and regulates autonomic responses to stress (76). GABAergic projections from CeA to LC (77) often co-localize the pro-stress peptides, CRF and dynorphin (78), and synapse onto NE neurons in LC (79), creating a feed-forward loop that is activated during stress and alcohol withdrawal (80, 81). These CeA neurons also express glucocorticoid receptors, suggesting regulation by neuroendocrine feedback from the HPA axis (82).

Dorsal Vagal Complex (DVC)—The DVC is composed of the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus (DMV), and is important for autonomic regulation. The CeA_M sends GABAergic projections to NTS and DMV (83, 84) that mediate autonomic (i.e., parasympathetic) responses to aversive stimuli (85) and contribute to chronic stress-induced hypertension (86).

THE CeA IN ANXIETY AND ALCOHOL EFFECTS

CeA Neurotransmission in Regulation of Anxiety Responses

Amygdala activation mediates emotional responses to fearful or anxiety-provoking stimuli in healthy humans (87), and this response is specific to stimuli with a negative valence, even when the valence is not consciously registered (88). Humans with an anxiety disorder (e.g., PTSD) often exhibit hyperactive amygdala responses to these types of stimuli (89). Similarly, chronically stressed rats exhibit hyperexcitability of the LA (90) and CeA lesion blocks chronic stress-induced increases in anxiety-like behavior (91).

Within the amygdala, optical stimulation and inhibition of BLA-to-CeA projection neurons bi-directionally modulates anxiety-like behavior in rodents (53). This may explain the strong correlation between BLA and CeA activation, as measured by ERK phosphorylation, observed in previously stressed animals exposed to a stress reminder (92). Human and animal studies also suggest that individuals that exhibit high reactivity (i.e., poor coping) to traumatic stress exhibit heightened functional connectivity between PFC and amygdala nuclei (89, 92).

CeA Neurotransmission in Fear Conditioning

Rodent fear conditioning experiments have significantly contributed to our understanding of the circuitry mediating anxiety disorders. Plasticity in the LA has a central role in fear conditioning (37), but the CeA also has roles in acquisition, expression, generalization, consolidation, and extinction of conditioned fear (93–97). CeA_L plasticity contributes to acquisition of conditioned fear, and CeA_M output neurons are excited by fear stimuli in a manner that decays with extinction and that is sensitive to the activity of somatostatin-positive CeA_L neurons (97–99).

Fear extinction relies heavily on descending projections from infralimbic cortex (ILC) to amygdala. Intercalated GABA cells are critical for mediating fear extinction via projections to CeA (100, 101). For example, CeA_M neurons of fear-extinguished animals exhibit greater synaptic inhibition by ITC cells, likely due to increased excitatory drive from BLA onto ITC cells, an effect that is contingent on ILC activity during extinction (102). The net result of fear extinction is reduced inhibitory output from CeA_M to brainstem effector regions, an effect due to either more inhibitory ITC input onto CeA_M neurons, less inhibitory ITC input onto CeA_L GABA neurons that project to CeA_M, or both (40, 103).

CeA Neurotransmission in Acute Alcohol Effects

Relative to the fear and anxiety literature, less is known about the molecular identity and projection pattern of specific CeA circuits mediating alcohol effects. Acute alcohol increases GABAergic transmission in the BLA via increased pre-synaptic GABA release (104, 105), which has implications for downstream CeA neurons via dense excitatory projections to CeA (45). An emerging story has been the potentially overlapping role of cortico-amygdalar projections in conditioning/extinction processes related to cues and contexts associated with both fear and alcohol/drugs. Specifically, prelimbic projections to NAc core and BLA facilitate expression of cocaine-seeking behavior and fear, respectively, whereas infralimbic projections to NAc shell and CeA (via ITC) facilitate extinction of cocaine-seeking behavior and fear, respectively (106). Recent data suggest that prelimbic and infralimbic cortices regulate extinction and reinstatement of alcohol-seeking behavior (107), and it is possible that these effects are mediated by projections to amygdala.

CeA neurons display two types of inhibition: phasic, which involves inhibitory postsynaptic currents (IPSCs) that reflect ‘point to point’ transmission; and tonic, which involves persistent inhibitory currents resulting from ambient GABA acting at highly-sensitized $GABA_A$ receptors (108, 109). Tonic inhibition regulates neural network activity (110), and is modulated by both acute and chronic alcohol (111, 112). Acute alcohol dose-dependently

and reversibly increases phasic GABA release in the CeA (113, 114), independent of $GABA_BR$ blockade (113). Acute alcohol also increases phasic and tonic inhibition in a population of CeA neurons that synapse onto CeA_M output neurons, resulting in disinhibition of CeA output to BNST (115).

CeA Neuroadaptations in Response to Chronic Alcohol

Offspring of alcohol-dependent humans exhibit reduced amygdala volume and reduced amygdala fMRI activation in response to fearful faces (116, 117). Furthermore, moderate-to-heavy drinking humans exhibit reduced amygdala activation during impulse control tasks (118). Alcohol-dependent humans that have endured more detoxifications and exhibit more loss-of-control over drinking also exhibit increased PFC-amygdala connectivity during attentional and executive function tasks (119).

Much of what is known about alcohol-induced neuroadaptations in CeA comes from studies on animals chronically exposed to intermittent bouts of alcohol with repeated withdrawal periods. This protocol accelerates the emergence of somatic, affective and motivational indices of alcohol dependence (120, 121). Relative to stress models, these dependence models may be most appropriately compared to findings from chronic stress studies. Indeed, alcohol dependence has been conceptualized in terms of a stress kindling process, in which CeA neuroadaptations play a central role (122).

Many studies on chronic alcohol effects on CeA neurotransmission utilize a chronic intermittent ethanol (CIE) vapor inhalation model in rodents (123). CIE augments spontaneous and evoked CeA GABA release via pre- and post-synaptic mechanisms (104, 114, 124). Alcohol-dependent rats exhibit increased GABA release in CeA during withdrawal, but do not exhibit tolerance to acute alcohol effects on CeA GABAergic transmission (114). Reductions in basal pre-synaptic $GABA_BR$ activity during withdrawal may account for increased baseline CeA GABAergic transmission in alcohol-dependent rats (125). Gabapentin, a structural analog of GABA, facilitates evoked GABAergic transmission in alcohol-naïve rats, an effect that is blocked by a $GABA_BR$ antagonist. Conversely, gabapentin decreases evoked CeA GABA transmission during alcohol withdrawal, suggesting that alcohol dependence-induced $GABA_BR$ neuroadaptations may account for the differential behavioral effects of gabapentin in dependent versus non-dependent animals (125).

CeA STRESS PEPTIDES IN ANXIETY AND ALCOHOL DEPENDENCE

Role of CeA Pro- and Anti-Stress Peptides in Anxiety

Humans with anxiety disorders exhibit altered levels of pro- and anti-stress peptides in the CNS and periphery. Here, we discuss a few examples in the context of human PTSD, an anxiety disorder that can manifest following an acute traumatic stress event and that is highly comorbid with AUD (126). Positive coping and stress resilience in PTSD veterans are each predicted by higher plasma levels of the anxiolytic NPY (127). PTSD is also associated with polymorphisms and methylation levels for the genes encoding the anxiogenic pituitary adenylatecyclase-activating polypeptide (PACAP) and its receptor PAC1, and PAC1 mRNA is upregulated in the amygdala of fear-conditioned mice (128).

As illustrated in Figure 2, CRF and NPY co-localize in the CeA, where CRF promotes anxiety-like behavior (131) an NPY reduces anxiety-like behavior (132). The acoustic startle reactivity (ASR) test can be used to assess control by specific EA regions (CeA, BNST) over generalized anxiety-like or stimulus-specific fear behaviors. NPY dampens basal ASR and fear-potentiated startle in rats, and facilitates extinction of fear-potentiated startle, effects likely mediated by the CeA (133). CRF increases ASR (134) and mediates stress-induced enhancement of ASR via CRF1s in BNST (135). Acute restraint or footshock stress increases CRF mRNA in rat CeA (136, 137), and CeA CRF is critical for consolidation of fear memories (138). Intra-amygdala injection of a CRF agonist produces an aversive state resembling that elicited by an environmental stressor, and both effects are blocked by intra-amygdala injection of NPY (139). Following exposure to predator stress, rats with maximally dysregulated behavior (e.g., hyperarousal and high anxiety-like behavior) exhibit reduced NPY in the amygdala (140), and treatment with either NPY or a CRF1 antagonist reduces behavioral dysregulation in rodents following exposure to predator stress (140,141).

CeA Pro- and Anti-Stress Peptides in Alcohol Dependence

Alcohol withdrawal is defined by a negative emotional state mediated in part by the recruitment of pro- and anti-stress peptides in the EA (30). CRF and NPY in CeA play critical roles in mediating negative affect and excessive alcohol drinking in dependent rodents (Figure 2). CRF and NPY are both likely produced locally in the CeA (142, 143) and/or imported to CeA from distal projection neurons, but it is not yet clear which peptide pools are dysregulated by alcohol dependence (or stress) to produce heightened anxiety-like behavior and escalated alcohol drinking.

CRF increases GABA release in the CeA of rats (124) and mice (144) via activation of pre-synaptic CRF1s. These effects are exaggerated during withdrawal (124), along with concomitant increases in CRF and CRF1 mRNA levels, and increases in CRF release in the CeA of alcohol-dependent rats (124, 145). CRF1 antagonism reverses withdrawal-induced increases in drinking in alcohol-dependent rats and mice (146, 147) via effects in CeA (148), and chronic CRF1 antagonism prevents escalation of alcohol drinking during the transition to dependence (124). Binge-like drinking increases CRF immunoreactivity in the CeA of mice (149), and CRF1 antagonists reduce binge-like drinking without affecting non-binge-like alcohol intake (150–152). Interestingly, the ability of CRF to increase CeA GABAergic transmission is blunted in binge-like drinking mice (149), in contrast to the sensitized CRF effects observed in CeA of alcohol-dependent rats (124). Binge-like alcohol drinking may abolish CRF effects on GABAergic transmission in CeA via internalization of CRF1s in response to elevated CRF levels in binge alcohol drinkers (149), as seen in the dorsal raphe following stress (153).

The complex alcohol effects on local CeA microcircuitry are illustrated in the differential ethanol sensitivity of CRF1+ CeA neurons possessing an ethanol-insensitive ongoing tonic conductance and CRF1- CeA neurons possessing a tonic conductance that is enhanced by acute alcohol (115). Accordingly, acute alcohol decreases firing of CRF1-neurons, but increases firing of CRF1+ neurons, suggesting a local CeA_M inhibitory microcircuit whose constituent neurons are differentially regulated by alcohol, similar to the CeA_L inhibitory

microcircuit described in the behavioral expression of conditioned fear (154). Future optogenetic studies will dissect the role of CeA microcircuitry in the behavioral consequences of alcohol dependence and as a locus for integration of anxiety and alcohol abuse.

NPY decreases GABAergic transmission in CeA, and also prevents and reverses acute alcohol-induced facilitation of evoked GABAergic transmission in the CeA of naïve and alcohol-dependent rats (155). Pharmacological experiments suggest that NPY exerts Y1 receptor (Y1R)-mediated post-synaptic effects on basal inhibitory transmission in CeA, whereas NPY blocks alcohol effects on GABA release in CeA via Y2 receptor (Y2R)-mediated pre-synaptic effects (155). Alcohol dependence produces neuroadaptations in CeA NPY systems, as evidenced by lower NPY levels in CeA of alcohol-dependent rats during withdrawal (156), and higher Y_1R levels in CeA of chronic alcohol-drinking mice 48 hours into abstinence (157). NPY reduces GABAergic transmission in the CeA of binge-like alcohol drinking mice, but not in alcohol-naïve mice (158). Chronic ventricular infusion of NPY during withdrawals early in the transition to dependence prevents excessive alcohol drinking during subsequent withdrawals (155), and NPY infused into the CeA reduces excessive drinking by alcohol-dependent rats (159), suggesting that NPY may blunt excessive drinking by alcohol-dependent rats via modulation of CeA GABAergic neurotransmission.

In summary, CRF and NPY in CeA are recruited during stress and alcohol dependence, and exert opposite but convergent effects on anxiety-like behavior and escalated alcohol drinking, likely via modulation of CeA GABAergic transmission. CRF1s mediate withdrawal-induced increases in anxiety-like behavior (160), alcohol drinking (147), and sensitization of anxiety-like behavior over repeated withdrawals (161). In contrast, intra-CeA NPY reduces withdrawal-induced increases in anxiety-like behavior (155, 159). Y2R antagonism attenuates withdrawal-induced increases in anxiety-like behavior but not escalated alcohol drinking in dependent rats, suggesting that anxiolytic effects occur via Y2R autoreceptor modulation of NPY release, whereas effects on alcohol drinking occur via Y2R heteroceptor modulation of GABA release (162). Although NPY antagonizes the behavioral effects of CRF in the amygdala, the cellular interactions of NPY and CRF in the CeA remain uncharacterized.

CeA Pro- and Anti-Stress Peptides in Stress-Alcohol Interactions

Although humans report drinking alcohol to reduce anxiety (163), animal research has produced a complicated picture of stress effects on alcohol drinking. Studies report stress-induced increases, decreases, and null effects on alcohol drinking according to type/modality of stressor, intensity/frequency of stressor, time between stress and alcohol access, species and strain of animal tested, and other factors (164). One common procedure utilizes stress to reinstate previously-extinguished alcohol-seeking behavior in a session where operant responses do not produce alcohol deliveries. Until recently, there has been a lack of studies explicitly investigating the interaction between a PTSD-like state (which takes into account individual differences in stress reactivity) and alcohol self-administration (165). Recently, the stress-enhanced fear-learning (SEFL) model of PTSD was used to show that a single

traumatic stress increases acquisition and maintenance of voluntary alcohol consumption in previously alcohol-naïve rats but does not alter drinking by rats previously trained to drink (166). Another study found that rats with high reactivity to predator odor stress exhibit escalated and compulsive-like alcohol drinking (167).

Evidence for the role of CeA stress peptides in stress-alcohol interactions comes from human genetics data showing that variation at the CRF1 locus contributes to increased stress sensitivity and may be associated with alcohol dependence susceptibility (167, 168). Alcohol-preferring rats exhibit increased stress sensitivity, increased extra-hypothalamic CRF1 signaling (169, 170), and increased basal spontaneous GABA release in CeA (171). Voluntary alcohol drinking by alcohol-preferring rats further increases GABA release and reduces sensitivity of the GABAergic system to CRF1 antagonism (171). Interestingly, stress-induced reinstatement of alcohol-seeking behavior is blocked by CRF receptor blockade and by NPY, but not by opioid receptor antagonists (172,173).

The CeA modulates autonomic and neuroendocrine responses to stress via reciprocal projections with LC and PVN (81, 174), suggesting that hypothalamic and extra-hypothalamic stress responses are coordinated (175). Alcohol-dependent humans exhibit a blunted HPA stress response (176, 177), and both alcohol-dependent rats and non-dependent drinkers exhibit blunted HPA response to an acute bolus alcohol injection (178). Unlike the PVN, abstinence in alcohol-dependent rats up-regulates GRs in CeA, thereby “sensitizing” extra-hypothalamic stress systems, which may provide new drug targets depending on the timing of therapeutic intervention (179). The critical determinant of whether glucocorticoids exert negative or positive feedback over specific brain regions remains unclear, but one possibility is that different splice variants of steroid coactivator (SRC)-1 work at GRs to negatively regulate gene expression in PVN, while increasing CRF gene expression in CeA (180,181).

CeA INTRACELLULAR SIGNALING PATHWAYS IN ANXIETY AND ALCOHOL DEPENDENCE

An emerging story is the role of stress peptide interactions with specific protein kinase C (PKC) isoforms in anxiety- and alcohol-related behaviors. Endogenous PKC epsilon (PKC) promotes anxiety-like behavior and expression of CRF mRNA and peptide in amygdala (182), and endogenous amygdalar PKC promotes alcohol consumption in mice (183). The PKC signaling pathway in CeA is activated by CRF1s, and the ability of acute alcohol to augment GABAergic transmission in CeA is contingent on the integrity of PKCε signaling pathways and the contribution of those pathways to vesicular GABA release (184, 185). Protein kinase A (PKA), which is activated by CRF1 (via G_s and G_q proteins), also plays an important role in facilitating CeA GABA release by acute alcohol (186), and PKA antagonists block CRF-induced increases in pre-synaptic CeA GABA release (186). CeA_L neurons positive for PKC-δ appear to gate the output of CeA_M neurons onto downstream effector regions (154), and NPY has been linked to PKC-δ signaling in brain (187). Future studies should examine potential crosstalk between PKA, PKCε and PKCδ pathways in regulating alcohol and peptide effects in CeA, especially as these pathways have been implicated in binge-like drinking and alcohol dependence (188, 189).

CONCLUSIONS

Anxiety disorders and AUDs are highly co-morbid in humans. A pre-existing anxiety disorder can precipitate alcohol abuse, and high anxiety is a hallmark symptom of alcohol dependence that manifests during withdrawal. Anxiety disorders and AUD in humans are both defined by altered amygdala structure and function, the end result of which may be disinhibition of downstream “effector” regions that regulate anxiety- and alcohol-related behaviors. Because the CeA is ascribed an important role in the aversive states and behavioral dysregulation associated with stress and alcohol dependence, it is critical to understand the overlapping and/or compounding effects of anxiety disorders and AUD on amygdala function. New research techniques combine traditional cellular, pharmacological, and anatomical approaches with sophisticated new genetic technologies, and will facilitate our understanding of how the amygdala is recruited in anxiety disorders and/or AUD, and in the tailoring of future treatment strategies.

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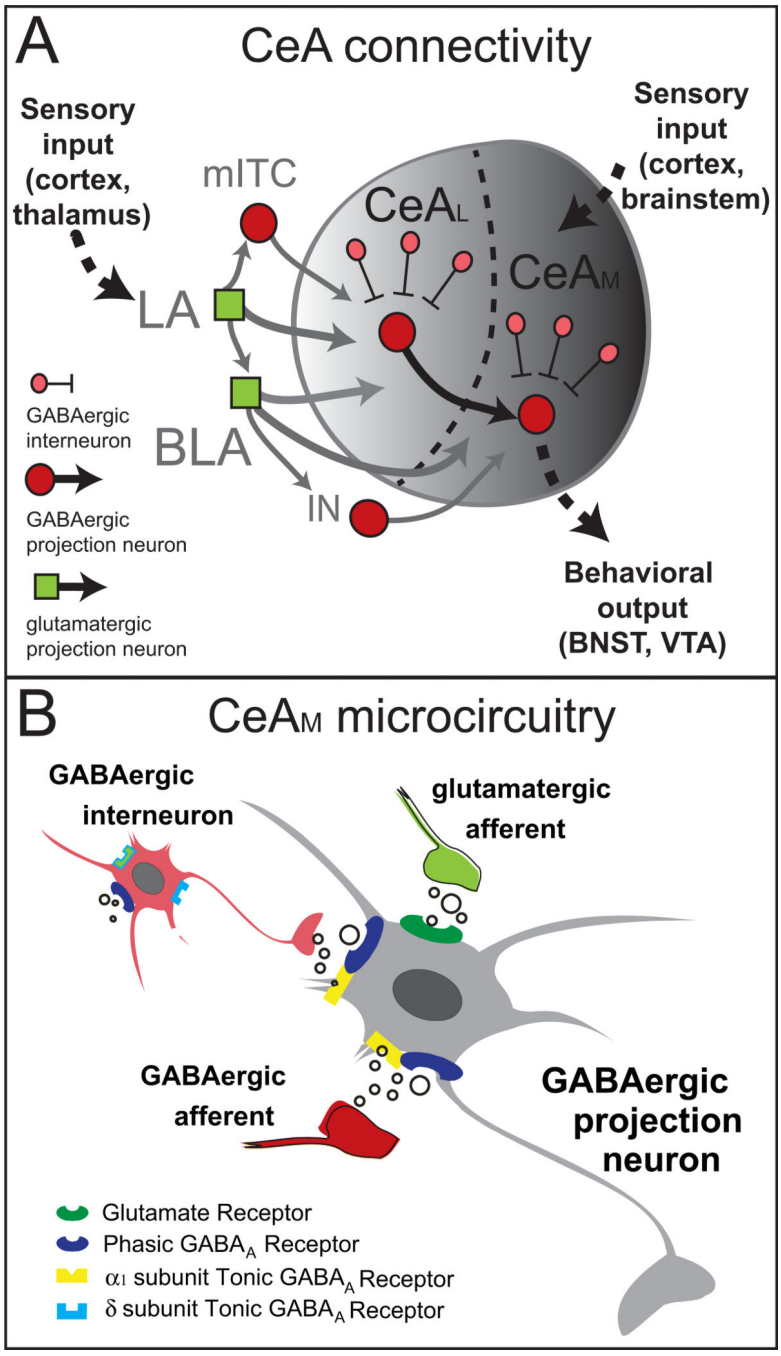

Figure 1.

(A) Schematic of amygdala circuitry showing inter- and intranuclear connectivity. Abbreviations: BLA- basolateral amygdala; CeA_M- medial central amygdala, CeA_L- lateral central amygdala; IN- main intercalated cell cluster; LA-lateral amygdala; mITC intercalated cell cluster. **B.** Microcircuitry of the CeA_M illustrating excitatory transmission by glutamatergic afferents (green) and phasic and tonic inhibitory transmission by GABAergic afferents (dark red) and local interneurons (light red).

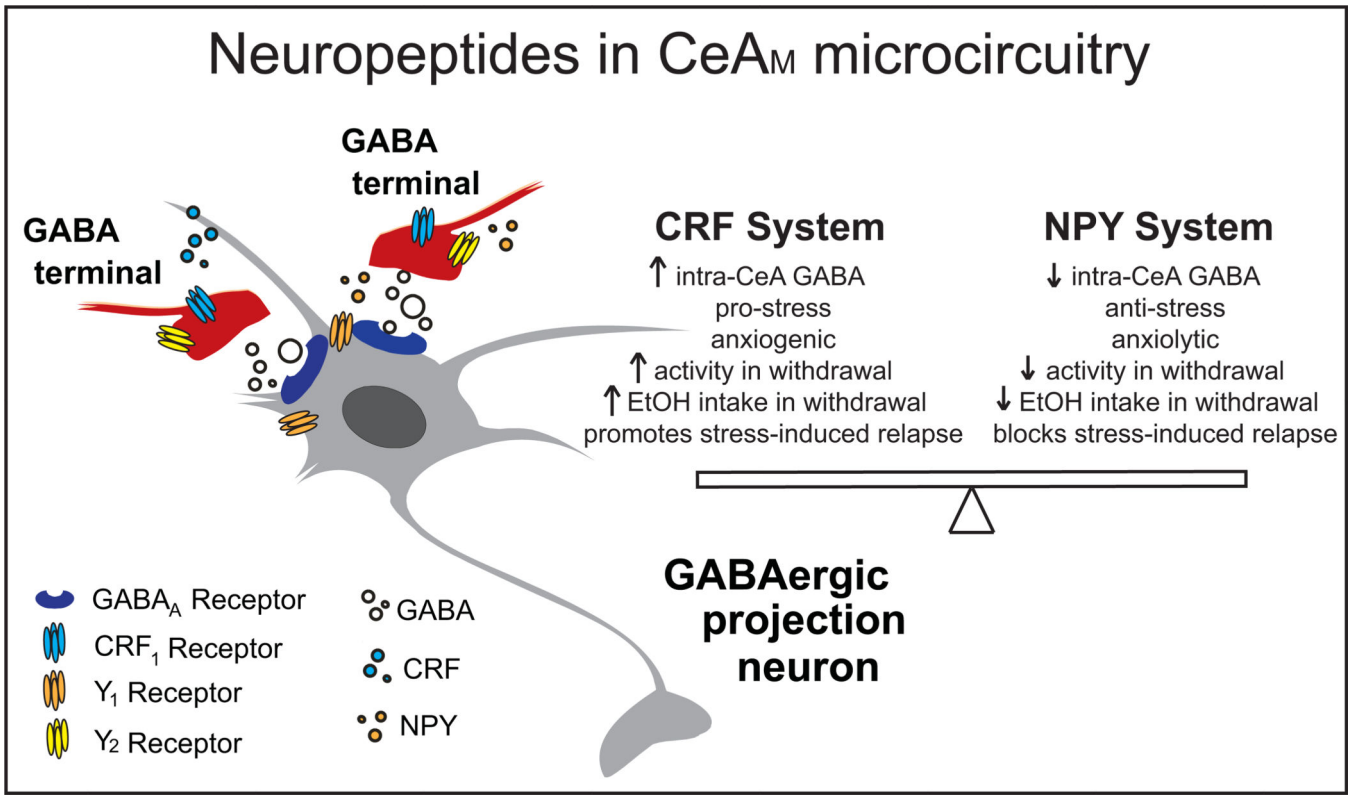

Figure 2.

Schematic illustrating location of neuropeptides and their receptors in the medial CeA synapse, and their proposed roles in stress, anxiety, and alcohol effects. Here and in the text, we focus on pro-stress pro-alcohol-drinking CRF and anti-stress anti-alcohol-drinking NPY systems, intended to provide a snapshot of what may be (or is) occurring with other stress peptides in CeA in response to stress and alcohol. Abbreviations: CeA_M- medial central amygdala, CRF1- corticotropin-releasing factor receptor 1, NPY- neuropeptide Y, Y_1 NPY Y_1 receptor, Y_2 - NPY Y_2 receptor.