Cocaine- and Amphetamine-Regulated Transcript (CART) Peptide Plays Critical Role in Psychostimulant-Induced Depression

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Abstract
Cocaine- and amphetamine-regulated transcript (CART) peptide is a widely distributed neurotransmitter expressed in the central nervous systems. Previously, several reports demonstrated that nucleus accumbal-injected CART peptide positively modulated behavioral sensitization induced by psychostimulants and regulated the mesocorticolimbic dopaminergic pathway. It is confirmed that CART peptide exerted inhibitory effect on psychostimulant-enhanced dopamine receptors signaling, Ca2+/calmodulin-dependent kinase signaling and crucial transcription factors expression. Besides modulation of dopamine receptors-related pathways, CART peptide also exhibited elaborated interactions with other neurotransmitter receptors, such as glutamate receptors and γ-aminobutyric acid receptors, which further account for attribution of CART peptide to inhibition of psychostimulant-potentiated locomotor activity. Recently, CART peptide has been shown to have anxiolytic functions on the aversive mood and uncontrolled drug-seeking behaviors following drug withdrawal. Moreover, microinjection of CART peptide has been shown to have an antidepressant effect, which suggests its potential utility in the mood regulation and avoidance of depression-like behaviors. In this review, we discuss CART pathways in neural circuits and their interactions with neurotransmitters associated with psychostimulant-induced depression.

Key Words: CART peptide, Addiction, Psychostimulant, Depression

INTRODUCTION
Fragment of cocaine- and amphetamine-regulated transcript (CART) peptide was first discovered by Spiess et al. (1981) in the extraction of hypothalamus in 1981. Douglass et al. identified increased CART mRNA expression within the striatum of psychostimulant-exposed rats (Douglass et al., 1995; Douglass and Daoud, 1996), suggesting the role of CART peptide on the drug abuse. The complete sequences of CART gene were available and showed highly conservation across species (Kuhar et al., 2000; Dallvechia-Adams et al., 2002). The CART gene is composed of 3 exons and 2 introns with alternatively splicing in rat and mouse (Kuhar et al., 2000). And the mouse CART promoter contains series of transcription factor binding site, such as E-box, SP1, overlapped STAT/ cyclic adenosine 5’-monophosphate (cAMP) response element (CRE)/AP1, SP2 sites (Kuhar et al., 2000), in which transcription factors including cAMP response element binding protein (CREB), cJUN, SP1 and AP2 may regulate expression of CART gene expression (Fig. 1). Surprisingly, expression of CART peptide dominates in the mesocorticolimbic dopaminergic (DA) system that extends from the ventral tegmental area (VTA) to the nucleus accumbens (NAC) and includes other limbic areas (amygdala, hippocampus, and frontal cortex), and is also widely distributed in the central nervous system (CNS) (Kuhar and Yoho, 1999; Kuhar et al., 2000). Compelling evidences also shows that repeated administration of psychoactive drugs enhances expression of CART peptide (Jaworski et al., 2003a; Hubert et al., 2008), which is supported by a study in which microinjections of CART peptide into NAc that
effectively attenuated the rewarding properties of psychostimulants (Jaworski et al., 2003b; Yoon et al., 2007; Peng et al., 2014; Fu et al., 2016). These observations suggested CART peptide plays a positive role in the regulation of behavioral sensitization induced by psychostimulants and led to thorough investigations of the modes of action of CART peptide with the object of identifying its potential use for the treatment of drug addiction. For example, microinjection of CART peptide into rat NAc significantly blocked psychostimulant-induced up-regulation of dopamine receptor (DR) and activation of downstream cAMP/protein kinase A (PKA)/cAMP response element binding protein (CREB) pathway (Peng et al., 2014; Fu et al., 2016; Xiong et al., 2018). Psychostimulant-induced Ca\(^{2+}\) influx and phosphorylated calcium/calmodulin-dependent protein kinase II (pCaMKII\(\alpha\)) expression have also been attenuated by CART peptide. In addition, interactions between pCaMKII\(\alpha\) and D3R blocked the inhibitory effect of D3R on the cAMP/PKA/CREB pathway and behavioral sensitization (Xiong et al., 2018). Recently, CART peptide has been suggested to positively and allosterically modulate \(\gamma\)-aminobutyric acid B receptors (GABA\(\beta\) R), based on the observation that it inhibited drug-depressed GABA\(\beta\) R-G-protein-coupled inwardly rectifying K\(^{-}\)-channel (GIRK) signaling. Thus, it has been suggested CART peptide modulates psychostimulant-induced hyperlocomotion through DR-related calcium signaling and GABA-R-associated pathways (Moffett et al., 2011; Upadhyya et al., 2012; Cai et al., 2014; Hu et al., 2015; Fu et al., 2016; Xiong et al., 2018). However, our understanding of CART pathways in neuronal circuits is lacking.

On the other hand, repeated psychostimulant intake may increase the risk of persistent drug-relapse accompanied by irritability, anxiety, and dysphoria (Koob and Le Moal, 1997; Koob et al., 1998). Furthermore, these addiction-related anxious and aversive emotions can lead to depression-like behaviors that may ultimately facilitate suicidal actions possibly mediated by GABAergic pathways (Stanek, 2006; Wiehager et al., 2009; Yoon et al., 2014). Interestingly, CART peptide has been closely linked with corticotropin-releasing factor (CRF) in the hypothalamic-pituitary-adrenal (HPA) axis and amygdala, the latter of which provides the interface between stress and addiction (Koob, 2008a). We hope this review of the role of CART in psychostimulants-induced anxiety-like behaviors will provide new avenues for the development of effective drugs for addiction and/or depression disorders based on understanding of CART pathways in neuronal circuits.

**RELATIONS BETWEEN CART CONTAINING NEURAL CIRCUITS AND DEPRESSION**

Drug addiction is considered as a psychiatric disorder that progresses from impulsivity to compulsivity, during which people undergo transformation from sense of pleasure or gratification in a positive reinforcement toward relief of anxiety or stress in negative reinforcement (Koob et al., 2004; Koob, 2008a, 2008b). On the other hand, drug cessation triggers protracted anxiety and depression-like symptoms due to counter-adaptive processes that include diminished functions of neurotransmitters in the neuro-circuits associated with acute drug reinforcing effects, such as, the dopamine signaling pathway. Chronic drug exposure results in within-system neuro-adaptations including decreased function of the same neurotransmitter in the same neuro-circuits involved in the acute reinforcing effect of the drug, such as the dopamine signaling pathway (Koob et al., 2004; Koob, 2008a, 2008b). According to the self-medication hypothesis, drug-addicted individuals suffer from...
deficits in self-esteem and emotion regulation, and cope with aversive and painful emotions by binging (Koob et al., 2004; Koob, 2008a, 2008b). This dysregulation may be a manifestation of altered information-processing, decision-making and behavioral motivation, all of which are associated with functional deficits in brain-stress and anti-stress systems (Koob et al., 2004; Koob, 2008a, 2008b). We later discuss the molecular mechanisms underlying disrupted mood regulation following psychostimulant abstinence and the effects of CART peptide on depressive-like emotions induced by drug withdrawal.

The Hypothalamic-Pituitary-Adrenal (HPA) axis

Pathophysiologic studies showed that quantities of CART immune-reactivity were synthesized and secreted from the anterior pituitary gland (Stanley et al., 2004) and hypothalamus (Smith et al., 2004). Stress regulates CART expression via CRF and glucocorticoids (Stanley et al., 2004). Conversely, the administration of CART peptide up-regulates circulating levels of ACTH and corticosterone in the HPA axis through the CRF-dependent mechanism (Vrang et al., 2000; Smith et al. 2004). Furthermore, multiple line of evidence shows that CART peptide plays a key role in the HPA-axis associated stress response (Vrang et al., 2000; Smith et al., 2004; Stanley et al., 2004; Job et al., 2011).

The HPA axis is composed of three major structures: the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland (Turnbull and Rivier, 1997; Zuloaga et al., 2015). CRF is synthesized and released by the medial parvocellular subdivision of the paraventricular nucleus to the portal blood vessels and then binds to the CRF 1 receptor on the pituitary corticotrophin to induce adrenocorticotrophic hormone (ACTH) release into the systemic circulation, which in turn stimulates cortical secretion of glucocorticoid from the adrenal gland (Herman et al., 2005). And the HPA axis is finely tuned by negative feedback from glucocorticoid, which activates glucocorticoid receptor within the paraventricular nucleus and the hippocampus (Turnbull and Rivier, 1997). Acute psychostimulants exposure behaves like stressors that can elicit the activation of HPA axis (Char- toff and Carlezon, 2014), and thus, induce the release of the above-mentioned molecules, which then exert immediate or delayed effects on the mesocorticolimbic system. However, acute withdrawal from chronic psychostimulants induces allosteric load in HPA axis, elevates secretion of CRF and ACTH, and decreases cortisol levels, which are hallmarks of depressive and anxiety spectrum disorders in man (Li et al., 2013a; Zuloaga et al., 2015). However, in depressed patients, regulation of HPA axis is disrupted, which leads to low level of cortisol concentration in serum via stress reactivity (Peng et al., 2015). Surprisingly, hypercortisolism is present in about 40%-60% of depressed adults (Carroll et al., 2007), which may explain the cause of disrupted hippocampal integrity and impaired memory function in the pathogenesis of depression. Several groups have reported intracerebroventricular or intraperiaamygdalar injection of CRF1 receptor antagonists could effectively attenuate the aversive states and anxiogenic effects induced by drug abstinence, and thus, inhibit drug self-administration (George et al., 2007; Specio et al., 2008; Greenwell et al., 2009).

Serotonin (5-HT) neurotransmitter systems

5-HT is a widely distributed neurotransmitter in the CNS, and has been linked with arousal, anxiety, aversive affect and depressive disorders (Graeff et al., 1996; Pompili et al., 2010). The 5-HT pathway originates from the dorsal raphe nucleus (DRN) and it extends to the amygdala and frontal cortex to facilitate conditioned fear (Graeff et al., 1996). 5-HT synthesis is catalyzed by tyrosine hydroxylase and tryptophan hydroxylase, and synthesized 5-HT is stored in the presynaptic vesicles, where monoamine oxidase (MAO) metabolites can inhibit its release. 5-HT binds to guanine nucleotide triphosphate-binding protein–coupled receptors (GPCR) to activate (AC)/cAMP/PKA and PI/PLC/DAG/PKC signaling pathways, and ultimately promotes the expression of the CREB and induces profound antidepressant effects (Ruhe et al., 2007). Therefore, any abnormality that exists within the mechanisms of 5-HT secretion, receptor transportation and signal transduction may result in anxiogenic and depressive-like disorders. In particular, withdrawal from cocaine self-administration has been associated with a decrease in extracellular 5-HT in the NAc sub-regions (Parsons et al., 1996), whereas acute withdrawal from ethanol has been shown to increase in the sensitivity of 5-HT1A autoreceptor to modulate 5-HT synthesis (Esteban et al., 2002). Moreover, 5-HT2C receptor antagonist blocked the inhibitory dorsal raphe 5-HT2C receptor, and this potentially attenuated cocaine withdrawal exacerbated GABA activity, thereby prevented anxiety-like behaviors (Craige et al., 2015).

The serotonergic system interacts with CART system originating from the lateral hypothalamus to innervate other brain areas associated with stress (Ruhe et al., 2007). Light microscopic studies from Lee and Lee (2014) found reciprocal connections between CART-immunoreactive, hypothalamic paraventricular nucleus and the serotonergic dorsal raphe neurons. Ma et al. (2007) performed a microdialysis approach, which can increase 5-HT efflux made by infusions of CART peptide into the dorsal raphe nucleus and NAc. In addition, activation of 5-HT receptors by 5-HT might enhance dopaminergic signaling and further enhance anti-depressant effects. Interestingly, some studies also investigated that activation of 5-HT1A receptor upregulated CART mRNA expression in the NAc via cAMP/PKA signaling pathway (Jean et al., 2007; Jean et al., 2012) These observations support the protective role of CART peptide on the depression-deprived serotonin system during drug addiction (Ma et al., 2007).

GABAergic systems

Immunoblotting results show CART peptide co-localizes with GABA in the nerve terminals in the VTA and substantia nigra (SN) (Dallvechia-Adams et al., 2002), suggesting the intricate relationship between CART peptide and GABA. GABA_B R is a ligand-gated ion channel mediating fast inhibitory synaptic transmission, especially in the dopaminergic brain areas such as VTA and substantia nigra compacta (Jiao et al., 2015). On the other hand, GABA_A R is a G-protein-coupled receptor composed of 2 subunits, GABA_A R1 and GABA_A R2, which are responsible for agonist or antagonist binding and G-protein activation, respectively (Kulik et al., 2003; Pin and Bettler, 2016). In addition, presynaptic GABA_A R inhibits Ca2+ influx whereas postsynaptic GABA_A R activates GIRK, which may cause neuron hyperpolarization leading to slow inhibitory post-synaptic current (IPSC) and a reduced synaptic activity (Padgett et al., 2012). It has been reported that withdrawal from chronic morphine exposure increases GABA release in the VTA, resulted in
a short-lived (1-3 days) GABA<sub>A</sub>-mediated inhibition, and up-regulation of cAMP-dependent proteins (Bonci and Williams, 1996; Bonci and Williams, 1997), all of which drive conditioned place aversion (Tan et al., 2012) and diminished GABA<sub>B</sub>-mediated inhibition (Bonci and Williams, 1996). Chronic methamphetamine and cocaine exposure can depress both GABA<sub>A</sub>R and GABA<sub>B</sub>R expression, and weaken GABA<sub>B</sub>R-GIRK signaling in VTA GABA neurons including glutamatergic neurons within the medial prefrontal cortex (mPFC) (Filip et al., 2015; Jiao et al., 2015). Previous studies indicated that injection of GABA<sub>B</sub>R agonist baclofen or GABAB<sub>R</sub> positive allosteric modulators can attenuate self-administration and drug craving in ethanol-dependent rats and human alcoholics (Addolorato et al., 2006; Knapp et al., 2007). Recently, we have shown the modulatory effect of intra-accumbally injected CART peptide on methamphetamine-induced depression of GABA<sub>B</sub>R-GIRK signaling and concomitant internalization and reduction of membrane GABA<sub>B</sub>R R and GIRK receptors in the VTA and mPFC neurons (Hu et al., 2015), which suggests the regulatory targets of CART peptide are similar to those of the positive allosteric modulator GABA<sub>B</sub>R R on GABA<sub>B</sub>R R in the context of rescue from drug-depressed GABA<sub>B</sub>R-GIRK signaling (Fig. 2).

Glutamatergic pathway

The excitatory neurotransmitter glutamate is essential for the excitation propagation and neuronal transmission (Javitt et al., 2011). There are two main classes of glutamate receptors, that is, metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs) (Javitt et al., 2011). mGluRs, are classified into group I, II and III subfamilies, and are seven transmembrane G-protein-coupled receptors (GPCRs) associated with protein kinase B (PKB), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), CaM signaling cascades, or coupled Ca<sup>2+</sup>, K<sup>+</sup> and Na<sup>+</sup> channels (Javitt et al., 2011). Conversely, iGluRs are composed of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors and share a voltage-gated ion channel function to enable cation influx (Javitt et al., 2011).

The lateral habenula (LHb) has recently attracted attention due to its modulatory role on depressive behaviors and drug abuse (Lecca et al., 2014). Anatomical studies indicated that LHb, which is positioned near the midline and surrounded by the thalamus, receives prominent glutamatergic afferents from the lateral hypothalamus, and cortical inputs, for example, from the high AMPA-R but low synaptic NMDA-R expressing neurons in medial prefrontal cortex (Lecca et al., 2014). Investigators have reported that aberrant LHb activity overactivates jCaMKII and contributes to aversive and depressive disorders (Li et al., 2013b), whereas the co-release of GABA and glutamate controls LHb activity and can be used to treat depression (Shabel et al., 2014). Cui et al. (2018) found the upregulation of astroglial Kir4.1 in the LHb depressed neuronal bursts in a rat model of depression, and Yang et al. (2018) found LHb burst required both NMDARs and low-voltage-sensitive T-type calcium channels (T-VSCCs) and that blockade of NMDAR or T-VSCCs by ketamine (a NMDAR antagonist) in the LHb induced a rapid antidepressant effect.

Previous reports on CART peptide showed similar pathways to those associated with glutamate receptors. Intra-ac-
cumulably injected CART peptide decreased the expression of α-CaMKII (Fu et al., 2016; Xiong et al., 2018), which after Ca\(^{2+}\) channel activation couples with NMDAR to enhance neuronal excitability (Liu and Murray, 2012). As discussed above, our recent experiments showed CART peptide has a significant positive effect on GIRK signaling pathways, whereby GIRK channels exert modulatory effects on depressive-like behaviors (Hu et al., unpublished data). In addition, NMDA receptors also activate GIRK channels. Taken together, it is apparent more efforts are required to identify the role of CART peptide on the depression-related LHb area and to determine whether the glutamatergic system is a key target for the inhibitory effect of CART peptide on rewarding properties and anxiety-like behaviors.

**CART Peptide and Depression Therapy**

Interest in the pathophysiological mechanisms of depression and treatment strategies is increasing, and in view of the many addiction and depression patterns exhibited, the anxiolytic effects of CART peptide might be useful in this context. Currently, the treatment of depression involves the prolonged use of high doses of antidepressants, such as, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs), or electroconvulsive therapy (ECT) (Kupfer et al., 2012). Furthermore, evidence indicates the effects of these drugs might be augmented by CART peptide (Job et al., 2011; Mao, 2011). It has been reported CART peptide levels are low in the cerebrospinal fluid of major depression disease patients, which suggests a close relationship between CART peptide and depression (Yoon et al., 2018), which is supported by marked reductions of CART-immunoreactive fibers in the paraventricular thalamic nucleus and locus coeruleus of socially isolated rats (Dandekar et al., 2009; Choudhary et al., 2018). Recently, it was reported CART-ergic neurons in the lateral hypothalamus innervated neurons of the paraventricular nucleus communicated with glutamatergic fibers in the NAc shell to modulate psychostimulant-induced reward behaviors, whereas intra-paraventricular hypothalamic infusions of CART antibody or intra-accumbal NMDA receptor antagonist (MK-801) injection blunted the modulatory effect of CART peptide (Choudhary et al., 2018). We have observed pretreatment of basal CaMKIIα-overexpressing NAc neurons with CART peptide injection decreased cocaine or amphetamine (stress)-enhanced pCaMKIIα expression (Fu et al., 2016; Xiong et al., 2018) and that these reductions were coupled with the activations of NMDA receptors, which suggests the inhibitory and modulatory effects of CART peptide on the glutamate receptor-Ca\(^{2+}\)/CAM-pCaMKII signaling pathway influences learning and memory formation. Furthermore, we previously showed CART peptide can promote hippocampal neuron survival by upregulating BDNF (Wu et al., 2006; Pae et al., 2007). In addition, some reports have demonstrated the availability of CART-specific binding sites within brain stress regions, suggesting selective CART peptide receptors can induce anxiolytic and antidepressant effects (Nagelova et al., 2014). These findings and their implications indicate more efforts are required to identify other regions influenced by the anxiolytic and antidepressant CART pathways.

**Conclusion**

Recent experimental findings and reports of associations between neural circuits and disrupted neurotransmissions and psychostimulant addiction and depression suggest CART peptide might be therapeutically useful for the treatment of addiction and depression (Job et al., 2011; Mao et al., 2012). Briefly, we summarize the pathways involved in CART peptide-induced amelioration of anxiety-like behaviors during drug withdrawal as follows: (1) CRF-dependent up-regulation of a disrupted HPA axis, (2) CART-induced increase 5HT efflux in the dorsal raphe nucleus and NAC and the subsequent activations of 5-HT autoreceptors and dopaminergic signaling, and (3) CART-induced rescue of the psychostimulant-depressed GABAergic signaling pathway within the VTA. (4) CART peptide-induced modulation of glutamate pathways in LHb. However, some studies have reported adverse side effects when CART peptide was used to alleviate anxious and depressive-related behaviors (Stanek, 2006; Job et al., 2011; Mao et al., 2012). Therefore, we suggest CART related pathways should be further investigated to elucidate the molecular mechanisms responsible for the anxiolytic and antidepressant effects of CART during drug withdrawal.

**Conflict of Interest**

All authors declare no conflict of interest.

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