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CART Peptide Regulates Psychostimulant-Induced Activity and Exhibits a Rate Dependency

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Since the identification of CART peptides in the 1990s [1], evidence has been steadily accumulating that they are involved in a great variety of physiologic processes. These include feeding and body weight, depression and anxiety, stress, hormonal control, psychostimulant (PS) action [2,3,4,5,6,7,8], and others. With regard to PS action, CART peptides appear to regulate the action of cocaine, amphetamine, and dopamine. Injection of CART peptide (CART55-102) into the nucleus accumbens (NAc) reduces the average effect of PSs on locomotor activity (LMA) and cocaine-induced reward [2,3,4,5,6,7,8,9].

While previous studies have focused on the *average* effect of CART peptide in groups of animals, a recent study from our laboratory examined the effect of the peptide on the action of PSs in *each individual* animal [10]. This approach gives more visibility to those animals that were not always stimulated by PSs, presumably because of the state of the animal. It was found that CART peptide, injected into the NAc, inhibited the LMA of animals that were stimulated by PSs as previously observed. But, it was also found that injection of CART peptide tended to stimulate or increase the activity of animals who did not respond to PSs (Figure 1). This finding reinforced our earlier hypothesis that CART peptides in the NAc regulate the action of PSs and dopamine [2,10]; when the PS effect on LMA was a significant increase, CART peptide inhibited the LMA, and conversely, when PS had little or no effect on LMA, CART peptide stimulated LMA. Thus, CART peptide seems to act to maintain PS-induced LMA within a certain window of activity. A schematic of this regulatory action is shown in Figure 2.

These recent findings can also be discussed according to “rate effects” or the “rate dependency” hypothesis of drugs. These interesting concepts have been discussed by Dews [11] and others, although it is acknowledged that the idea of rate dependency has its shortcomings [11,12,13,14,15].

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Conflict of interest

The first author is the Editor-in-Chief of this journal; accordingly, Dr. Kuhar and the coauthor were blind to the details of the review. The authors have no other conflicts of interest.

Branch [12] suggests that rate dependency can mean that a given drug can have different effects depending on the baseline rate of the observed behavior. We find that CART peptide can be inhibitory or excitatory depending on the baseline cocaine-induced LMA of the animals (Figure 1). Thus our data are compatible with rate dependency although they do not contribute to understanding the possible mechanism of the effect. This rate effect has not been noted previously for CART peptide and represents an additional property of CART peptides. It further suggests that given the effect of cocaine on LMA, one can predict the effect of CART peptide.

In summary, a new analysis of data on the effects of CART peptide on cocaine-induced LMA [10] supports the previous hypothesis that CART regulates the effects of PSs, and also shows that CART peptide exhibits a rate dependency.

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References

1. Douglass J, McKinzie AA, Couceyro P. PCR differential display identifies a rat brain mRNA that is transcriptionally regulated by cocaine and amphetamine. *J Neurosci.* 1995; 15:2471–2481. [PubMed: 7891182]
2. Rogge G, Jones D, Hubert GW, Lin Y, Kuhar MJ. CART peptides: regulators of body weight, reward and other functions. *Nat Rev Neurosci.* 2008; 9:747–758. Erratum in *Nat Rev Neurosci*, 11 (2010), 218. [PubMed: 18802445]
3. Zhang M, Han L, Xu Y. Roles of cocaine- and amphetamine-regulated transcript in the central nervous system. *Clin Exp Pharmacol Physiol.* 2012; 39:586–592. [PubMed: 22077697]
4. Parker JA, Bloom SR. Hypothalamic neuropeptides and the regulation of appetite. *Neuropharmacology.* 2012; 63:18–30. [PubMed: 22369786]
5. Abels M, Riva M, Bennet H, Ahlqvist E, Dyachok O, Nagaraj V, et al. CART is overexpressed in human type 2 diabetic islets and inhibits glucagon secretion and increases insulin secretion. *Diabetologia.* 2016; 59:1928–1937. [PubMed: 27338624]
6. Kuhar MJ. CART peptides and drugs of abuse: A review of recent progress. *J Drug Alcohol Res.* 2016; 5 art235984.
7. Balkan B, Gozen O, Koylu EO, Keser A, Kuhar MJ, Pogun S. Region- and sex-specific changes in CART mRNA in rat hypothalamic nuclei induced by forced swim stress. *Brain Res.* 2012; 1479:62–71. [PubMed: 22960117]
8. Upadhyaya MA, Nakhate KT, Kokare DM, Singh U, Singru PS, Subhedar NK. CART peptide in the nucleus accumbens shell acts downstream to dopamine and mediates the reward and reinforcement actions of morphine. *Neuropharmacology.* 2012; 62:1823–1833. [PubMed: 22186082]
9. Jaworski JN, Hansen ST, Kuhar MJ, Mark GP. Injection of CART (cocaine- and amphetamine-regulated transcript) peptide into the nucleus accumbens reduces cocaine self-administration in rats. *Behav Brain Res.* 2008; 191:266–271. [PubMed: 18485497]
10. Job MO, Kuhar MJ. CART peptide in the nucleus accumbens regulates psychostimulants: Correlations between psychostimulant and CART peptide effects. *Neuroscience.* 2017; 348:135–142. [PubMed: 28215744]
11. Dews PB. Studies on behavior. IV. Stimulant actions of methamphetamine. *J Pharmacol Exp Ther.* 1958; 122:137–147. [PubMed: 13502838]

12. Branch MN. Rate dependency, behavioral mechanisms, and behavioral pharmacology. *J Exp Anal Behav.* 1984; 42:511–522. [PubMed: 6520580]
13. Sanger DJ, Blackman DE. Rate-dependent effects of drugs: A review of the literature. *Pharmacol Biochem Behav.* 1976; 4:73–83. [PubMed: 4819]
14. Cook L, Sepinwall J. Reinforcement schedules and extrapolations to humans from animals in behavioral pharmacology. *Fed Proc.* 1975; 34:1889–1897. [PubMed: 238869]
15. Langer SZ, Trendelenburg U. Studies on veratrum alkaloids. XXXIX. Interaction of veratramine and accelerating agents on the pacemaker of the heart. *J Pharmacol Exp Ther.* 1964; 146:99–110. [PubMed: 14221234]

Figure 1. Rate dependency of CART peptide's effects on cocaine (COC)-induced LMA

Each circle represents data from one individual animal. The experiments were carried out as described by Job and Kuhar [10]. The left or *y*-axis is the "CART peptide effect" which is determined as the difference between (1) the cocaine-induced LMA with CART peptide and (2) the cocaine-induced LMA without CART peptide. When the effect is positive (above the dotted line) the peptide is stimulatory. When the effect is negative (below the dotted line) the peptide is inhibitory. Note that when cocaine-induced activity is low in a given animal, say less than 4,000 on the *x*-axis, then CART peptide tends to be stimulatory. When the cocaine-induced activity tends to be high in a given animal, say around 8,000, CART peptide tends to be inhibitory. Thus the CART peptide effect shows a rate dependence on cocaine-induced LMA. The figure shown is Figure 2(c), females, reproduced from Job and Kuhar [10], with permission.

Figure 2. The regulation of cocaine-induced LMA by CART peptide (CARTp)

When an animal is given cocaine which causes an increase of dopamine (DA) levels in the synapse, the animal will exhibit a certain level of activity. Because of its variability, this level of activity is likely to depend on the state of the animal as influenced by various unknown factors (? Factors). CART peptide injection into the NAc can then have either a positive effect or a negative effect depending on the level of activity without the peptide.