

Commentary

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

Michael J. Kuhar¹ and Martin O. Job²

¹Yerkes National Primate Research Center, Emory University, 954 Gatewood Road, NE Atlanta, GA 30329, USA

²Psychobiology Section, Molecular Neuropsychiatry Research Branch, National Institute on Drug Abuse,

Intramural Research Program, NIH, Baltimore, MD 21224, USA

Address correspondence to Michael J. Kuhar; mkuhar@emory.edu

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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

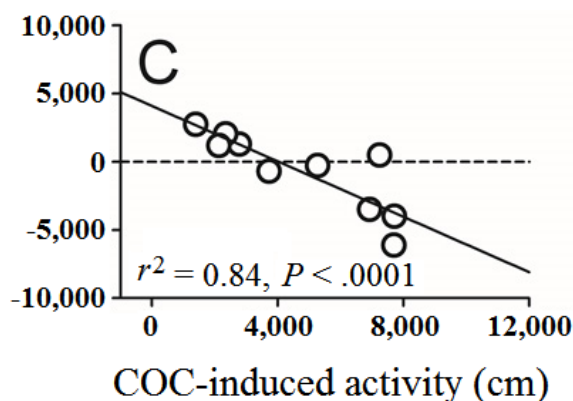


Figure 1: Rate dependency of CART peptide's effects on cocaine (COC)-induced LMA. Each circle represents data from one individual animal. The experiments were carried out as described by Job and Kuhar [10]. The left or *y*-axis is the “CART peptide effect” which is determined as the difference between (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.

idea of rate dependency has its shortcomings [11,12,13,14,15].

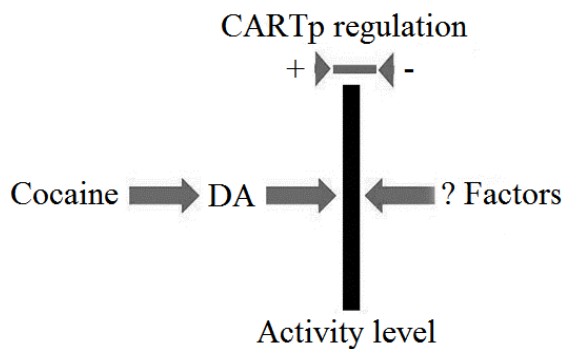


Figure 2: The regulation of cocaine-induced LMA by CART peptide (CARTp). When an animal is given cocaine which causes an increase of dopamine (DA) levels in the synapse, the animal will exhibit a certain level of activity. Because of its variability, this level of activity is likely to depend on the 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.

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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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.

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