available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/peptides

Review

Cocaine- and amphetamine related transcript (CART) and anxiety

Lisa M. Stanek *

Emory University School of Medicine, Yerkes National Primate Research Center, Department of Neuroscience, Yerkes Research Center, 954 N. Gatewood Drive, Atlanta, GA 30329, United States

ARTICLE INFO

Article history:
Received 2 January 2006
Accepted 17 January 2006
Published on line 13 June 2006

Keywords:
Cocaine- and amphetamine-regulated transcript
CART
Anxiety

ABSTRACT

CART is a neuropeptide that appears to play an important role in a variety of physiological processes. The major research focus into the function of CART peptide has been on feeding behavior, modulation of mesolimbic dopamine, and actions of psychostimulant drugs. The neuroanatomic expression profile of CART does however suggest other functions as well, and its presence within the limbic system points to a possible role in emotionality. There are now several published reports which describe a new role for CART as a mediator of anxiety-like behaviors in rodents. This review will summarize these findings and speculate on the mechanisms by which CART might be involved in the modulation of these behaviors. We will also consider what future studies need to be done to further clarify the role of this peptide in anxiety.

Contents

1. Introduction

Cocaine- and amphetamine related transcript (CART) is an abundantly expressed and widely distributed neuropeptide that has been implicated in a number of physiologic processes. This peptide neurotransmitter has been shown to play a role in reward and reinforcement, feeding and satiety, stress, endocrine regulation, sensory processing, and most recently, anxiety [1,2,4,10,15,35,42,51–54]. The existence of a CART peptide fragment was first reported by Spiess et al. in 1981 [59]. In the rat, alternative splicing of the CART transcript gives rise to two peptides containing either 129 or 116 amino acids. The predicted signal sequence consists of 27 amino acid residues resulting in a prohormone of 102 or 89 residues [19]. In humans, only the short form is expressed, whereas the rat brain contains both the short 89 amino acid residue form, as well as the longer splice variant, containing a 13 amino acid insertion [1,23,51]. This long splice variant is referred to as

* Tel.: +1 404 727 5052; fax: +1 404 727 3278.
E-mail address: lstanek@emory.edu.
0196-9781/$ – see front matter © 2006 Published by Elsevier Inc.
doi:10.1016/j.peptides.2006.01.027

rlCART, or rat long form CART. The C-terminal end of CART, consisting of 48 amino acid residues and three disulfide bonds, is thought to constitute the biologically active part of the molecule, and several fragments, notably, rlCART 55–102 and rlCART 62–102, have been shown to be active in vivo [6,50].

Research on this peptide has focused largely on the involvement of CART in the action of psychostimulant drugs, and CART was originally described to be an mRNA acutely upregulated in the striatum after cocaine or amphetamine administration in rats [23]. Unfortunately the studies that originally gave CART its name (cocaine and amphetamine-regulated transcript) have been difficult to replicate, although it has recently been shown that binge administration of cocaine did significantly elevate CART message in the nucleus accumbens [9,25,37]. In addition to its role as a mesolimbic modulator, CART has also been shown to play a much more reliable and robust role as a mediator of feeding, satiety, and body weight [22,36,40,62,66]. CART is an anorectic peptide that produces tonic inhibition of feeding behavior when injected intracerebroventricularly (i.c.v.) into rats [50,62]. This manipulation has also been shown to induce c-Fos activity in brains areas related to feeding and energy expenditure [64,65]. Not surprisingly, CART mRNA is abundantly expressed within hypothalamic structures involved in feeding control, and its role in regulation of body weight is now well documented.

Interest in CART as a modulator of anxiety was generated in part by its well known role as an anorectic peptide. The hypothalamus produces several neuropeptides that stimulate (orexigenic factors) or inhibit (anorectic factors) feeding [7,8]. These peptides include neuropeptide Y (NPY), the melanocortin system (which includes α-melanocyte stimulating hormone, α-MSH and agouti related protein, AgRP), corticotropin-releasing hormone (CRH), melanin-concentrating hormone (MCH), and orexins, in addition to CART. These peptide systems interact with each other as well as with signals from the periphery, allowing the hypothalamus to sense the status of body energy stores and regulate food intake and energy expenditure [61].

An increasing number of these appetite-regulating peptides are now being implicated in the regulation of anxiety. In many cases, anorectic peptides act as anxiogenic factors to facilitate anxiety-like reactions, whereas appetite stimulating orexigenic peptides typically act as anxiolytics to reduce anxiety. For example, intracerebroventricular (i.c.v.) injection of NPY produces anxiolytic and orexigenic actions, whereas α-MSH produces anorexia and anxiety [16,26,31,32,41]. It would therefore not be unreasonable to expect that CART, an appetite suppressing peptide, might have anxiogenic actions and act to enhance anxiety. Both feeding behavior and regulation of body weight are closely tied with emotional states, and thus it is possible that a broad acting peptide such as CART may be playing a dual role as an endogenous factor mediating the effects of anxiety on appetite.

2. CART and anxiety: neuroanatomical evidence

CART peptides are highly abundant, and widely but discretely distributed in the brain, gut, pituitary, adrenals, and pancreas. The high density of CART immunoreactivity in a variety of brain areas suggests that the role of CART is not restricted to the regulation of food intake, reward/reinforcement, and hormone secretion. The anatomical localization of CART mRNA and protein has been extensively reviewed elsewhere [13,14,47,48,53,64]. Much of the research into the proposed function of CART peptide has been inspired by its location in the brain. The presence of CART immunoreactivity in specific brain regions has led to the discovery of CART peptides many diverse functions.

CART mRNA and protein are found in abundance within specific nuclei of the hypothalamus important for regulation of feeding and body weight [27,48,64]. Specifically CART is found in the ventromedial nucleus (VMN), dorso-medial nucleus (DMN), lateral hypothalamus (LH), arcuate nucleus (Arc), and the paraventricular nucleus (PVN). The discovery of CART in these brain regions led to a number of functional studies to examine the affects of i.c.v.-injected CART on feeding behavior in rodents. Together these studies have revealed that CART is a strongly anorectic peptide involved in satiety and regulation of body weight in rats [39,50,62]. Since then, studies of both transgenic animals and humans have demonstrated a linkage to both obesity and anorexia, further confirming a critical role for CART in feeding and satiety.

Similarly, CART has also been found to be abundantly expressed within sub-regions of the mesolimbic dopamine system including the ventral tegmental area (VTA), nucleus accumbens, and the amygdala [47]. The discovery of CART in these brain areas associated with reward and reinforcement, in addition to its dynamic regulation in the VTA following cocaine overdose, led to a number of functional studies examining the relevance of CART peptide to drug addiction. These studies have served as the basis for the understanding that CART may be involved in modulating the actions of psychostimulant drugs through interactions with the mesolimbic dopamine system [9,23,25,38].

In addition to its abundant expression in the feeding and reward areas, CART mRNA and peptide immunoreactivity are highly expressed within the limbic system, a collection of brain regions important in the modulation of emotionality. CART immunoreactivity has been found in areas such as the central and basomedial nucleus of the amygdala (CeA, BM), the bed nucleus of the stria terminals (BNST), and the hippocampus [14,47,48] (see Fig. 1). The presence of CART in these brain regions suggests a possible role for this peptide in emotionality, and has been the motivation for several functional studies examining the behavioral effects of CART infusion on anxiety-like behaviors in rodents.

3. CART and anxiety: functional evidence

The first report implicating a role for CART in anxiety was published by Kask et al. in 2000 [42]. This study examined anxiety-like behaviors in rats following i.c.v. injection of CART. The authors sought to examine the role of CART in drinking (as a measure of non-feeding ingestive behavior) and locomotion, in addition to its role in anxiety. They first tested whether anorectic doses of the $CART_{89–103}$ fragment would affect locomotor activity and modulate stress responses in a novel environment.