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Review Article

Cocaine- and Amphetamine-regulated Transcript (CART) Peptide and the Mesolimbic and Nigrostriatal Dopaminergic Systems

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Abstract

Cocaine- and amphetamine-regulated transcript (CART) peptide was discovered in the treatment of cocaine and amphetamine addiction in rats and received its name from this relationship. The functional role of CART peptide is strongly associated with feeding behaviors, and reward and reinforcement. Recently, a number of studies have shown that mesolimbic and nigrostriatal dopaminergic neuronal activities are also under the regulation of CART peptide. In this mini-review, we will introduce the current knowledge on the neuroanatomical, neurochemical and behavioral aspects of interactions of CART peptide with the mesolimbic and nigrostriatal dopamine pathways. Overall, it is clear that there are functional interactions among CART peptide, dopamine, and psychostimulants. The next step is to clarify the receptor(s) and mechanisms of CART peptide to develop potential therapeutic drugs. (*Tzu Chi Med J* 2008;20(4):248–252)

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1. Introduction

In 1981, Spiess et al reported a previously unknown sequence of peptide that was extracted from ovine hypothalamus (1). At that time, they did not know the physiologic function or the exact localization of this novel peptide. Fifteen years later, Douglass et al used differential display techniques and found that an mRNA transcript was elevated by acute administration of cocaine and amphetamine into rat striatum (2), but two other studies (3,4) could not reproduce their work. The peptide following mRNA transcript coding was named cocaine- and amphetamine-regulated transcript (CART) peptide. CART peptide is a well-identified neurotransmitter. It is produced by neurons (1), and packaged in vesicles (5). Michael Kuhar's laboratory has shown that CART peptide affects the downstream ERK pathway of G protein-coupled receptors (6,7). The next steps in identifying the CART peptide as the real neurotransmitter would be discoveries of CART receptor(s) and understanding the clearance mechanism(s). Recently, Jones and Kuhar, using primary neuronal cell culture, showed that the CART peptide receptor is a G protein-coupled receptor (8). Although there remains controversy about whether CART peptide or its mRNA expression is related to drug abuse, there is no doubt

that CART peptides are involved in reward and reinforcement, feeding and satiety, stress, endocrine regulation, sensory processing and other physiological processes [3,9–12]. The physiological role of CART peptide in the nucleus accumbens and striatum is still unclear, however, although recent studies have shown that CART peptide may play a regulatory role in the mesolimbic and nigrostriatal dopamine systems.

2. Anatomical point of view

High densities of CART immunoreactivity are found in the nucleus accumbens, striatum and various hypothalamic regions of rats and monkeys, and a large number of varicose terminals with CART immunoreactivity are located throughout the nucleus accumbens and form axodendritic synapses; ultrastructural observations further revealed CART immunoreactivity in dense varicosities and many interspersing perikarya [2,13–19]. In addition, electron microscopy showed that tyrosine hydroxylase (the rate limited enzyme of catecholamines)-containing nerve terminals synapse on CART-containing neurons in the nucleus accumbens [13]. The major midbrain dopaminergic systems can be divided into three major categories. These dopaminergic neurons are the long projections linking the ventral tegmental area and substantia nigra neurons with three principal sets of targets, which are the nucleus accumbens, prefrontal cortex, and striatum. These three groups have frequently been termed the mesolimbic, mesocortical, and nigrostriatal dopaminergic systems, respectively, and play different physiological roles in the central nervous system. For instance, the nigrostriatal dopamine system plays an important role in the regulation of the extrapyramidal motor system, and the mesocortical and mesolimbic dopamine systems are associated with the regulation of reinforcement, reward, and incentive motivation. Therefore, it has been speculated that CART peptide plays regulatory roles in the mesolimbic and nigrostriatal dopaminergic systems.

CART immunoreactive cell bodies are found in the nucleus accumbens and these neurons project to the substantia nigra, suggesting that CART peptides provide a significant modulation of a primary output center of the basal ganglia [14,18]. The substantia nigra contains two anatomical divisions: the substantia nigra pars reticulata, which contains basal ganglia output GABAergic neurons; and the substantia nigra compacta, which contains dopamine neurons that project to the striatum forming the nigrostriatal dopaminergic system. In the rat, CART immunoreactive axons and terminals are found throughout the entire ventral midbrain, but neither the ventral tegmental area nor the substantia nigra contains CART immunoreactive cell bodies or CART mRNA, suggesting extrinsic sources of CART-containing innervation to these regions [15,16]. Surprisingly, less than half of CART-containing terminals in the ventral tegmental area form synapses with dopaminergic neurons in the rat [20]. The greater part of CART-containing terminals have contact with non-dopaminergic neurons [20]. Similarly, in the substantia nigra, only one fifth of CART-containing terminals form synapses with the dendritic processes and cell bodies of dopaminergic neurons [14,20]. In common, the majority of CART-containing terminals in both the ventral tegmental area and substantia nigra do not have contact with the dopaminergic systems, but are apposed with the GABAergic neurons. Therefore, it was hypothesized that the effects of CART peptide on the midbrain dopaminergic systems may be through direct and indirect pathways. The direct mechanism of CART peptide on mesolimbic and nigrostriatal dopaminergic neuronal activities could be through direct stimulation of dopaminergic neurons. In contrast, the indirect influence of CART peptide on the neuronal activities of the mesolimbic and nigrostriatal dopaminergic systems could be through inhibition of GABAergic neuronal activity, followed by similar stimulating effects in the dopaminergic systems.

3. Neurochemical and behavioral points of view

Kimmel et al [21] found that direct administration of CART peptide into the ventral tegmental area produced significant psychomotor stimulant-like effects, including increases in locomotor activity and conditioned place preference. After this study, others reported the effects of CART peptide on the central dopaminergic systems, especially midbrain mesolimbic and nigrostriatal dopaminergic neuronal activities [22–25]. In fact, most of these studies provide indirect evidence, or focus on behavioral responses following CART peptide treatments. Shieh [24] reported that dopamine turnover in the nucleus accumbens and striatum was elevated 15 minutes after central administration of CART peptide. However, only dopamine turnover in the nucleus accumbens was increased 45 minutes following CART peptide treatment, while that in the striatum was not. Using the ratio of the major dopamine metabolite (3,4-dihydroxyphenylacetic acid [DOPAC]) to dopamine as an index of dopaminergic neuronal activity showed a similar trend (Fig. 1). Using microdialysis, Yang et al [25] also found that the major dopamine metabolites in the nucleus accumbens of conscious rats were significantly elevated after central injection of CART peptide. Interestingly, these stimulating effects of CART peptide on the dopamine turnover of the mesolimbic and nigrostriatal systems are influenced by the gonadal hormones, including

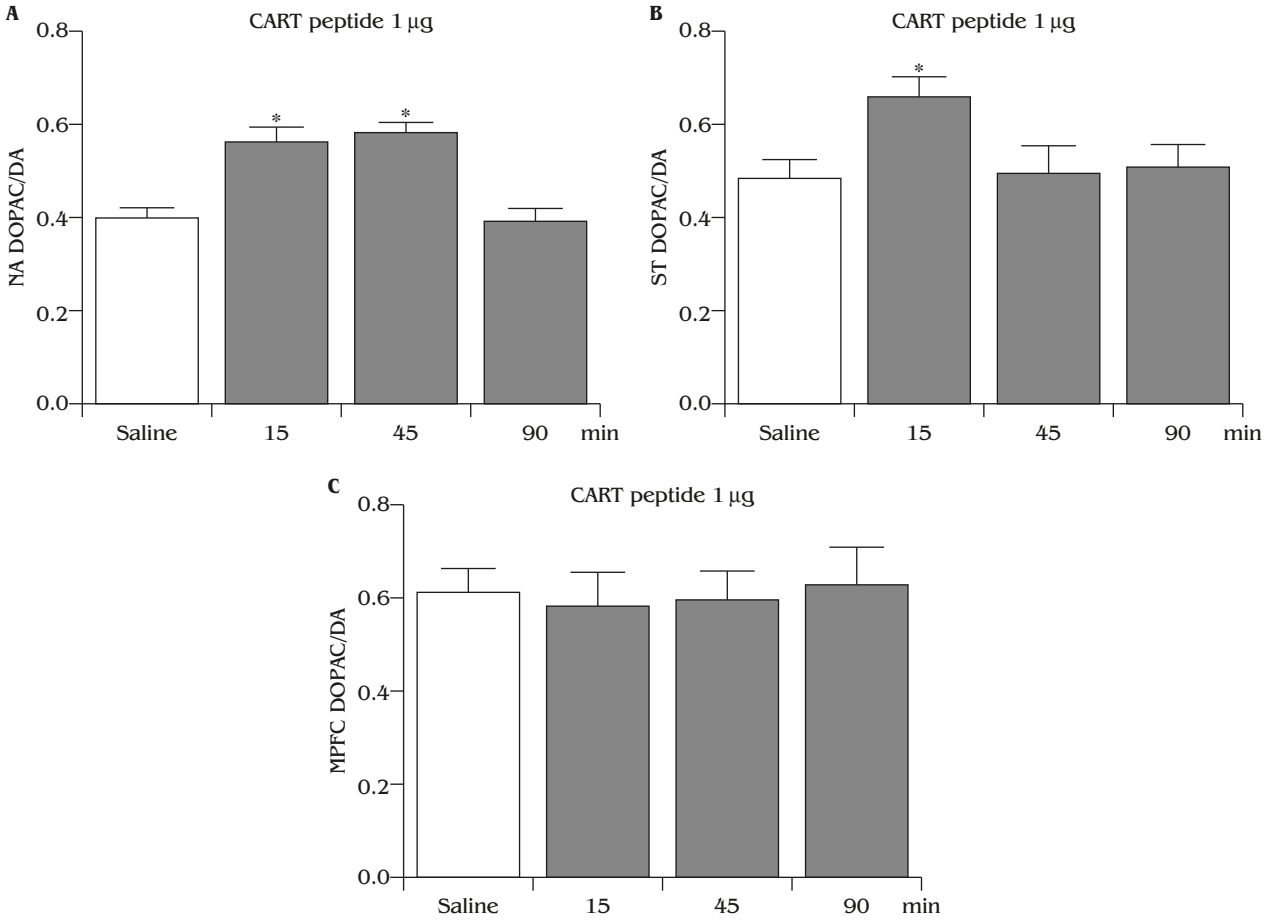

Fig. 1 — Dopamine turnover in the: (A) nucleus accumbens (NA); (B) striatum (ST); and (C) medial prefrontal cortex (MPFC) in male rats following central injection of cocaine- and amphetamine-regulated transcript (CART) peptide as measured by using the DOPAC/DA ratio. CART peptide (1 μg) was given in the morning, and the rats were decapitated 15, 45 or 90 minutes later. Detailed information on the materials and methods has been reported in previous studies [24–28,31]. The vertical line above each bar represents the standard error of the mean (n=6). *p<0.05 compared with the DOPAC/DA ratio in saline-treated controls (white bar).

testosterone and estradiol. For instance, intracerebroventricular administration of CART peptide increased dopamine turnover in the nucleus accumbens and striatum in male rats [26,27]. Stimulation of dopamine turnover in the nucleus accumbens and striatum by CART peptide was found in intact male rats, but not in castrated male rats [27]. This stimulation was restored in castrated male rats by testosterone or dihydrotestosterone priming. These restoring effects were blocked by a testosterone antagonist, but not by an estradiol antagonist [27]. Moreover, similar stimulation by CART peptide on the dopamine turnover of the mesolimbic and nigrostriatal systems in female rats was also influenced by estradiol [28]. Stimulation of nucleus accumbens and striatum dopamine turnover by CART peptide was found in ovariectomized female rats after estradiol priming, but not in ovariectomized female rats without priming. Therefore, the gonadal hormones, testosterone and estradiol, play regulatory roles in stimulation of CART peptide in the mesolimbic and nigrostriatal dopaminergic systems.

On the other hand, mesocortical dopaminergic neuronal activity was not affected by CART peptide. For example, the dopamine turnover of the medial prefrontal cortex showed no changes at 15 and 45 minutes (Fig. 1), and this is similar to previous studies [24–28]. Previous anatomical evidence has shown that a high density of CART peptide exists in the nucleus accumbens and striatum, the major projection sites of the mesolimbic and nigrostriatal dopaminergic systems [13,14,17]. In contrast, low-to-extremely low levels of CART peptide immunoreactive fibers and CART mRNA were found in the medial prefrontal cortex, the major projection site of the mesocortical dopaminergic system, in both humans and rats [17, 29,30]. Taken together, these reports indicate that CART peptide may also act as a psychostimulant or at least plays a stimulatory role on the mesolimbic and

nigrostriatal, but not the mesocortical dopaminergic systems.

4. Conclusion

Neuroanatomical, neurochemical and behavioral evidence has shown close relationships between CART peptide and the mesolimbic and nigrostriatal dopaminergic systems. Although studies have also reported that CART peptide might play a regulatory role on other dopaminergic systems, such as the hypothalamic tuberoinfundibular dopamine system (24,26,31), further data are still needed. Taken together, the role for CART peptide involved in modulating the reward and reinforcing effects of psychostimulants, feeding behavior and central dopaminergic systems is clearer. There is a great potential for CART as a therapeutic target for the treatment of eating disorders and psychostimulant addiction. In the past, the major challenge in studies of CART peptide was the absence of a particular CART receptor; however, it is expected that the recent discovery of a CART peptide receptor (8) might greatly facilitate the development of useful agonist(s)/antagonist(s) of CART peptide for future therapeutic purposes.

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