Neuropeptides xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Neuropeptides

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

News and Reviews

Cardiovascular functions of central corticotropin-releasing factor related peptides system

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ARTICLE INFO

Keywords:
CRF related peptides
CRFR1
CRFR2
Cardiovascular functions

ABSTRACT

The corticotropin-releasing factor (CRF) related peptides system has widespread distributions in central nervous system, to perform many physiological and pathophysiological functions, including cardiovascular functions. A complex connection exists between the central CRF related peptides system and cardiovascular system. There are multiple pathways and mechanisms through which the central CRF related peptides system influences cardiovascular functions. A dysfunction in the central CRF related peptides system may lead to a wide range of alterations in cardiovascular functions. Though there are difficulties or limitations in establishing exact modulatory roles of the central CRF related peptides system in cardiovascular functions. The central CRF related peptides system as target to prevent cardiovascular diseases is being pursued with increasing interest. In this review, we summarize recent understanding on cardiovascular functions of the CRF related peptides system in limbic forebrain, hypothalamus and brain stem structures, discuss mechanisms of the central CRF related peptides system in control of cardiovascular functions, and suggest that the central CRF related peptides system may be a potent candidate for prevention of cardiovascular diseases.

1. Introduction

Mammalian corticotropin-releasing factor (CRF) related peptides including CRF, urocortin 1, urocortin 2 and urocortin 3, have been extensively studied and implicated as neuropeptides in central nervous system. CRF 1 type receptor (CRFR1) and CRF 2 type receptor (CRFR2) mediate actions of CRF related peptides. CRF related peptide was injected into intracerebroventricular to increase blood pressure (BP) and heart rate (HR) (Briscoe et al., 2000; Brown and Fisher, 1983; Kalin et al., 1983; Nijsen et al., 2000; Overton et al., 1990a, 1990b; Overton and Fisher, 1989; Richter and Mulvany, 1995; Scoggins et al., 1984), and produce a reduction in baroreflex sensitivity (Fisher, 1988, 1989; Turnbull et al., 1993) in conscious or anesthetized animals. In addition, microinjection of CRF related peptides receptors antagonist into intracerebroventricular decreased pressor and tachycardia responses and reduction in baroreflex sensitivity induced by diverse stimulations (Dedeoglu and Fisher, 1994; Dong et al., 2001; Kregel et al., 1990; Nakamori et al., 1993; Tan et al., 2003; Wang et al., 2018; Yamada et al., 2009). Intracerebroventricularly administered CRF related peptide influenced neuronal activities of central autonomic structures (Bittencourt and Sawchenko, 2000; Daniels et al., 2004; Yakabi et al., 2014; Yamaguchi and Okada, 2009). Thus, activities of autonomic nervous system may be primarily responsible for cardiovascular functions of central CRF related peptides system. In contrast, it had also been demonstrated that intracerebroventricular injection of CRF produced bradycardia response (Stiedl and Meyer, 2002), and intracerebroventricular pretreatment with nonselective CRF related peptides receptors antagonist attenuated repeated restraint stress induced increase in baroreflex sensitivity (Conti et al., 2001). Thus, we believed that central CRF related peptides system in different central cardiovascular structures play distinct roles in regulation of cardiovascular functions.

CRF related peptides and their receptors have been demonstrated to be distributed in multiply central regions and exert their roles at different central cardiovascular structures including limbic forebrain, hypothalamus and brain stem structures, pointing towards roles of the central CRF related peptides system in regulation of cardiovascular functions. This present review will describe the state of knowledge on cardiovascular functions of the central CRF related peptides and their receptors in different central cardiovascular structures, discuss the pathways and mechanisms underlying modulation of the central CRF related peptides system on cardiovascular functions, and provide new

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https://doi.org/10.1016/j.npep.2019.03.006
Received 6 October 2018; Received in revised form 26 February 2019; Accepted 19 March 2019

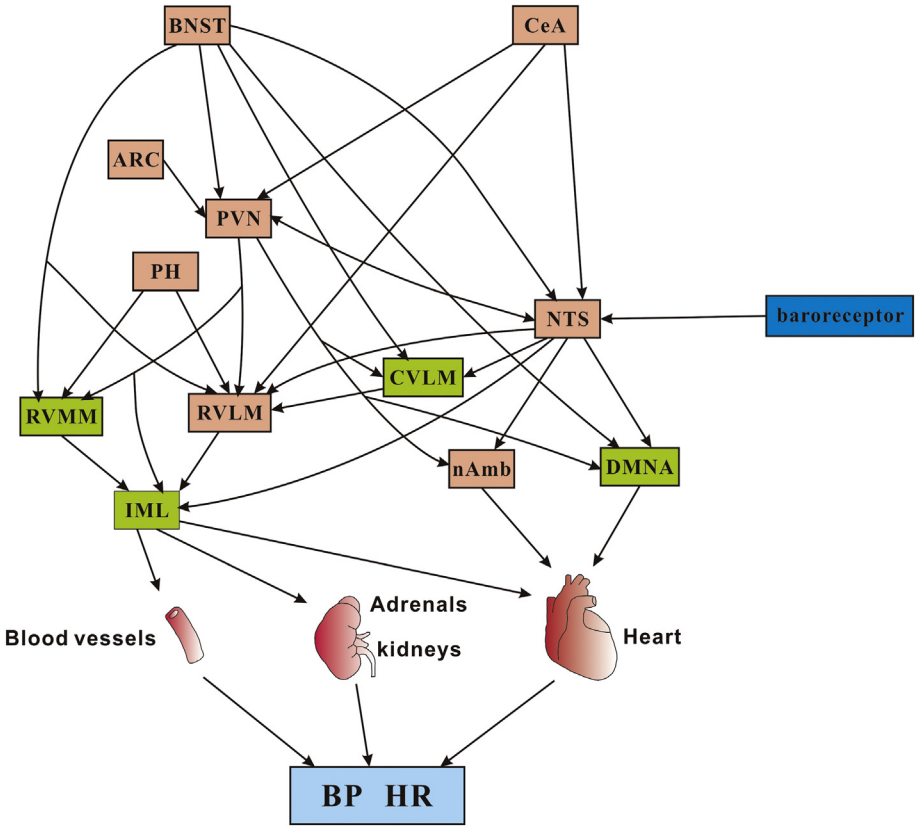

Fig. 1. Schematic illustrating the pathways from central cardiovascular structures to peripheral cardiovascular system involved in cardiovascular functions. CRF related peptides are involved in regulation of cardiovascular functions in central cardiovascular structures including rostral ventrolateral medulla (RVLM), nucleus ambiguous (nAmb), nucleus of the solitary tract (NTS), paraventricular hypothalamic nucleus (PVN), hypothalamic arcuate nucleus (ARC), posterior hypothalamic nucleus (PH), central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST). CVLM, caudal ventrolateral medullary; RVMM, rostral ventromedial medulla; DMNV, dorsal motor nucleus of vagus; IML, intermediolateral cell column of thoracolumbar spinal cord.

insights into pathogenesis and therapeutic targets of cardiovascular diseases.

2. CRF related peptides system and regulation

CRF was initially characterized in 1981 by Vale and colleagues (Vale et al., 1981). Fourteen years later, CRF related peptides family member urocortin 1 was described in 1995 by Vaughan and colleagues (Vaughan et al., 1995) followed by discovery of urocortin 2 (or stresscopin-related peptide) (Hsu and Hsueh, 2001; Reyes et al., 2001) and urocortin 3 (or stresscopin) (Hsu and Hsueh, 2001; Lewis et al., 2001) in 2001. CRF related peptides act by two different class B subfamily of seven-transmembrane receptors, CRFR1 and CRFR2. CRF is a high affinity ligand for CRFR1 and a lower affinity ligand for CRFR2. Urocortin 1 binds with high affinity to both CRFR1 and CRFR2. Urocortin 2 and urocortin 3 are preferred ligands for CRFR2 (Haass-Koffler, 2017; Henckens et al., 2016). CRF binding protein (CRF-BP) in central nervous system is able to bind CRF, urocortin 1 and urocortin 2, but unable to bind urocortin 3 (Haass-Koffler, 2017; Henckens et al., 2016). Biological role of CRF-BP in brain is not limited solely to being a CRF related peptides scavenger that would decrease free CRF related peptides synaptic concentration and prevent CRF related peptides receptors activation. CRF-BP buffer, inhibit, or enhance effects of CRF related peptides binding to their receptors (Haass-Koffler et al., 2016; Slater et al., 2016a; Slater et al., 2016b). The types of effects produced by CRF-BP may rely on localization and concentration (Seasholtz et al., 2002).

Both CRFR1 and CRFR2 signal by coupling to G proteins which include G_s, G_q, G_i, G_o, $G_{i1/2}$ and G_z. Different G proteins binding to different CRF related peptides activated receptors activate distinct signal pathways including adenylyl cyclase - cyclic AMP - protein kinase A pathway, phospholipase C - 1,2-diacylglycerol - protein kinase C pathway, phospholipase C - inositol (1,4,5)-trisphosphate (IP3) - Ca^{2+} pathway, extracellular signal regulated kinase - mitogen activated protein kinase pathway and other pathways, and subsequent downstream events including gene transcription and intracellular Ca^{2+} mobilization (Dautzenberg and Hauger, 2002; Grammatopoulos and Chrousos, 2002; Henckens et al., 2016; Hillhouse and Grammatopoulos, 2006; Waters et al., 2015). Thus, the effects of CRF related peptides may be regulated through interaction with different types of CRF related peptides receptors and depend on CRF related peptides receptors localization and cellular context. Besides, after CRF related peptides receptors coupling to G proteins, G proteins related kinases phosphorylate the receptors to desensitize the receptors. And phosphorylation of CRF related peptides receptors rapidly enhance affinity of the receptors for β-arrestin. The receptors signaling can be terminated by β-arrestin. The complex of CRF related peptide -CRFR-β-arrestin is internalized. Desensitized and internalized CRF related peptides receptors are dephosphorylated by specific phosphatases, and resensitized receptors are recycled to plasma membrane. The CRF related peptides receptors activities are also modulated by interactions with carboxy-terminal PDZ-domain. Membrane-associated guanylate kinases binding to PDZ-domain influence the localizations of CRF related peptides receptors and may anchor CRF related peptides receptors to larger signaling complexes. Many other regulatory systems seem to modulate CRF related peptides receptors activities but need further study (Henckens et al., 2016; Waters et al., 2015).

3. Effects of CRF related peptides in different central cardiovascular structures

Although it is well established that the central CRF related peptides system regulates cardiovascular functions, a number of recent studies have challenged that CRF related peptides system plays distinct cardiovascular functions in different central cardiovascular structures. Here we review the studies of the CRF related peptides in brain regions mediated cardiovascular functions: rostral ventrolateral medulla (RVLM), nucleus ambiguous (nAmb), nucleus of the solitary tract

(NTS), paraventricular hypothalamic nucleus (PVN), hypothalamic arcuate nucleus (ARC), posterior hypothalamic nucleus (PH), central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST).

RVLM contains presympathetic neurons which innervate sympathetic preganglionic neurons located in intermediolateral cell column of thoracolumbar spinal cord (IML) and receive strong excitatory and inhibitory inputs from other central cardiovascular structures and inhibitory input from baroreceptor input pathway. Thus, RVLM is necessary for maintenance and mediation of tonic and reflex cardiovascular functions. Presympathetic neurons of RVLM release glutamate and other neurotransmitters including catecholamines. These neurons regulate sympathetic outflow which execute commands to heart, kidney, adrenal medulla and blood vessels and therefore play critical roles in cardiovascular functions (Fig. 1). Studies had reported that microinjection of CRF into RVLM increased BP and HR (Ku et al., 1998; Ku et al., 2006; Milner et al., 1993). CRF related peptides binding to their receptors in RVLM may change other neurotransmissions into RVLM to affect presympathetic neurons or directly affect presympathetic neurons, which in turn, regulate sympathetic outflow to regulate cardiovascular functions. Intra-RVLM microinjection of non-selective CRF related peptides receptors antagonist reduced pressor or tachycardia responses of CeA, ventromedial hypothalamic nucleus or dorsomedial hypothalamic nucleus to Glu (Wu et al., 1999). Thus, RVLM appears to be critical sympathoexcitatory efferent target for CRF related peptidergic inputs to play excited role in BP and HR. CRFergic neurons with axonal project to RVLM originating from PVN, NTS, lateral hypothalamic area, lateral parabrachial nucleus, dorsomedial hypothalamic nucleus and local neurons of RVLM (Lee et al., 2013; Milner et al., 1993) which are involved in regulation of cardiovascular functions. However, the roles and mechanisms of CRFergic innervation and CRF related peptides receptors of RVLM involved in cardiovascular control are still unknown.

nAmb, a key source nucleus contains premotor cardiac vagal neurons which innervate heart and play an essential role in regulation of HR by tonic and reflex control (Fig. 1). The great majority of premotor cardiac vagal neurons of nAmb are silent. Synaptic connections to premotor cardiac vagal neurons along with neurotransmitters and postsynaptic receptors are responsible for cardiac vagal activity to regulate HR. Premotor cardiac vagal neurons of nAmb receive glutamatergic excitatory input (Neff et al., 1998), GABAergic (Wang et al., 2001a; Wang et al., 2001b) and glycinergic (Batten, 1995; Venkatesan et al., 2003; Wang et al., 2003) inhibitory inputs to play pivotal roles in regulation of HR. In normal rats, microinjection of urocortin 1 into nAmb elicited bradycardia response which was mediated via activation of CRFR1, through increasing in cardiac vagal activity. And in mid-collicular decerebrate rats, urocortin 1 in nAmb elicited bradycardia response, which was not statistically different from those elicited in normal rats (Chitravanshi and Sapru, 2011). Thus, the brain structures located rostral to brainstem are not necessary for urocortin 1 induced bradycardia response in nAmb. A major input to nAmb originates from NTS located in brainstem. Actually, the glutamatergic excitatory input to premotor cardiac vagal neurons of nAmb arises from NTS (Neff et al., 1998). Activation of glutamatergic excitatory input system of nAmb was involved in urocortin 1 binding to CRFR1 mediated increase of cardiac vagal activity to reduce HR (Chitravanshi and Sapru, 2011). In nAmb, urocortin 3 elicited bradycardia response which was mediated via activation of CRFR2, through increasing in cardiac vagal activity (Chitravanshi et al., 2012). Activation of glutamatergic excitatory input system and inhibitions of GABAergic and glycinergic inhibitory inputs systems to nAmb were involved in urocortin 3 acting on CRFR2 mediated increase of cardiac vagal activity to reduce HR (Chitravanshi et al., 2012). In addition, urocortin 3 activated CRFR2 which couples with $G_{i/o}$ protein, in turn, induced an phospholipase C activation in nAmb neurons, and promoted Ca^{2+} influx via voltage-gated P and Q channels and Ca^{2+} release via IP3 receptors (Brailoiu et al., 2012). Thus, urocortin 2 may affect presynaptic glutamatergic excitatory input and GABAergic and glycinergic inhibitory inputs to nAmb or affect postsynaptic glutamate receptors, GABA receptors and glycine receptors or directly affect nAmb neurons activities. Bradycardia response of microinjection of urocortin 1 or urocortin 3 into nAmb appear to depend on doses injected. Urocortin 1 or urocortin 3 injection into nAmb elicited U-shaped dose–response in HR (Chitravanshi et al., 2012; Chitravanshi and Sapru, 2011). Higher dose of CRF related peptides binding to a modulator site other than the primary site which results in attenuated responses could explained the type of dose-response.

NTS is also critical for cardiovascular functions. NTS accepts several central cardiovascular structures inputs and baroreceptor nerve afferent, and innervates nAmb and dorsal motor nucleus of vagus (DMNV) which include cardiac vagal preganglionic neurons, and projects to caudal ventrolateral medullary (CVLM) which in turn, GABAergic CVLM neurons send axons to RVLM, and directly projects to PVN, RVLM and IML (Fig. 1). Microinjection of urocortin 1, urocortin 2 or urocortin 3 into NTS elicited decreases in BP and HR which were mediated by decrease in sympathetic nerve activity and increase in vagal nerve activity (Nakamura et al., 2009; Nakamura and Sapru, 2009; Yamazaki et al., 2008). CRF related peptides acting on their receptors may excite NTS neurons, which, in turn, excite GABAergic neurons located in CVLM, then, GABA is released in RVLM, decreasing activity of RVLM neurons. Ultimately, activity of excitatory input from RVLM neurons to sympathetic preganglionic neurons located in IML is decreased. CRF related peptides may also excite NTS neurons which directly excitatory project to vagal preganglionic neurons located in nAmb and DMNV to increase vagal nerve activity. In addition, CRF related peptides may excite NTS neurons which directly inhibitory project to RVLM or IML to decrease sympathetic nerve activity or excite NTS-PVN pathway to decrease sympathetic nerve activity and increase vagal nerve activity.

NTS expresses high level of CRFR2 and relatively lower level of CRFR1 (Van Pett et al., 2000; Wang et al., 2018). Cardiovascular responses to CRF related peptides in NTS are mediated via CRFR1 and CRFR2. CRFR2 is mainly CRF related peptides receptor to mediate cardiovascular responses of CRF related peptides in NTS (Nakamura and Sapru, 2009; Wang et al., 2019). Depressor and bradycardia responses to activation of CRFR2 in NTS by microinjection of urocortin 3 were mediated via ionotropic glutamate receptors (Nakamura and Sapru, 2009). A study has demonstrated that CRFR2 presynaptically expresses on afferent terminals of NTS (Lawrence et al., 2002). In addition, CRF induced increase of intracellular calcium level in NTS which mediated by CRFR2 was reproduced in presence of TTX (tetrodotoxin) (Wang et al., 2018). Thus, CRFR2 also postsynaptically expresses on NTS neurons. CRF related peptides acting on presynaptic CRFR2 increase glutamate releasing and acting on postsynaptic CRFR2 activate glutamate receptors to enhance excitatory of NTS neurons. Depressor and bradycardia responses to activation of CRFR1 and CRFR2 in NTS by microinjection of urocortin 1 were only partially mediated via ionotropic glutamate receptors (Nakamura and Sapru, 2009). CRF related peptides may also activate CRFR1 to affect other neurotransmitters mechanisms or directly activate CRFR1 located on NTS neurons which affect NTS neurons to modulate cardiovascular functions.

However, activation of PVN-NTS CRF containing projection increased BP and HR (Wang et al., 2019). Thus, CRF releasing into NTS from PVN play diverse roles in regulation of cardiovascular functions comparing with injection of CRF related peptides into NTS. In addition, urocortin 1 or urocortin 3 injection into NTS elicited inverted U-shaped dose–response in depressor and bradycardia responses (Nakamura et al., 2009; Nakamura and Sapru, 2009). NTS is heterogeneous in regulation of cardiovascular functions. NTS neurons express a diverse array of neurotransmitters and receptors for neurotransmitters, and plays distinct cardiovascular roles through different pathways. This heterogeneity is probably responsible for controlling different cardiovascular functions.

PVN, a pivotal central cardiovascular area is a mixed population of neurons composing magnocellular neurons and parvicellular neurons. Many magnocellular neurons synthesizing vasopressin and oxytocin project to posterior pituitary which serve as a site for secretion of vasopressin and oxytocin directly into circulation (Swanson and Sawchenko, 1980). Vasopressin and oxytocin into circulation promote renal tubular reabsorption of water and contract blood vessels, and hence increase BP. Magnocellular terminal fibers releasing excitatory or inhibitory neurotransmitters are associated with NTS and DMNV and sympathetic preganglionic neurons located in IML (Pyner, 2009; Sawchenko and Swanson, 1982) which regulate tonic and reflex sympathetic and vagal nerve activity to regulate cardiovascular functions. Parvicellular neurons comprise pre-autonomic neurons and neuroendocrine neurons. Parvicellular pre-autonomic neurons synthesizing excitatory or inhibitory neurotransmitters project to key central cardiovascular structures including NTS, CVLM, DMNV, RVLM, rostral ventromedial medulla (RVMM) and sympathetic preganglionic neurons located in IML (Dun et al., 2004; Pyner, 2009) (Fig. 1) which involve in modulatory actions of tonic and reflex sympathetic and vagal nerve activity to regulate cardiovascular functions. Parvicellular neuroendocrine neurons synthesizing CRF project to median eminence where they regulate secretion of adrenocorticotropin hormone from anterior pituitary, that will have an effect on cardiovascular functions (Blair et al., 1996; Pyner, 2009; Swanson and Sawchenko, 1980).

Moderate level of CRFR2 is expressed in PVN (Chalmers et al., 1995). Microinjection of urocortin 3 into PVN significantly increased BP, HR and renal sympathetic nerve activity (Li et al., 2010). It is known that PVN is an important brain structure regulating efferent sympathetic nerve activity (Coote, 2005; Kenney et al., 2003). Therefore, CRFR2 may express in PVN which regulate sympathetic nerve activity to mediate CRF related peptides induced increase of sympathetic outflow. Besides, PVN neurons expressing CRFR1 adjacent to CRFergic neurons of PVN which form synapses on neighboring CRFR1 expressed neurons and activate them by releasing CRF. CRFR1 expressed neurons of PVN make GABAergic synapses on parvocellular and magnocellular neurons of PVN and also make long range glutamatergic synapses in autonomic nucleus such as the NTS (Jiang et al., 2018). Thus, CRF and CRFR1 in PVN may be involved in complex control of cardiovascular functions.

ARC has been implicated in regulation of cardiovascular functions. CRF related peptidergic nerve terminals and CRFR1 and CRFR2 have been found in ARC (Campbell et al., 2003; Fekete and Zorrilla, 2007; Van Pett et al., 2000). Urocortin 1, urocortin 2 or urocortin 3 in ARC activating CRFR1 and/or CRFR2 elicited depressor and bradycardia response which were mediated via increase in vagal activity and decrease in sympathetic nerve activity. However, in barodenervated rats, urocortin 1 in ARC activating CRFR1 and CRFR2 elicited pressor and tachycardia responses (Chitravanshi et al., 2013). These cardiovascular responses induced by CRF related peptides in ARC were accordant with previous studies, both pressor and depressor responses could be elicited by chemical stimulation in ARC (Sapru, 2013). The directions of cardiovascular responses (increase or decrease) elicited by chemical stimulation in ARC depend on level of baroreceptor activities which are determined by baseline BP. ARC neurons directly project to many central cardiovascular structures including PVN, NTS, CVLM, RVLM, and sympathetic preganglionic neurons located in IML. But, direct projections from ARC to NTS, CVLM, RVLM, and sympathetic preganglionic neurons located in IML are sparse. PVN is the main central cardiovascular structure which mediate cardiovascular functions of ARC (Sapru, 2013) (Fig. 1). Activation of ARC-PVN projections regulating baroreceptor input pathway may be involved in cardiovascular functions of CRF related peptides in ARC.

PH, caudal and dorsal hypothalamic region, plays important roles in cardiovascular functions. Our studies have demonstrated that both CRFR1 and CRFR2 are co-localized in PH neurons. CRF in PH directly activating CRFR1 and CRFR2 excited PH neurons to increase HR rather than BP and renal sympathetic nerve activity. Tachycardia response to microinjection of CRF into PH was mediated via cardiac sympathetic nerve activity. Furthermore, microinjecting CRF into PH primarily increased neuronal activity of RVLM and RVMM, does not influence that of DMNV (Gao et al., 2016). Thus, activation of CRF related peptides receptors within PH neurons modulate cardiovascular functions through PH-RVLM/RVMM-cardiac sympathetic nerve pathway rather than PH-DMNV-vagus nerve pathway (Fig. 1).

CeA is a limbic forebrain structure and an important part of neural circuitry mediating cardiovascular functions, and plays critical roles in integration and coordination of cardiovascular functions (Saha, 2005). CRF related peptidergic nerve terminals and CRFR1 and CRFR2 have been identified in CeA (Brown and Gray, 1988; Li et al., 2002). CRF in CeA could increase BP and HR (Ku et al., 1998; Wiersma et al., 1993). CRF related peptides in CeA linking to presynaptic or postsynaptic CRFR1 and CRFR2 affected glutamatergic neurotransmission into CeA to affect CeA neurons (Fu and Neugebauer, 2008; Liu et al., 2004; Silberman and Winder, 2013). Glutamatergic neurotransmission in CeA plays an important role in cardiovascular functions (Saha, 2005). Thus, cardiovascular regulation of microinjection of CRF into CeA may be mediated via glutamatergic neurotransmission into CeA. A study had showed that CRF in CeA increased plasma catecholamine concentrations (Brown and Gray, 1988) suggesting that in CeA, CRF may be involved in regulation of sympathetic outflow to affect cardiovascular functions. However, another study had demonstrated CRF injecting into CeA caused an increase in HR without affecting plasma epinephrine and noradrenaline (Wiersma et al., 1993) suggesting that CRF in CeA regulated HR probably by affecting vagal outflow. NTS and RVLM are main central cardiovascular structures known to receive projections from CeA (Saha, 2005). Thus, activations of CRF related peptides receptors within CeA modulating cardiovascular activity may be mediated through CeA-NTS/RVLM- sympathetic nerve pathway or CeA-NTS-vagus nerve pathway. In addition, CeA directly or indirectly project to PVN, which in turn, send projection to brainstem or spinal cord to mediate cardiovascular functions of CRF related peptides in CeA (Fig. 1).

BNST is also a limbic forebrain structure which plays important roles in cardiovascular functions. High density of CRF and moderate density of urocortin 1 and urocortin 3 nerve terminals are located in BNST (Beckerman et al., 2013; Bittencourt et al., 1999; Li et al., 2002; Sakanaka et al., 1986). Both CRFR1 mRNA and CRFR2 mRNA express in BNST (Dabrowska et al., 2011; Van Pett et al., 2000). Endogenous CRF related peptides releasing within BNST is involved in cardiovascular response. CRFR1 and CRFR2 distinctly mediate endogenous CRF related peptides induced cardiovascular response. Microinjection of selective CRFR1 antagonist into BNST decreased baroreflex bradycardia response without affecting reflex tachycardia, conversely, CRFR2 antagonist decreased baroreflex tachycardia without affecting reflex bradycardia (Oliveira et al., 2017). Microinjection of CRFR1 antagonist into BNST reduced pressor and tachycardia responses caused by restraint, CRFR2 antagonist reduced increased BP without affecting increased HR (Oliveira et al., 2015). Thus, CRF related peptides in BNST regulate distinct cardiovascular functions which be mediated by CRFR1 or CRFR2 through different neural pathways. However, A study had showed that microinjection of nonselective CRF related peptides receptors antagonist into BNST potentiated tachycardia induced by footshock (Nijsen et al., 2001). CRF related peptides neurotransmission systems in BNST display adverse roles in control of cardiovascular activity during different stresses. Another study had demonstrated that CRF at dose of 0.07 nmol increased restraint-evoked cardiovascular responses, but microinjection of a higher dose (0.15 nmol) did not evoke any cardiovascular change in restraint responses (Oliveira et al., 2015). Thus, CRF related peptidergic inputs systems in BNST play complex cardiovascular functions.

BNST plays complex cardiovascular functions mediated by different BNST subregions and different BNST neural pathways (Crestani et al.,

2013). Fibers inputs of BNST arise from brain structures which including CRF related peptides neurons involve in stress such as PVN, CeA and hippocampus. Thus, different nerve terminals into BNST may be connected to different roles in regulation of cardiovascular activity in different stress. CRF signaling increases glutamatergic neurotransmission to activate neurons of BNST (Kash et al., 2008; Nobis et al., 2011; Oliveira et al., 2018). Glutamate in BNST plays bi-directional cardiovascular functions which may be mediated by different BNST subregions (Crestani et al., 2013). CRF also enhances GABAergic neurotransmission in BNST (Kash and Winder, 2006; Nagano et al., 2015; Oberlander and Henderson, 2012). Therefore, it is possible that different BNST subregions and different BNST neural pathways mediate CRF related peptidergic inputs systems in BNST induced complex cardiovascular functions. Furthermore, direct projections from BNST reach central cardiovascular structures including PVN, NTS, CVLM, DMNV, RVLM and RVMM (Dabrowska et al., 2016; Giancola et al., 1993; Gray and Magnuson, 1987; Hatam and Ganjkhani, 2012) which play roles in cardiovascular functions. Thus, activations of CRF related peptides neurotransmission systems in BNST effect neurons of BNST to modulate complex cardiovascular functions through pathways from BNST to these central cardiovascular structures which play distinct cardiovascular roles (Fig. 1).

4. Conclusion and future perspectives

The CRF related peptides system has emerged as crucial neurotransmission in many central cardiovascular structures. The central CRF related peptides and their receptors play distinct roles in cardiovascular functions in different central cardiovascular structures. However, the underlying pathways and mechanisms of the central CRF related peptides which regulate cardiovascular functions in central cardiovascular structures are still not well understood and need to be further investigated.

The central CRF related peptides system may be considered as potential therapeutic target for cardiovascular diseases. The neurophysiological mechanisms linking the CRF related peptides system and cardiovascular diseases risk remain largely uncertain. We know that acute stress and chronic stress induced cardiovascular response may initiate or exacerbate pathophysiological changes in cardiovascular diseases. The central CRF related peptides system really plays pivotal roles in stress induced cardiovascular response. Many brain regions containing CRF related peptidergic neurons and nerve terminals are involved in stress and cardiovascular activity (Ku, 2006). Although, the neural mechanisms that mediate the central CRF related peptides system involved stress induced cardiovascular response are poorly understood. Thus, the central CRF related peptides system may contribute to the generation and development of cardiovascular diseases. Further studies that determine the roles and mechanisms of the central CRF related peptides system in stress induced cardiovascular response and the generation and development of cardiovascular diseases are essential.

Training significantly attenuates elevations of BP and HR in response to stress and elevations of BP induced by central injection of CRF (Overton et al., 1991). Thus, training may change the central CRF related peptides system to reduce stress induced cardiovascular response. Electroacupuncture also contribute to reduce stress induced cardiovascular response (Yang et al., 2002). The roles and mechanisms of the central CRF related peptides system in training and electroacupuncture reduced stress induced cardiovascular response to prevent cardiovascular diseases need to be further investigated.

Investigating the neurobiological mechanisms linking the central CRF related peptides system with cardiovascular function and cardiovascular disease would support ongoing efforts to develop a comprehensive understanding of brain structure-function relationships. Additionally, training and electroacupuncture studies would likely implicate novel targets to improve health outcomes.

Funding

This work was supported by the Natural Science Foundation of Anhui University of Chinese Medicine (grant numbers 2018zrzd02).

Conflict of interest

The authors declare that they have no conflict of interest

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