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Review

Role of the hypothalamic arcuate nucleus in cardiovascular regulation

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ABSTRACT

Recently the hypothalamic arcuate nucleus (Arc) has been implicated in cardiovascular regulation. Both pressor and depressor responses can be elicited by the chemical stimulation of the Arc. The direction of cardiovascular responses (increase or decrease) elicited from the Arc depends on the baseline blood pressure. The pressor responses are mediated via increase in sympathetic nerve activity and involve activation of the spinal ionotropic glutamate receptors. Arc-stimulation elicits tachycardic responses which are mediated via inhibition of vagal input and excitation of sympathetic input to the heart. The pathways within the brain mediating the pressor and tachycardic responses elicited from the Arc have not been delineated. The depressor responses to the Arc-stimulation are mediated via the hypothalamic paraventricular nucleus (PVN). Gamma aminobutyric acid type A receptors, neuropeptide Y1 receptors, and opiate receptors in the PVN mediate the depressor responses elicited from the Arc. Some circulating hormones (e.g., leptin and insulin) may reach the Arc via the leaky blood–brain barrier and elicit their cardiovascular effects. Although the Arc is involved in mediating the cardiovascular responses to intravenously injected angiotensin II and angiotensin-(1-12), these effects may not be due to leakage of these peptides across the blood–brain barrier in the Arc; instead, circulating angiotensins may act on neurons in the SFO and mediate cardiovascular actions via the projections of SFO neurons to the Arc. Cardiovascular responses elicited by acupuncture have been reported to be mediated by direct and indirect projections of the Arc to the RVLM.

Contents

Abbreviations: Arc, hypothalamic arcuate nucleus; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropin; AgRP, agouti-related peptide; Alpha-MSH, alpha-melanocyte stimulating hormone; AMPA, ±-α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid hydrobromide (non-NMDA receptor agonist); AMPK, adenosine monophosphate-activated protein kinase; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; CART, cocaine and amphetamine-regulated transcript; CVLM, caudal ventrolateral medullary depressor area; D-AP7, D(−)-2-amino-7-phosphono-heptanoic acid (NMDA receptor antagonist); DMN, hypothalamic dorsomedial nucleus; GSNA, greater splanchnic nerve activity; IML, Intermediolateral cell column of the spinal cord; LSNA, lumbar sympathetic nerve activity; nAmb, nucleus ambiguus; NBQX, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo-[f]quinoxaline-7-sulfonamide (non-NMDA receptor antagonist); NMDA, N-methyl-D-aspartic acid; NPY, neuropeptide Y; NPY1R, neuropeptide type 1 receptor; NTS, nucleus tractus solitarius; OPR, opiate receptor; PAG, periaqueductal gray; POMC, proopiomelanocortin; PVN, hypothalamic paraventricular nucleus; RSNA, renal sympathetic nerve activity; RVLM, rostral ventrolateral medullary pressor area; SFO, subfornical organ; VMH, ventromedial hypothalamus; VMN, hypothalamic ventromedial nucleus.

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1. Introduction

The hypothalamus lies below the thalamus on both sides of the third ventricle and extends from the optic chiasm rostrally to the midbrain tegmentum caudally. In the anterio-posterior direction, the hypothalamus can be arbitrarily divided into three regions: anterior, tuberal and posterior regions. It is a complex structure and contains several groups of neurons. The preoptic and suprachiasmatic nuclei are located in the anterior region. The periventricular, paraventricular (PVN), anterior, supraoptic, dorsomedial (DMN), ventromedial (VMN) and arcuate (Arc) nuclei are located in the tuberal region. The posterior nucleus and mammillary body are present in the posterior region. The lateral nucleus extends from the tuberal to the posterior regions. All of these hypothalamic nuclei are located on both sides of the third ventricle (Siegel and Sapru, 2011).

Among other vital functions, the hypothalamus plays a critical role in the regulation of cardiovascular function (Coote, 2004). Extensive literature is available on the role of the paraventricular, dorsomedial, lateral and posterior hypothalamic nuclei in the regulation of cardiovascular function (Coote, 2004). However, information regarding the role of the Arc in cardiovascular regulation and autonomic functions is just beginning to be accumulated.

The main focus of this review is to discuss available literature on the participation of the Arc in cardiovascular regulation. However, other information relevant to the role of Arc in autonomic regulation has also been included. In the beginning, basic neuroanatomy of the Arc, its projections and chemical phenotypes of its neurons are presented. This description is followed by a discussion of different types of cardiovascular responses elicited by the chemical stimulation of the Arc and the pathways mediating these responses. Next, cardiovascular effects of microinjections of leptin, angiotensin II (Ang II), angiotensin-(1-12) (Ang-(1-12)) and insulin into the Arc are discussed. The role of the Arc in mediating cardiovascular responses to these circulating hormones is also discussed in the context of leaky blood–brain barrier of the ventromedial part of this nucleus. Finally, the role of Arc in mediating the cardiovascular effects of acupuncture is discussed.

2. Basic anatomy of the Arc

The Arc is located in the ventral hypothalamus on both sides of the base of the third ventricle. Ventrally it has a short extension into the median eminence of the tuber cinereum. In the rat, the Arc extends along the base of the 3rd ventricle from 1.72 to 4.36 mm caudal to the bregma (about 2.64 mm length in rostro-caudal direction). In the rostral regions (1.72 to 3.36 caudal to the bregma), the Arc has been divided into dorsal, medial and lateral regions. In the caudal regions (3.48 to 4.36 mm caudal to the bregma), only the medial and lateral regions of the nucleus are prominent (Paxinos and Watson, 2007). The neurons in the Arc are generally polymorphic and small to medium in size. They usually give rise to 2–3 dendrites which do not arborize extensively. In a majority of Arc neurons (72%), the axons arise from the perikarya while in some neurons (28%) they arise from the proximal dendrites. The axons of some Arc neurons synapse locally while other neurons project to the median eminence and other nuclei in the central nervous system (CNS). In the rostral part of the Arc, the axons of some neurons cross under the third ventricle to the contralateral Arc (Carpenter and Sutin, 1983; Bleier and Byne, 1985).

A large percentage of the total tissue volume of the Arc consists of tanycytes which are descendants of radial glial cells. The cell bodies of tanycytes are located either in the lateral walls or floor of the third ventricle and their main processes proceed ventrally and end on blood vessels or pial surface. Tanycytes have been implicated in the transport of hormones from the cerebrospinal fluid to the capillaries of the hypophyseal portal system and from hypothalamic neurons to the cerebrospinal fluid (Peruzzo et al., 2004). This function may involve the process of transcytosis in which materials are taken up by the tanycyte on one end by endocytosis and moved to the opposite side where they are released through the plasma membrane by exocytosis.

3. Arc projections

Anatomical tracing techniques have revealed that neurons in the Arc project to the forebrain (the nucleus accumbens, bed nucleus of stria terminalis, lateral septal nucleus and amygdaloid nucleus), thalamus (the paraventricular and centromedian nuclei), hypothalamus, midbrain (ventrolateral periaqueductal gray; vlPAG), pons (the lateral parabrachial nucleus, dorsal raphe nucleus and locus coeruleus) and medulla (the nucleus raphe magnus and pallidus, nucleus reticularis gigantocellularis and nucleus tractus solitarius) (Sim and Joseph, 1991; Li et al., 2006a, 2009). Some retrogradely labeled cells were found in the lateral portion of the Arc after microinjections of Fluoro-Gold (FG) or fast blue dye (tracers) into the intermediate gray matter and adjacent lateral funiculus of the spinal cord at T1–T4 level in adult rats suggesting that some Arc cells may project directly to the intermediolateral cell column of the spinal cord (IML) (Cechetto and Saper, 1988; Elias et al., 1998). Electrophysiological experiments and anatomical tracing studies have shown that neurons located in the subfornical organ (SFO) can be activated or inhibited by electrical or chemical stimulation of the Arc and that Arc neurons may directly project to the SFO (Rosas-Arellano et al., 1993, 1995, 1996). Arc neurons also project to the median eminence for endocrine modulation (Van den Pol and Cassidy, 1982).