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Sexual dimorphism of cardiopulmonary regulation in the arcuate nucleus of the hypothalamus

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ABSTRACT

The arcuate nucleus of the hypothalamus (ANH) interacts with other hypothalamic nuclei, forebrain regions, and downstream brain sites to affect autonomic nervous system outflow, energy balance, temperature regulation, sleep, arousal, neuroendocrine function, reproduction, and cardiopulmonary regulation. Compared to studies of other ANH functions, how the ANH regulates cardiopulmonary function is less understood. Importantly, the ANH exhibits structural and functional sexually dimorphic characteristics and contains numerous neuroactive substances and receptors including leptin, neuropeptide Y, glutamate, acetylcholine, endorphins, orexin, kisspeptin, insulin, Agouti-related protein, cocaine and amphetamine-regulated transcript, dopamine, somatostatin, components of renin-angiotensin system and gamma amino butyric acid that modulate physiological functions. Moreover, several clinically relevant disorders are associated with ANH ventilatory control dysfunction. This review highlights how ANH neurotransmitter systems and receptors modulate breathing differently in male and female rodents. Results highlight the significance of the ANH in cardiopulmonary regulation. The paucity of studies in this area that will hopefully spark investigations of sexually dimorphic ANH-modulation of breathing.

Contents

1. Introduction

This review focuses on the role of hypothalamus especially the arcuate nucleus in sexual dimorphic regulation of cardiopulmonary function. A brief introduction describes the neuroanatomy of the hypothalamic nuclei and their role in maintaining homeostasis. Functions such as energy balance, arousal, and thermoregulation, regulated by several hypothalamic nuclei, can also influence indirectly cardiopulmonary function. Several disorders such as Prader-Willi Syndrome and hypothyroidism have as part of their presentation abnormalities of control of breathing and involve the arcuate nucleus and other hypothalamic nuclei. Moreover, several hypothalamic nuclei show sexually dimorphic anatomical and/or functional characteristics. Potential factors such as sex steroid hormones and their receptors, genetic and epigenetic factors that may influence these sexually dimorphic traits and contribute to cardiopulmonary regulation are discussed. Results indicate that there is a paucity of information about sexual dimorphic regulation of breathing in the AN. Hopefully this review will spark future studies of this clinically relevant hypothalamic region.

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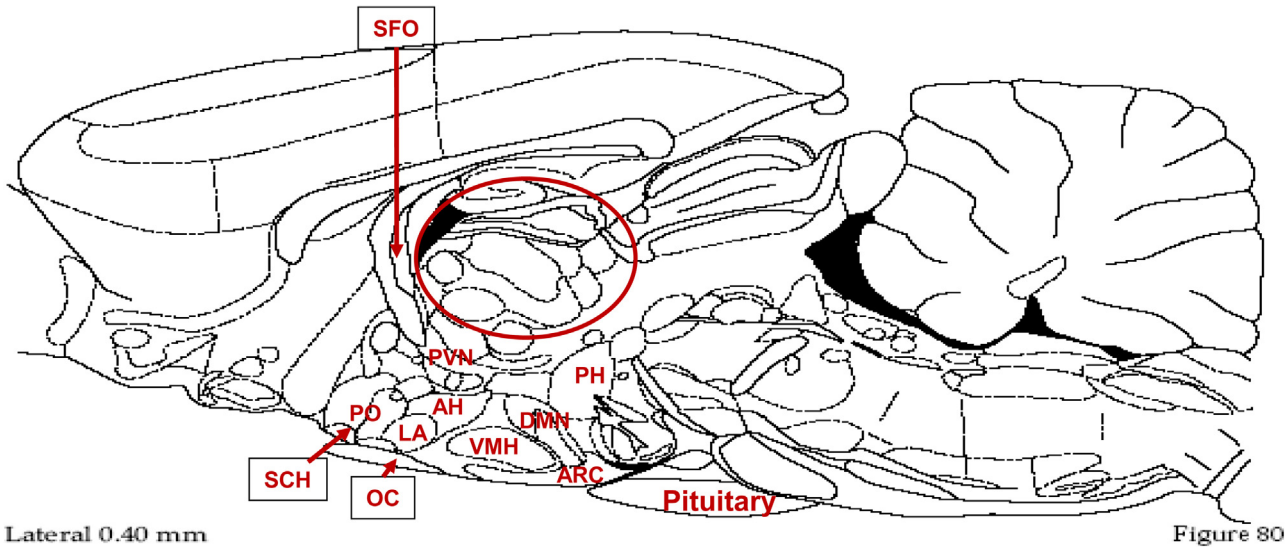

Fig. 1. Sagittal section of a rat brain illustrating the location of some hypothalamic nuclei. Modified with permission from Paxinos and Watson, The Rat Brain in Stereotaxic Coordinates, 2nd Edition. Academic Press, Orlando FL. The encircled area denotes the thalamus. Abbreviations: SFO = subfornical organ, PVN = paraventricular nucleus of the hypothalamus, SCH = superchiasmic nucleus, PO = preoptic nuclei, OC = optic chiasm, LA = Lateroanterior hypothalamic nucleus, AH = anterior hypothalamic nucleus, PH = posterior hypothalamic nucleus, VMH = ventromedial hypothalamic nucleus, DMH = dorsomedial hypothalamic nucleus, ARC = arcuate nucleus.

2. Hypothalamic nuclei: anatomy

The hypothalamus is located below the thalamus (Fig. 1, (Paxinos and Watson, 1986) and consists of a large number of nuclei involved in modulating the functions of the neuroendocrine system, feeding and satiety, reproduction, autonomic nervous function, stress responses, metabolism, thermoregulation, pain, and cardiopulmonary regulation (Dampney, 2015; Li and Longhurst, 2010; Seoane-Collazo et al., 2015). Hypothalamic nuclei that are located in more anterior locations include the median preoptic nuclei, subfornical organ (SFO), the lateral terminalis (LT), organum vasulosum of the LT, suprachiasmatic nuclei, arcuate nucleus, the median eminence (ME) and the PVN. The posterior nuclei include the dorsomedial nucleus, the posterior hypothalamic region, the lateral hypothalamus, the perifornical areas and mammary nuclei. Importantly, the ME, SFO and the organum vasulosum of the LT, are circumventricular organs, meaning that they lack a blood-brain barrier (Ganong, 2000). Thus, these regions "taste" the circulating factors in the blood that can in turn affect their function and the nuclei that they innervate.

3. Methods to evaluate the physiological and behavioral role of hypothalamic nuclei

To ascertain the function of hypothalamic nuclei, a number of approaches are utilized. These include electrical stimulation of specific nuclei (seminal studies in cardiopulmonary regulation were conducted by Kabat (Kabat, 1936), electrophysiological recordings from brain regions in the hypothalamus (Waldrop and Porter, 1995) and investigating interacting circuits by stimulating specific regions using optogenetic methods, and overexpressing or knocking enzymes necessary to produce neurotransmitters and/or specific receptors (Candlish et al., 2015; Han et al., 2015). Another approach involves microinjection of specific neurotransmitter receptor agonists or antagonists (examples are given in later sections on cardiopulmonary regulation in this review). Many older studies were conducted in anesthetized animals, but more recent studies investigated the effects of stimulation or inhibiting the function of specific areas in freely behaving animals avoiding potential effects of anesthesia. Many respiratory studies using conscious animals cited below were conducted using plethysmography (Tenney and Leiter, 1995). Other approaches to investigate the contribution of a specific nucleus on cardiopulmonary regulation include lesioning sites using electrical or chemical methods or blocking the production of chemicals (using viral vectors, antisense, and neurotoxins (Holloway et al., 2015; McCarthy et al., 2000; Takakura et al., 2008). Importantly, smaller lesions are more efficacious in discerning the function of specific hypothalamic areas in understanding their roles in physiological functions(Dreshaj et al., 2003). Finally, individual studies currently employ a variety of techniques to help elucidate underlying interactions among brain regions (Takeuchi et al., 2016). In the papers presented in this review the use of some of these approaches are discussed.

4. Sexual dimorphism of hypothalamic nuclei

A number of hypothalamic nuclei, including the arcuate nucleus, exhibit anatomic and/or functional sexual dimorphic characteristics (Kermath et al., 2014; Leal et al., 1998). Sexual dimorphism may be modulated at different times during development and aging by the presence and amount of sex steroid hormones such as estrogen and testosterone and their respective receptors as well as the substrates and enzymes necessary for their production both in gonads and within the brain itself (Behan and Kinkead, 2011; Leal et al., 1998; Panzica et al., 2007).

Systemically circulating sex steroid hormones that can freely enter the brain and act on a number of different receptors including estrogen receptors alpha and beta, and androgen receptors (Ciofi et al., 2007; Majdic and Tobet, 2011). Moreover, more recent studies denote the role that chromosomal and epigenetic factors play in determining the sexually dimorphic structure and function of hypothalamic nuclei (Matsuda et al., 2012; Panzica and Melcangi, 2016). Several studies illustrate the large number of sexually dimorphic nuclei in the hypothalamus (such as the bed nucleus of the stria terminalis, arcuate nucleus, ventral medial hypothalamus, sexually dimorphic nucleus of the preoptic area, anteroventral periventricular nucleus, (Scott et al., 2015; Wright et al., 2010), as well as in other brain regions (Ball et al., 2014; de Carvalho et al., 2016). Thus, it is important to elucidate how sexually dimorphic substrates in

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