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Review

Circumventricular organs: Targets for integration of circulating fluid and energy balance signals?

Andrea Mimee, Pauline M. Smith, Alastair V. Ferguson *

Queen's University, Department of Biomedical and Molecular Sciences, Kingston, Ontario, Canada K7L 3N6

HIGHLIGHTS

- SFO interfaces with circulating signals that do not cross the blood brain barrier.
- Circulating indicators of cardiovascular/metabolic status influence SFO neurons.
- Sensitivity to these circulating signals is modified by physiological state.
- We suggest integrative roles for SFO neurons in controlling ingestive behavior.

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ABSTRACT

The subfornical organ (SFO), as one of the sensory circumventricular organs (CVOs), is among the only central nervous system structures which interfaces directly with circulating substances that do not cross the blood brain barrier. Here we describe a growing literature showing that circulating indicators of cardiovascular (angiotensin II, osmolarity, calcium, sodium) and metabolic (adiponectin, amylin, glucose, ghrelin, leptin) statuses influence the excitability of single SFO neurons. Single cell electrophysiological studies from our laboratory have demonstrated excitatory effects of angiotensin II on individual SFO neurons, and changes in angiotensin II receptor expression in this CVO in hypertensive states emphasize the dynamic contribution of SFO neurons to the regulation of fluid balance. Furthermore, we have shown both depolarizing and hyperpolarizing effects of the adipokines adiponectin and leptin in SFO cells, and highlight that conditions of fasting in the case of adiponectin, and obesity in the case of leptin, alter the sensitivity of SFO neurons to these circulating factors. The results examined in this review provide evidence for a role of the SFO as a mediator and integrative structure in the maintenance of cardiovascular and metabolic functions.

Contents

1. Introduction

It is now well established that numerous molecules in the peripheral circulation play important roles in signaling both fluid and energy

* Corresponding author. Tel.: +1 613 533 2803; fax: +1 613 533 6880.
E-mail address: avf@queensu.ca (A.V. Ferguson).

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balance status to the central nervous system (CNS). More specifically, osmolarity, concentrations of sodium and calcium in the blood, and circulating levels of regulatory hormones, including angiotensin II, endothelin and vasopressin, play critical roles in signaling fluid balance status to important control centers within the brain. Similarly, homeostatic regulation of energy balance requires that the CNS receive information from the periphery regarding glucose concentrations, as well as levels of circulating adipokines, such as leptin and adiponectin, and regulatory hormones, including amylin, ghrelin, and cholecystokinin (CCK). Intriguingly, many of these circulating signaling molecules influence the brain despite their inability to cross the normal blood brain barrier (BBB). Several potential mechanisms as to how these circulating factors may influence protected neuronal regions have been proposed. For example, the gut hormone CCK has been shown to influence the CNS via vagal afferents to the caudal brainstem [1], while selective transporters for leptin [2] and insulin [3] from blood to brain have been described, though their physiological function remains largely unknown. Transendothelial cell signaling represents another potential mechanism by which circulating factors may influence the brain, as this occurs when molecules act on the luminal side of the cerebral vascular endothelial cell and induce the release of a second, different, signaling molecule (i.e. nitric oxide) on the other side of the barrier [4,5]. Finally, work in our laboratory has focused on the hypothesis that circumventricular organs (CVOs), structures which lack the normal BBB, offer a direct route by which circulating molecules may access the CNS. In this review we will consider the current evidence suggesting important roles for the CVOs, with a specific focus on the subfornical organ (SFO), as relay centers through which peripheral information is collected and transmitted to critical autonomic control centers protected by the BBB.

2. The subfornical organ

The SFO, a midline sensory CVO located on the floor of the third ventricle dorsal to the anterior commissure, is primarily known for its well established roles in cardiovascular and neuroendocrine regulation [6,7]. Sensory CVOs are specialized CNS structures characterized firstly by a cerebral vasculature in which fenestrations are found between endothelial cells (similar to the rest of the non-brain systemic vasculature), thus allowing even large, lipophobic, substances, including peptides and proteins, to cross from blood to neural tissue without having to cross the cell membrane [8], and secondly by the presence of exceptionally dense aggregations of a variety of different receptors for peripheral signals. These unique properties make the CVOs, including the SFO, ideally suited to detect and monitor the presence of regulatory molecules in the peripheral circulation. Specifically, the SFO then communicates this information on peripheral signals to numerous hypothalamic autonomic control centers, including the paraventricular nucleus (PVN), supraoptic nucleus (SON), median preoptic nucleus, and the OVLT [9–11]. The SFO also sends more minor projections to the zona incerta, raphe nuclei, infralimbic cortex, rostral and ventral portions of the bed nucleus of the stria terminalis, lateral preoptic area, lateral hypothalamus/dorsal perifornical region and, of significance to fluid and energy homeostasis, the arcuate nucleus [9,12,13]. Anatomical data suggests that SFO neurons have relatively compact dendritic trees and limited neural inputs [14], which, in most cases, originate from the same areas that receive SFO efferents. Specific excitatory projections have been found to vasopressin and oxytocin neurons in the SON and PVN, as well as to parvocellular areas of the PVN that in turn project either to the median eminence, the medulla, or the spinal cord [15].

Roles for the SFO in food intake, anorexia, emaciation and the regulation of energy balance [16], cardiovascular function and hypertension [10,17–26], immune regulation [27], the febrile response (see [28] for review), drinking [29–33], osmoregulation [34], and reproduction [35,36] have all been suggested.

In the remainder of this review we will focus on data suggesting that single neurons in the SFO play important roles in sensing factors which provide information regarding energy and fluid balance. Specifically, we will describe the literature demonstrating that neurons in the SFO sense levels of circulating angiotensin II, as well as the adipokines adiponectin and leptin.

3. Cardiovascular and fluid balance signals

3.1. Angiotensin II

Landmark studies conducted in the late 1970s and early 1980s established the SFO as a critical central site of circulating angiotensin II actions and, as such, provided the background for our understanding of the important roles of the CVOs in sensing circulating signals which regulate both fluid balance and cardiovascular parameters. These microinjection and lesion studies identified the SFO as the primary central nervous system site where angiotensin II acts to induce both drinking [37,38] and increases in blood pressure [25]. Correspondingly, later autoradiographic studies demonstrated the SFO contains the highest density of angiotensin II binding sites in the CNS [39], thus providing anatomical evidence of the critical contribution of the SFO in mediating the central actions of angiotensin II. Importantly, the central effects of angiotensin II on drinking [32,40], blood pressure [25,41], and the secretion of vasopressin [42] and oxytocin [43] are all abolished by lesions of the SFO.

Taken together, these in vivo studies indisputably highlight the SFO as an essential central site of angiotensin II effects and thus led to a deeper cellular analysis of the mechanisms through which angiotensin II influences the excitability of SFO neurons to ultimately regulate drinking, cardiovascular function, and neuroendocrine responses. Extracellular recordings [44] and whole cell patch-clamp recordings from dissociated SFO neurons [45] have both demonstrated exclusively excitatory effects of angiotensin II on the majority (>60%) of SFO cells, consistent with the findings of high AT_1 receptor density in this CVO. These cellular actions of angiotensin II have been shown to be mediated via the AT_1 receptor, as pharmacological pre-treatment of neurons with the AT_1 receptor antagonist, losartan, abolished the excitatory effects of angiotensin II on SFO neurons [44]. It is also interesting to note the expression levels of AT_1 receptors in the SFO have been reported to be decreased in hypertensive states [46], thus highlighting the dynamic nature of angiotensin II effects on SFO neurons in accordance with the cardiovascular status of the organism. Finally, patch-clamp recordings have revealed that angiotensin II modulates numerous conductances to exert its central effects, namely by inhibiting the transient potassium conductance I_A [47], and potentiating both a non-selective cation conductance [48] and voltage-gated calcium channels [49].

3.2. Additional fluid balance signals

Since these studies demonstrating SFO neurons to be critical sensors of circulating angiotensin II, considerable additional evidence has highlighted roles for this CVO in responding to many other circulating signals of importance to cardiovascular regulation and fluid balance. For example, c-Fos studies have indicated that the SFO is activated by changes in circulating osmolarity [50,51]. We have further characterized the osmosensitivity of SFO neurons at the single cell level using patch-clamp techniques, and have shown that SFO cells are excited by increases in extracellular osmolarity [34]. In addition, increases in circulating levels of Ca^{2+} [23] or of Na^{+} [52] have been shown to increase the activity of SFO neurons. Finally, numerous other regulatory hormones have been shown to influence the excitability of SFO neurons. More specifically, vasopressin induces both depolarizing and hyperpolarizing effects on these cells [53,54], while atrial natriuretic peptide suppresses the activity of SFO neurons [55,56] and endothelin excites these cells [22,57]. Taken together,