Neuroscience Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

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

Review article

Sodium sensing in the subfornical organ and body-fluid homeostasis

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ARTICLE INFO

Article history:
Received 30 April 2016
Received in revised form 22 July 2016
Accepted 28 July 2016
Available online xxx

Keywords:
Circumventricular organs
Subfornical organ
Na_x
Body-fluid homeostasis
Hypernatremia

ABSTRACT

The brain monitors conditions of body fluids and levels of circulating neuroactive factors to maintain the systemic homeostasis. Unlike most regions in the brain, circumventricular organs (CVOs) lack the blood–brain barrier, and serve as the sensing center. Among the CVOs, the subfornical organ (SFO) is the sensing site of Na^+ levels in body fluids to control water and salt intake. The SFO harbors neuronal cell bodies with a variety of hormone receptors and innervates many brain loci. In addition, the SFO harbors specialized glial cells (astrocytes and ependymal cells) expressing Na_x, a Na^+-level-sensitive sodium channel. These glial cells wrap a specific population of neurons with their processes, and control the firing activities of the neurons by gliotransmitters, such as lactate and epoxyeicosatrienoic acids (EETs), relevant to water/salt-intake behaviors. Recent advances in the understanding of physiological functions of the SFO are reviewed herein with a focus on the Na^+-sensing mechanism by Na_x.

Contents

1. Introduction

The brain needs to continuously monitor circulating substances to know body conditions. Therefore, the brain has entry points for these signal substances at limited loci that lack a blood–brain barrier (BBB); endothelial cells of capillaries form BBB to protect neurons and glial cells from potentially harmful circulating substances. In mammals, seven loci around the cerebral ventricle are known to have fenestrated capillaries lacking a BBB. These loci were the subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT), area postrema (AP), median eminence (ME), pineral gland, subcommissural organ, and neurohypophysis (Dellmann, 1987), and collectively designated as the circumventricular organs (CVOs). These tissues are commonly featured by extensive vascularization and atypical ependymal cells lining the cerebral ventricle (Dellmann, 1987).

Among the CVOs, only the SFO, OVLT, and AP are termed sensory CVOs, because they harbor neuronal cell bodies and have afferent and efferent neural connections with many other areas of the brain (Johnson and Gross, 1993) (Fig. 1A). In addition, expressions of a variety of hormone receptors, including angiotensin II (Ang II) receptors, have been reported in the sensory CVOs (McKinley et al.,

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http://dx.doi.org/10.1016/j.neures.2016.07.007
0168-0102/

Please cite this article in press as: Hiyama, T.Y., Noda, M., Sodium sensing in the subfornical organ and body-fluid homeostasis. Neurosci. Res. (2016), http://dx.doi.org/10.1016/j.neures.2016.07.007

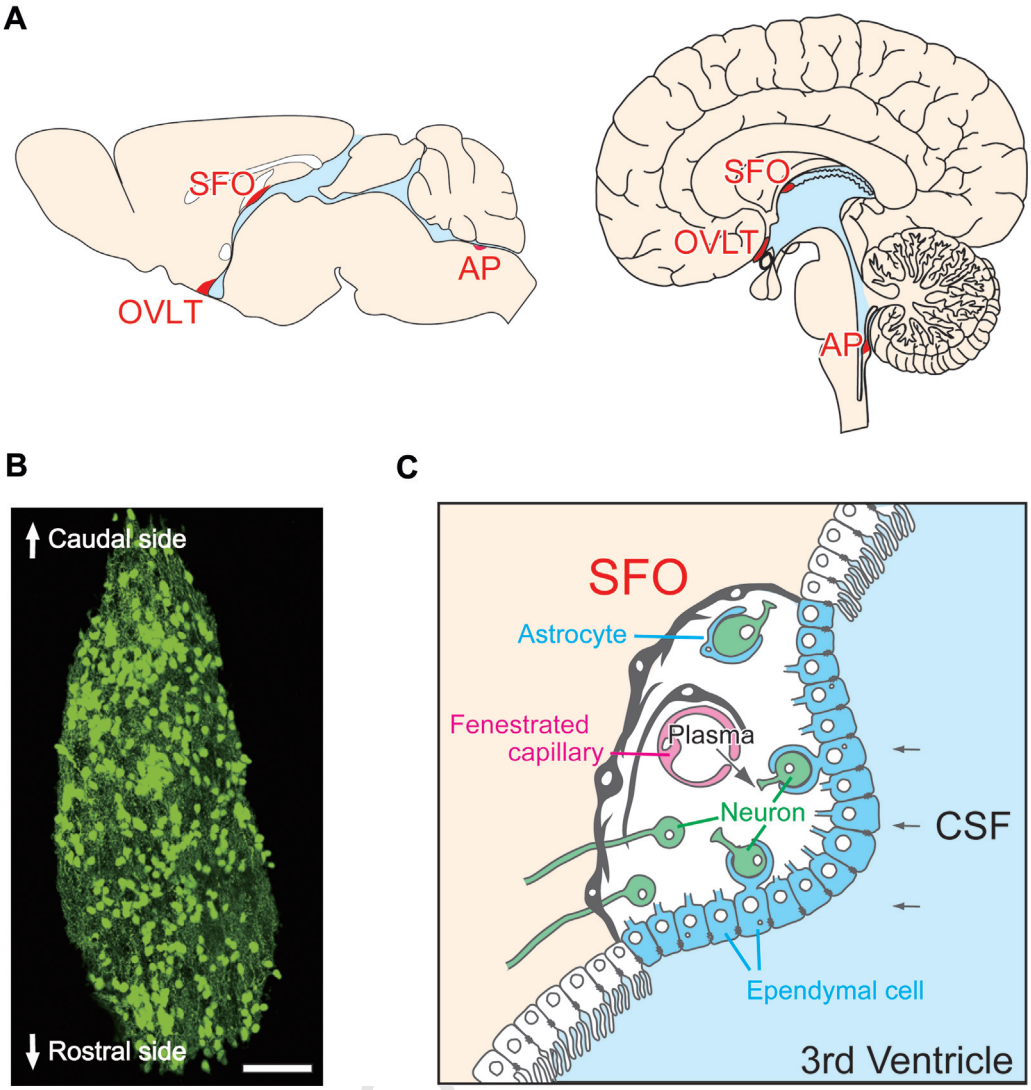

Fig. 1. Position of the sensory CVOs and structure of the SFO. (A) Schematic drawings indicating the position of sensory CVOs (red) in a sagittal view of the mouse (left) and human (right) brains. (B) Whole image of the SFO of GAD-EGFP mice, in which GABAergic neurons are visualized with enhanced green fluorescent protein (EGFP) fluorescence (green). The view from the ventricular side along with the axis perpendicular to the fornix. Scale bar, 100 μm. (C) Schematic drawing indicating the structure of the SFO.

2003; Premer et al., 2013; Song et al., 1992). Among the sensory CVOs, the SFO is the principal site for monitoring Na^+ levels ($[Na^+]$) in body fluids in order to control salt-intake behaviors. This review provides an overview of the SFO and its $[Na^+]$-sensing mechanism by summarizing a series of studies on Na_x by our research group.

2. Location and structure of the SFO

The SFO is a translucent tissue situated on the dorsal aspect of the anterior wall of the third ventricle, which is a part of the hippocampal commissure (fornix) (Fig. 1B; McKinley et al., 2003). The caudal part of the SFO is surrounded by the choroid plexus, which produces cerebrospinal fluid (CSF) by filtering the blood through epithelial cells (Dellmann, 1987). The SFO is located near to the interventricular foramen, through which CSF flows from the lateral to the third ventricle, and has contacts with the CSF through a single layer of Na_x-positive ependymal cells (McKinley et al., 2003).

Blood vessels that branch from the anterior cerebral artery bifurcate into the SFO and form an intricate capillary network with sub-ependymal capillary loops (a capillary plexus) (Dellmann and Simpson, 1976). Some of the capillary have fenestrated capillary endothelium with an expanded perivascular space; this structure markedly enhances the blood-to-tissue transfer of circulating agents (Gross, 1991) (Fig. 1C). Recent studies have indicated that continuous angiogenesis occurs in the SFO of adult rodent brains (Morita et al., 2015; Miyata, 2015), which may contribute to the maintenance of fenestrated capillaries. The ependymal surface of the SFO markedly differs from the surrounding ependymal cells; they are flattened, lack the copious cilia of normal ependymal cells, and have tight junctions between adjacent cells, which block the diffusion of substances between the parenchyma of the SFO and third ventricle (Lind, 1987; Tsuneki et al., 1978). These structural features of the SFO may be suitable for the sensing of plasma and CSF components.

3. SFO as the primary locus of $[Na^+]$ sensing by Na_x

Na_x is an atypical Na channel that was initially classified as a subfamily of voltage-gated Na channels and called Na_v2 (Fig. 2A; Noda and Hiyama, 2005, 2015b). However, the primary structure of Na_x markedly differed from that of the other Na_v channel members, including the key regions for voltage sensing and inactivation (Goldin et al., 2000; Noda and Hiyama, 2015b), and all attempts to

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