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Review

Molecular responses to acidosis of central chemosensitive neurons in brain

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Abstract

Significant advances have been made in understanding how neurons sense and respond to acidosis at the cellular level. Decrease in pH of the cerebrospinal fluid followed by hypercapnia (increased arterial CO_2) is monitored by the chemosensory neurons of the medulla oblongata. Then the intracellular signalling pathways are activated to regulate specific gene expression, which leads to a hyperventilatory response. However, little is known about molecular details of such cellular responses. Recent studies have identified several transcription factors such as c-Jun, Fos and small Maf proteins that may play critical roles in the brain adaptation to hypercapnia. Hypercapnic stimulation also activates c-Jun NH_2-terminal kinase (JNK) cascade via influx of extracellular Ca^{2+} through voltage-gated Ca^{2+} channels. In addition, several transmembrane proteins including Rhombex-29 (rhombencephalic expression protein-29 kDa) and Past-A (proton-associated sugar transporter-A) have been implicated in regulation of H^+ sensitivity and brain acidosis-mediated energy metabolism, respectively. This review discusses current knowledge on the signalling mechanisms and molecular basis of neuronal adaptation during acidosis.

Keywords: H^+-sensitivity; Ventral medullary surface of the medulla oblongata; Hypercapnia-induced genes; Nuclear transcription factor; c-Jun NH_2-terminal kinase; Ca^{2+} channels; Differential display; Glucose homeostasis

Contents

Abbreviations: ASIC, acid-sensing ionic channel; AP-1, activator protein 1; ATF-2, activating transcription factor-2; bZIP, basic leucine zipper; Ca^{2+}/CaM, Ca^{2+}/calmodulin; CRE, cyclic AMP response element; ERK, extracellular signal-regulated kinase; GLUT, glucose transporter; IP_3, inositol triphosphate; JNK, c-Jun NH_2-terminal kinase; MAP, mitogen-activated protein; OGR1, ovarian cancer G-protein-coupled receptor 1; Past-A, proton associated sugar transporter-A; PKC, protein kinase C; PLCβ, phospholipase C-β; VMS, ventral medullary surface.

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1. Introduction

The main components of the respiratory control responsible for autonomic respiration are located in the medulla oblongata [1]. Two defined groups of respiratory neurons are known, the dorsal and ventral medulla. The dorsal group of neurons is located in and near the nucleus of the tractus solitarius (NTS). A change in the arterial partial pressure of CO_2 (P_{CO_2}), O_2 (P_{O_2}) or H^+ regulates the activity of the dorsal group of neurons. The ventral group is a long column of neurons that extends through the nucleus ambiguous and retroambiguous in the ventrolateral medulla. In addition to reacting to peripheral stimuli, the ventral neurons detect changes in the H^+ and CO_2 concentrations in the cerebrospinal fluid (CSF) and brain interstitial fluid. The capacity to detect these changes is called central chemosensitivity.

The H^+ concentration seems to be a stimulant of central chemosensitivity, because the discharge frequency of ventral medullary surface (VMS) neurons in cats increased with lowered pH of CSF [2–5]. Furthermore, according to a review by Ganong [6], the chemoreceptors monitor the H^+ concentration of CSF, including the brain interstitial fluid. Carbon dioxide readily penetrates membranes, whereas H^+ and HCO_3^- penetrate slowly. The CO_2 that enters the brain and CSF is promptly hydrated. The H_2CO_3 dissociates, so that the local H^+ concentration rises. Therefore, the effects of CO_2 on respiration are mainly due to CO_2 movement into the CSF, where it increases the H^+ concentration and stimulates receptors/sensors for H^+. Thus, the direct stimulant of the central chemosensitive neurons may be H^+ rather than CO_2 [7,8].

Whether there are H^+-sensitive neurons in the brainstem is not known. In the last 40 years, many attempts have been made to clarify the localization of H^+-sensitive neurons. The central chemosensitive neurons responsible for respiratory regulation are distributed over the VMS, which is bathed in CSF, and that these neurons are stimulated by excess H^+ and CO_2 to induce a hyperpneic or tachypneic response [5,8–10]. Mitchell et al. [8] initially reported that respiration was stimulated when pledgets soaked with fluid containing high concentrations of CO_2 and H^+ were placed on circumscribed areas in the VMS. Then, many investigators tried to show that the VMS neurons are sensitive to CO_2 and H^+ [5,8,9]. The application of acid or electrical stimulation to the VMS increased ventilation [10]. The firing rate of the VMS neurons was increased by reducing the extracellular fluid pH [2]. On the other hand, many investigators have shown that H^+-sensitive neurons also exist in the extra-VMS regions, specifically in the deep ventrolateral medulla [11,12], NTS [13–15], the vicinity of the NTS [12,16], nucleus raphe [17,18], nucleus locus caeruleus (LC) [19], the vicinity of the LC [15], and the retrotrapezoid nucleus [20]. The discoveries of chemosensitive neurons in many nuclei disproved that the VMS was the unique site of central chemosensitive neurons.

It is still not clear how H^+ excites the H^+-sensitive (chemosensitive) neurons in the VMS. There is some evidence for H^+-sensing ionic channels in sensory neurons: H^+ activates Na^+ conductance in small neurons of the rat trigeminal ganglion [21]; H^+ activates Ca^{2+} channel in rat sensory neurons [22]; a stepwise reduction in extracellular pH induced an increase in Na^+ current in small dorsal root ganglion cells of the frog [23]; and H^+ and capsaicin share a common mechanism of neuronal activation in rat dorsal root ganglion cells [24]. The H^+-sensitive neurons in the VMS may also have H^+-sensing ionic channels/sensors or similar mechanisms for reacting to extracellular H^+ changes. Few studies have investigated the identification of chemosensitive molecules responsible for respiratory regulation in the VMS. Recently, Waldmann et al. succeeded in cloning the H^+-gated cation channel (ASIC, for acid-sensing ionic channel) that belongs to the amiloride-sensitive Na^+ channel/degenerin family of ion channels [25]. ASIC is expressed in dorsal root ganglia and is also distributed widely throughout the brain. The H^+-gated cation cannel is activated transiently by rapid extracellular acidification and induces cation (Na^+, Ca^{2+}, K^+) influx. More recently, it has been shown that ovarian cancer G-protein-coupled receptor 1 (OGR1), previously described as a receptor for sphingosylphosphorylcholine, acts as an H^+-sensing receptor stimulating inositol phosphate (IP) formation [26]. The receptor is stabilized in an inactive state at pH 7.8 and fully activated at pH 6.8. Pertussis toxin did not inhibit IP formation measured at pH 7.0, indicating that OGR1 acts through Gq. Ovarian cancer G-protein-coupled receptor 4 (OGR4) also responds to pH changes, the receptor promotes cAMP formation through Gs. ASIC, OGR1 and 4 are candidates for chemosensitive molecules responsible for respiratory regulation in the VMS. However, it has been no evidence that these channel/receptors are involved in the central chemosensitivity for respiratory regulation.

Until now, detailed mechanisms responsible for central chemosensitivity in the ventral medulla has been an exceedingly difficult task. In this review, to clarify the H^+-sensitive mechanism of respiratory regulation, we will present our results and discuss the following points:

1. Detection of H^+-sensitive neurons.
2. Analysis of intracellular signalling pathway for H^+-induced c-Jun expression.
3. Profiling of H^+-induced genes.