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Review

Regulation of pH in the mammalian central nervous system under normal and pathological conditions: Facts and hypotheses

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Abstract

The maintenance of pH homeostasis in the CNS is of key importance for proper execution and regulation of neurotransmission, and deviations from this homeostasis are a crucial factor in the mechanism underlying a spectrum of pathological conditions. The first few sections of the review are devoted to the brain operating under normal conditions. The article commences with an overview of how extrinsic factors modelling the brain at work: neurotransmitters, depolarising stimuli (potassium and voltage changes) and cyclic nucleotides as major signal transducing vehicles affect pH in the CNS. Further, consequences of pH alterations on the major aspects of CNS function and metabolism are outlined. Next, the major cellular events involved in the transport, sequestration, metabolic production and buffering of protons that are common to all the mammalian cells, including the CNS cells. Since CNS function reflects tight interaction between astrocytes and neurons, the pH regulatory events pertinent to either cell type are discussed: overwhelming evidence implicates astrocytes as a key player in pH homeostasis in the brain. The different classes of membrane proteins involved in proton shuttling are listed and their mechanisms of action are given. These include: the Na^+/H^+ exchanger, different classes of bicarbonate transporters acting in a sodium-dependent- or -independent mode, monocarboxylic acid transporters and the vacuolar-type proton ATPase. A separate section is devoted to carbonic anhydrase, which is represented by multiple isoenzymes capable of pH buffering both in the cell interior and in the extracellular space. Next, impairment of pH regulation and compensatory responses occurring in brain affected by different pathologies: hypoxia/ischemia, epilepsy, hyperammonemic encephalopathies, cerebral tumours and HIV will be described. The review is limited to facts and plausible hypotheses pertaining to phenomena directly involved in pH regulation: changes in pH that accompany metabolic stress but have no distinct implications for the pH regulatory mechanisms are not dealt with. In most cases, the vast body of knowledge derived from *in vitro* studies remains to be verified in *in vivo* settings.

Keywords: pH; Astrocytes; Neurons; Na^+/H^+ exchanger; Bicarbonate transporters; Monocarboxylate transporters; V-ATPase; Carbonic anhydrase; Epilepsy; Hyperammonemia; Cerebral tumours; Hypoxia; HIV

1. Introduction

The maintenance of pH homeostasis is essential for all mammalian cells because the hydrogen ion is ubiquitously involved in cell metabolism and function. With regard to metabolism the areas of the involvement include: protonation and deprotonation of protein molecules, modulation of membrane lipid fluidity, maintenance of the ionic status of cell metabolites, signal transduction within and between cells, ATP production, control of DNA and protein synthesis, cell volume regulation, apoptosis and posttranslational modification of proteins and sorting of lipids. At the functional level, protons are a factor in exocytosis, proliferation and fertilization. These diverse roles of the hydrogen ion have been exhaustively reviewed in a number of articles that have appeared in the last decade (Kaila and Ransom, 1998; Demaurex, 2002; Chesler, 2003; Lagadic-Gossmann et al., 2004; Paroutis et al., 2004; Peracchia, 2004; Mulkidjanian et al., 2005; Schreiber, 2005; Orlov and Hamet, 2006).

In the central nervous system (CNS), changes in pH modulate events specific for its function: neuronal excitability, synaptic transmission, neurotransmitter uptake and intercellular communication through gap junctions. The pH sensitivity is a feature of many membrane proteins that are of key importance for neurotransmission. It has also been suggested that pH gradients may be important in neuronal differentiation,

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development of growth cones and neurites, regulation of pH in dendrite spines, learning and memory (Sánchez-Armáss et al., 2006). Therefore, maintenance of adequate pH is a key factor in the functioning of the CNS.

2. Extrinsic factors causing pH shifts in the CNS cells

2.1. Amino acid neurotransmitters or their analogues

Glutamate (Glu) and its receptor agonists, *N*-methyl-D-aspartate (NMDA) and kainate (KA), cause acidification of neurons and astrocytes (Hartley and Dubinsky, 1993; Irwin et al., 1994; Wang et al., 1994; Brune and Deitmer, 1995; Canzoniero et al., 1996; Rose and Ransom, 1996; Zhan et al., 1997, 1998). A fall in intracellular pH (pH_i) evoked by Glu is followed by a biphasic alkaline-acid shift of extracellular pH (pH_e) (Chen and Chesler, 1992a). Mechanism of glutamate-induced pH shifts are proposed to be HCO_3^--independent, as an increase of pH_e is amplified by inhibition of carbonic anhydrase (CA) (Chen and Chesler, 1992b). In neurons, intracellular acidification caused by Glu may be a result of elevated production of metabolic acids (carbon dioxide and lactate) and activation of mitochondrial Ca^{2+}/H^+ exchange (Wang et al., 1994; Werth and Thayer, 1994). The acidification of astrocytes by Glu is due to the fact that uptake of Glu is coupled to inward transport of H^+ (Brune and Deitmer, 1995; Rose and Ransom, 1996). The details of the mechanisms underlying ion exchange and its implications for pH regulation will be discussed in the following sections.

Activation of group I metabotropic glutamate receptors (mGluRs) by metabotropic glutamate receptor agonist, (1S,3R)-1-aminocyclopentane-1,3-dicarboxcylic acid, modulates pH_i of astrocytes and neurons (Amos et al., 1998). The effect occurs in bicarbonate buffered medium and while the pH of neurons increases slightly, astrocytes become considerably alkaline. The authors propose that the pH shift is executed by a Ca^{2+}-dependent mechanism: activation of subtype 5 metabotropic glutamate receptor would be the cause of elevation of $[Ca^{2+}]_i$ (Amos and Chesler, 1998). The above mechanism is proposed to supplement the more commonly recognised mechanism underlying the depolarization-induced alkalinization (DIA) of glial cells (see Section 2.4).

D-Aspartate, a non-metabolizable analog of L-glutamate, was shown to acidify the cytoplasm of rat astrocytes (Brune and Deitmer, 1995; Rose and Ransom, 1996). Since D-aspartate does not interact with Glu receptors of any class and does not evoke an increase in $[Ca^{2+}]_i$ (Brune and Deitmer, 1995), D-aspartate-induced acidification appears to result from uptake-related base extrusion but not from H^+ influx.

2.2. Gamma-aminobutyric acid

Stimulation of both neurons (Pasternack et al., 1993, 1996; Trapp et al., 1996a) and astrocytes (Kaila et al., 1991, 1992) by gamma-aminobutyric acid (GABA) leads to acidification of cytoplasm. Intracellular acidification and the accompanying extracellular alkalization induced by GABA are mediated by $GABA_A$ receptor-coupled Cl^- channels that allow for HCO_3^- efflux out of the cell (Chesler and Chen, 1992; Bonnet and Bingamnn, 1995). Inhibition of carbonic anhydrase, the enzyme producing HCO_3^- (see Section 5.5) reduced the GABA-induced acidification (Pasternack et al., 1993).

2.3. Glycine

Lückermann et al. (1997) corroborated earlier findings that glycine (Gly) induces a substantial decrease of pH_i of respiratory neurons. Gly is an inhibitory neurotransmitter whose receptors are permeable to both chloride and bicarbonate (Bormann et al., 1987). Therefore it was proposed that, like with GABA, acidification is due to the efflux of HCO_3^-. Green et al. (2003) reported that the dynamics of glycine-evoked pH changes in neurons depends upon the presence or absence of bicarbonate. When bicarbonate is present, Gly-induced acidification is preceded by alkalinization, while in the nominal absence of bicarbonate Gly produces instant acidification. In the presence of bicarbonate Gly induces a biphasic response in membrane potential: hyperpolarization followed by depolarization. These authors proposed that acidification is a result of membrane depolarization causing calcium influx but not bicarbonate efflux (although the initial alkalinization may be the result of bicarbonate influx). Gly receptors are likewise sensitive to pH: protons inhibit the Gly-receptor-mediated currents (Aubrey et al., 2000; Chen et al., 2004).

2.4. Extracellular K^+ or electrical stimulation

In neurons, depolarizing stimuli in most cases evoke an increase in pH_e and a decrease in pH_i (Chen and Chesler, 1992c; Grichtchenko and Chesler, 1996), although sporadically a rise of their intracellular pH has been observed (OuYang et al., 1995). Neuronal activity results in a decrease of pH_i due to (i) H^+ influx caused by activation of the Ca^{2+}/H^+ pump, (ii) HCO_3^- efflux through ligand-gated anion channels and stimulation of metabolism and in consequence and (iii) increased production of lactate and CO_2 (for a review see Bevensee and Boron, 1998). The influx of H^+ mediated by the plasmalemmal Ca^{2+}/H^+-ATPase is associated with excitation whereas the efflux of HCO_3^- through activated GABA- or Gly-gated anion channels is related to the inhibition (for a review see: Ballanyi and Kaila, 1998). The depolarisation-induced acidification of neuronal cytoplasm may be an effect secondary to Ca^{2+} extrusion (Benham et al., 1992; Khodorov et al., 1995; Trapp et al., 1996a,b; Lückermann et al., 1997), a step that deserves more specific comment. Ca^{2+}/H^+ pump is the major mechanism of Ca^{2+} extrusion in neurons: it mediates the ATP-dependent exchange of extracellular H^+ for intracellular Ca^{2+}. Therefore, extrusion of Ca^{2+} is connected with acidification of cell cytoplasm (Trapp et al., 1996b). In neurons an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is paralleled by a fall in pH_i or vice versa—high pH_e inhibits the activity of plasmalemmal Ca^{2+}/H^+ pump (Deitmer and Rose, 1996); an increase in intracellular H^+ concentration ($[H^+]_i$) may cause an increase in $[Ca^{2+}]_i$ due to reverse activity of the Na^+/Ca^{2+}