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REVIEW ARTICLE

The Value of pH Sensors in Maintaining Homeostasis of the Nervous System

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Abstract—Maintaining pH homeostasis is vital for all mammalian cells since hydrogen and hydroxyl ions perform important functions in the regulation of metabolism. Today, it is believed that maintaining the pH in the neutral range (pH 7.2–7.6) in the nervous system is necessary for its normal functioning, while small changes in pH affect the excitability of neurons, synaptic transmission, neurotransmitter transport and intercellular communication. Sensitivity to changes in pH is a feature of many membrane proteins that play a key role in neurotransmission. Recent studies have revealed the presence in the nervous system of protein molecules, which are sensors of a significant change in the pH of the extracellular environment in both acidic (to pH 5) and alkaline (to pH 9) areas. It has been established that a change in the pH of the extracellular environment causes various cellular responses in which ion channels, ionotropic receptors, G protein-coupled receptors, connexins and receptor tyrosine kinases are involved. The presence of these proteins in the nervous system suggests that local acid–base balance shifts are one of the key factors regulating neuronal activity. This review describes the properties of neuronal pH-sensitive proteins.

Keywords: acid–base balance, pH in the nervous system, pH sensors, IRR

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INTRODUCTION

Maintaining pH homeostasis is vital for all mammalian cells, as hydrogen and hydroxyl ions play important roles in regulating metabolism. The processes that take place depending on the balance of acid–base balance include: protonation and deprotonation of protein molecules, regulation of enzymatic activity, modulation of membrane fluidity, maintaining the ionic status of cellular metabolites, signal transmission inside and between cells, ATP synthesis, control of DNA synthesis and proteins, regulation of cell volume, apoptosis, posttranslational modification of proteins and lipid sorting.

It has been experimentally established that a change in the pH of the extracellular medium causes various cellular responses in which ion channels, ionotropic receptors, G protein-coupled receptors, receptor tyrosine kinases, connexins are involved. The presence of these proteins in the nervous system suggests that local shifts in acid–base balance are one of the key factors that regulate neuronal activity. This review describes the properties of neuronal pH sensors and evidence supporting this hypothesis.

Maintaining pH homeosasis in the nervous system. The pH values of the blood and, especially, the brain are maintained at a fairly stable level [1–3]. The regulation of acid–base balance involves several processes related to the buffer properties of blood, excretory function of the kidneys, and gas exchange in the lungs. Buffer properties are determined by the content in the blood or other liquids of bicarbonates, inorganic phosphates and proteins, which combine with an excess of acids or bases and form substances that do not affect pH. The kidneys regulate acid–base balance by increasing or decreasing the concentration of ions HCO_3^- and H^+ in body fluids. At the same time, pH changes occur slowly, over several hours or even days. A much faster regulation of pH (a few minutes) occurs through gas exchange. Depending on the state of acid–base balance, the respiratory cycle changes so that through an increase or decrease in the supply of oxygen and the release of carbon dioxide, the acid–base balance of the brain can be normalized.

Change in pH (or pCO_2) induces a coordinated response in the nervous system that modulates respiration control to maintain arterial pCO_2 levels. This phenomenon is known as central chemoreception and involves activation of neurons sensitive to H^+ ions or CO_2 through several yet poorly studied molecular pro-

Abbreviations: ASIC, acid-sensitive ion channel; RTN, retrotrapezoid nucleus, Kir, Inwardly-rectifying potassium channels; VGCC, voltage-gated calcium channel; NMDAR, *N*-methyl-D-aspartate receptor; GABA receptor, gamma-aminobutyric acid receptor; IRR, insulin-related receptor; IR, insulin receptor; IGF-IR, insulin-like growth factor I receptor; IGF-I, insulin-like growth factor I; NGF, nerve growth factor.

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cesses in different parts of the hindbrain, including the retrotrapezoid nucleus (RTN), parafacial respiratory group (pFRG), Bötzinger nucleus, pre-Bötzinger complex (preBötC), rostral and caudal ventral respiratory group (rVRG and cVRG), caudal nucleus tractus solitarious (cNTS), lateral hypothalamus (LHA), fastigial nucleus (FN), medullary raphe and locus coeruleus [4, 5]. At the molecular level, the sensitivity of neurons to pH changes is determined by the expression of ion channels, ionotropic receptors, and G protein-coupled receptors. Recent studies also point to the important role of astrocytes in maintaining the physiological pH level in the brain. Several mechanisms of chemoreception of astrocytes have been proposed. To a change in the concentration of H^+ TRP ion channels (transient receptor potential channels) expressed on the surface of astrocytes may be sensitive [6], Ca^{2+}-activated K^+ channels, voltage-dependent K^+ channels and potassium channels Kir [7]. Carbonic anhydrase catalyzes the conversion of CO_2 into carbonic acid, which in turn dissociates to form HCO_3^- and H^+. Increased intracellular concentration of H^+ ions can activate ion channels, transporters and exchangers, thus causing a cellular response to an increase in pCO_2 [5]. CO_2 can directly affect connnexins of pH-sensitive astrocytes. It has also been shown that acidification activates Na^+/HCO_3^- transporter in astrocytes of the brain stem, which leads to an increase in the transport of Na^+ ions inside the cell. Increased intracellular Na^+ activates Na^+/Ca^{2+} exchanger, Na^+ is removed from the cell in exchange for Ca^{2+} ions. Increased intracellular Ca^{2+} concentration leads to an increase in exocytosis of vesicles containing ATP [8]. ATP, in turn, leads to the activation of chemosensitive neurons RTN [9, 10]. In the following, pH-sensitive proteins expressed in the brain will be examined in detail.

EXTRACELLULAR pH SENSORS IN THE BRAIN

Ion Channels

ASICs. The response of neurons to acidification of the extracellular medium was discovered more than 25 years ago, but the physiological significance of this observation is still incomprehensible [11]. Key receptors for extracellular protons are ion channels ASIC (acid-sensing ion channels) (Table 1). These channels belong to the Degenerin/Epithelial Na^+ family of channels and are widely expressed in the nervous system of animals. There are seven known ASIC isoforms encoded by the four genes ASIC1a, ASIC1b, ASIC1b2, ASIC2a, ASIC2b, ASIC3 and ASIC4 [12]. These channels function both homo-and hetero-multimers. Homomultimers of ASIC1a, activated by extracellular protons, conduct Na^+ and Ca^{2+} ions [13]. ASIC1b conducts Na^+ and K^+ ions while other forms conduct only Na^+ ions [14]. Different ASIC isoforms have different pH sensitivity (Table 1), ASIC1a and ASIC3 are activated when the pH drops below 7, ASIC1b at pH below 6.5, and ASIC2a at pH below 5 [15].

It has now been shown that ion channels ASIC mediate most physiological and pathological functions associated with acidosis. It was shown that the ASIC1a channel mediates cell death caused by acidosis in coronary artery disease [12, 13]. The nature of ASIC activation in the ischemic brain, leading to cell death, is rather complicated and involves the participation of endogenous amines and other pH-sensitive proteins, which leads to an increase in the intracellular concentration of calcium ions and cell death [12]. ASIC channels also play various roles in the pathophysiology of pain, ischemic stroke, and psychiatric diseases [16]. Experimental data indicate the important role of ASIC channels in chemoreception in various regions of the brain. Acidification in the lateral hypothalamus stimulates respiration by activating the ASIC1a channel on the surface of orexin neurons [17]. The role of ASIC in respiration regulation is also shown in NTS neurons (nucleus tractus solitarious) [18] and ventrolateral medulla (VLM) [19]. Acidification of the rat ventrolateral medulla by microinjection of artificial cerebrospinal fluid with pH 6.5 stimulated respiration, amiloride and PcTx1 inhibited this effect, suggesting the participation of homomeric ASIC1a or heteromeric ASIC1a/2 channels in central chemoreception [19].

Two-Pore Domain Potassium Channels (K_{2P} channels). Another example of ion channels that respond to pH changes are the two-pore potassium channels TASK, TALK, TREK. In the nervous system, the pH-sensitive channels TASK-1, TASK-2 and TASK-3 are detected. Moreover, TASK-2 is expressed only in some areas of the brain stem, including RTN (retrotrapezoid nucleus) [20]. The RTN is a cluster of neurons that are activated by hypercapnia (high CO_2 in the blood) and stabilize arterial P_{CO_2} by regulating the ventilation of the lungs. For these channels, the currents are maximum at alkaline pH values; with decreasing pH, the channel conductivity decreases significantly. It was shown that for TASK-1 at pH 7.7, 90% of the maximum possible current is observed, while at pH 6.7 only 10% [21]. In the case of TASK-3, with a decrease in extracellular pH from 7.2 to 6.4 and to 6.0, a decrease in current by 74 and 96% was observed, respectively. [22]. TASK-2 shows 90% of the maximum possible current at pH 8.8 and only 10% at pH 6.5 [23].

For the TASK-1 and TASK-3 channels, a histidine residue was found at position 98, which is responsible for the pH sensitivity of the channel; it is located next to the ion-conducting pore. Mutation of this residue leads to a loss of pH sensitivity of the channels [22]. The pH sensitivity mechanism of TASK-2 is different. In a similar position of the TASK-2 channel, the

Table 1. pH sensors in the nervous system

		$pH_{0.5}$/pKa	pH effect	Links
			Ion channels	
ASICs	ASIC1a	5.8–6.6	Activated by decreasing extracellular pH < 7	[15]
	ASIC1b	6.1–6.2	Activated by decreasing extracellular pH < 6.5	
	ASIC2a	4.5–4.9	Activated by decreasing extracellular pH < 5	
	ASIC3	6.4–6.6	Activated by decreasing extracellular pH < 7	
K_{2P} channels	TASK-1	7.3	Inhibited by a decrease in extracellular pH < 8.4	[21]
	TASK-3	6.0–6.6	Inhibited by a decrease in extracellular pH < 7.4	[22, 123]
	TASK-2	8.0–8.3	Inhibited by extracellular pH < 9.1	[23, 124]
	TALK-1	–	Activated by extracellular pH > 7.8 (max above 10)	[35]
	TALK-2	9.5	Activated by extracellular pH > 7.8 (max above 10)	[36]
	TREK-1	7.3	Activated by extracellular pH > 6.9	[37]
		6.0	Activated by decreasing intracellular pH < 7.2	[38]
	TREK-2	7.3	Activated by decreasing extracellular pH < 8.5	[37]
		–	Activated by decreasing intracellular pH < 7.2	[39]
	TRESK	–	Activated by increasing extracellular pH in the range of 5.6–9	[40]
		–	Activated by increasing intracellular pH in the range of 5.6–9	
Kir	Kir1.1	6.5–7.2	Inhibited by lowering intracellular pH	[48]
	Kir2.3	6.8–7.4	Inhibited by a decrease in extracellular pH < 7–7.5	[48]
		6.7	Inhibited by lowering intracellular pH < 7	[48]
	Kir2.4	7.14	Activated by an increase in extracellular pH > 6 (max 8.5–9)	[125]
	Kir4.1	6.0–6.1	Inhibited by lowering intracellular pH	[48]
	Kir4.2	6.7–7.1	Inhibited by lowering intracellular pH	
	Kir4.1–Kir5.1	6.8–7.5	Inhibited by lowering intracellular pH	
	Kir4.2–Kir5.1	7.6	Inhibited by lowering intracellular pH	
	Kir6.1	7.1	Activated by lowering intracellular pH	[14]
	Kir6.2	7.2	Activated by lowering intracellular pH	[14]
Voltage-dependent K^+ channels	Kv1.2	4.9	Activated by extracellular pH > 4	[45, 46, 48]
	Kv1.3	–	Activated by increasing extracellular pH	[44]
	Kv1.4	6.3/7.5	Activated by extracellular pH > 5.5	[45, 48]
	Kv1.5	6.2–7.2	Activated by extracellular pH > 5.5	[46, 48]
	Kv2.1	<6.2	Activated by increasing extracellular pH	[48]
	Kv11.1	–	Acidification [extracellular pH (pHo) 8.5–6.5] accelerated HERG deactivation	[47]
TRPs	TRPV1	5.4	Activated by increasing extracellular pH	[126]
	TRPV4	5–5.4	Activated by increasing extracellular pH	[127]
	TRPC4	7.2 (activation)	Activation with a decrease in pH below 8.0, 6.5–6.0 maximum activation, inhibition <6.0–4.2	[49]
		5.2 (inhibition)		
	TRPC5	7.3 (activation)	Activation with a decrease in pH below 8.0, 6.5—maximum activation, inhibition <6.5–5.5	[49]
		6.0 (inhibition)	Inhibited by decreasing extracellular pH	
	TRPC6	5.7	It is activated when the pH rises above 6.0, the activation maximum is 9.0, a further decrease in pH to 10.0 inhibits the channel	[49]
	TRPP2	7.5 (activation)		[52]

Table 1. (Contd.)

		$pH_{0.5}$/pKa	pH effect	Links
			Ionotropic receptors	
GABA	α1β2γ2 α3β2γ2	7.7	It is inhibited by lowering the pH in the range from 8.5 to 6.4	[56]
NMDAR		6.9–7.3	Inhibition upon lowering pH from 8.4 to 6	[65, 66]
P2X	$P2X_1$	6.3	Inhibition upon lowering of extracellular pH	[59]
	$P2X_2$	7.1–7.3	Activated by lowering pH	[59]
	$P2X_3$	6.0	Inhibition upon lowering pH	[59]
	$P2X_4$	6.8	Inhibition upon lowering pH	[59]
	$P2X_5$	–	Inhibition upon lowering pH in the range of 8 to 5.5	[128]
	$P2X_7$	6.1	Inhibition upon lowering pH	[59]
	$P2X_{2/3}$	–	Activated at pH 6.3, inhibited at pH 8.3	[59]
	$P2X_{2/6}$	7.1 (activation)	It is activated by lowering the pH from 8 to 6.3, when lowering the pH below 6.3 it is inhibited	[60]
	$P2X_{1/5}$	–	Inhibited at pH above and below 7.3	[59]
			G protein-coupled receptors	
GPCRs	OGR1	7.48	Activated by decreasing extracellular pH, maximum 6.8–7, at pH below 6.5 inhibition	[70]
	GPR4	7.55	Activated by decreasing extracellular pH, maximum 6.8–7, at pH below 6.5 inhibition	[70]
	TDAG8	7.0–7.1	Activated by decreasing extracellular pH, 6.5–6.8—maximum, below 6.5 inhibition	[72]
	G2A	–	Activated by decreasing extracellular pH below 7.6	[71]
			Receptor tyrosine kinases (RTK)	
RTK	IRR	8.4	Activated by extracellular pH above 7.9	[77]
	ErbB2	8.6	Activated by extracellular pH above 8	[96]
	c-Met	8.4	Activated by extracellular pH above 8	[102]
			Other proteins	
Connexins	Cx26	7.2–7.3	Activated by extracellular pH above 6.6	[112]
	Cx43		Activated by increasing extracellular pH from 7.4 to 8.5	[111]
	Cx45	7.0	Activated by increasing intracellular pH > 6.4	[115]
	Cx57	7.4	Activated by increasing intracellular pH > 7.2	[114]
	Cx50 > Cx46 > Cx45 > Cx26 > Cx37 > Cx43 > Cx40 > Cx32	7.2–6.5	Inhibition with a decrease in intracellular pH	[113]
Receptor guanylyl cyclase	GCY-14		Activated in pH range 8–10.9	[118]
Cl^- channel	SsCl	7.55	Activated by extracellular pH > 6.5	[129]
	pHCl	7.33	Activated by extracellular pH > 6.5	[130]

asparagine residue is located, the replacement of which with histidine leads to a paradoxical decrease in the channel's pH sensitivity. It has been shown that several charged amino acid residues from the loop between the first transmembrane domain and the pore-forming domain contribute significantly to the pH sensitivity of the channel [24]. It is suggested that the physiological role of TASK channels is to control cellular excitability [25]. It has been shown that increased expression of TASK, in particular, TASK-3 contributes to K^+ dependent apoptosis of cerebellar neurons [26]. Apoptosis can be prevented if cells are cultured at acidic pH values that inhibit TASK activity [26]. The physiological importance of TASK-3 is also

indicated by increased expression of the ion channel in various types of human tumors [27, 28]. Specific expression and experimental data with knockout animals indicate that TASK-2 is one of the main mediators of respiratory chemosensitivity, the brain's ability to sense CO_2 and/or pH and in accordance with this change respiration, thereby regulating the gas composition of the blood and pH [29, 30]. It has been shown that HCO_3^- ions can directly regulate the activity of chemosensitive neurons RTN, presumably through TASK-2 [31].

TASK-1 and TASK-3 mRNAs were detected in neurons of locus coeruleus and raphe nuclei [32]. Recent studies indicate that TASK-1 and TASK-3 also contribute to central regulation of respiration, acting together in the perception of local pH changes in VLM neurons. TASK blocking by microinjection of the non-selective TASK antagonist bupivacaine (BUP), the specific TASK-1 antagonist anandamide (AEA), or the specific TASK-3 antagonist ruthenium red (RR) in the VLM, increased phrenic nerve discharge (iPND), decreased respiratory time (Ti), and enhanced the respiratory drive (iPND/Ti). Microinjection of an alkaline artificial cerebrospinal fluid reduced the activity of the respiratory center, this effect was inhibited by the addition of AEA [33]. In addition, in mice with double knockout for the genes encoding TASK-1 and TASK-3, a respiratory phenotype was observed that was different from the phenotypes with single knockouts TASK-1 and TASK-3. This phenotype was characterized by a markedly increased tidal volume and an abnormal increase in ventilation during hyperoxia (100% O_2) TASK-1 and TASK-3 appear to perform various specific tasks in the complex processes underlying chemoreception and respiratory control [34].

The channels TALK-1, TALK-2 (TASK-4) also have pH sensitivity. These channels are activated by alkalizing the extracellular medium in the pH range 7.5–10. The pH sensitivity of TALK-1 and TALK-2 is shifted to the alkaline side compared to TASK-1, TASK-3, and TASK-2. Their currents are largely (TALK-1) or almost completely (TALK-2) inhibited at physiological pH 7.4, and maximum activation is achieved above pH 10 [35, 36]. The ion channels TREK-1 and TREK-2 are sensitive to changes in both extracellular and intracellular pH. TREK-1 is activated when an increase in extracellular pH > 6.9, reaching a maximum of activation at a pH of about 8. TREK-2, on the contrary, is activated when the pH drops below 8.5, with a maximum of activation at a pH of about 6 [37]. In this case, intracellular acidification below pH 7.2 causes activation of both channels [38, 39].

TRESK channels are blocked by extracellular and intracellular acidification and are activated by extracellular and intracellular alkalization of the medium [40]. Changes in extracellular pH from 7.3 to 5.6 and 8.9 led to inhibition (80%) and increase (120%) of TRESK currents, respectively, from the channel activity observed at pH 7.3. The same effect was observed with changes in intracellular pH. Changes in pH from 7.3 to 5.6 and 8.9 led to inhibition (39%) and increased (140%) of TRESK currents, respectively [40]. TRESK is the main background channel K_{2P} in DRG neurons; knockout of the TRESK gene showed that this channel plays a role in the regulation of the excitability of DRG neurons [14].

Potassium channels Kir. Another potassium channel that responds to pH changes is the Kir potassium channel (Inwardly-rectifying potassium channels). These channels are characterized in that the incoming current of potassium ions passes through them with greater ease than the outgoing current. The Kir channel family consists of at least 16 different subunits, which are divided into seven subfamilies (Kir1.x–Kir7.x). All Kir channels consist of 4 α-subunits forming homomeric or heteromeric channels with different properties [41]. Kir potassium channels regulate various processes, including cellular excitability, vascular tone, heart rate [41]. Kir2.3 is expressed in the brain, mainly in the forebrain and olfactory bulb. Extracellular protons inhibit currents Kir2.3, at the same time, at alkaline pH 8.5 an increase in the incoming current was observed [42]. Kir2.3 can also be activated by increasing intracellular pH in the range from 6 to 7. Potassium channel Kir 2.4 is activated by increasing extracellular pH > 6, peaking at pH 8.5–9. pH-sensitive potassium channels are also expressed in the brain Kir1.1, Kir4.1, Kir4.2, Kir5.1, Kir6.1, Kir6.2. These channels are highly sensitive to changes in intracellular pH in the physiological range. The activity of potassium channels Kir1.1, Kir4.1, Kir4.2 and Kir5.1 is inhibited by decreasing intracellular pH. Kir6.1 and Kir6.2 are activated by decreasing intracellular pH, reaching a maximum of activation at pH 6.5–6.8, with a further decrease in pH, the channel is inhibited [14]. Kir5.1 subunits do not form functional homomeric channels, but predominantly heteromerize with Kir4.1 subunits in astrocytes, in situ hybridization shows a high level of expression of Kir4.1 and Kir5.1 in RTN. pH-sensitive currents were recorded in RTN astrocytes, which were inhibited by the addition of specific inhibitors of Kir4.1 and Kir5.1 channels [43]. Thus, the heteromeric Kir4.1–Kir5.1 channels are considered as possible candidates for the role of pH sensors in RTN astrocytes. Since these channels are sensitive to changes in intracellular pH, it is assumed that the effect observed in RTN astrocytes is mediated by the Na^+/HCO_3^- cotransporter [43].

Voltage-dependent K^+ channels (Kv). Other pH-sensitive molecules in neurons are Kv channels. Kv channels, consisting of subunits containing six transmembrane segments, are regulated by changes in membrane potential. Inactivation of the activated channel Kv1.3 is delayed by a decrease in extracellular pH [44] whereas inactivation of the Kv1.2, Kv1.4,

Kv1.5 and Kv11.1 channels is accelerated by extracellular acidosis [44–47], but sensitivity to changes in pH varies widely among Kv channel subunits. Kv1.2 and Kv2.1 are relatively insensitive to inhibition upon lowering extracellular pH, with pK 5 and <6.2 [48]. In contrast, Kv1.4 and Kv1.5 are more sensitive to inhibition by decreasing extracellular pH, with pK 6.3 [45] and 6.2–7.2 [48], respectively. Interestingly, Kv1.4 appears to be very sensitive to inhibition when lowering intracellular pH with a pK of 7.5 [48]. The effect of acid pH on Kv1.2 currents depends on the potential, the more positive the potential, the less inhibition. Whereas the effect of acid pH on Kv1.4 currents was independent of voltage [45].

The role of Kv channels in central chemoreception is not clear. The fact that these channels are sensitive to changes in both intracellular and extracellular pH makes them possible targets in hypercapnia. TEA and 4-aminopyridine Kv channel inhibitors have been shown to reduce the effect of hypercapnia on chemosensitive neurons in the LC and NTS regions, suggesting the participation of Kv channels in chemoreception [48].

TRPs. To a change in the concentration of H^+ TRP ion channels (transient receptor potential channels) can be sensitive. There are seven families of TRP channels: TRPC, TRPV, TRPM, TRPA, TRPP, TRPML and TRPN. These channels are widely expressed on the plasma membrane in various cells, including neurons. Extracellular stimuli that activate TRP channels are also diverse. pH-sensitive channels include TRPV1, TRPV4, TRPC4, TRPC5 and TRPC6 channels. TRPV1 is a nonselective cation channel that is activated at a pH below 6 and predominantly conducts Ca^{2+} ions. According to some reports, TRPV1 can conduct H^+ ions causing intracellular acidification, which can activate other ion channels sensitive to intracellular pH [14]. Like TRPV1, the TRPV4 channel also is activated when the pH drops below 6. Channels TRPC4 and TRPC5 are activated at more physiological pH values from 7.4 to 6.5. With a further decrease in pH below 6.5–6.0, inhibition of channels is observed. TRPC6 is inhibited by lowering pH [49]. Studies indicate the role of TRP channels in response to changes in pH/pCO_2 in glial cells, activation of channels is suggested with a decrease in intracellular pH [6]. Moreover, in neurons of locus coeruleus (LC), which are involved in the regulation of respiration in response to an increase in pCO_2 in the blood, it was shown that the TRPC5 channel is activated by extracellular and Ca^{2+}-dependent intracellular acidification [50]. The use of SKF-96365 specific TRPC channel inhibitors, in the presence of which LC neurons did not respond to pH changes, indicates the role of TRPC channels in chemoreception in LC neurons [50]. With the use of capsaicin-specific TRPV1 agonist, a negligible contribution of TRPV1 channels to central chemoreception was shown. [51]. Unlike the ion channels TRPV1, TRPV4, TRPC4, TRPC5 and TRPC6, the ion channel TRPP2 is activated by alkaline pH. When TRPP2 was expressed in HEK293T cells, an increase in currents was observed in the pH range from 8 to 9, a further increase in pH to 10 decreased TRPP2 currents [52]. TRPP2 is expressed in many tissues, including the brain. However, the role of TRPP2 in central chemoreception remains the subject of study.

Ionotropic Receptors

GABA. One of the receptors that respond to changes in pH is the $GABA_A$ receptor. The $GABA_A$ receptor is an ionotropic receptor whose endogenous ligand GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter of the central nervous system. When activating $GABA_A$ receptors selectively conducts Cl^- ions, which leads to hyperpolarization of the neuron and inhibition of synaptic transmission. $GABA_A$ receptors are composed of five subunits. The existence of six α, three β, three γ, one δ, one ε, one θ, one π and three ρ subunits determines the variety $GABA_A$ receptors with different composition of subunits, with different localization and with different pharmacological properties [53]. However, most $GABA_A$ receptors are composed of two α, two β and one γ2 subunit. Changes in pH cause allosteric changes in the receptor molecule, leading to a change in ligand-dependent activity. Interestingly, depending on the composition of the subunits, different forms of receptors have different sensitivity to changes in the pH of the extracellular environment. In general, there is a decrease in receptor activity at acidic pH values, while in some cases this effect is minimal [54, 55]. Compared to the control at pH 7.3, with increasing pH to 8.4, the GABA current was increased by 3 and 2.6 times in the GABA receptors α1β2γ2 and α3β2γ2, respectively. Acidification of extracellular pH had the opposite effect; at pH 6.4, GABA currents decreased by 2 times [56].

There is no direct evidence for the role of the GABA receptor as a pH sensor in central chemoreception. However, it is known that GABA-expressing neurons inhibit serotonin neurons, which play an important role in pH/CO_2 chemoreception in the area of medullary raphe, with the participation of $GABA_A$ and $GABA_B$ receptors. CO_2 in turn inhibits GABA-expressing neurons, thus with a change in pH/CO_2 in addition to the direct activation of serotonin neurons, there is no effect of their inhibition resulting in stimulated respiration [57].

P2X. P2X purineceptors are ATP-dependent ionotropic channels. When binding extracellular ATP P2X Na^+, K^+, Ca^{2+} ions are non-selectively carried out. P2X subunits form homo- or heterotrimers. Seven P2X subunits ($P2X_1$–$P2X_7$) are currently identified. Their membrane topology is characterized by two

transmembrane domains; between them there is a very long extracellular polypeptide loop, which consists of approximately 280 amino acids and is rich in cysteine. N- and C-ends of the protein are oriented inside the cell [58]. $P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$ and $P2X_7$ subunits react to pH changes [14, 59]. A decrease in pH decreases the efficiency of ATP binding of homo-multimeric $P2X_1$, $P2X_3$, $P2X_4$, $P2X_5$ and $P2X_7$ receptors, an increase in pH has no effect. On the contrary, acidification sensitizes $P2X_2$ homomultimeric receptors to the activating effect of ATP, whereas at alkaline pH values above 7.5, the effectiveness of the action of the agonist on homomultimeric $P2X_2$ receptors declines [14]. P2X subunits are specifically expressed in various parts of the brain; there are both homo- and heteromultimeric complexes that differ in pH-sensitive properties. Heteromultimer complex $P2X_{2/6}$ activated by lowering the pH from 8 to 6.3 and inhibited by a further decrease in pH below 6.3 [60]. Heteromultimer complex $P2X_{2/3}$ is also activated by lowering the pH from 8.3 to 6.3 [59]. The $P2X_{1/5}$ complex is inhibited at pH above and below 7.3 [59]. A high expression of $P2X_2$ in areas of the brain responsible for respiratory activity, including preBötC and VRG [61] make $P2X_2$ a likely candidate for the role of a pH sensor, which plays a role in central chemoreception. Although there is no direct evidence for this, numerous experimental data indicate the role of purine receptors in mediating the cellular response of chemosensitive respiratory neurons to an increase in H^+ concentrations and CO_2. Increased extracellular ATP concentration in response to a change in pH/pCO_2 activates purine receptors and the corresponding signaling pathways in the respiratory regions of the brain, which as a result stimulates respiration [10, 62, 63].

NMDAR. Other receptors that respond to extracellular pH changes are NMDAR receptors (N-methyl-D-aspartate receptors). NMDAR receptors are involved in controlling memory formation, plasticity of synaptic connections, malfunctioning of receptors, both hyper-activation and hypo-activation associated with many neurological and psychiatric diseases, including pathological pain, epilepsy, Alzheimer's disease, schizophrenia, depression and dementia [64]. NMDAR receptors are large heterotetrameric membrane complexes. Various ligands and allosteric compounds, binding to large extracellular domains of receptors, regulate the activity of the transmembrane domain, which is an ion channel. The activity of NMDAR receptors is highly dependent on changes in extracellular pH. At pH 8.4, receptors are fully activated, while lowering the pH to 6 completely inhibits the receptor [65–67]. There is evidence that a significant portion of the postsynaptic NMDAR current depends on the extracellular alkalization generated by Ca^{2+}-ATPase plasma membrane (PMCA) [68]. Inhibition of NMDAR receptors in extracellular acidosis helps to reduce damage to cortical neurons caused by toxic effects of glutamate [67]. It has been shown that astrocytes in the medulla oblongata region can synthesize, store and release D-serine, an NMDAR agonist, in response to increased CO_2 levels. The administration of D-serine increased the respiration rate of mice; blocking of NMDAR inhibited this effect, indicating the role of NMDAR in central chemoreception [69].

G Protein-Coupled Receptors

Acid-sensing G protein-coupled receptors include the G2A/OGR1 minifamily receptors, consisting of G2A, GPR4, OGR1/GPR68 and TDAG8/GPR65. The first identified G protein-coupled receptors that respond to pH changes were OGR1 and GPR4 receptors. At pH 7.8, receptors are inactive, while at pH 6.8 they are fully activated. However, lowering the pH causes various cellular responses. Activation of OGR1 results in the formation of inositol phosphate, while activation of GPR4 stimulates the formation of cAMP [70]. The G2A receptor, activated by extracellular protons, causes the formation of inositol phosphate [71] while activation of TDAG8 leads to cAMP accumulation [72]. It is worth noting that activation of the G2A receptor by protons, as well as its belonging to this minifamily of receptors, is called into question by some authors [73].

G2A/OGR1 family receptors are thought to be involved in maintaining acid–base homeostasis. Early research indicates the most important receptor functions in the body. Thus, the important role of OGR1 in bone and muscle tissues, GPR4 in vascular endothelial tissue, TDAG8 in the immune system was demonstrated [73]. It is known that OGR1 is expressed in the nervous system, but receptor function in the brain has not been studied, as well as its ability to be activated by protons [73]. It has been shown that TDAG8 is expressed in the brain, namely in the forebrain, and is activated at acidic pH values. Upon receptor activation, an increase in the concentration of cAMP and pCREB is observed [74]. Recent studies have shown the crucial role of GPR4 in the brain. GPR4 is expressed in the chemosensory neurons RTN (retrotrapezoid nucleus), which maintain the acid–base balance in the body through regulation of respiration. Removal of the GPR4 gene disrupted acidosis-dependent activation of RTN neurons and increased the frequency of suffocation. Thus, GPR4, along with the TASK-2 ion channel mentioned above, also expressed in RTN neurons, is one of the main respiratory chemosensitivity mediators [30].

Receptor Tyrosine Kinases

IRR. An insulin receptor-related receptor (IRR) is a member of the insulin receptor minifamily, which also includes an insulin receptor (IR) and an insulin-like growth factor receptor (IGF-IR). Receptors of the insulin receptor minifamily exist on the membrane in

the form of homologous dimers connected by disulfide bonds. Upon maturation, both monomers undergo proteolysis in the near-membrane zone of the extracellular part. As a result, the receptor molecule consists of two pairs of covalently linked α and β subunits. In the extracellular *N*-terminal part of the α-subunit, at all three receptors, there are two leucine-rich domains L1 and L2, between which there is a furin-like cysteine-rich domain C. Next, follow three type-III fibronectin repeats: FnIII-1, FnIII-2, and FnIII-3. The *C*-terminal intracellular portion of the β subunit contains a catalytic domain capable of phosphorylating tyrosine, which is a common property of receptor tyrosine kinases.

The physiological role of the IRR receptor was not known until recently as attempts to find a natural ligand of protein or peptide nature were unsuccessful [75]. We have established that IRR can be directly activated by a slightly alkaline extracellular medium pH > 7.9. Activation of IRR with an alkaline medium is specific, dose-dependent, and is also caused by conformational changes in the extracellular part of the receptor with increasing pH of the extracellular medium [76, 77].

Of obvious fundamental interest is the question of what determines the striking differences between the functions of the IR and IGF-IR receptors having protein ligands, on the one hand, and IRR, on the other.

Chimeric protein experiments in which individual IRR domains have been replaced by homologous regions of the IR and IGF-IR receptors [78–80] demonstrated the crucial role of the extracellular domains of L1C, L2 in the pH sensitivity of the receptor. The role of fibronectin domains in IRR receptor activation has also been shown. Replacing FnIII-2 and FnIII-3 domains with homologous regions of IR led to a significant decrease or disappearance of the pH sensitivity of the chimeric receptor [81] and mutations of amino acid residues, potential glycosylation sites, on Ala in chimeric proteins led to a partial restoration of pH sensitivity [82]. It has been suggested that IRR activation includes two separate pH-dependent centers in the ectodomain of the receptor, which act together to induce conformational changes in the IRR molecule leading to autophosphorylation of the intracellular kinase domains of the receptor [81].

The function of IRR as a sensor of an alkaline extracellular medium is confirmed by physiological experiments. In mice with targeted gene inactivation *insrr* encoding the IRR receptor, there was a violation of the regulation of acid–base balance. In gene knockout mice *insrr*, the alkaline load on the body was accompanied by metabolic alkalosis and decreased secretion of bicarbonate in the urine [77]. Wild type and knockout animals *insrr* reacted differently to acute experimental alkalosis caused by the introduction of bicarbonate into the blood. It is interesting that in mice with IRR knockout, as well as in wild-type mice, alkalosis compensation is observed, judging by the decrease in blood pH, but this does not occur due to secretion of excess bicarbonate in the urine, but as a result of an increase in the concentration of CO_2 in the blood, which is apparently caused by a slowdown in breathing or an acceleration of metabolism [83].

Unlike their close homologs of the IR and IGF-IR receptors, which are expressed in a wide range of tissues and cells, the expression of IRR is specific; the receptor is found in some organs, in certain types of cells. The largest amount of IRR was found in the kidney. In lower concentrations of mRNA, IRR was found in the brain, stomach, and pancreas. In the nervous system, IRR mRNA is found in sensory and sympathetic neurons, where IRR is coexpressed with the tyrosine kinase receptor of nerve growth factor (NGF) TrkA [75]. Expression of IRR and TrkA appears at the perinatal stage of development in the basal neurons of the forebrain, with mRNA of both receptors found in the developing nervous system only together. There is also evidence of IRR expression in forebrain cholinergic neurons, where coexpression with the TrkA receptor is also observed [75]. In addition, IRR has been detected in neuroblastomas. IRR expression was significantly correlated with a favorable prognosis for neuroblastoma [84].

According to the Allen Brain Atlas (http://mouse.brain-map.org) the highest expression of IRR is observed in the thalamus region, namely in the PVT region, the paraventricular nucleus of thalamus; a smaller amount was found in the brain stem region, Area Postrema, and the core region of the XII pair of cranial nerves. The PVT area contributes to the regulation of behavior, stress, motivation, mood, and appetite. Anatomical data are also presented that show that PVT transmits information from neurons involved in the visceral or homeostatic function [85, 86]. The area postrema (AP), the region of the medulla oblongata, is one of the circumventricular organs that provides a link between the central nervous system and the circulatory system in the area where the blood-brain barrier is the most permeable. AP provides the transfer of information about the chemical composition of blood to other areas of the nervous system. The location of the AP outside the blood-brain barrier makes this part of the brain vital in controlling the autonomic functions of the central nervous system. AP is involved in the autonomic control of many physiological systems, including the cardiovascular system and systems that control nutrition and metabolism [87]. It is known that AP is responsible for the vomiting reflex and forms a complex with the neighboring NTS region, which is involved in the regulation of respiration and pH maintenance [88]. According to the electronic resource (http://www.emouseatlas.org), IRR was also found at the embryonic stage of mouse development in large numbers in trigeminal ganglion (trigeminal V ganglion), glossopharyngeal nerve (glossopharyngeal IX

ganglion), cerebrospinal nerve (dorsal root ganglion) and pancreas, to a lesser extent in the renal tubules. Also, IRR expression was shown in neurons of the cerebrospinal ganglia of adult mice (6–8 weeks) using the RNA sequencing method of individual cells, and a high level of TrkA receptor expression is observed in the same cells [89]. Using the RT-PCR method (reverse transcription PCR), the expression of the IRR receptor, as well as other members of the IR and IGF-IR family, was shown in unicellular and blastocyst mouse embryos, which also suggests the role of the receptor in the development of the body [90].

Since IRR and TrkA are located adjacent to the chromosome and have common regulatory elements located between these two genes, it was suggested that IRR does not play a specific role in the nervous system, and its presence is determined only by TrkA expression [91]. However, significant changes in extracellular pH in the nervous tissue occur both during normal physiological functioning and in pathological conditions such as epilepsy, stroke, diabetes, etc. Significant alkalosis in the tissues of the peripheral or central nervous system can occur during hypoglycemia, ischemia, or renal failure. In particular, tissue alkalosis is one of the hallmarks of brain damage caused by hypoglycemia [92]. It can be assumed that one of the functions of IRR is neuroprotective signal transmission that promotes cell survival in response to acute alkalosis of nerve tissue as a result of pathophysiological conditions.

In mice knocked out with the IRR gene, a behavioral phenotype was found, consisting in a deficit of aggressive-defensive behavior of animals [93]. The extent to which this phenotype is associated with the function of IRR as a physiological pH sensor remains a subject of study.

ErbB2 and c-Met. ErbB2 is an oncogenic receptor tyrosine kinase associated with breast cancer. It is a member of the epidermal growth factor receptor (EGFR) minifamily. The EGFR minifamily consists of four members of ErbB1-4. ErbB2 is currently regarded as an orphan receptor, since it alone does not bind EGF-like ligands and can only be activated when overexpressed in malignant cells or in complex with ErbB3, another member of the EGFR minifamily. As structural studies have shown, ErbB2 is not able to bind a ligand, since its extracellular ligand-binding domain is already in the conformation associated with the ligand, thereby blocking the access of any other peptide ligand to this region [94]. ErbB2 activation occurs at nonphysiologically high levels of expression (for example, in cancer cells), which leads to phosphorylation of the ligand-independent receptor. ErbB2 activation has been observed in cancer cells of the bladder, lung, stomach, ovary, prostate, and breast. This phenomenon is associated with the amplification of the ErbB2 gene, which leads to overexpression of the ErbB2 protein on the cell surface [95]. Recent studies have shown that ErbB2 can be activated by treatment with an extracellular, slightly alkaline medium (pH > 8). Thus, a new ligand-independent ErbB2 receptor activation mechanism has been described [96]. ErbB2 is expressed in small amounts in nervous tissue. ErbB2 is expressed in the cerebellum [97]. Expression of ErbB2 and ErbB3 is observed in the ganglia of the spinal cord of a mature rat, while ErbB1 and ErbB4 showed low expression. With damage to the peripheral nerve, a significant increase in the expression of ErbB2 and ErbB3 was observed compared with an intact nerve [98]. ErbB receptors are known to be expressed in Schwann cells, and their expression is regulated by damage to nerve tissue [99]. Recent studies have shown that activation of the ErbB2 receptor in Schwann cells contributes to an increase in the regeneration of spinal axons during damage [100].

Another alkali-activated receptor tyrosine kinase is c-Met (Met). Met was discovered as a receptor for hepatocyte growth factor (HGF), also known as scatter factor (SF). Ligand binding activates the Met kinase domain by dimerization Met subunits and leads to autophosphorylation. Activation of the Met signaling pathway has been shown to lead to a wide range of cellular responses, including angiogenesis, wound healing, tissue regeneration, proliferation, survival, scattering, motility and invasion [101]. Using immunoaffinity chromatography with an antiphosphothyrosine antibody, phosphorylation of the endogenous Met receptor was detected by alkaline treatment in the CAKI-1 cell line. Met alkali activation is observed at pH > 8.0 and is dose-dependent. The specificity of the Met response to alkali was confirmed by treatment with the Met kinase inhibitor SU11274, as well as by knockout of the Met receptor using the CRISPR/CAS9 genome editing system. Both approaches completely blocked Met phosphorylation in CAKI-1 cells in response to alkaline treatment of cells [102].

The Met receptor is expressed in both the central and peripheral nervous systems [103, 104]. Met receptor tyrosine kinase is involved in many processes of the development of the nervous system, including cell migration, the development of dendrites and axons, and synaptogenesis [105, 106]. Met expression was detected at the prenatal stage of development in the brain stem: including a subpopulation of neurons in the cranial nuclei (nVII, nA and nXII), subgroup B6 dorsal raphe, the Barrington nucleus, and in a small subset of neurons in the nucleus of a single tract (nucleus of solitary tract). Unlike Met, neither the full-sized form nor the known spliced forms of HGF were found in the prenatal brain stem. HGF expression was detected in target tissues of Met-expressing brain stem neurons, suggesting that MET in these neurons could be activated by HGF from peripheral sources [107]. One can also suggest a ligand-independent method for activating the Met receptor in the brain stem. Together, these data suggest that MET sig-

naling can influence the development of neurons that are involved in central regulation of gastrointestinal function, tongue movement, swallowing, speech, stress and mood. Studies of long-term changes in the expression of mRNA of the HGF protein and its Met receptor after spinal cord injury in rats revealed an increase in the expression of both HGF and Met. HGF mRNA expression was significantly increased seven days after injury in the damaged segment, and the peak was seven days later. Met mRNA expression was increased one day after injury and peaked after 14 days [108].

Changes in the expression of ErbB and Met receptors in damaged tissues seem to play an important role in the subsequent regeneration of nerve tissue. Tissue alkalosis that occurs with some brain damage can be a factor that activates the ErbB2 and Met receptors, which activate the regeneration processes.

Connexins

Connexins are a family of membrane proteins that form connexons. The subunit of connexin consists of four transmembrane domains, two extracellular loops, one intracellular loop, while both ends of the protein are oriented inside the cell. Six protein subunits form connexon. Connexons of neighboring cells form a continuous channel (hemichannel), which provides transmembrane transport of small molecules such as ATP, NAD^+, glutamate, prostaglandin E2, glucose. Twenty-one connexins isoforms are found in the human genome, which are widely expressed in many body tissues [109]. Connexins play an important role in the development and homeostasis of the organism [109, 110]. It was found that the hemichannel formed by connexin Cx43 expressed in HeLa cells is activated by an alkaline extracellular medium with an increase in extracellular pH from 7.4 to 8.5. Channel activation leads to an influx of Ca^{2+} ions into the cage [111]. The pH sensitive channel also includes Cx26. At pH 8, the channel is active, while lowering the pH to 6.5 inhibits the channel [112]. Cx26, along with other connexins, is also sensitive to changes in intracellular pH. Intracellular acidification inhibits the channels formed by connexins Cx50 > Cx46 > Cx45 > Cx26 > Cx37 > Cx43 > Cx40 > Cx32. Most sensitive to pH changes Cx50 (pK_a 7.2), then the channels are arranged in order of decreasing pH sensitivity, for Cx32 pK_a 6.5 [113]. Channels formed by Cx45 and Cx57 are activated when the intracellular pH rises above 6.4 and 7.2, respectively [114, 115]. High expression of connexins Cx26, Cx32, Cx36, Cx43 in the chemosensory regions of the brain suggests their participation in central chemoreception [109]. In addition, connexins of pH-sensitive astrocytes can interact directly with CO_2. So, connexins 26, 30, 32 (Cx26, Cx30, Cx32) contain a CO_2 binding site. With an increase in pCO_2 hemichannels open and release ATP [116, 117], which in turn activates chemosensitive neurons RTN [9, 10].

Guanylate Cyclase Receptor

It was found that the transmembrane receptor guanylate cyclase GCY-14 expressed in chemosensory neurons *C. elegans* senses alkaline pH in the range of 8 to 10.9. Upon activation of GCY-14, cyclic guanosine monophosphate (cGMP) is formed, which binds to cGMP-dependent channels, which in turn conduct Ca^{2+} ions inside the cell, which leads to the activation of a neuron [118]. Guanylate cyclase receptors consist of a large ligand-binding extracellular domain, one transmembrane domain, an intracellular domain similar to the kinase and *C*-terminal guanylate cyclase domain. Site-directed mutagenesis shows the role of the His174 residue in the extracellular domain of GCY-14 in the pH sensitivity of the protein. In animals, seven forms of membrane guanylate cyclases are expressed, GC-A, GC-B, GC-C, GC-D, GC-E, GC-F and GC-G. There is evidence that GC-D is activated by CO_2 or HCO_3^- and GC-G by HCO_3^- [119].

Ligand-Dependent Chloride Channels

pH sensitive Cl^--channels are members of the family of ligand-gated ion channels. Their membrane topology is characterized by four transmembrane domains and a large extracellular *N*-terminal part. Invertebrates have two pH-sensitive Cl^- channels, pHCl and SsCl, which are activated by extracellular alkaline pH (with an increase in pH greater than 6.5). The pHCl chloride channel is expressed in Drosophila neurons. When expressing pHCl in *Xenopus oocytes* or insect cells Sf9 Cl^- currents were observed when pH changes from neutral to 9.0, while extracellular acidification to pH 5.8 inhibited these currents. Chloride Channel SsCl Tick *Sarcoptes scabiei* expressed in *Xenopus oocytes* is also reversibly activated by extracellular alkaline pH [120].

CONCLUSIONS

In the framework of the main dogma of homeostasis, it is believed that the pH of the blood and extracellular environment of the body should be close to neutral values, and deviations in physiological conditions are minimal. The continuous process of metabolism and food intake cause shifts in acid–base balance and require the removal of excess acids or bases. Within the framework of a whole organism, the removal of a part of acids or bases in a small volume is impossible without extreme changes in the pH of the excreted extracorporeal fluids, in particular, the renal filtrate [121]. A directed change in pH is also necessary for certain extracellular functions, such as digestion. Within one cell, pH changes in organelles are possible from acidic

(lysosomes) to alkaline (mitochondria). Thus, with tight control of the pH of the main body fluids, significant shifts of acid–base balance are possible in separate locations.

Today, it is believed that maintaining the pH in the neutral range (pH 7.2–7.6) in the nervous system is absolutely necessary for its normal functioning, while small changes in pH affect the excitability of neurons, synaptic transmission, absorption of neurotransmitters, and intercellular communication [2, 3]. Sensitivity to changes in pH is a feature of many membrane proteins, which play a key role in neurotransmission. In addition, it has been suggested that small pH gradients may be relevant in the processes of neuronal differentiation, development, learning, and memory [3].

In particular, the main cause of pH fluctuations in synapses is the strong acidification of synaptic vesicles with a vacuolar H^+-ATPase, which provides energy to the process of loading neurotransmitters into synaptic vesicles. Exocytosis of synaptic vesicles leads to the release of protons into the synaptic cleft. Thus, synaptic transmission causes a relatively short but strong acidification of the synaptic cleft. Increased synaptic/neuronal activity can also cause acidification of the extracellular environment due to increased cellular metabolism [122]. It is also known that various pathological conditions such as ischemia, inflammation, cancer or trauma are associated with a decrease in extracellular pH [3].

Recent studies have revealed the presence of protein molecules in the nervous system, which are sensors of a significant change in the pH of the extracellular environment in both the acidic (up to pH 5) and alkaline (up to pH 9) regions. It is difficult to explain the expression of these proteins in the nervous system within the framework of modern ideas about the control of acid–base balance. It is possible that local changes in pH are possible in the nervous system, both under normal and pathological conditions, which are currently poorly understood and underestimated.

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COMPLIANCE WITH ETHICAL STANDARDS

The study contains no research using people or animals as objects of study.

Conflict of Interests

The authors declare they have no conflict of interests.

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