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Proton Mechanisms of Neurotransmission and Calcium Signalling for Impulse Initiation, Development and Propagation

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Abstract

Protons are gaining increasing attention as neurotransmitters due to their extraordinary abilities to rapidly transfer electrical charge, mobilize cellular calcium and modulate ion channels. How all this is possible is currently the subject of in-depth studies and discussions concerning not only neurophysiology, but also biological materials for artificial intelligence.

This review describes some biochemical mechanisms by which protons, in combination with calcium, can initiate firing in sensory neurons and transmit impulses across synapses, thus supporting the action of Na⁺ and K⁺ ions shown by Hodgkin and Huxley. Furthermore, mechanisms are put forward concerning how many hydrolases and neurotransmitters, particularly glutamate, gamma-aminobutyric acid, adenosine triphosphate and acetylcholine, are able to generate protons.

The results of the numerous experimental works taken into consideration indicate that protons can play a fundamental role both in the generation and in the transmission of the sensory nerve impulse.

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1. Introduction

The importance of Na⁺ and K⁺ ions for nerve transmission was demonstrated by eighteen years of experimental work by Hodgkin and Huxley (A. Hodgkin & Huxley, AF, 1952). Other ion, such as H⁺ and Ca²⁺, were studied less, although Hodgkin and Huxley noted the significant role of Ca²⁺ as far back as 1949 (A. L. Hodgkin, 1976) (Fig.7). Subsequent studies confirmed the fundamental role of Ca²⁺ in proper transmission (Augustine et al., 2003; Bagur & Hajnóczky, 2017; Brini et al., 2014; Clapham, 2007; Moccia et al., 2023; Neher & Sakaba, 2008; Pozzan et al., 1994). Dysfunctions in Ca²⁺ homeostasis and abnormal Ca²⁺ concentration levels characterize the pathological states of acidosis and alkalosis. Acidosis and alkalosis are consequences of opposite, extended changes in H⁺ concentration, i.e. in pH, and can cause neurodegenerative diseases (Brini et al., 2014; Verma et al., 2022; Zündorf & Reiser, 2011) and cancer (Papavassiliou & Papavassiliou, 2021; Salucci et al., 2023; Zheng et al., 2023). In fact, acidification in acidosis depletes cellular calcium stores and depleted stores release a reduced quantity of Ca²⁺ in response to stimuli. On the contrary, in alkalosis, calcium stores are overloaded and this can produce an excessive response. Only a steady-state cell with adequately full calcium stores can respond with the right release of Ca²⁺ to the stimulus, thus transducing the signal correctly. The pathological consequences of poor/excessive responses to stimuli in acidosis/alkalosis are beyond the scope of this review; here the focus is on the physiological chemical mechanisms of neurotransmission, which underlie the rapid and highly localized transient changes in H⁺ and Ca²⁺ concentrations, triggered by stimuli. Unfortunately, the *in vivo* analytical quantification of H⁺ and Ca²⁺ ions is very difficult, as they can interact with a multitude of atomic and molecular species. Moreover, fast nerve impulses can last no more than 10 ms (Lemaréchal et al., 2022; Wolfel & Schneggenburger, 2003), intracellular pH transients and calcium spikes less than 2 ms. Consequently, H⁺ and Ca²⁺ ions require sophisticated instruments for their study (Bekku & Salzer, 2021; Horiuchi et al., 2020; L. Zhang et al., 2016).

The interest in H⁺ ions, identified below with the current terminology as “protons”, picked up after 1980 (Bevan, S & Yeats, J, 1991; Gruol et al., 1980; Krishtal & Pidoplichko, 1980) and particularly with the technical progress of the last 25 years (Barth & Corrie, 2002; Freeman et al., 2023; Steinegger et al., 2020).

Protons are tiny ionic particles that in an aqueous environment are acidic and highly mobile, able to rapidly transfer positive charges and to temporarily modify pH, Ca²⁺ concentration, electrical potential and the protein structure, as a result activating numerous receptors. Due to these extraordinary chemical and physical properties they are used in the preparation of organic electro-conductive materials (Song et al., 2020; Yao et al., 2020) and are attracting increasing attention as neurotransmitters (Beg et al., 2008; Davies et al., 1988; Diering & Numata, 2014; J. Huang et al., 2010; Kier, 2017; Ruffin et al., 2014; Soto et al., 2018; Tombaugh & Somjen, 1996; Traynelis & Cull-Candy, 1991; Uchitel et al., 2019; Ueno et al., 1992; Willoughby & Schwiening, 2002; Zeng & Xu, 2012). Protons have been shown to have an essential role at the synaptic level (Du et al., 2014; Fillafer & Schneider, 2016; González-Inchauspe et al., 2017; Highstein et al., 2014; Uchitel et al., 2019) and it has been posited that they are responsible for conduction in axons (Kier, 2017). Some authors have also posited a significant role in the transmission and modulation of the signal in the nervous system generally (Malchow et al., 2021; Ruusuvoori & Kaila, 2014; Soto et al., 2018; Zeng et al., 2015). However, the endogenous sources of the protons have yet to be determined. There are four candidates: Na-H exchangers, V-ATPases, carbonic anhydrases and AE3 chloride-bicarbonate exchangers (Country & Jonz, 2017; Soto et al., 2018; Warren et al., 2016; Zeng & Xu, 2012), but they appear to be insufficient (Country & Jonz, 2017). Specifically, Soto and colleagues (Soto et al., 2018)

rightly observe: “A problem of classifying protons as neurotransmitters is related to the fact that its regulated release is always a co-release with classical neurotransmitters”. In addition, some criticisms have been levelled against the theory of Hodgkin and Huxley; for example, it does not explain the origin of the firing of neurons (Deng, 2017). These problems could be overcome more simply if neurotransmitters and second messengers (Newton et al., 2016) were included among the possible sources of protons, given that these molecules can generate protons, i.e., new mobile charges.

The double purpose of this review is: 1) to highlight several endogenous sources of protons, which have so far been overlooked; 2) to suggest some biochemical pathways for sensory impulse initiation/transmission that can be activated by protons and Ca^{2+} ions. Specifically, subsection 2.3 lists in Table 1 some important enzymatic proton sources for cell signalling. Subsection 2.4 describes how protons are able to trigger the depolarization of sensorial neurons by directly opening ionotropic channels or activating GPCR receptors, via PLC/IP₃ and the mobilization of Ca^{2+} , thereby contributing to the generation of the action potential and the exocytosis of the vesicles. Subsection 2.5 describes the mechanisms by which neurotransmitters in the vesicles, such as glutamate (Glu), gamma-aminobutyric acid (GABA), adenosine 5'-triphosphate (ATP) and acetylcholine (ACh), are able to become the sources of protons, generating them and, via the protons, fostering the transmission of the impulse through the synaptic cleft to the postsynaptic termination and beyond.

2. Results and Discussion

A review and critical assessment was made of the scientific publications dealing with the topic between 01.01.1943 and 31.12.2023, all available online.

2.1. Properties of protons

With an atomic mass about 23 times lower than sodium and a radius of about 0.08 nm, the proton is the smallest and most mobile ion, despite the limitations of its solvation structure, thanks to its diffusion coefficients, in bulk water (Silverstein, 2021). In its hexahydrate form proton has a radius of about 0.25 nm against 0.95 nm of Na^+ . It diffuses faster along and across membranes than in the cytoplasm (Silverstein, 2021). The level of proton permeability across the phospholipid membrane is tightly controlled and depends on the lipids and proteins in the membrane (DeCoursey & Hosler, 2014; Endeward et al., 2014; Kratochvil et al., 2023). There are several different routes for proton permeation, via both passive and active transport. Due to different experimental conditions, the results of many existing studies are inconsistent, however, in most measurements the proton permeability was \geq that of Na^+ (Bozdaganyan et al., 2019). Studies with weak acids on artificial vesicles revealed that protons diffuse more rapidly than other ions through lipid bilayers, mainly in the undissociated acidic form (Anderson Norris & Powell, 1992; Tivony et al., 2022). Alternatively, in living cells, protons can cross the plasma membrane much more rapidly through specific channels, such as voltage-gated proton channels (Hv1), gramicidin A channels, and mutated aquaporins (DeCoursey, 2018; DeCoursey & Hosler, 2014). Also, the existence of CO_2 -permeable aquaporins has been proved, but the permeation mechanism of CO_2 through aquaporins is not yet resolved (J. Chen et al., 2023). Carbonic anhydrases, which have a fundamental role in proton generation from CO_2 in the whole organism, including brain (Ruusuvauro & Kaila, 2014), could be less available with

regards to aquaporins (J. Chen et al., 2023). Besides these routes, active transporters such as pumps and exchangers can drive protons across the plasma membrane (Doyen et al., 2022; Ruusuvoori & Kaila, 2014).

The elemental charge of the proton is the same as for other individual monovalent cations, at 1.602×10^{19} C. Anyway, protons can transport the charge much more quickly (Brünig et al., 2022; Volkov et al., 2020), via proton-hopping (Agmon et al., 2016; Silverstein, 2021). In addition to interacting with water and the three channels mentioned above, protons can modulate (J. R. King et al., 2018) a large variety of channels and receptors. Such as Voltage Gated Calcium Channels (VGCC/CaV) (Sharma et al., 2023; Simms & Zamponi, 2014), Store Operated Calcium channels (SOC) (Kraft, 2015), calcium-activated potassium channels (K_{Ca}) (Guéguinou et al., 2014; Sancho & Kyle, 2021), inward rectifier potassium channels (Kir) (Hibino et al., 2010; Ye et al., 2016), TWIK-related acid-sensitive K^+ channel (TASK) (Duprat, 1997), proton gated Acid Sensing Ion Channels (ASIC) (Rook et al., 2021; Storozhuk et al., 2021; Zeng et al., 2015), multimodal Transient Receptor Potential channels (TRP) (Cao, 2020; Kweon et al., 2015), Pannexin 1 channels (Panx1) (Whyte-Fagundes & Zoidl, 2018), G-protein Coupled Receptors (GPCR) (Sisignano et al., 2021) and P2X2 purinergic receptors (Burnstock, 2018). Furthermore, GLIC channels in prokaryotes are proton-gated. The interaction depends on the species, the extracellular or intracellular position of the protons, their concentration and the type of channel (de la Roche et al., 2013). Many channels, including ASIC and TRPV1, mainly trigger activation; others, such as VGCC (Almanza et al., 2008), Panx1 (Vroman et al., 2014), and TRPV5 (Fluck et al., 2022), have a control or inhibitory function. X-ray crystallography and cryo-electron microscopy have revealed the structure of many ion channels in the inactivated/open state and, in some cases, the amino acid residues involved in gating (Catterall et al., 2020). However, a knowledge of the structures of the intermediate states at the atomic level is required in order to better understand the origin of the movement of charges in the gating mechanism (Catacuzzeno & Franciolini, 2022). Numerous studies on proton mobility prove that protons can move and interact in very short times with several chemical players before neutralization. Therefore, the opinion that the variations in proton concentrations are physiologically negligible because they are quickly neutralized is inexact.

2.2. The H^+/Ca^{2+} correlation

It is known that both Ca^{2+} ions and protons are ubiquitous in organisms, at concentrations that are strictly correlated (Deplazes et al., 2019; Molinari & Nervo, 2021; Swietach et al., 2013). As mentioned in the introduction, a widespread lasting increase in their concentration produces the pathological condition known as acidosis (Hamroun et al., 2020), whilst a local and temporary increase is used currently by cells as a signal, in physiological conditions (Ruusuvoori & Kaila, 2014; Soto et al., 2018; Zeng & Xu, 2012). In comparison with proton and Na^+ ion, Ca^{2+} has a higher atomic mass (40 Da), carries a double positive charge and possesses much less mobility. In cells, most calcium is normally bound and the cytosolic concentration of free Ca^{2+} is very low. Its unique chemical characteristics have allowed calcium to become a key element in cellular signalling (Carafoli & Krebs, 2016). The correlation between protons and Ca^{2+} ions is fundamental for the transmission of the signal and depends on the high degree of solubility in an acid environment of calcium-buffering molecules. In steady cells, most calcium is bound within Ca^{2+} buffers, which are either stationary or mobile (Eisner et al., 2023). When the stimulus reaches the cell membrane activating an acidifying enzyme, such as a lipase or an esterase, the

enzymatic action produces protons and hence locally and temporarily lowers pH (Molinari & Nervo, 2021). The acidity quickly dissolves part of the Ca^{2+} buffers and Ca^{2+} can therefore pass into the solution, producing calcium spikes (Molinari & Nervo, 2021), of intensity and duration proportional to the quantity of protons released (Garciaarena et al., 2018; S. Huang et al., 2023; OuYang, JB et al., 1994; Swietach et al., 2013). It has been calculated that in mitochondria a fall of one unit of pH produces a 100-fold increase in the concentration of Ca^{2+} (Nicholls & Chalmers, 2004). Similarly, protons produce the release of other bivalent and trivalent ions, such as Zn^{2+} , Mg^{2+} , or Fe^{3+} and Mn^{3+} . The intracellular increase in proton concentrations produced by esterases and lipases can transiently affect the structures of channels and pumps, by modifying their conformation and action. Clearly, the acidifying power of lipases and esterases, including phosphatases, is a very important characteristic that allows the transformation of the chemical signal into transient electrical charges and the continuation of the signal both through the release of Ca^{2+} from cellular stores and through the influx of extracellular Ca^{2+} . However, scientific publications have almost entirely ignored this characteristic. The existence in biological membranes of voltage-sensing phosphatases (VSP) that produce the opposite transformation from an electrical signal to a chemical signal (Okamura et al., 2018) may not be coincidental. This allows us to argue that protons are at the basis of the transformation of the signal from chemical to electrical and vice versa.

2.3. Endogenous sources of H^+ ions, overlooked until now

In two prior articles, we have described how protons may be generated in different cells by second messengers with the chemical structure of an ester or anhydride, such as IP_3 , ATP, NAADP, cADPR, cAMP or cGMP, by the hydrolytic action of specific enzymes (Molinari, 2015; Molinari & Nervo, 2021). The hydrolysis of an ester or anhydride produces an acid, in most cases a phosphoric acid derivative, which can rapidly dissociate, releasing protons. Table 1 provides some examples of lipases and esterases and the acids they produce, which can solubilize calcium at the cellular level. Schematic representations of the reaction are available in many cases, for example for ATP (Feng, equation 5) (Feng, PX, 2017), IP_3 (Huang, Supplementary information, Fig.S1) (J. Huang et al., 2010), cAMP (Barbosa, Fig.3) (Barbosa et al., 2011) and cGMP (Rybalkin Fig.1) (Rybalkin et al., 2013). However, it is not easy to find the complete representation, because most texts inexplicably fail to mention protons. Worse yet, the names *phosphate* and *phosphoric acid* are often used interchangeably.

Table 1. Examples of lipases and esterases, as possible sources of protons and Ca^{2+} spikes

enzyme	substrate	acid product	reference
phospholipase A ₂	PC	arachidonic acid	Sun (G. Y. Sun et al., 2004)
phospholipase C	PIP ₂	acid IP ₃	Molinari, Fig.1A (Molinari, 2015)
phospholipase D	PC	phosphatidic acid	Cazzolli (Cazzolli et al., 2006)
ecto-ATPase	ATP	ADP + acid phosphate	Kreitzer (Kreitzer et al., 2023)
phosphodiesterase	cAMP	acid AMP	Delhaye (Delhaye & Bardoni, 2021)
phosphodiesterase	cGMP	acid GMP	Delhaye (Delhaye & Bardoni, 2021)
cADPR cyclase	cADPR	acid ADPR	Young (Young & Kirkland, 2008)
VSPs	phosphoinositides	acid inositol phosphate	Okamura (Okamura et al., 2018)
inositol 5-phosphatase	IP ₃	not yet identified*	Ooms (Ooms et al., 2009)
S1P phosphatase	S1P	not yet identified*	Wollny (Wollny et al., 2017)
alkaline phosphatase	NAADP	not yet identified*	Schmid (Schmid et al., 2012)
acetylcholinesterase	ACh	acetic acid	Fillafer (Fillafer et al., 2021)

*See the discussion in the section below.

Abbreviations: PC, phosphatidylcholine; PIP₂, phosphatidylinositol 4,5-bisphosphate; IP₃, inositol 1,4,5-trisphosphate; ATP, adenosine 5'-triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; cADPR, cyclic adenosine diphosphate ribose; VSP, voltage-sensing phosphatase; S1P, sphingosine 1-phosphate; NAADP, nicotinic acid adenine dinucleotide phosphate; ACh, acetylcholine.

The products of enzymatic hydrolysis, listed in the third column of Table 1, are acidic and can therefore release protons, by dissociation. The ability of an acid to generate protons and consequently Ca²⁺ spikes depends on its dissociation constant (K_a): the higher the K_a, the stronger the acid and the number of dissociated protons. Dissociation is also largely influenced by environmental pH and the pK_a corresponds to the pH value at which the acid is half dissociated.

Theoretically, all lipases and esterases can generate protons, but only hydrolysis that produces an acid with pK_a lower than the cellular pH will substantially release protons under physiological conditions. The Drug Bank reports pK_a 4.54 and 4.82 for acetic acid and arachidonic acid, respectively. The three pK_as of phosphoric acid are 2.1, 7.2, and 12.3. Its partially esterified derivatives, such as phosphatidic acid and the acids produced by hydrolysis of cyclic nucleotides, have lower pK_{a1} and pK_{a2}, since “the replacement of a phosphoric acid hydrogen by a non-acidic group leads to an increase in the acid strength” (Kumler & Eiler, 1943).

Therefore, in physiological conditions, phospholipases (i.e. PLA₂, PLC, and PLD), triphosphatases (i.e. ecto-ATPase) and phosphodiesterases are acidifying enzymes, since their acid derivatives have lower pK_as than the cellular pH. Numerous experimental studies support this statement. Some doubts may arise about the acidifying power of phosphomonoesterases (phosphatases), due to the possible high pK_a values of their two products: the alcohol and the inorganic acid phosphate. However, the mechanism of hydrolysis of phosphomonoesters by phosphatases can be of considerable importance. Phosphoric esters are stable compounds and their spontaneous hydrolysis is very slow. Monoester monoanions with a typical second pK_a of 6-7 and dianions are relatively reactive (Kirby & Nome, 2015)

(Scheme 6 and respectively Scheme 5). The reaction is a nucleophilic substitution SN_2 (P) which begins with the deprotonation of the nucleophile (water) and proceeds through a transition state (TS) in which the phosphoryl group forms a pentacoordinate intermediate (Duarte et al., 2016). This involves a redistribution of charges and electrostatic effects (De Vivo et al., 2007), with consequent stabilization of the TS. Alcoholic leaving groups having $pK_a < 7$ can promote the reaction (Duarte et al., 2016; Kirby & Nome, 2015) and release the proton after hydrolysis (Duarte et al., 2016; Onyido et al., 2023). Protein phosphatases such as inositol phosphatase (EC 3.1.3.25) can enhance the rate of hydrolysis by a factor of $\approx 10^{21}$ (Lad et al., 2003). They generally use Zn^{2+} or Mg^{2+} as cofactors (Gill et al., 2005), (Kimura, 2012) (Fig 11, Fig 15 and Fig 16). These data taken together suggest that the physiological hydrolysis of phosphomonoesters can be acidifying, similar to triesters and diesters. Unfortunately, experimental confirmation is still lacking, as is the certain identification of the acid products of the hydrolysis of important monoesters, such as IP_3 , S1P and NAADP. The acidifying power of phosphatases has so far been studied in plant roots, soil microorganisms and earthworms (Moro et al., 2021; Tibbett, 2002; Vos et al., 2023) where the improvement of calcium and phosphates solubility is important for plant nutrition. For soils with pH around 6.0 a decrease in pH was shown, specifically related to phosphodiesterases and phosphomonoesterases activity (Moro et al., 2021). Unfortunately, the authors do not measure the contribution of phosphodiesterases and phosphomonoesterases separately.

2.4. Pre-synaptic transmission of the impulse in sensory neurons

Protons can contribute to the generation and transmission of impulses in sensory neurons via biochemical mechanisms that differ in modality and effects (Silbering & Benton, 2010).

In the specific case of neurons sensitive to a sour taste, it has been shown in mammals that protons can directly cause firing by opening the OTOP1 channel (Chang et al., 2010; Teng et al., 2022; Tu et al., 2018).

"In response to acidic stimuli, the sour receptor, OTOP1, conducts protons into the cell cytosol. This changes the membrane potential directly, and the change in intracellular pH blocks KIR2.1 K⁺ channels, which further depolarizes the membrane potential. With sufficient depolarization, voltage-gated Na⁺ channels open causing a train of action potentials that open voltage-gated calcium channels and lead to neurotransmitter release" (Liman & Kinnamon, 2021).

The pathway is more complex in the case of sensory neurons with GPCR-type metabotropic receptors at the distal termination of the axon. These are very common in mammals (Imenez Silva & Wagner, 2022; Liccardo et al., 2022) for the transmission of visual stimuli (Xue et al., 2011), nociceptive stimuli (Geppetti, P et al., 2015), odor (G. Liu et al., 2006; Szebenyi et al., 2014) and taste, limited to taste/flavour perceptions of sweet, bitter, umami and kokumi (Ahmad & Dalziel, 2020; Deshpande et al., 2010; Lee & Owyang, 2017). In these cases, the biochemical mechanism begins with the activation of a phospholipase C (PLC) (Balla, 2010; Weernink et al., 2007) which hydrolyzes the phosphatidylinositol (4,5)-bisphosphate of the neuronal membrane. The reaction for several enzyme isoforms is pH- and Ca^{2+} -dependent (Banno & Nozawa, 1987; Nakamura & Fukami, 2017; Roy et al., 1991). This means that the reaction can be acidifying and

autocatalytic (Thakur et al., 2020), because the hydrolysis produces IP_3 and protons (J. Huang et al., 2010; Molinari, 2015; Randall et al., 2015), which in turn produce Ca^{2+} release (W. Chen et al., 2001; Križaj et al., 2011; Nedergaard, 1995; OuYang, JB et al., 1994; Thakur et al., 2020), hence promoting a rapid increase in enzymatic activity. The acidifying action has been confirmed experimentally at the presynaptic termination (Caldwell et al., 2013; Rossano et al., 2013; L. Zhang et al., 2016).

The increase in cytosolic Ca^{2+} concentration, induced by the direct proton influx or by the acidifying action of PLC, can have a threefold contribution:

1. Solubilization of cytosolic Ca^{2+} buffers (Molinari & Nervo, 2021; OuYang, JB et al., 1994)
2. Ca^{2+} release from endoplasmic reticulum stores (Woll & Van Petegem, 2022)
3. Ca^{2+} influx by stimulation of the SOCs (D. Wei et al., 2017)

The latter is fundamental for neurotransmission, since the influx of Ca^{2+} as well as the influx of protons can constitute the first step of depolarization.

A second step may follow rapidly with the opening of:

- low threshold VGCC/ CaV channels (Dolphin, 2020; Harding & Zamponi, 2022; Ramachandran et al., 2022; Tombaugh & Somjen, 1997) permeable to Ca^{2+}
- TRP (Cao, 2020; Henrich & Buckler, 2009; J. Huang et al., 2010; Zeng & Xu, 2012) and ASIC (X. Liu et al., 2020) channels permeable to Ca^{2+} and Na^+ (Hu et al., 2021).

These new influxes of Ca^{2+} and Na^+ can further promote depolarization. Moreover, the increase in Ca^{2+} concentration in the cytosol modulates calcium-activated potassium channels (Hou et al., 2008; Orfali & Albanyan, 2023; Shah et al., 2022).

The above studies jointly demonstrate that protons, together with Ca^{2+} ions, can start the process of membrane depolarization not only in neurons sensitive to a sour taste, but also in many other neurons with GPCR-type receptors. It is likely that the three ions, H^+ , Ca^{2+} and Na^+ contribute cooperatively (Dixon et al., 2022; Moreno et al., 2016) and to varying degrees to depolarization until the threshold value is reached.

When the threshold value is exceeded Voltage Gated Sodium Channels (NaV) open, generating the action potential (Catterall et al., 2005; A. Hodgkin & Huxley, AF, 1952). This produces the exocytosis of the vesicles and the release of the neurotransmitters into the synaptic cleft (Ge et al., 2022; Wu et al., 2014).

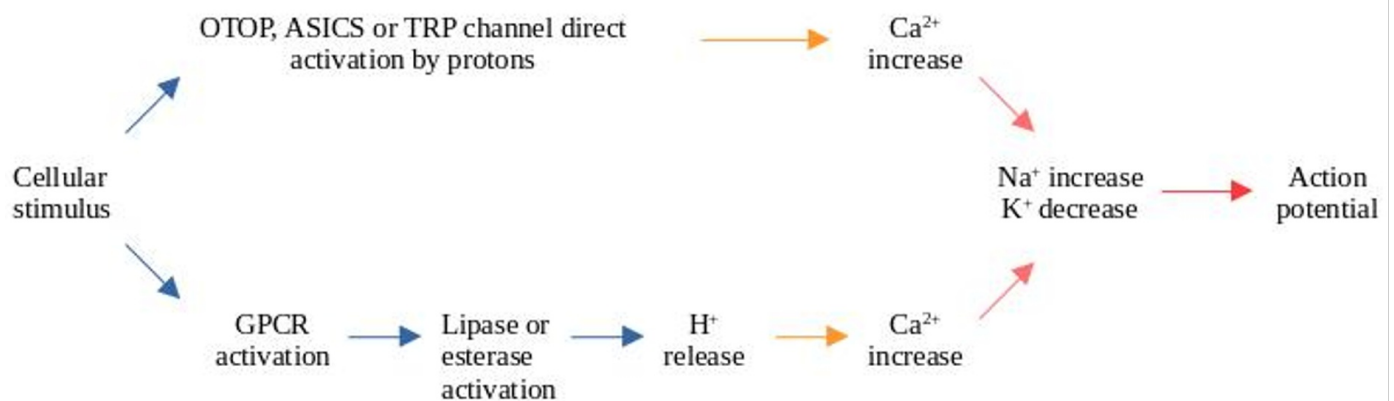
In the following repolarization phase the NaV channels close and the Kv (Grider et al., 2022; A. Hodgkin & Huxley, AF, 1952; Kariev & Green, 2022), K_{Ca} and $Hv1$ proton channels (DeCoursey, 2018; Han et al., 2022) open enabling the efflux respectively of the K^+ ions and the protons leading to the rebinding of Ca^{2+} and the return to static conditions. Pumps and exchangers contribute to the control of the entire process (Brini et al., 2014).

In the eye, the activation of GPCRs via the PLC/ IP_3 pathway occurs by means of the cells containing melanopsin, whilst

the cells of the retina containing rhodopsin and the cells of the auricular cochlea follow a different pathway, via PDE/cGMP (C.-K. Chen et al., 2015; Marchetta et al., 2022). In this case, the protons are generated by the hydrolysis of cGMP and the dissociation of acid glutamate, as described below in subsection 2.5. The role of protons in hair cell transmission is currently under debate (Contini et al., 2022).

In relation to the sensory neurons that transmit mechanical stimuli, it is believed that in mammals these neurons generally respond via mechano-electrical channels (Douguet & Honoré, 2019). The physical stimulus induces the opening of ionic channels enabling the influx of Ca^{2+} , depolarization and the generation of the action potential. The mechanisms for the activation of the channels are not clear (Bavi et al., 2017). In some cases, ASIC channels (Cheng et al., 2018) or GPCR receptors (Lin et al., 2022) are involved. Moreover, it has been shown that the G protein-coupled receptor OGR1 (GPR68) responds to mechanical stimuli and to protons via the PLC/ IP_3 pathway (Iliff, AJ & Xu, XZS, 2018; W.-C. Wei et al., 2018).

To sum up, for the above sensorial neurons, with ionotropic channels of the OTO, TRP, ASIC type or metabotropic channels of the GPCR type, protons are essential to increase the cytosolic Ca^{2+} concentration. For all these cases it is therefore possible to find a response with reference to the criticism advanced by Deng (2017), according to which the Hodgkin-Huxley theory does not explain the origin of firing. The response is: Protons, inducing with Ca^{2+} the initial depolarization steps, via proton influx and/or proton-induced calcium influx, may be at the origin of firing. Scheme 1 provides a comprehensive, simplified representation of the mechanisms of proton action at the cellular level. Orange-colored arrows represent the increasing depolarization.



Scheme 1 – Mechanisms of proton actions at cellular level: in both the alternative pathways protons (H^+) are essential for the increase of Ca^{2+} concentration, depolarization and the generation of the action potential.

2.5. Synaptic transmission of the impulse

Neurotransmitters include compounds, shown in Table 1, with an ester, anhydride or acid-type structure that can therefore generate protons. Below, four fundamental neurotransmitters are considered, released in the ribbon-type synapses by vesicle exocytosis: ACh, ATP, GABA and Glu. ACh is an ester, ATP is a phosphoanhydride, GABA and Glu are amino acids. It is worth clarifying something regarding the latter: glutamate is the name given to a neutral salt and this can lead to confusion. In fact, for the acid strength GABA and Glu are very similar amino acids: they have respectively 4.0 and 4.3

pKa. For that reason, in vesicles where the pH is acidic (Anderson & Orci, 1988; Egashira et al., 2016; Fuldner, HH & Stadler, H, 1982; Michaelson, DM & Angel, I, 1980; Miesenbock, G & De Angelis, DA, 1998), they are both partially undissociated, in the protonate form; therefore, for the sake of coherence, like GABA, Glu should be called acid glutamate. When they are released in a neutral or slightly alkaline environment, such as the synaptic cleft in the static state, these undissociated acid molecules tend to dissociate, each in its respective anion and a proton, as shown in Table 2.

Table 2. Protonated and deprotonated states of acid neurotransmitters		
VESICLE LUMEN		SYNAPTIC CLEFT
acid glutamate	⇌	glutamate ⁻ + H ⁺
γ-aminobutyric acid	⇌	γ-aminobutyrate ⁻ + H ⁺

Therefore, it is evident that vesicle exocytosis produces inter-synaptic acidification (Ahdut-Hacohen et al., 2004; DeVries, 2001; Kolen et al., 2023; Miesenbock, G & De Angelis, DA, 1998; Palmer et al., 2003; Soto et al., 2018; Uchitel et al., 2019) through the release of protons due to the acid content of vesicles and that the two acid neurotransmitters Glu and GABA may be, in glutamatergic or respectively GABAergic vesicles, the principal source of the protons. The importance of this source is shown by the fact that the organism consumes energy to recycle the deprotonated Glu and GABA in the vesicles sufficiently rapidly to protonate and reuse them (Eriksen et al., 2016; Marx et al., 2015; Pathak et al., 2015; Pulido, C & Ryan, TA, 2021).

ATP is an important signalling molecule (Burnstock, 2020; Dunn & Grider, 2023) as well as being a fundamental source of cellular energy, produced by mitochondria and other cellular structures (Morelli et al., 2020). Unlike Ca²⁺, its concentration is high inside the cell and low outside. As an extracellular neurotransmitter, ATP can be released, or co-released from synaptic vesicles and activates two families of purinergic receptors, P1 and P2, for adenosine and ATP/ADP, respectively (Burnstock, 2020). The hydrolysis of ATP produces energy, ADP and acid phosphate, which in turn releases a proton. Similarly, one more step can lead to AMP. The products of hydrolysis can have a modulatory effect on retinal synapses (Kreitzer et al., 2023; Vroman et al., 2014) or, if in excess, cause inflammation and brain disorders (Di Virgilio et al., 2023; Dias et al., 2023; Vultaggio-Poma et al., 2022).

Regarding the ACh, the protons are released by the acetic acid produced by the hydrolytic split of the ester bond by the cholinesterases: acetylcholinesterase and butyryl-cholinesterase. The reaction is very rapid and produces choline and acetic acid. For a long time, it was believed that the acetic acid and choline, constituting the ACh, were neurologically inactive molecules. It is still believed that the activity of ACh concerns the entire molecule because the limited use of anticholinesterases inhibits the response in direct proportion to the inhibitor dose and the response increases with the accumulation of ACh (Malik, 1970). From this standpoint, cholinesterases have the sole function of rapidly eliminating the ACh, after its action. Today, we know that both constituents, choline and acetic acid, carry out a specific neurologically significant action (Mike, A et al., 2000; Wang et al., 2011) and that acetylcholinesterase may be indispensable for the

action of ACh (Fillafer et al., 2021; Fillafer & Schneider, 2016). In addition, it has been posited that cholinergic transmission is due to the protonation of the postsynaptic membrane, caused by the acetic acid derived from the hydrolysis of ACh (Fillafer et al., 2021).

If the hypothesis that ACh can also act via its constituents were confirmed, it would be easier to clarify a number of questions that have been perplexing for some time. In addition, the fact that the four neurotransmitters ATP, ACh, Glu and GABA can release protons explains the observation of Soto et al. regarding co-release (Soto et al., 2018), as cited in the introduction.

The protons released by Glu, GABA, ATP or ACh acidify the inter-synaptic space and can activate acid-sensitive receptors at the postsynaptic termination together with specific receptors for Glu, GABA, ATP and ACh. There are numerous proton-sensitive receptors in the postsynaptic termination (Holzer, 2011), both ionotropic such as ASICs (Cheng et al., 2018; Rook et al., 2021), TRPV1 (Kweon et al., 2015; Leffler, A et al., 2006; Ryu et al., 2007; Semtner et al., 2007), CaV3 (Lipkin et al., 2021) and metabotropic, of the TASK type (Fan et al., 2022) and GPCRs (Sisignano et al., 2021). The proton activation of the postsynaptic receptor can foster the opening of ionic channels (Boillat, A et al., 2014; Henrich & Buckler, 2009), depolarization and the generation of a new action potential, enabling the impulse to continue (Burke & Bender, 2019; Fillafer et al., 2021; Highstein et al., 2014).

Furthermore, many ligand receptors, specific for Glu, GABA and ACh, of the GPCR type, such as Group1 Glu (Suh et al., 2018; Y.-G. Sun et al., 2016), GABAb (Negri et al., 2022), nicotinic $\alpha 7$ (J. R. King et al., 2018; Papke, RI & Lindstrom, JM, 2020) and muscarinic M1, M3 and M5 (Brown, 2019; Sam & Bordoni, 2022) receptors are activated by protons generated by PLCs. Ionotropic GABA_A are also activated by the PLCs (Nicholson et al., 2018). On the contrary, most ionotropic postsynaptic receptors of glutamate are inhibited by the protons, particularly AMPARs (Ihle, Eva C. & Patneau, Doris K., 2000), Kainate receptors (Mott et al., 2003) and NMDARs (Dravid et al., 2007; J.-B. Zhang et al., 2018).

It is evident that protons may act at the synaptic level in various ways and via a large number of receptors. However, since they are highly mobile and reactive but have low specificity, it is logical to attribute to protons mainly the quantitative aspects of the mechanisms of neurotransmission. Whilst the qualitative aspects could be modulated by variations in the frequency, intensity and duration of the proton impulse, by a parallel series of events such as variations in the concentration of other ions, the type of other neurotransmitters involved, the receptors activated, their interrelations and their responses. In line with the general principle of co-release and co-transmission (Hunt et al., 2022; Svensson et al., 2019).

Scheme 2 provides a comprehensive, simplified representation of the possible processes of proton action at the synaptic level. Orange-colored arrows represent the increasing depolarization.

3. Conclusions

The results of the numerous experimental works cited in this review, taken together, provide an answer to the dual

objective of the work and support the hypothesis that protons, with Ca^{2+} ions, may play a fundamental role in both the generation and the biochemical transmission of the nerve impulse. Protons are small, charged particles that are very mobile and can have many, different endogenous sources. At the cellular level, the transient and localized increase in protons and Ca^{2+} concentrations can activate Na^+ and K^+ channels and promote depolarization thus generating the action potential. Likewise, at the synaptic level protons and Ca^{2+} can activate post-synaptic channels and generate action potential.

These conclusions open a new perspective on neurotransmission; nevertheless, much remains to be discovered. In particular, two relevant questions require experimental answers for a better evaluation of the role of protons in neurotransmission: a) Are phosphomonoesterases able to release protons and consequently increase the Ca^{2+} concentration in physiological conditions? b) Are cholinesterases essential for the action of ACh, i.e. are the protons released by cholinesterases essential for the action of ACh? The tests to answer the two questions do not seem very difficult, especially the first one. Hopefully, somebody will perform them.

Often, experimental studies on ionic neurotransmission consider only a single step of the process of neurotransmission and a single ion. This leads to partial knowledge and the need to connect them like dominoes. For better knowledge, at least two ions should ideally be determined at the same time, in subsequent steps. The interdependence of protons and Ca^{2+} ions due to their chemical properties suggests always measuring their concentration together. The articles of Swietach et al. (P. Swietach, 2013) and Liu et al. (X. Liu et al., 2020) can be useful examples for planning experimental works on the reciprocal roles of protons and Ca^{2+} ions in neurons. At present, several fluorescent probes are available to measure organellar pH (Freeman et al., 2023) and photostimulation techniques are often used to study Ca^{2+} (Moccia et al., 2023). Mathematical models can also provide valuable help (J. King et al., 2021).

To conclude, the role of protons in neurotransmission may be more important than has so far been believed. New studies on the topic could lead to fundamental discoveries and improvements in therapeutic agents for the treatment of neurological diseases.

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