

Proton Signaling Biology From Ancient Bioenergetics to Neural Communication: An Exploration of Keratan Sulfate as a Potential Proton-Modulatory Molecule

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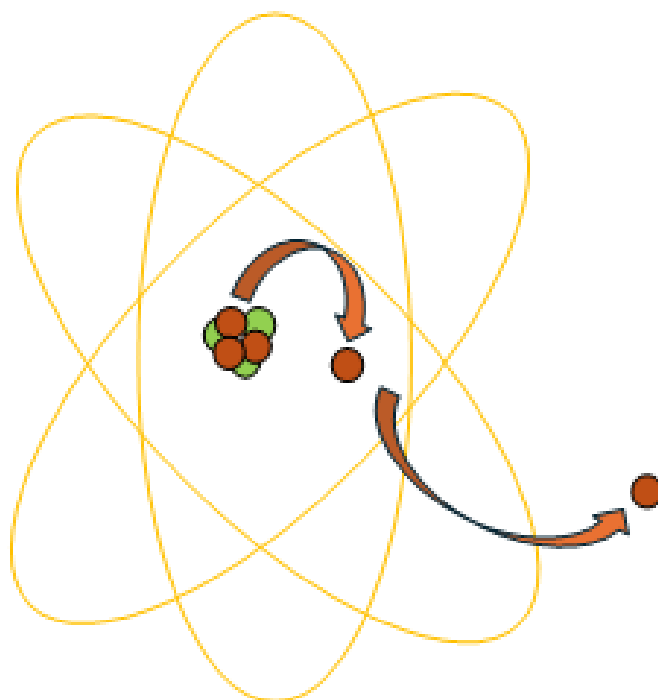
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This mini review examines the potential roles of proton signaling in the peripheral and central nervous systems and its proposed regulation by keratan sulfate (KS). Protons are central to bioenergetics and rapid chemical signaling, linking metabolism to membrane excitability and receptor activity across tissues. Nanoscale-to-microscale pH transients may add a further layer of intercellular communication in the nervous system through proton-sensitive ion channels and receptors. Extracellular matrix glycosaminoglycans may influence this signaling by buffering and transporting protons. Keratan sulfate has an unusually high capacity to bind and conduct protons. Evidence from electrolocation biology, proton-conductive biomaterials, and brain proton sensors suggests that keratan sulfate may act as a local proton reservoir and shuttle within defined microenvironments, thereby shaping pH-dependent neuromodulatory processes in health and disease. KS-substituted proteoglycans have the potential to act as neuron modulatory molecules mediating effects on cellular metabolism. KS shows considerable promise as a neuromodulatory molecule. Further electrophysiological studies are warranted using KS knockout animal models to test this hypothesis and validate the proposed role of KS as a potential regulatory neural interface molecule.

Keywords: proton; glycosaminoglycan; keratan sulfate; neural regulation; Grotthuss proton shuttling; proton wire

The proton the energetic communicator



Protons belong to an ancient bioenergetic system that emerged with the origin of life. They signal to cells through multiple receptors and in neurons support neurotransmission.

Graphical Abstract

Introduction

The structure, neuromodulatory roles, and conductive properties of keratan sulfate have previously been reviewed as discussed later; however, much needs to be learned about this fascinating glycosaminoglycan (GAG). The proton interactive properties of KS are particularly interesting and relevant to neural function and synaptic transmission. The proton is one of the three basic subatomic particles, alongside neutrons and electrons [1] with fundamental roles in early life evolution [2], in health and disease [3]. Neurons are highly energy-demanding [4]. Mitochondrial dysfunction is implicated in neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, frontotemporal dementia, Huntington's disease, and amyotrophic lateral sclerosis [5]. G-protein coupled receptors act as cellular proton sensors [6] linked to mechanosensation, inflammation, cancer [7], hematopoiesis, pain, and cytoskeletal remodeling in tissue development [8]. Proton gradients and local pH shifts drive chemical and biological processes regulating molecular interactions and cellular behavior [9,10,11].

Strategic Roles of the Chemistry of Water in Early Life Evolution

The chemistry of water was one of the most crucial determinants that shaped the evolution of life on earth [12]. An important chemical feature of water was its dissociation into protons and hydroxyl ions. It was this presence of relatively high proton concentrations in ambient solution that eventually resulted in the emergence of proton pumps during the dawn of life on earth [13] and the early development of cellular bioenergetic systems. These proton pumps maintained a neutral pH inside early cells and had a fundamental role in the generation of electrochemical proton gradients across their membranes. The proton-motive force so generated promoted dynamic electrochemical properties in membranes essential for the evolution of early bioenergetics [14] and the survival of the earliest unicellular organisms. The emergence of membrane bioenergetics equipped membranes with essential ion transport properties for the provision of life promoting metabolite delivery and the removal of metabolic waste products and also led to the development of active sensory systems [15].

Roles for Proton Gradients in Life Events Still Relevant to Neuroregulation Today

During the early evolution of life proton gradients emerged as an energy source that early forms of mitochondria subsequently harnessed to develop an energy production system [16]. It is postulated that during early evolution a symbiotic partnership progressed with pre-mitochondria via cellular fusion to generate a chimeric or hybrid cell with a membrane bound internal structure that was the forerunner of the nucleus. This hybrid cell type was the precursor of what would become the eukaryotic cell [17,18]. Subsequent evolution of the mitochondrial electron transport system and the harnessing of the proton motive force by ATP synthase to synthesise ATP in early bioenergetic events is now a universal energy production system in all mammalian cells [14].

Protons and Cell Regulation

Protons are essential for cellular homeostasis and influence many physiological processes. Metabolically generated proton levels vary with environmental factors and diet. Protons are metabolic by-products, that act as potent regulators, affecting enzyme activity, ion channel function, receptor–ligand binding, and local ion availability. These processes are highly pH-sensitive and multicellular organisms tightly regulate pH using ion channels, pH sensitive receptors and proton pumps that move protons across membranes.

Mitochondria establish a proton gradient by using the electron transport chain, a series of protein complexes embedded in the inner mitochondrial membrane. As electrons move through the electron transport chain, complexes I, III, and IV transfer protons (H^+) from the matrix into the intermembrane space, generating an electrochemical gradient (the proton-motive force). ATP synthase then uses this proton gradient to drive the synthesis of ATP from ADP and inorganic phosphate [19]. Neurons and photoreceptors are energetically demanding cell types and contain high mitochondrial numbers to service their high energetic needs.

Proton Interactions With Multiple Receptors in the Brain

In the CNS, transporter activity and increased production of CO_2 and metabolites (e.g., lactate) can generate substantial nano- and micro-scale pH shifts, providing a potential intercellular communication system [11]. Acid-sensing ion channels (ASICs) are proton-gated cation channels that detect and signal increases in proton concentration and modulate neuronal activity [20]. ASICs act as specialized detectors in proton-signaling networks, responding to extracellular pH changes across a broad pH range (pH 5–8). Through proton detection, ASICs modulate neuronal excitability during synaptic transmission, supporting extracellular proton-based signaling [21]. Emerging evidence indicates that protons are produced and regulated in spe-

cific brain niches, suggesting they have roles in physiological and pathological processes in the brain ranging from nociception to cognitive learning and memory. Extracellular protons may contribute to signal transmission by acting on adjacent cells or by modulating the cell they originated from. Protons have modulatory effects on a number of receptors in the brain. Protons modulate ASICs and voltage-gated Ca^{2+} channels (VGCCs). Binding of protons to acetylcholine ionotropic receptors opens a distantly located ion channel through a change in the conformation of the M2 domain, a process termed allosteric activation which supports pore dilation [22,23]. Gating of the $\alpha 1\beta 3\delta\gamma$ -aminobutyric acid A ($GABA_A$) receptor channel is modulated by protons [24]. The beta sub-unit TM2 and TM3 domains mediate the modulation of $GABA_A$ receptors [25,26,27]. N-methyl-D-aspartate receptors (NMDARs) play essential roles in memory formation, neuronal plasticity, and brain development. Dysfunction in NMDAR function is linked to a range of neurological disorders, pH is a physiological allosteric modulator of NMDARs [28,29,30]. This modulatory activity of protons highlights their importance in brain function under normal and pathological physiological conditions (Fig. 1).

Examples of Proton Responsive Receptors

ASIC Ion-Channels

ASICs are activated by a decrease in extracellular pH leading to the binding of protons to the channels in its extracellular domain [31]. This induces a conformational change in the channel opening the ion conductive pore promoting an influx of primarily Na^+ and Ca^{2+} to a lesser extent which leads to membrane depolarization and neuronal excitation. The influx of Ca^{2+} can also activate voltage gated calcium channels (VGCC) promoting an increase in intracellular $[Ca^{2+}]$ which constitutes part of the neuronal activation process. Cellular responses to ASIC channel activation can influence a range of physiological processes [32]. ASIC channels are widely but differentially expressed in the CNS/PNS, most neurons express at least one ASIC sub-unit and have crucial roles in neuronal signaling in a wide range of physiological and pathological processes. Activation of neurons by protons leads to cellular excitation. ASIC channels are assembled from several different sub-units (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, ASIC4, ASIC5) as homo or heteromeric trimeric assemblies. ASIC1a trimeric channels allow entry of Na and Ca ions and can trigger multiple cellular processes in glial cells [33].

Postsynaptic receptors such as glutamate receptor, metabotropic 6 (mGluR6) in bipolar neurons are activated by protons co-released with glutamate by photoreceptors in the ribbon synapse and these play an essential role in visual processes and sensory hair auditory cells in the cochlea [34,35,36]. Co-release of protons and glutamate also act

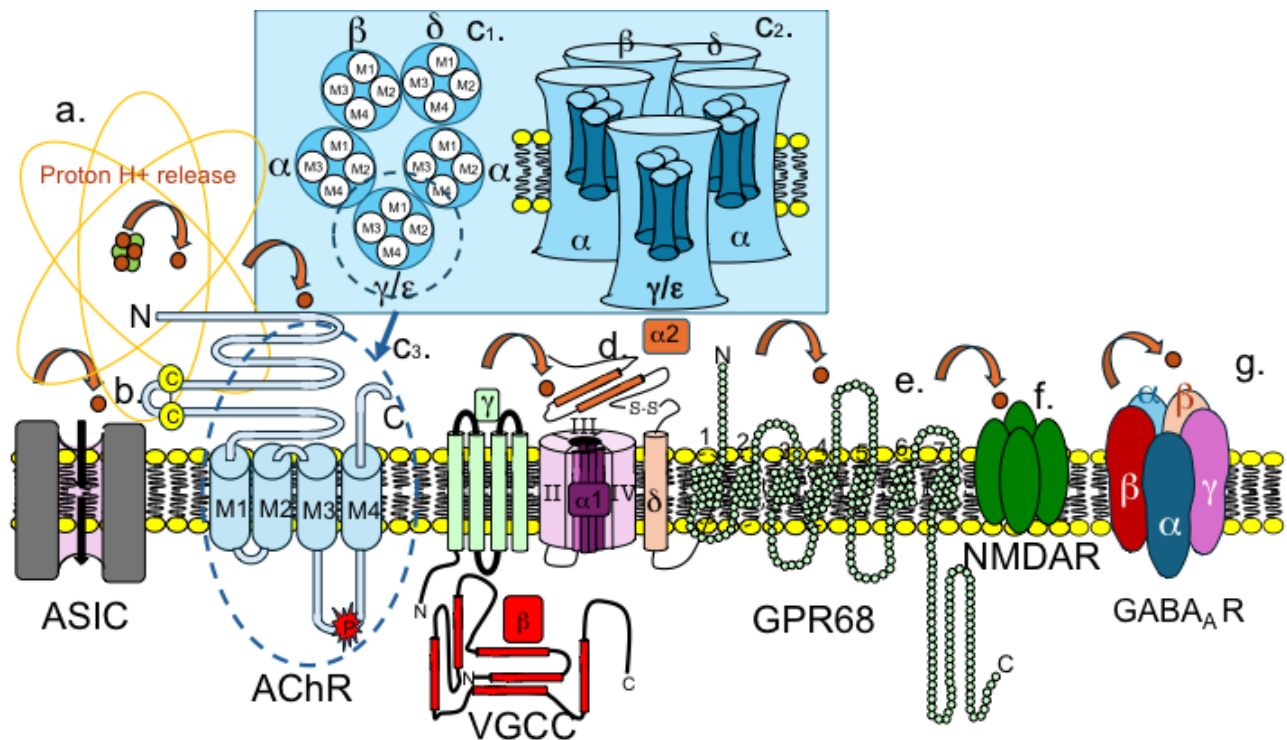


Fig. 1. A schematic depiction of some examples of cell receptors and ion channels known to be regulated by protons. A schematic of a cell nucleus with a released proton (a). Acid sensing ion channels (ASIC) (b), acetyl choline receptor (AChR) and its five sub-units each containing M1–M4 transmembrane domains (c1–c3), c1 is a plan view; transmembrane voltage gated calcium channel (VGCC) and its 5 sub-units (d), G-protein coupled 7 span transmembrane receptor for sphingosylphosphorylcholine proton-sensing receptor, (GPR68) (e), *N*-methyl-D-aspartate receptor, a glutamate receptor and Ca^{2+} ion channel found in neurons (NMDAR) (f), GABA_A R, for the neurotransmitter gamma aminobutyric acid (GABA) (g). Calcium has crucial roles in membrane depolarization and activation of the neuron and transport of neurotransmitters in synaptic vesicles to the synaptic cleft during neurotransmission. The figure was created by the author using Microsoft PowerPoint (version 16.111, Redmond, WA, USA).

as as modulators of synaptic transmission at glutamatergic synapses and GABAergic synapses in synaptic plasticity, memory and learning. Dysfunction in this system contributes to pathological functional changes in neuronal tissues in conditions such as epilepsy, mood disorders and Alzheimer's disease.

Acetylcholine Receptors

Brain acetylcholine receptors (AChRs) are expressed in pre-synaptic nerve terminals where they regulate neurotransmitter release by co-ordinating the clustering, fusion and acidification of brain synaptic vesicles which regulates synaptic neurotransmitter release [37]. The AChR consists of five subunits including the fetal specific γ -subunit or the adult specific ϵ -subunit. Each subunit has four helical transmembrane domains M1–M4 [38]. Protons interact with multiple extracellular sites on $\alpha\beta\gamma$ nAChRs regulating their gating properties [39]. AChRs are further regulated by an N-terminal extracellular domain which contains a Cys-loop, four transmembrane domains and a cytoplasmic loop domain between M3 and M4. This is a consensus sequence in AChR for phosphorylation by protein kinase

A and is only present in the M3–M4 loop of the ϵ -subunit [38]. AChR alpha subunit gene expression is regulated by electrical activity and this process also involves protein kinase C and Ca^{2+} . Proton transfer promotes conformational changes in the cysteine-loop receptor channel to regulate the gating process. During cholinergic transmission acetylcholinesterase hydrolyses acetylcholine however this also generates protons. It has been proposed that lipid membrane state change is induced by this catalytic protonation and this promotes cholinergic transmission [40].

Voltage-Gated Ca^{2+} Channels

VGCCs mediate Ca^{2+} influx to trigger neurotransmitter release at specialized presynaptic sites termed active zones. VGCCs are assembled from several different subunits (α_1 , $\alpha_2\delta$, β_{1-4} , and γ). The α_1 subunit forms the ion-conducting pore while the other sub-units surround this sub-unit and modulate its gating properties providing an off/off molecular switch that regulates the secretion of Ca^{2+} . Synaptotagmin binds to the α_1 pore-sub-unit to regulate release of Ca^{2+} [41]. Synaptotagmin is a crucial calcium sensory glycoprotein that regulates neurotransmitter

release and hormone secretion by facilitating vesicle fusion in response to calcium ions [42,43] co-operating with the SNARE protein complex to promote synaptic vesicle fusion with the pre-synaptic membrane to regulate release of neurotransmitters into the synaptic gap during neurotransmission [44].

Sphingosylphosphorylcholine Proton-Sensing Receptor (GPR68)

GPR68 (ovarian cancer G protein coupled receptor 1, Sphingosylphosphorylcholine receptor) is a proton-sensing G-protein coupled receptor that has an activation threshold between pH values of 6.5–7.0 and is widely expressed by many normal and cancer cell types. These GPCR receptors interact with lipid molecules such as sphingosylphosphorylcholine, lysophosphatidylcholine, and psychosine as well as protons. The expression of GPCRs are significantly elevated in macrophages and monocytes in inflammatory bowel disease. GPR68 modulates inflammatory responses affected by the Gp/11-phospholipase C- inositol 1,4,5-triphosphate (IP3)/Ca²⁺ cell signaling pathway. Gp/11 (Gp alpha sub-unit) is a heterotrimeric protein of the GPCR signaling pathway that activates phospholipase-C. An acidic extracellular pH promotes GPR68 coupling to Gp/11 elevating phospholipase-C activity and IP3 synthesis. This results in Ca²⁺ release from the ER and activation of calmodulin dependent kinase and calcineurin activity which induces, or nuclear factor kappa B (NF-κB) and nuclear factor of activated T-cells (NFAT) nuclear translocation upregulating inflammatory mediator (interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), cyclooxygenase-2 (COX-2)) production exacerbating inflammatory signaling pathways and promoting age related diseases such as OA, atherosclerosis, chronic kidney disease, AD, PD, glioblastoma and pancreatic cancer [45]. Elevation in GPR68 activity also mediates visceral pain [46] and pain generation in osteoarthritis (OA) [47] and may influence gene expression in articular cartilage exacerbating pathological changes in this tissue in OA [47,48]. GPR68 has been proposed as a therapeutic target in the treatment of cancer [49].

N-methyl-D-aspartate Receptors

NMDARs are heterotetrameric assemblies of different combinations of the GluN1, GluN2 (A-D), and GluN3 (A-B) subunits and are ionotropic glutamate and Ca²⁺ gated receptors and ion channels critical for synaptic transmission and plasticity. NMDARs coordinate brain vascular development [50] and are widely expressed in the CNS playing key role in brain development and plasticity [51]. Over or under activation of NMDAR activity is harmful to neuronal function and has roles in the development of neuropsychiatric disorders including autism spectrum disorders, epilepsy, intellectual disability, and schizophrenia. Protons inhibit NMDARs and may be useful for therapeutic applications.

GABA Receptor

Gamma-aminobutyric acid (GABA) is the major inhibitory CNS neurotransmitter that reduces the excitability of neurons thus it has the opposite properties of glutamate which is an excitatory neurotransmitter and collectively these are important neuroregulatory compounds.

GABA receptors occur as ionotropic (GABA_A) and metabotropic (GABA_B) isoforms with different functional properties. The GABA_A receptor acts as a chloride gated ion channel facilitating hyperpolarization of post synaptic neurons. GABA_A is a heteropentameric receptor assembled from α, β, γ, σ, ε sub-units and is the major GABA receptor with over 800 GABA_A receptor sub-types identified in the human brain. The β subunits of GABA_A receptors form proton-gated chloride channels [27,52,53]. Protons regulate GABA_A receptors through pH-dependent changes that vary with subunit composition. By altering ion conductance and receptor sensitivity to GABA, protons can modify inhibitory signaling. This effect depends partly on specific subunit residues, such as histidine H267 in the β subunit, which contributes to proton-induced enhancement of GABA responses. Receptor assemblies such as αβ, αβδ, and αβγδ also differ in chloride-current kinetics and agonist potency. As a result, proton-sensitive GABA_A receptors may have distinct pharmacological properties and could represent targets for drug development [53]. The GABA_B receptors are GPCRs that mediate slow and prolonged inhibitory action, through activating inwardly rectifying K⁺ channels, inactivation of voltage-gated Ca²⁺ channels, and inhibition of adenylate cyclase [54,55,56].

Proton Regulation of Brain Cellular Activity

Protons help regulate neurons, astrocytes, photoreceptors and neurovascular unit, including endothelial cells and pericytes, by generating local niche microenvironments that modulate nearby cellular activity and by acting as intercellular messengers [21]. Proton-sensitive G-protein-coupled receptors (GPCRs) such as GPR68 can be neuroprotective during acidosis and ischemic conditions, in part through protein kinase C (PKC)-dependent signaling, underscoring the complexity of acid signaling and its influence on brain cellular behavior, cognition, and memory [47,57].

Roles for Protons in Synaptic Processes

Extracellular pH changes provide signals for neuronal communication [58]. During synaptic transmission changes in pH in the synaptic cleft regulate presynaptic Ca²⁺ currents through multivesicular neurotransmitter release in ribbon-synapses. Protons act as neurotransmitters in synaptic neuronal communication in CNS regions such as the amygdala, nucleus accumbens, and brainstem. Protons released by nerve stimulation activate postsynaptic ASICs [31]. Changes in intracellular Ca²⁺ also play important roles in photoreceptor signaling and neuronal acti-

vation. Metabotropic glutamate receptors have important roles in glutamate signaling that prime bipolar neurons for neurotransmission and transfer of visual signals from photoreceptors through the retinal neural network to the ganglionic neurons and transfer via the optic nerve to the brain for visual interpretation [34].

The Impact of Protons on Neuronal Function

The high energy requirements of neurons and an inability to produce sufficient ATP by glycolysis in some disorders, shows a dependency on functional mitochondria to maintain normal neuronal activity [4]. Under normo-stasis the adult human brain consumes a significant and disproportionate amount of energy substrates (20–25% of total glucose and oxygen) [59]. It achieves this through oxidative phosphorylation using ATP synthase which generates a proton gradient (the proton motive force) via proton-coupled electron transfer processes in the multi-component electron transport chain. The proton motive force generated proton gradients drives the ATP biosynthetic process by ATP synthase, a rotary nan-machine protein [19,60]. However, reactive oxygen species, produced as part of the respiration process within mitochondria, can lead to oxidative stress, compromising neuronal survival and tissue function and may lead to mitochondrial dysfunction in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) [61]. Mitochondria have their own genome, the mitochondrial DNA (mtDNA). Inherited solely from the mother, this genome is affected by mutations, and by an absence of an effective repair system. Mutations in mtDNA are associated with endocrine, metabolic, neurodegenerative diseases, and even cancer. Mitochondrial gene therapy is a promising strategy since it focuses specifically on the cause of mitochondrial disorders arising from oxidant stress [62].

Proton Release in the Ribbon Synapse Regulates Neural Responses

The ribbon synapse is an electron-dense highly specialized synapse that tethers synaptic vesicles containing encapsulated neurotransmitters close to the active zone in the synaptic cleft where they are subsequently released in a highly regulated process as part of the neurotransmission process [63]. Tight vesicle channel coupling ensures rapid highly efficient neurotransmitter release and sustained signal transmission enabling extremely fast, precise and sustained neurotransmission critical for the function of high precision senses such as vision and hearing. Ribbon synapses are found in retinal photoreceptor, vestibular organ receptors and sensory cochlear hair cells, retinal bipolar neurons and pinealocytes.

Proton Receptors and Ion-Channels in Cartilage Pathobiology

Acid sensing receptors and ion channels are implicated in pain generation in OA [47,64]. Proton-sensing channels and receptors are implicated in pH-driven nociceptor activation, through direct causal demonstration in human OA [65]. GPR68 Couples to Gq/phospholipase C mitogen-activated protein kinase (PLC-MAPK), cAMP response element-binding protein (cAMP-CREB), G12/13-Ras homolog family member A (RhoA)-Rho-associated coiled-coil kinase (ROCK) signaling pathways, and is expressed most prominently in articular cartilage, with additional expression reported in synovium, bone, vasculature, and some neuronal populations [47,48].

Keratan Sulfate Is a Multifunctional Glycosaminoglycan Relevant to Neuron Biology

Keratan sulfate (KS) is a sulfated glycosaminoglycan present in specialized tissues including the cornea, cartilage, and nervous system [66,67,68]. Its structural heterogeneity, including differences in sulfation and linkage to proteoglycan core proteins, contributes to its physicochemical and biological properties. Of particular relevance to the present review, the high negative charge density of sulfated KS may facilitate interactions with protons and influence the ionic microenvironment surrounding cells. Detailed aspects of KS structure, isoforms, and glycodynamics have been reviewed previously [67,68,69,70] and are therefore not discussed further here.

Sulfation of KS is an Important Functional Determinant

The sulfation pattern of KS is an important determinant of its charge density and molecular interactions [68]. Variations in sulfation and chain organization influence the physicochemical properties of KS and may therefore affect its capacity to bind and transport protons. KS also interacts with multiple neuroregulatory proteins and extracellular matrix components [71,72,73,74]; however, these broader signaling functions have been reviewed elsewhere and are beyond the scope of the present discussion.

Keratan Sulfate Conveys Diverse Functional Properties to Proteoglycans

Brain KS chains can be linked to several proteoglycan core proteins, including keratocan, lumican, and fibromodulin, which are distributed in neural and other extracellular matrix environments [75,76]. These KS-containing proteoglycans have diverse structural and regulatory functions that have been reviewed previously [77,78,79]. In the context of the present review, their relevance lies primarily in the possibility that KS-containing extracellular matrices may influence local proton availability and proton-dependent neural responses [10,58,80].

Roles for GAGs in Cell Signaling Processes Modulated by Proton Activity

All GAGs can bind protons to some degree although KS is the most potent proton binder [80,81]. Extracellular matrix proteoglycans with their attached GAG side chains may act as proton reservoirs and transporters helping to buffer and regulate the pH of the extracellular environment. Keratan sulfate traps and transports protons through a process that has been termed Grotthuss shuttling. This process utilises the hydrogen bonding network that surrounds KS chains and the sulfate groups on KS chains attached to GlcNAc and Galactose to transport protons in proton wires. Protons are co-released with neurotransmitters into the synaptic cleft when synaptic vesicles fuse with the depolarized pre-synaptic gap membrane. KS has a particularly high proton-binding capacity and proton conductivity [80] and can bind and conduct protons through a hydrogen-bonding network, with sulfate groups acting as proton donors/acceptors, enabling rapid transfer via structural diffusion [82]. In this scenario, KS has been proposed to form part of a neural interface that can modulate proton availability and thereby influence electro sensory processes and optimise neurotransmission in selected tissue niches [9,83].

Proton Interactive Properties of KS: Grotthuss Proton Shuttling

The Grotthuss proton shuttling mechanism [70,84] explains diffusion through hydrogen bonded solvated networks in electroconductive molecules and was reviewed by Cukierman [85] and Popov et al. [82] (Fig. 2). It was later supported by NMR [84], dielectric spectroscopy, quasielastic neutron ion mobility-mass spectrometry and light scattering [82,86]. This proton-hopping process has been proposed as a message-delivery system for nerve conduction [58], while conductive hydrogels may regulate neural activity and tissue function [87]. Experiments show that all GAGs conduct protons to varying degrees through hydrogen-bond networks between water and hydrophilic residues [80]. Hydrated bovine corneal KS has proton conductivity comparable to KS-glycoconjugate gel in the Ampullae of Lorenzini and is among the highest known natural proton conductors [81,88]. Shark KS enables exceptionally sensitive electrolocation, detecting conductivities as low as 5 nV/cm, and KS is the most proton-conductive GAG. Natural ion-conducting materials are promising neuronal bioelectronic interfaces [89], and natural-compound biotransducers can regulate pH-responsive enzymatic reactions [90], supporting a role for KS as a local proton reservoir and shuttle that shapes pH-dependent neuromodulation in health and disease.

Roles for KS in Electrolocation, an Ultrasensitive Proton Detection System

A low-sulfation, mucin-like glycoconjugate hydrogel in the ampullae of Lorenzini skin sensory pores of elasmobranch fish (sharks and rays) supports electro-sensing by enabling detection of extremely weak electric fields generated by muscular activity of prey species [81,88,91]. Measurements of ampullae jelly indicate unusually high proton conductivity among biological materials [88], and KS has been proposed as a contributor through its sulfate-rich, proton-conductive chemistry [81,91]. Sharks use these weak bioelectric fields for electrolocation during hunting. Mammals no longer have the ability to electrolocate, these aforementioned examples nevertheless illustrate the ultrasensitive properties of KS as a proton detection device.

Future Research on KS as a Potential Biotherapeutic Delivery Vehicle to Treat Neurodegeneration

Despite progress made in the last few decades in our understanding of a growing number of genetic and molecular causes of CNS disease, therapies that diminish or halt neuronal dysfunction/death are rare. The genetic complexity of such neurological disorders has challenged the development of effective neuroprotective strategies that also preserve mitochondrial homeostasis. Besides having an essential role in energy production and oxidative stress, mitochondria also have indispensable roles in many cellular processes, including amino acid metabolism, biosynthesis of iron-sulfur clusters, calcium homeostasis, intrinsic programmed cell death (apoptosis), and cell signaling. Innovative biotherapeutic delivery systems are now revolutionising diagnostic approaches with the use of novel engineering platform technologies to treat mitochondrial disorders. KS-based drug-delivery systems such as nanoliposomes, microspheres, microcapsules and nanoparticles have also been developed however they have yet to be applied in mitochondrial therapies [92]. These delivery vehicles have the potential to improve the delivery of medications increasing efficacy and reduction of side effects and show potential in the treatment of mitochondrial neurodegenerative disorders warranting further assessment. Protons can act as neurotransmitters and regulate neuronal cell signaling [10] through proton mediated effects on neuronal receptors such as GABA_A [27,53], NMDAR [30], GPCRs [7,8,46] and ASICs [93] thus the regulatory properties of KS over protons is important.

Recent studies on mitochondrial therapy have focused on the targeting of individual ribosomal proteins either by gene therapy or by direct delivery into the brain to treat neurological disorders [94,95,96]. Mitochondrial ribosomal proteins are essential for the translation of mitochondrial-encoded effects in the oxidative phosphorylation system, that are critical regulators of neuronal homeostasis and sur-

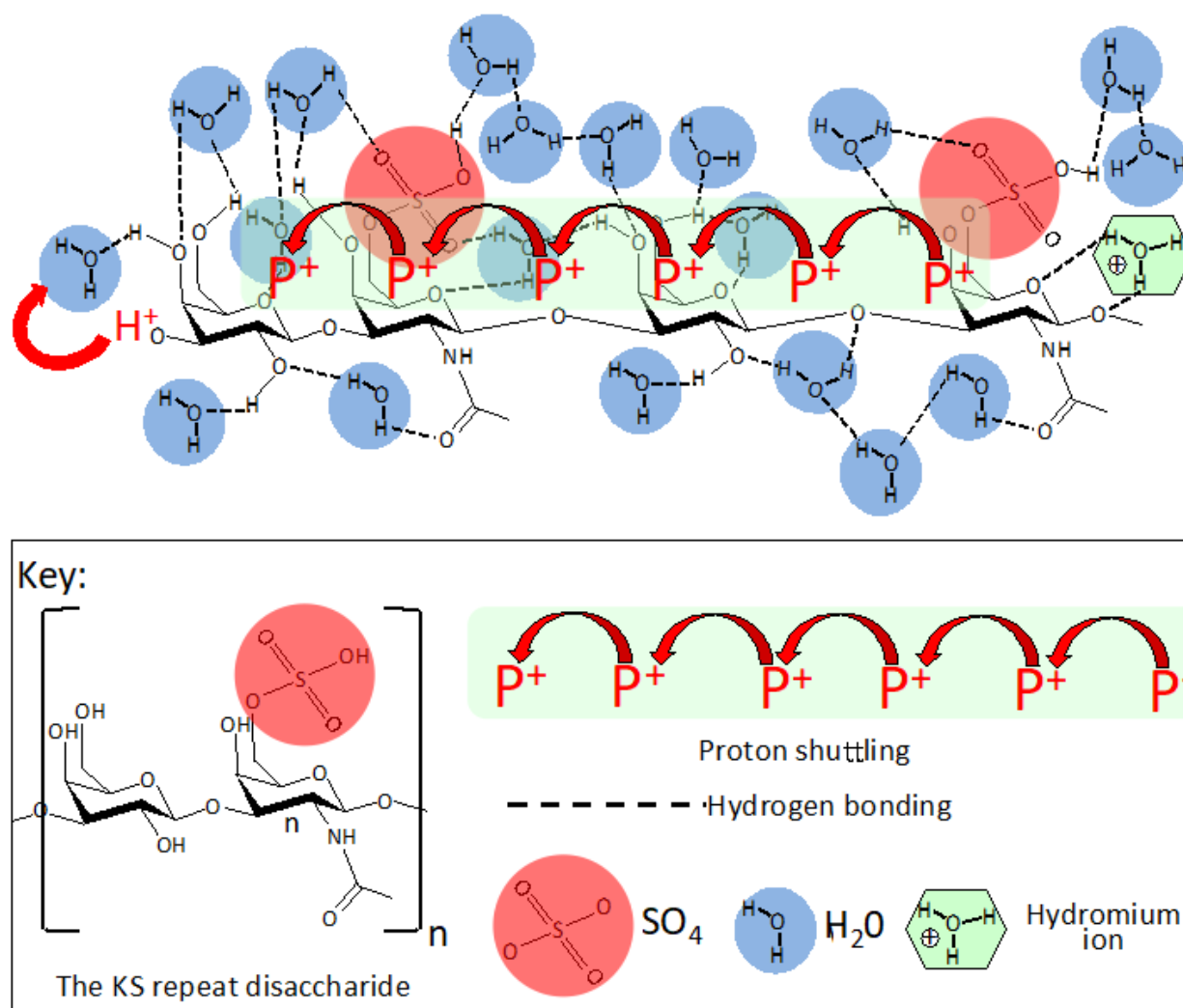


Fig. 2. Diagrammatic representation of Grotthuss proton hopping or shuttling forming a proton wire and the H-bonding cloud surrounding a KS chain that facilitates this. This involves the hydronium ion and water acceptor molecules that interact with sulfate groups and components of the H-bonding cloud of KS to transfer protons. The figure was created by the author using Microsoft PowerPoint (version 16.111, Redmond, WA, USA).

vival and implicated in autism spectrum disorder, motor neuron disease, encephalopathy, epilepsy, stroke, ataxia, AD, ALS, HD, and PD. The beneficial anti-oxidant, neuroprotective and neuroregulatory properties of KS suggest that this targeting strategy may also be useful in such therapeutic approaches. Neuroglobin, is found at high levels in the brain, the eye, and the cerebellum and localizes to mitochondria where it has roles in electron transfer, oxygen storage and defence against oxidative stress similar to those proposed in this study for KS.

Innovative Interventions With Nanozymes Preventing the Generation of Oxidant Stress and Neuroinflammation in Neurodegenerative Disorders

Medical treatment of neurodegenerative diseases such as AD, PD, MS, ALS and HD offer significant challenges. Current pharmacological interventions for these disorders

are unsatisfactory. All of these disorders are propagated by oxidative stress, protein misfolding, and neuroinflammation, leading to neuronal damage and death. Advancements in nanotechnology with the introduction of nanozyme engineered synthetic enzymes offer a promising innovative approach to the treatment of these disorders [97,98,99,100]. The potent antioxidant properties of nanozymes effectively scavenge reactive oxygen species (ROS) and restores redox balance, offering neuronal protection and recovery of normal neuronal function.

Conclusions

Cells depend on signals from their surroundings to survive and function. Protons participate in an ancient signaling system and act as intracellular and extracellular messengers. This review proposes that KS may interact with

protons and facilitate their local transfer to neurons, thereby modulating neuronal activity and neurotransmission. A clearer understanding of cellular proton regulation may reveal new therapeutic approaches for neurobiological disorders. Further research should therefore examine how KS regulates proton activity and whether this glycosaminoglycan contributes to neural bioregulation. The proposal that KS functions as a neural communicating molecule should be tested in KS-deficient animal models, including the β -1,3-N-acetylglucosaminyltransferase-7-null mouse cornea model. Priority studies include: electrochemical measurements of proton binding and transport; physiological assessment of neuronal responses; and behavioural studies of sensory and neural function. Together, these studies would clarify the contribution of KS to proton-mediated processes.

Availability of Data and Materials

Not applicable.

Author Contributions

JM is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author has received consultation fees from Arthroparm Pharmaceuticals, Bondi Junction, Sydney. This company had no input into the writing or interpretation of this study. The author has no conflict to report.

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