Pharmacology & Therapeutics 245 (2023) 108403

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The emerging science of Glioception: Contribution of glia in sensing, transduction, circuit integration of interoception

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ARTICLE INFO

Available online 5 April 2023

Associate editor: S.J. Enna

Keywords:
Interoception
Glioception
TRPV
AQPs
Astrocytes
Glia
Pain

ABSTRACT

Interoception is the process by which the nervous system regulates internal functions to achieve homeostasis. The role of neurons in interoception has received considerable recent attention, but glial cells also contribute. Glial cells can sense and transduce signals including osmotic, chemical, and mechanical status of extracellular milieu. Their ability to dynamically communicate "listening" and "talking" to neurons is necessary to monitor and regulate homeostasis and information integration in the nervous system. This review introduces the concept of "Glioception" and focuses on the process by which glial cells sense, interpret and integrate information about the inner state of the organism. Glial cells are ideally positioned to act as sensors and integrators of diverse interoceptive signals and can trigger regulatory responses via modulation of the activity of neuronal networks, both in physiological and pathological conditions. We believe that understanding and manipulating glioceptive processes and underlying molecular mechanisms provide a key path to develop new therapies for the prevention and alleviation of devastating interoceptive dysfunctions, among which pain is emphasized here with more focused details.

Abbreviations: 15dPGJ2, 15-deoxy-delta-prostaglandin J2; 2-NBDG, 2-[N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-D-glucose; A1R, adenosine A1 receptors; ACh, acetylcholine; AQP4, aquaporin 4; AQP4ex, aquaporin 4 extended isoforms; ASD, autism spectrum disorder; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; ATP, adenosine triphosphate; BA40, Brodmann's area 40; BA9, Brodmann's area 9; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; Ca^{2+}, calcium cation; CB, carotid body; CBX, carbenoxolone; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C chemokine receptor type 2; CCR3, C-C chemokine receptor type 3; CD11b, integrin α_M; CGRP, calcitonin gene-related peptide; Cl^-, chloride anion; CNS, central nervous system; CO_2, carbon dioxide; COX-1, cyclooxygenase-1; CREB2, cAMP responsive element binding protein-2; CSF, cerebrospinal fluid; CVOs, circumventricular organs; Cx, connexin; Cx30, connexin 30; CX3CL1, chemokine (C-X3-C motif) ligand 1; Cx43, connexin 43; CXCL1, chemokine (C-X-C motif) ligand 1; D1, dopamine 1; D2, dopamine 2; DBS, deep brain stimulation; DRG, dorsal root ganglia; EF, endfeet; ER, endoplasmic reticulum; Erk1/2, extracellular signal-regulated kinases 1/2; EtBr, ethidium bromide; GABA, gamma-aminobutyric acid; GAT2, γ-aminobutyric acid transporter 2; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GLAST, glutamate transporters; GLT1, glutamate transporters 1; GLUT-1, glucose transporter type 1; GLUT-2, glucose transporter type 2; GlyRs, glycine receptors; GSNO, S-nitrosoglutathione; H_2O, dihydrogen monoxide; HIV, human immunodeficiency virus; IBA1, ionized calcium-binding adapter molecule 1; IFN-γ, interferon-gamma; IL-1, interleukin 1; IL-1β, interleukin 1 beta; IL-33, interleukin 33; IL-6, interleukin 6; IP_3, inositol 1,4,5-trisphosphate; IP_3Rs, inositol 1,4,5-trisphosphate receptor; K^+, potassium cation; KATP, adenosine triphosphate-sensitive K^+; Kir 4.1, inwardly rectifying potassium; LC, locus coeruleus; LRRC8A, leucine-rich repeat-containing protein 8A; MAPK, mitogen-activated protein kinases; MBP, myelin basic protein; MHC II, major histocompatibility complex class II; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; MMS, magneto-mechanical stimulation; MPO, median preoptic nucleus; Na^+, sodium cation; NCX, sodium-calcium exchanger; NG2, neuron-glia antigen 2; NM2B, non-muscle myosins 2B; NM2C, non-muscle myosins 2C; NMJ, neuromuscular junction; NMO, neuromyelitis optica; NTS, nucleus of the solitary tract; NVU, neuro-vascular unit; O_2, oxygen; OAPs, orthogonal arrays of particles; Olig2, oligodendrocyte transcription factor 2; ONs, osmosensory neurons; OPCs, oligodendrocyte progenitor cells; OVLT, organum vasculosum laminae terminalis; OXY, oxytocin; P2, purinergic; P2X7, purinoceptor 7; P2Y1, purinoceptor 1; Panx1, pannexin 1; PCO_2, partial pressure of carbon dioxide; PDGFRa, platelet derived growth factor receptor alpha; PER, period; PNS, peripheral nervous system; PO_2, partial pressure of oxygen; POMC, pro-opiomelanocortin; PP, posterior pituitary; PVN, paraventricular nucleus; RAS, renin-angiotensin system; RTN, retrotrapezoid nucleus; RVD, regulatory volume decrease; RVLM, rostral ventro-lateral medulla; SCs, Schwann cells; SCN, suprachiasmatic nucleus; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; SFO, subfornical organ; SGCs, satellite glia cells; SON, supraoptic nucleus; SP, substance P; Src, Steroid Receptor Coactivator; ST2, suppression of tumorigenicity 2; tDCS, Transcranial direct cranial stimulation; TG, trigeminal ganglia; TGF-β1, transforming growth factor beta 1; TIM, timeless; TNF-α, tumor necrosis factor alpha; TNF, tumor necrosis factor; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV, transient receptor potential vanilloid; TTX, tetrodotoxin; VNS, vagus-nerve stimulation; VP, vasopressin; VRAC, volume regulated anion channel.

https://doi.org/10.1016/j.pharmthera.2023.108403
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Contents

1. Introduction

The Nervous System controls the regulation of vital inner processes, including blood pressure, temperature, sleep, digestion, osmoception, volume sensing and breathing, by responding to both external and internal stimuli (Berntson & Khalsa, 2021; Chen et al., 2021). Neuroscience investigations of the past decades have strongly contributed to the clarification of how we sense and interact with the external world. However, knowledge of the nervous system ability to represent our internal world remains limited (Chen et al., 2021; Quadt, Critchley, & Garfinkel, 2018). Recently, the concept of interoception has arisen as a bidirectional interplay between brain and body allowing the nervous system to sense, interpret, integrate, and regulate information about the inner state of the body, in order to maintain homeostasis (Berntson & Khalsa, 2021; Cameron, 2001; Sherrington, 1906).

The function of "sensing" indicates the bottom-up communication from cells that transduce responses to stimuli to the brain, through ascending pathways, whereas the function of "regulating" refers to the top-down flow from the brain to other physiological systems via descending and bidirectional pathways (Fig. 1). Brain regions, including the brainstem, hypothalamus, thalamus, and ultimately insula and somatosensory cortex, are primarily responsible for "interpreting" and "integrating" the signals arising from body tissues to form a representation of the internal world. Visceral sensory afferents and regulatory efferent signals travel along neural pathways, somatic and autonomic, including cranial, autonomic and spinal nerves. It has been reported that vagal nerves mainly transport mechanosensory and chemosensory autonomic information, while spinal nerves conduct signals mainly related to temperature, pain, and tissue injury (Saper, 2002).

Interoceptive information is exchanged also by non-neural pathways. Signals received from/ delivered to the peripheral organs include humoral pathways that are components of the vascular and lymphatic systems (Critchley & Garfinkel, 2017).

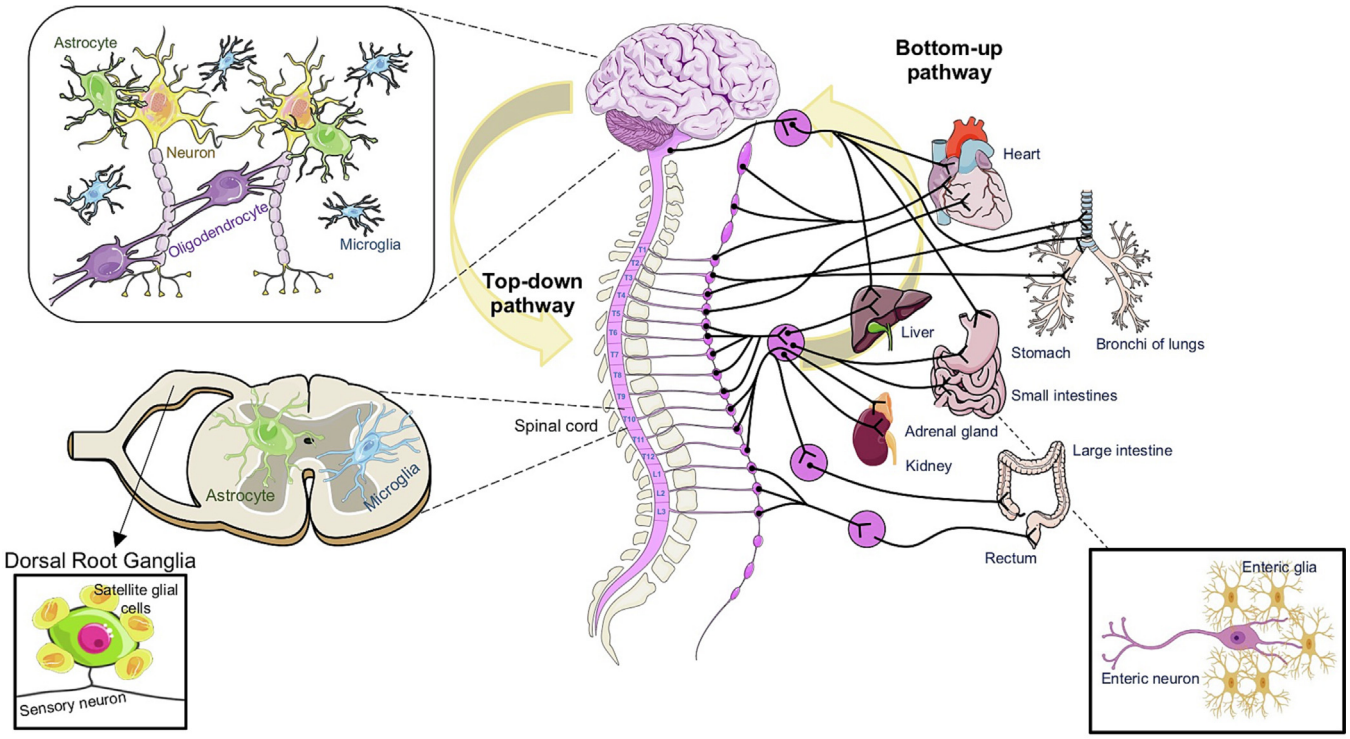

Fig. 1. Schematic representation of the glioceptive mechanisms. Bottom-up processing (illustrated to the right in the figure) begins with the retrieval of sensory information from our internal organs through the dorsal root ganglia, the spinal cord and then to the brain and higher cortical centers. Top-down pathway (illustrated to the left) is the interpretation and processing of incoming information by the brain. Upper inset shows glia of the CNS (astrocytes, microglia and oligodendrocytes), lower inset shows satellite glial cells (SGCs) surrounding neurons in sensory and autonomic ganglia. Enteric ganglia drawn at lower right contain neuronal plexuses surrounded by enteric glia. Drawing created by smart.servier.com.

Interoception was traditionally differentiated from exteroceptive senses, such as vision and audition, which process information about the external world, and more proximal senses, such as proprioception, touch, and taste, by which the body samples and interprets the external environment. However, the boundaries between interoception and some exteroception modalities are obscure, as in the case of proprioception, somatosensation, thermoception and nociception. Neural activities originating in tissues below the skin, including muscular and connective tissues, which participate in proprioception function, may be considered a form of interoception (Tuthill & Azim, 2018).

The sensing of metabolic substances in the gastrointestinal system presents more of an indicator of internal status than a representation of the external environment (Mei, 1983). Another example is the vestibular system, which typically achieves the internal balance of an organism, thus belonging to interoception rather than exteroception (Shinder & Newlands, 2014).

Ascending neural pathways intersect with the central and autonomic network on multiple subcortical and spinal levels and ultimately carry interoceptive information to the cerebral cortex (Azzalini, Rebollo, & Tallon-Baudry, 2019), thus suggesting that interoceptive sensitivity is determined also by the affective, cognitive, motivational, and arousal state of an individual (Wei & Van Someren, 2020). Indeed, studies on the functional anatomy of the lamina I spinothalamocortical system, where projection of ascending fiber occurs, indicate that interoception should be also redefined as the sense of the physiological condition of the whole body, not just the viscera (Craig, 2002). This system is a homeostatic pathway carrying signals from primary afferents that represent the physiological status of all body tissues. It projects first to autonomic and homeostatic centers in the brainstem and the spinal cord, in that way providing the long-elusive afferent complement of the efferent autonomic nervous system. Together with afferent activity that is delivered by the nucleus of the solitary tract (NTS), it produces a direct thalamocortical representation of the body state in primates, which is paramount for temperature, pain, itch and other somatic feelings. This complex anatomy shows that "how we feel "is a highly resolved representation of ongoing homeostasis, depicting the physiological condition of the body itself-an evolution of the concept that pain and temperature are simply aspects of touch (Craig, 2002). Data collected by functional imaging substantiate an interoceptive cortical image and suggest that this tight and highly organized representation in the anterior insular cortex of the right hemisphere could be correlated with evolution, as it is possibly unique in humans. It is intriguing to speculate that insular cortex might participate in human ability of integration of sensorial stimuli and achieve unique subjective cognitive function abilities, including self-perception.

Sensing, regulation, and maintenance of osmotic and chemical concentration of our internal milieu is an interoceptive function. The role of non-neuronal cells, especially astrocytes, as brain interoceptors has been proposed previously (Gourine & Kasparov, 2011), as they are major players in sensing and transduction processes in the Central Nervous System (CNS) (Bazargani & Attwell, 2016; Benfenati et al., 2007; Benfenati et al., 2011; Dossi, Vasile, & Rouach, 2018; Maiolo et al., 2021; Navarrete et al., 2013). However, fundamental understanding is lacking on how internal changes are sensed, transduced and integrated, on scales ranging from cellular and circuitry to organ and whole-body levels. In this context, we review the literature and question if there could be a role for glia in interoceptive signaling not only in the brain, but also in the peripheral nervous system (PNS) and in other organs.

To this end, in the present work, we critically review abundant existing literature on the ability of glia to sense, transduce and integrate environmental stimuli and propose that glial cells are key players in sensing, transduction, integration, and processing of interoceptive signals.

We define the potential roles of glia in interoception as glioception and hope that this review of molecular, cellular, circuitry, functional, and behavioral analyses may provide foundation for future translational studies.

2. Why glial cells?

Mounting evidence has shown that some glial cell types in CNS and PNS can communicate with internal organs via both neural and humoral systems, by secreting bioactive molecules and signaling mechanisms, modulating glia-glia and/or glia-neuron interaction in CNS (Parpura et al., 2012; Verkhratsky & Nedergaard, 2018) and PNS (Hanani & Spray, 2020).

Moreover, glial cells are equipped with interoceptive sensory channels, including chemoreceptors, osmoreceptors, glucose receptors, mechanoreceptors, thermoreceptors and humoral receptors, as well as electro- and electromagnetic transducers, which mediate visceral pain and other interoceptive sensations (Benfenati et al., 2007; Ciura et al., 2018; Long et al., 2021; Parpura et al., 2012; Turovsky et al., 2020).

Among glial cells, astrocytes occupy a strategic position in the CNS where they can function as an interface between neurons and blood vessels, as well as synaptic and non-synaptic neuronal domains and cerebrospinal fluid (CSF) (Navarrete and Araque, 2011). This location allows them to act as interoceptors, as they may sense variations in the internal microenvironment and contribute to the homeostatic processes coordinated by neuronal circuits (Verkhratsky, Rodríguez and Parpura, 2012). Moreover, astrocytes are connected to one another and to oligodendrocytes via gap junction channels, forming a panglial syncytium extending long distances within the brain. Recent evidence indicates the involvement of astrocytes in the central nervous control of breathing, metabolic functions, sleep and visceral pain (Teschemacher, Gourine, & Kasparov, 2015).

Microglia cells are the resident immune system of the CNS. They constantly sense and survey the surrounding environment to remove damaged cells or infectious factors and to maintain tissue homeostasis (Colonna & Butovsky, 2017).

Oligodendrocytes are the myelinating cells of the CNS. They produce myelin, a multi-layered insulating sheath spirally arranged around the axons, enabling the fast propagation of the electrical impulse. In the healthy human brain, oligodendrocytes are continuously generated (Nave & Werner, 2014) and respond to perturbations in neuronal activity by regulating myelin production (Ronzano, Thetiot, Lubetzki, & Desmazieres, 2020). They derive from oligodendrocyte precursor cells (OPCs), which proliferate and differentiate into mature glial cells. OPCs respond differently to neuronal activity, depending on the developmental stage and the anatomical area (Kalafatakis & Karagogeos, 2021). Oligodendrocytes sense the myelin demand in the brain and ensure the remodeling and homeostasis of myelin throughout the organism life, by the generation of myelin during development, adaptive myelination in adulthood and remyelination after damage (Kuhn, Gritti, Crooks, & Dombrowski, 2019; Tsai & Casaccia, 2019). In the peripheral nerves, myelination is achieved by Schwann cells.

Schwann cells (SCs) include a heterogeneous population of myelinating and non-myelinating cell types, with a plethora of diverse functional roles in the development, sensory perception and nerve repair of PNS in vertebrates. Myelinating SCs accelerate the conduction velocity of the propagating action potentials in peripheral nerve circuits, and drive the architecture and health of axons, by providing them metabolic support and protection from mechanical stress. Non-myelinating SCs wrap multiple small-diameter axons forming bundles of fibers, called "Remak" bundles, surrounding sensory C and sympathetic/parasympathetic fibers. Terminal non-myelinating perisynaptic SCs present in the motor axon endings at the neuromuscular junction (NMJ), actively participate in the growth, functional support and regeneration of NMJ. Due to their plasticity and sensing properties, SC contribution is critical after nerve injury, as SCs can sense degenerative stimuli and orchestrate a regenerative program for nerve repair (Bosch-Queralt, Fledrich, & Stassart, 2023; Ko & Robitaille, 2015).

Satellite glia cells (SGCs) closely envelop cell bodies of neurons in peripheral ganglia, which include sensory ganglia, and sympathetic and parasympathetic ganglia in the autonomic nervous system.

The main sensory ganglia are the Dorsal Root Ganglia (DRG), trigeminal ganglia (TG) and nodose ganglia. Sensory ganglia form SGC-neuron units located adjacent to the spinal cord and contain the somata of peripheral neurons that innervate most body parts, including internal organs. The unique organization of these clusters of cells is not found elsewhere in the nervous system and enables mutual neuron-SGC interactions, playing a crucial role in the control of neuronal homeostasis and pain (Hanani & Spray, 2020; Spray & Hanani, 2019). However, emerging controversy exists about the origin and fate of SGCs as precursor cells, and further investigation is needed to characterize their lineage and nature, thus providing new insights on their staminal properties and potential ability to replenish damaged neurons (Lu, Wang, Xu, Zhang, & Yu, 2023).

Enteric glial cells form a peripheral glial population lying under the intestinal epithelial cells throughout the gastrointestinal tract. Their unique position allows enteric glia to act as regulators of diverse gastrointestinal processes. They are central modulators of homeostasis of the intestine, and the bidirectional communication between enteric glia and neurons dynamically modulates the activity in neuronal circuits underlying reflexes but also controls mucosal permeability (Seguella & Gulbransen, 2021).

3. Glial cells and interoceptive signals, interoceptors and sensing processes

Glial cells are involved in sensing and transduction of diverse types of information, that is used to modulate intrinsic function and outputs of the cardiovascular, gastric, and respiratory pathways (Fig. 2). Here we will focus on the responsiveness of glia to several types of mechanical stimuli (osmotic swelling, stretch due to locomotion of vascular or gastrointestinal smooth muscle, fluid shear stress accompanying perivascular and parenchymal glymphatic flow), and by other stimulus modalities (thermal, chemical and metabolic). The role of glia in cognitive performance as well as in metabolism is briefly overviewed as it has been described in detail elsewhere (Magistretti, 2006; Santello, Toni, & Volterra, 2019). We then describe glioception as a potential therapeutic target for pain, as an example of an interoceptive pathology. Finally, we outline the possibility of using non-pharmacological strategies to target glial signaling and to treat or modulate interoceptive signals.

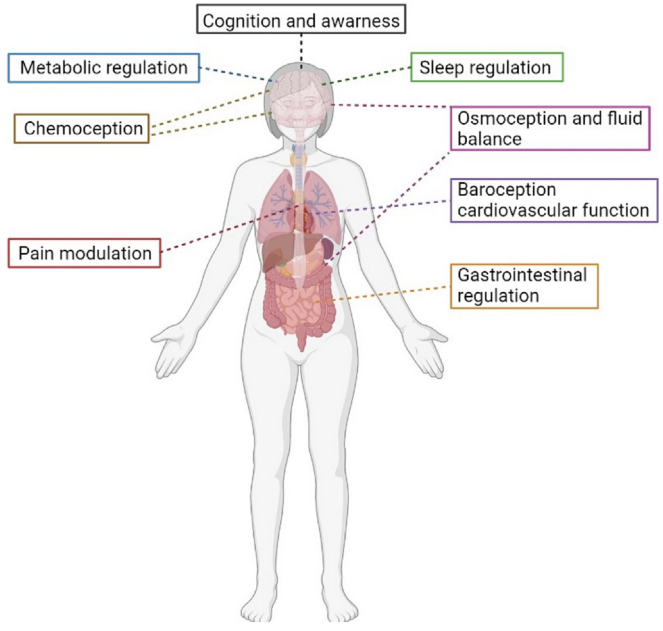

Fig. 2. Scheme of proposed glial mediated interoception. Organ systems are pointed out in which glioception is proposed to play a major role in the indicated interoceptive functions. Drawing created by Biorender.com.

3.1. Mechanosensory signaling and transduction

Glial cells can sense and respond to the physical/mechanical forces of their microenvironment and transduce them into internal molecular signals that drive the homeostasis of ions and water in cerebral blood flow, the mechano-modulation of nuclear events regulating oligodendrocyte progenitor gene expression and myelination, as well as the motility, cytoskeletal rearrangement, and morphological shaping of activated microglia during inflammation (Bruno et al., 2021; Tsai & Casaccia, 2019; Turovsky et al., 2020).

3.1.1. Forces that glia "feel"

All glia cells are exposed to mechanical stresses, including rhythmic pressure differentials in CSF driven by the cardiac cycle, trauma such as concussive brain injury or mild multiple impacts as in soccer heading, and interactions with substrates of varying stiffness, as in glial scar or hetero cellular scaffolds. Indeed, astrocytes function as intracranial baroreceptors since their membrane is specialized to sense mechanical stimuli (Marina et al., 2020). Moreover, perfusion of narrow extracellular space creates shear forces. Anisotropic flow may exist in fiber tracts or around enclosed structures such as perisynaptic web or peripheral astrocyte processes. The most widespread system, anatomically arranged to provide shear force, is the covering of cerebral vasculature by astrocyte endfeet (EF) processes (Abbott, Rönnbäck, & Hansson, 2006). This coverage forms a glia limitans that separates perivascular space from brain parenchyma, and this boundary constitutes a diffusion barrier in the neurovascular unit that is in series to that provided by endothelial tight junctions (Owens, Bechmann, & Engelhardt, 2008). Studies of blood brain barrier (BBB) permeability have almost exclusively focused on tight junctions sealing endothelial cells lining the vessel wall; however, the discovery of so-called glymphatic circulation through perivascular space and across astrocyte EF into the brain parenchyma (Iliff et al., 2012) provides evidence for shear flow forces acting on the astrocytes (Fig. 3). Whereas the normal high resistance and low permeability of the endothelial layer are critical for the prevention of access by infectious agents, immune cells, large molecules and bulk water and solutes from systemic circulation, the diffusion of water and solutes from perivascular space across and between the EF is driven by the flow of intracranial fluid. CSF from subarachnoid space enters the perivascular space (glymphatics), conveying fluid and solutes across the astrocyte EF into the brain parenchyma, with glymphatic flow driven by blood pressure pulses in the arteriole-venule direction (for a recent discussion of controversies, see (Thomas, 2019)). Additionally, EF are exposed to both hypotonic and hypertonic solutions, to which they respond by swelling or shrinkage followed by regulatory volume recovery (Mola et al., 2021) and astrocytes undergo circadian volume changes, leading to diurnal dilation of extracellular space (Nicholson & Hrabetova, 2017; Xie et al., 2013).

The topology, volume and content of perivascular space through which the glymphatic circulation flows have been subjects of considerable experimental research and hydraulic modeling studies. Whereas electron microscopy has revealed a basement membrane between endothelial cells and astrocyte EF that are generally quite thin (<0.1 μm) and filled with dense matrix (Morris et al., 2016), this narrow space reflects collapse as a consequence of fixation and is at odds with functional studies (Nicholson & Hrabetova, 2017). In vivo measurements of tracer flow and tracks followed by single nanoparticles injected into CSF reveal that flux through the perivascular space is rapid, indicating that, despite its dense appearance in electron micrographs, the pathway is not filled with material that impedes flow appreciably (Thomas, 2019).

The existence of perivascular flow implies shear stress at the EF surface, and CSF pressure, vascular pressure and osmotic stimuli are

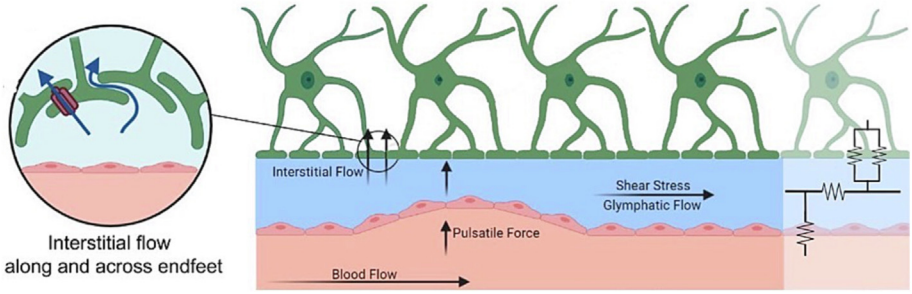

Fig. 3. Forces to which astrocytes are exposed. This highly schematic diagram shows a simplified section through a small cerebral vessel (salmon-colored), bounded by endothelial cells at upper vessel edge. Astrocytes (green) project endfeet that are separated from the endothelium by a basement membrane (light blue) that provides perivascular glymphatic flow (horizontal arrow in right hand diagram). Left: pathways for flow of water and solutes into and among endfeet are indicated by a channel representing both intracellular influx through AQP4 water channels, ion channels and transporters and the intercellular diffusion throughout the gap junction-coupled network. The more tortuous path illustrated by the curved arrow is that between the endfoot processes and represents interstitial flow at the endfoot and in the parenchyma. Right: Astrocytes shown lining vessel segments with arrows indicating contributions of transmural and interstitial pressures and shear force. Simple equivalent circuit at far right shows flow barriers at both endothelial and glia limitans boundaries. Drawing by David Gomes using Biorender software.

expected to drive interstitial flow and cause membrane stretch. Previous studies measured astrocyte Calcium (Ca^{2+}) responses to focal pressure pulses (Turovsky et al., 2020), pressures across the arteriolar wall (Kim et al., 2015; Kim & Filosa, 2012) and brief high intensity concussive forces (Maneshi et al., 2017; Maneshi, Sachs, & Hua, 2015; Maneshi, Sachs, & Hua, 2018; Ravin et al., 2012; Ravin et al., 2016; Ravin et al., 2019).

Molecular components of mechanosensory apparatus in astrocytes include Piezo channels, which sense membrane stretch, osmoresponsive channels considered in more detail below, and Transient Receptor Potential (TRP) cation channels. TRP channels are widely expressed in neuronal and glial cells and have been proposed as the most important ion channel family for the detection and transmission of different types of stimuli (Benfenati et al., 2007; Benfenati et al., 2011; Butenko et al., 2012; Filosa & Iddings, 2013; Kugler, Greenwood, & MacDonald, 2021).

Within the neuro-vascular unit (NVU), a multi-cellular structure composed of neuronal, glial, endothelial, and mesenchymal cells, astrocytes are key regulators of neurovascular coupling (Iadecola & Nedergaard, 2007). Among astroglial TRP channels, TRP Vanilloid 4 (TRPV4) has a crucial role in the regulation of neurovascular coupling as evidenced by its altered function or expression in pathological states, such as ischemia and stroke (Butenko et al., 2012; Filosa & Iddings, 2013; Kugler et al., 2021). Accumulating evidence indicates the importance of TRPV4 as a critical molecular determinant in modulating vascular tone in cerebral arterioles (Filosa & Iddings, 2013). It has been shown that through TRPV4-mediated mechanism, astrocytes sense mechanical stimulation of parenchymal blood vessels or direct pressure/flow-induced vasoconstriction (Kim et al., 2015; Turovsky et al., 2020). Astrocytes can also exhibit elevations in intracellular Ca^{2+} in response to acute decreases in blood perfusion, in presence of high intracranial pressure (Marina et al., 2020). Dunn et al. examined the effects of TRPV4 channels on Ca^{2+} dynamics in the endfoot microdomains of astrocytes and assessed their role in neurovascular coupling. They identified local TRPV4-mediated Ca^{2+} oscillations in the astrocytic EF that were amplified and propagated by a Ca^{2+} induced-Ca^{2+} release from Inositol Trisphosphate Receptors (IP_3Rs). They demonstrated that TRPV4-mediated Ca^{2+} influx promotes the EF Ca^{2+} response to neuronal activation and thus intensifies the concomitant vasodilation. Their investigation identified a dynamic synergy between TRPV4 channels and IP_3Rs in astrocytic EF and showed that TRPV4 channels are associated with and contribute to neurovascular coupling (Dunn, Hill-Eubanks, Liedtke, & Nelson, 2013). In order to study the underlying mechanosensory transduction mechanisms of the function of astrocytes as intracranial baroreceptors, Turovsky and collaborators used both in vitro and in vivo models. They mechanically stimulated cultured astrocytes by applying ejections of extracellular media via pressurization of a patch pipette localized near the cell membrane, and by generating a magnetic field in astrocytes coated with magnetite particles. The mechanical forces caused membrane stretching and triggered cellular Ca^{2+} responses. Pharmacological agents suggested that mechanosensory signaling in astrocytes is mediated by activation of TRPV4 channels leading to ATP release through Cx43 gap junction hemichannels. This release activates P2Y1 receptor and, in turn, induces Ca^{2+} recruitment from the intracellular compartments. The identified mechanism was supported by studies of mice lacking Cx43 in astrocytes, which displayed lower heart rates when cerebral perfusion pressure was altered, resulting in reduced cardiac sympathetic activity (Turovsky et al., 2020). However, acute decreases in brain perfusion did not change the profile and the magnitude of heart rate suggesting that other astrocyte ATP release pathways can functionally compensate for the absence of Cx43.

Thus, mechanosensing by ventral brainstem astrocytes is critical for increasing heart rate and blood pressure in response to a fall in intracerebral pressure. Communication with neurons of CNS sympathetic circuits occurs through Ca^{2+} signals, using ATP and lactate which pass through connexin (Cx) and pannexin (Panx) hemichannels (Scemes, Suadicani, Dahl, & Spray, 2007). This action of astrocytes on neurons and vasomotor tone is responsible for increasing vasomotor and cardiac sympathetic activities, indicating an essential role of astrocytes in the interoceptive modulation of cardiovascular function (Fig. 4) (Haidey et al., 2021; Kim et al., 2015; Turovsky et al., 2020).

Among glial cells, oligodendrocytes can also sense and transduce mechanical stimuli in their microenvironment. Recent studies have shown that mechano-transduction regulates the differentiation of oligodendrocyte progenitor cells into mature oligodendrocytes having myelin sheaths. Kim et al. demonstrated that physical strain applied by mechanical stretch causes transient myelin protein loss in differentiated oligodendrocytes. However, oligodendrocytes subsequently regain the ability to express myelin proteins. Biochemical analyses showed that resumption of protein synthesis is mediated by Ca^{2+} release from the Endoplasmic Reticulum (ER) and is followed by a Ca^{2+}-dependent activation of extracellular signal-regulated kinases 1 and 2 (Erk1/2). These findings characterize an Erk1/2-dependent mechanotransduction pathway in mature oligodendrocytes that alters the myelination program (Domingues et al., 2020; Kim et al., 2020).

A major role in the sensing and actuation of mechanosensory signals in oligodendrocytes has been attributed to the cytoskeleton. Specifically, actin dynamics have been proposed as the driving force for the myelination of axons (Nawaz et al., 2015; Zuchero et al., 2015). Recent work has also suggested that myosin and actinomyosin drive oligodendrocyte differentiation and finely tune the response of oligodendrocytes to internal tension via non-muscle myosins 2B and 2C (NM2B and NM2C). The latter are suggested as nanomechanical modulators of cell

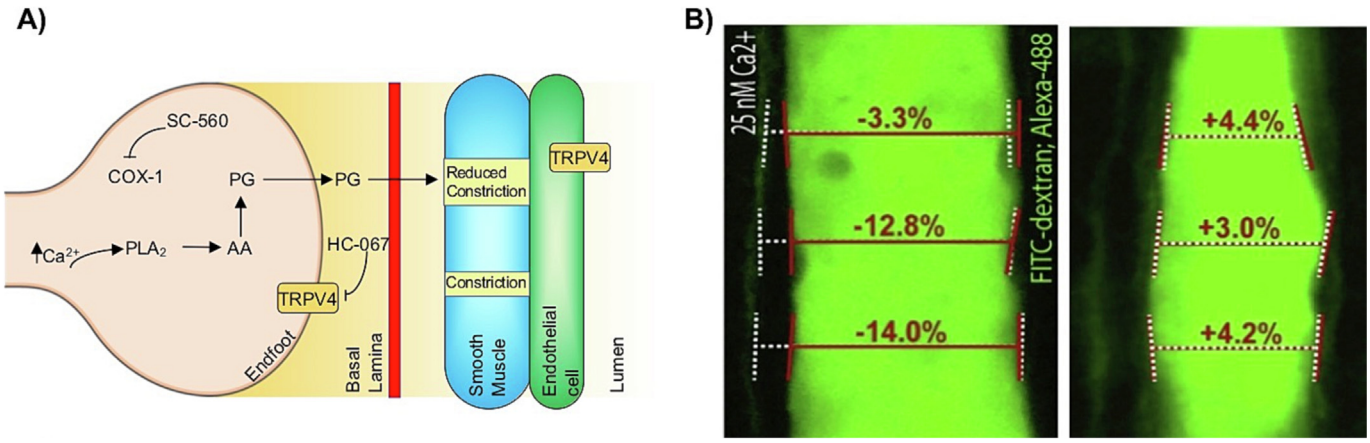

Fig. 4. Mechano-glioception in Cardiovascular function. A) Cartoon depicting potential mechanism of arteriole tone increase via astrocyte TRPV4 channels: arteriole tone induces astrocyte COX-1-mediated vasodilators via a TRPV4-Ca^{2+}-mediated mechanism. Drawing created by smart.servier.com, adapted from Haidey et al., 2021. B) Effect of TRPV4 on increasing/reducing constriction of the arteriole. Constriction of arteriole increases astrocyte endfoot Ca^{2+} via TRPV4 channels, to activate a negative feedback, mediated by astrocytic COX-1, that reduces the degree of arteriole vasoconstriction. Measurements of arteriole diameter in response to 25 nM Ca^{2+} astrocyte clamp in rat slice, before (white, dashed) and after (red, solid) the stimulus, in a pre-constricted arteriole (left) and in presence of COX-1 inhibitor (right). Adapted from Haidey 2021, under the Creative Commons CC-BY license, Copyright © 1969, Elsevier. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

tension that guide myelin membrane expansion at different cell stages (Domingues et al., 2020).

In astrocytes, a new in vitro study defined a correlation between actin dynamic response to homeostatic challenges that also induce mechanical stimulation (cell membrane stretch, alteration in the cell volume), such as hypotonicity and high concentration (40 mM) of potassium (K^+) (O'Neill et al., 2023). Interestingly, the astrocytic actin cytoskeleton was more dynamic and more active in nano and microdomains, while cortical actin and the whole cell fibers were almost quiescent. Thus, as happens in vivo, mechanical sensing and actuation might be confined at the periphery of the cell without the need for proprioception but limited to local membrane stretch. However, unpublished observations and in vivo studies indicate that Ca^{2+} waves might be generated by local response to changes in the pressure at the interface resulting in membrane tension. Thus, further studies will need to clarify if actin dynamics are involved in the process of integration of information or just act as local transducers and actuators. It would be interesting to explore if NM2B or C are involved in the response to mechanical stimuli also in astrocytes, as is the case in oligodendrocytes.

The response of astrocytes to external mechanosensory signals has also been investigated by using nanostructured interfaces made by hydrotalcites or by using a dispersion of nanoparticles made of 2D materials namely single-walled carbon-nanotubes or graphene nanoflakes in the bath (Bramini et al., 2018; Gottipati, Verkhratsky, & Parpura, 2014; Mola et al., 2021; Posati et al., 2016; Saracino et al., 2020). Notably, cytoskeletal dynamics of actin were more quiescent in astrocytes differentiated by exposure to these nanostructures, while Ca^{2+} signaling mediated by TRPV4, AQP4-mediated water transport, chloride current mediated by LRRC8A and regulatory volume processes were all upregulated (O'Neill et al., 2023; Posati et al., 2016; Mola et al., 2021). These data seem to indicate that astrocytes act as multiscale interoceptors in a confined micro-nano environment and that they then connect (and possibly integrate) the perceived sensory signals through the panglian syncytium throughout the brain via modulation of chemical synaptic transmission by the release of gliotransmitters (Covelo & Araque, 2016; Maiolo et al., 2021).

Along the bottom-up pathway of glioceptive processing, mechanosensitive non-neuronal cells are found to surround mechanoreceptor terminals of sensory end-organs located in the skin, raising the possibility they actively participate in touch sensation/transduction. Among these, cutaneous sensory Schwann glia can provide structural and functional support in the formation of a glio-neural end-organ interface in the skin. SCs anchor mechanoreceptor nerves to epidermis layers and feel and transduce the mechanical forces applied to the skin, as essential elements in pressure sensation and somatic response to mechanical stimuli (Ojeda-Alonso et al., 2022).

Mechanosensitive Piezo receptors were identified in SCs in the sciatic nerve and in afferent terminals innervating the skin (Shin et al., 2021). PIEZO1 and PIEZO2 are the mechanosensitive channels mostly expressed by SCs, as crucial mediators in mechanosensation as well in myelin formation in the PNS. PIEZO1 mediates shear stress and mechanically activated transmembrane currents in touch-sensitive non neuronal cells, whereas PIEZO2 has been mainly found in primary sensory neurons. However, PIEZO2 has emerged as a crucial mediator of mechanotransduction process for sensing and transducing touch, vibration, and proprioception, as well as, more recently, of mechanical nociception. Also, it was observed that the inhibition of PIEZO2 causes a delay in myelin generation, suggesting that PIEZO2 possibly regulates the myelination process in myelinating SCs (Abdo et al., 2019; Acheta et al., 2022; Bosch-Queralt et al., 2023; Shin et al., 2021; Silva et al., 2018).

3.2. Osmosensory signaling

Osmosensation is an important interoceptive function which allows the maintenance of the water balance and homeostasis of the organism. Osmoregulation is achieved by the changes occurring in volume and solute concentration that are modulated by a hypothalamic interoceptive circuit (Farrell et al., 2011).

Glial cells in the organum vasculosum laminae terminalis (OVLT), located in the hypothalamic area, seem to be essential elements in this interoceptive circuit by detecting modifications in extracellular fluid osmolality. In particular, astrocytes are believed to be the initial players that sense hypotonic conditions leading to inhibition of activity in primary osmosensory neurons (ONs) (Fig. 5) (Ciura et al., 2018; Vivas, Chiaraviglio, & Carrer, 1990).

Astrocytes express all the proteins involved in osmosis modulation, such as aquaporin 4 (AQP4) and a variety of TRP channel family members (Benfenati & Ferroni, 2010; Scemes, Suadicani, & Spray, 2000). The main changes in the brain in response to dehydration or hyperosmolarity occur in the Supra Optic Nucleus (SON) of the hypothalamus, where astrocytes were observed to retract their processes from the vasopressin neurons, creating a network between "naked" dendrites, connected through chemical synapses and gap junctions.

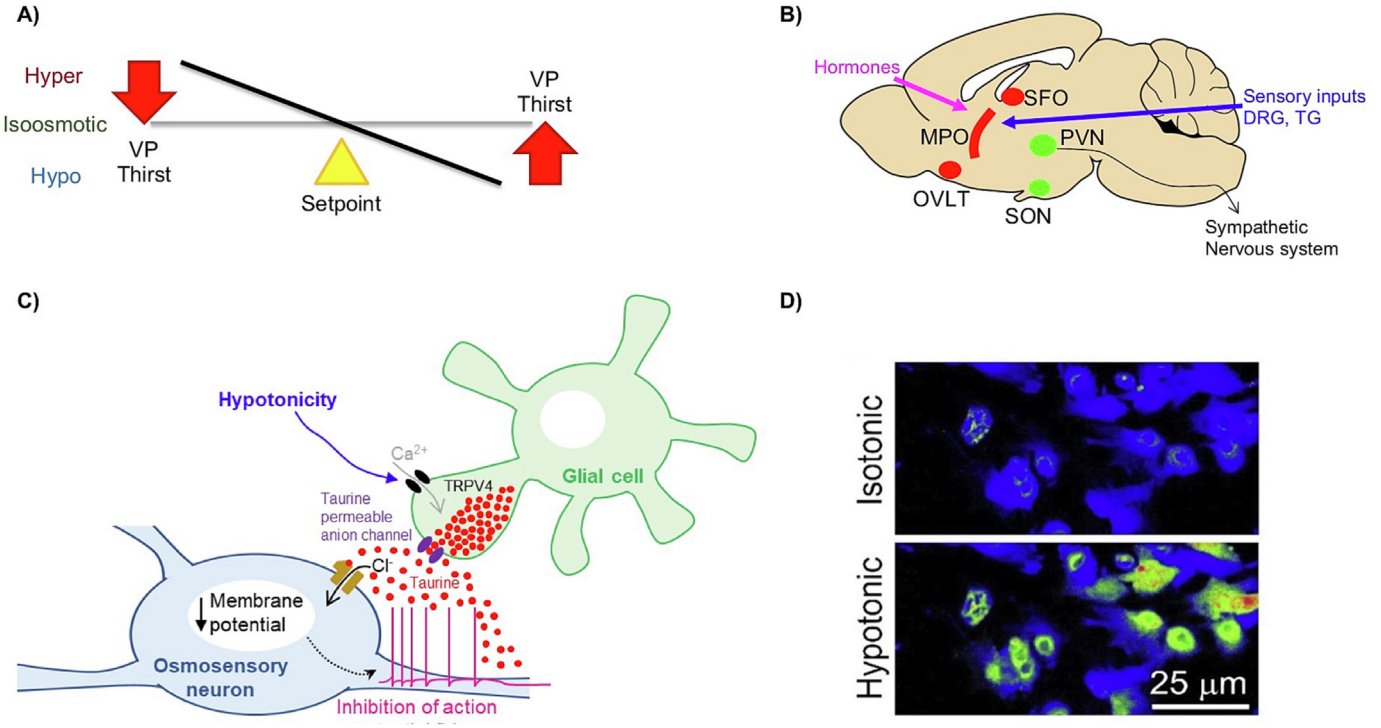

Fig. 5. Glial interoceptive control of water balance and osmolarity. A) Water loss leads to systemic hyper-osmolality, with higher levels of vasopressin (VP), antidiuresis and thirst. Water intake reduces serum osmolality, reducing thirst, VP levels and promoting diuresis. Isosmotic setpoint can be restored by compensatory changes in thirst and VP levels (upward and downward red arrows). B) Highly simplified illustration of relative locations of the neurons involved in the osmosensing interoceptive circuit. The nuclei of the circumferential organs (red: subfornical organ SFO, median preoptic nucleus MPO and organum vasculosum of the lamina terminalis OVLT) respond to plasma osmolarity and hormonal stimulation and receive sensory input from gastro-intestinal tract, baroreceptors and mouth. They connect to VP and OXT secreting neurons in supraoptic nucleus SON, paraventricular nucleus PVN (green). These neurons project to the posterior pituitary (PP), where hormones are released to act primarily on kidney and cardiovascular systems to regulate ion secretion and blood volume and pressure. PVN also projects to the autonomic nervous system to regulate other aspects of water balance. C) Osmoception in fluid balance is mediated by TRPV4 that activates hypotonic inhibition of central osmosensory neurons via taurine gliotransmission. Hypotonicity leads to opening of TRPV4 channels, admitting Ca^{2+}, leading to the release of taurine (red dots). Taurine permeates through Cl^- channels to hyperpolarize target neurons and inhibit their activity. Drawing created by smart.servier.com, adapted from Ciura et al., 2018; D) Measurement of rise in glial intracellular Ca^{2+} levels (indicated by change from blue to green/yellowcolor) in the osmosensory zone caused by hypotonicity. Adapted from Ciura et al., 2018, under the Creative Commons CC-BY-NC-ND license, Copyright © 2018 The Author(s). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

(Hatton, 1997). Hypoosmolality generates the opposite changes, in fact in this situation the astrocytic processes elongate and isolate/segregate vasopressin neuron dendrites.

The mechanisms by which glia modulate osmosensory neurons in the transduction of osmosensory signals are being investigated. Astrocytes in the SON present osmoceptive microdomains that sense and perceive perturbations in water homeostasis (Simard & Nedergaard, 2004). In particular, membranes in specific regions of astrocytes are equipped with channels and transporters including TRPV4 and other TRP receptors, including TRP Ankyrin 1 (TRPA1), AQP4, VRAC (LRRC8A), the gap junction proteins Panx1, Cx43 and Cx30, purinergic (P2) receptors, and K^+ channels such as Kir4.1, that mediate interoceptive responses to nearby neurons. Glia in the SON and in the circumventricular organs (CVOs) express AQP4, that colocalizes with TRPV4, forming the AQP4/TRPV4 complex that is demonstrated to be essential for cell-volume control in astrocytes (Benfenati et al., 2011). Tools such as optical and electrical devices have been used to drive ionic flow and water dynamics and thereby study osmoceptive mechanisms. Borrachero-Conejo and collaborators demonstrated as infrared laser or electrical stimuli provided by organic devices act on cell volume and on TRPV4 channels eliciting astrocytic Ca^{2+} responses (Borrachero-Conejo et al., 2020, 2019). Also, the nanoscale environment surrounding glia locally can rearrange microdomains altering AQP4 and Kir4.1 expression, VRAC current and anisotonic induced Ca^{2+} responses. The latter changes in ions and water concentration might be used as a model to mimic what happens during osmoceptive sensing where cellular surface and volume change (Posati et al., 2016; Saracino et al., 2020). The regulation of osmosensing and volume in astrocytes is strictly linked to the interaction between TRPV4 and AQPs, which seem to be primarily responsible for the neuron-glia interchanges during osmoceptive processes (Benfenati et al., 2007; Benfenati et al., 2011; Mola et al., 2021; Posati et al., 2016). Hypotonicity or cell volume triggers the activation of TRPV4 channels on the astrocyte cell membrane and Ca^{2+} is accumulated in the intracellular space (Liedtke et al., 2000; Vriens et al., 2004; Watanabe et al., 2003). Intracellular Ca^{2+} increase in astrocytes induces the opening of transmembrane hypotonicity-activated anion channels, allowing the release of taurine (Takano et al., 2006; Jo et al., 2015; Reichenbach and Bringmann, 2013; Ryskamp, Iuso, & Križaj, 2015; Ryskamp et al., 2014; Benfenati et al., 2011; Mola et al., 2016; Thrane et al., 2011). The interplay and partnership with AQP4 modulate the hypotonicity, volume sensitivity of TRPV4 and regulatory volume mechanisms magnitude and efficiency (Križaj et al., 2014).

Glial cells can accumulate high concentrations of taurine (Olson & Li, 2000; Pasantes-Morales, Alavez, Olea, & Morán, 1993) that can be secreted to mediate regulatory volume decrease (RVD) in response to hypotonic conditions (Pasantes-Morales et al., 1993). RVD is the homeostatic process by which the cell faces swelling challenges by extruding solutes, such as taurine. Millimolar levels of extracellular taurine (Hussy, Deleuze, Pantaloni, Desarménien, & Moos, 1997) activate glycine receptors (GlyRs) in osmosensory neurons promoting their inhibition (Ciura et al., 2018). Thus, TRPV4 activation and taurine release in response to cell swelling mediate osmoregulatory roles of astrocytes and their ability to sense and control the internal fluid osmolarity. This capability critically impacts renal function to maintain the water-electrolyte balance within the organism.

In the brain, dopamine and dopamine receptor agonists released by neurons act on astrocytes and microglia to regulate the activity of the renin-angiotensin system (RAS), an important regulator of blood pressure and fluid balance (Chugh, Pokkunuri, & Asghar, 2013). Both astrocytes and microglial cells express angiotensin AT1 and AT2 receptors, as well as dopamine D1 and D2 receptors. Dopamine and angiotensin are the two key renal factors and their counterregulatory interactions are important to maintain water and sodium balance in the kidney. Dopamine receptor activation can modulate astrocytic and microglial activity via glial renin-angiotensin system in vitro, causing the up- or down-regulation of angiotensinogen production by astrocytes. The effect of renal dopaminergic system on astrocytes and microglia activity supports the functionality of glia, as osmoregulators of the body fluid balance, and, thus, as controllers of blood pressure (Dominguez-Meijide, Rodriguez-Perez, Diaz-Ruiz, Guerra, & Labandeira-Garcia, 2017).

3.3. Glial involvement in chemosensing, signaling and response

Several studies have highlighted the role of brainstem astrocytes in central respiratory chemoreception (Erlichman, Li, & Nattie, 1998; Holleran, Babbie, & Erlichman, 2001). PCO_2 is detected by peripheral carotid and aortic chemosensors. However, ventilatory response to CO_2 is also mediated by respiratory chemosensors located within the CNS (Fig. 6).

Astrocytes display a locally distributed chemosensitivity in the brain. In absence of neuronal cues, ventral medullary astrocytes respond to differences between pH/PCO_2 levels of the arterial blood and those of the brain parenchyma. When astrocytes detect small physiological decreases in pH, intracellular Ca^{2+} increases lead to a release of ATP possibly via vesicles or through Panx1 or Cx channels. Through this gliotransmitter, the information is shared with the brainstem respiratory network. Interestingly, astrocytes from other brain regions seem to be insensitive to similar pH challenges (Teschemacher et al., 2015). CO_2-evoked ATP release from ventral surface astrocytes in the medulla oblongata thus contributes to respiratory chemosensing by activating chemosensitive retrotrapezoid nucleus (RTN) neurons (Gourine et al., 2010; Gourine, Llaudet, Dale, & Spyer, 2005; Wenker, Kréneisz, Nishiyama, & Mulkey, 2010). Evidence that a gap junction blocker (Carbenoxolone, CBX) decreases chemosensitive RTN neuronal activity proportionally to pharmacological inhibition by P2 receptor antagonists, suggests that astrocytes provide the purinergic activation of RTN neurons. This pathway is hypothesized to depend on gap junction hemichannels although Panx1 channels, which are also blocked by CBX, cannot be excluded (Koyanagi et al., 2016). Another study validated the significance of purinergic signaling for CO_2 chemosensitivity in the medulla oblongata (Wenker, Sobrinho, Takakura, Moreira, & Mulkey, 2012), and also concluded that ATP release from astrocytes is carried out by Cx hemichannels (Huckstepp et al., 2010). Finally, some studies suggest that astrocytes located in other brain areas, such as NTS, might also detect pH changes in activity of other transport mechanisms, that are not fully understood (Huda, McCrimmon, & Martina, 2013).

Sympathoexcitatory neurons in the rostral ventro-lateral medulla (RVLM) sense variations in PO_2 and contribute to increases in sympathetic vasomotor tone and cardiac output during systemic hypoxia (Spyer & Gourine, 2009). Heart failure progression impairs not only circulation but also respiration, since 38% of heart failure patients present episodes of central sleep apnea (Bradley & Floras, 2003). Recurrent periods of hypoxia can trigger the release of ATP from chemosensitive regions in the medulla oblongata (Gourine et al., 2005). However, the effects of fluctuations of O_2 levels on signaling mediated by non-excitable cells remain to be determined.

Interestingly, it has been demonstrated that during heart failure progression, hypoperfusion and hypo-oxygenation of the brain, aggravated by frequent episodes of sleep apnea, cause the activation of astrocytes located in the ventral medulla. Hypoxia can mobilize Ca^{2+} from intracellular stores in astrocytes with increased intracellular Ca^{2+} leading to the release of ATP and even the generation of ATP-mediated propagating Ca^{2+} waves (Aley, Murray, Boyle, Pearson, & Peers, 2006;

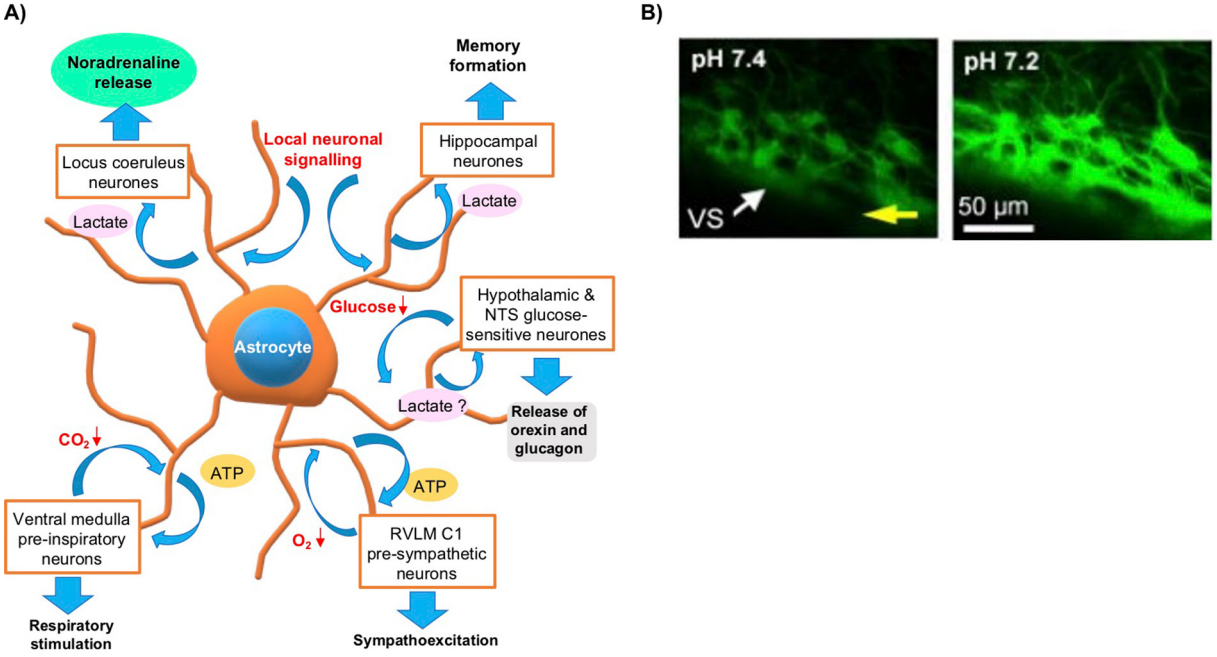

Fig. 6. Glial chemoception in respiratory function. A) Schematic representation of the astrocytic interface between the microenvironments of the brain, local neuronal network and blood vessels. Their strategic position allows the important astrocytic role in sensing and integrating respiratory gases and metabolic signal changing and modulating different neuronal circuits dedicated to the regulation of homeostasis. Drawing created by smart.servier.com, adapted from Teschemacher et al., 2015. B) Left panel: fluorescent imaging of astrocyte intracellular Ca^{2+} response in the ventral surface of the medulla oblongata (VS) evoked by pH changes. Right panel shows brighter staining, indicating that intracellular Ca^{2+} varies in response to extracellular pH change from 7.4 to 7.2, demonstrating pH-sensitivity of VS astrocytes. Arrows point at pH-responsive astrocytes. Adapted with permission from Gourine et al., 2010, Copyright © 2010, The American Association for the Advancement of Science.

Smith et al., 2005). This could evoke an increase in the extracellular concentration of ATP, enhanced activity of the RVLM sympatho-excitatory neurons and increased central sympathetic drive (Marina et al., 2012). Astrocytes in the RVLM can contribute, via ATP release, to sympathetic hyperactivity, which is characteristic of heart failure. The activation of this pathway, induced by low brainstem parenchymal PO_2, is one of the pathogenic mechanisms that contribute to the progression of this pathology (Marina et al., 2012). By extension, procedures or treatments suppressing activation of astroglia and/or interfering with ATP-mediated signaling in brain regions that regulate cardio-respiratory homeostasis may have a significant beneficial effect on the failing heart, as well as on pathological hypoxia conditions (Marina et al., 2012; Teschemacher et al., 2015).

Chemoreceptors for respiratory gases and pH are also found in peripheral structures such as the carotid body (CB), an O_2 and CO_2 sensor formed by a cluster of glomus cells located at the bifurcation of the carotid artery. CB glomus cells are enveloped by processes of glia-like, sustentacular type II cells, which are essential for sending information to the chemoreceptive afferents in the nodose/petrosal ganglia to maintain arterial homeostasis (Iturriaga, Alcayaga, Chapleau, & Somers, 2021).

Chemosensing and chemotransduction activity of CB glia is implicated in the synaptic crosstalk among glomus cells, type II cells, and the sensory nerve endings, three elements of a complex circuit resembling a tripartite synapse (Nurse, Leonard, & Salman, 2018; Retamal, Reyes and Alcayaga, 2014). Moreover, there is surprising evidence supporting the neurogenic potential of sustentacular type II glia-like cells in the CB. It is hypothesized that these cells can sense O_2, CO_2 and pH changes in the arterial blood environment and compensate for hypoxia exposure through mitosis and cell proliferation, inducing CB growth and generating new glomus cells.

Several studies have explored the role of the petrosal ganglion neurons in the CB chemotransduction and chemoreflex. These neurons have been historically considered as the main connection elements for signaling transmission from CB to the CNS. However, there is emerging evidence on the participation of glial cells present in the sensory ganglia in modulating respiratory information and chemosensing transduction processes. Retamal, Alcayaga, et al. (2014) have reported that in the nodose-petrosal-jugular complex from rat and mouse models Cx43 and Panx1 channels and P2X7 receptors can mediate paracrine glia-neuron transmission between SGCs and sensory neurons projecting to the vagus nerve. Due to the importance of SGCs in sensing and tuning the excitability of ganglion neurons to modulate CB input to the CNS, understanding the interoceptive roles of glia in CB chemosensing and chemoreflex circuits, as well as its involvement in pathologies, might help improve knowledge in this field and promote future investigations on recovering glioceptive functionality in cardio-respiratory diseases (Del Rio, Iturriaga, & Schultz, 2015; Retamal, Alcayaga, et al., 2014; Retamal, Reyes, & Alcayaga, 2014).

Intriguingly, some analogies in sensing capabilities and development between glomus cell and chromaffin cells located in adrenal medulla have been discovered (Hockman et al., 2018). Similarly to glomus cells, adrenal chromaffin cells exhibit a glial phenotype, deriving from multipotent peripheral glia cells, named Schwann cell precursors, (Furlan et al., 2017), and that S-100 positive cells from human adrenal medulla display features typical of SGCs (Lauriola, Maggiano, Sentinelli, Michetti, & Cocchia, 1985). Chromaffin cells fulfill a central role in the hormonal control of the "fight or-flight" body reaction, by sensing and modulating catecholamines, oxygen, and glucose systemic levels in response to stressful or dangerous events to adjust the internal homeostasis of organs and tissues.

Considering their chemosensing properties, such as hypoxia and hypercapnia sensitivity or neurotransmitter uptake, the opportunity to exploit the contribution of glial-derived adrenal medulla and glomus cells could be intriguing to decode and modulate the complex inner mechanisms of autonomic, unconscious, responses of the nervous system. Remarkably, the possibility to target "glial-like" neurogenic systems in the PNS, as an interoceptive pathway more accessible than CNS ones, could be useful to reduce the invasiveness of biomedical technologies for repairing internal organs and tissues after injury (Hockman et al., 2018; Pardal, Ortega-Sáenz, Durán, & López-Barneo, 2007).

4. Glial regulation of interoception

4.1. Metabolite sensing, metabolic regulation, and metabolite transport

Acting as functional brain interoceptors, glial cells modulate not only breathing function and sympathetic tone but also blood glucose levels (Teschemacher et al., 2015) by neurotransmitter receptors, transporters, and ion channels expressed on their membrane (Fig. 7) (Verkhratsky & Nedergaard, 2018).

Astrocytes can function as metabolic sensors since they can sense glucose levels and rewire hypothalamic circuits to ultimately balance energy metabolism (Kim et al., 2014).

The hypothalamus is the monitoring center of systemic metabolism. In this brain area, neurons and glia, including astrocytes, tanycytes and microglia, interact to control energy metabolism (García-Cáceres et al., 2019). Astrocytes transport and sense levels of glucose via gap junctions (Allard et al., 2014), a unique glucose transporter type 1 (GLUT-1) (Chari et al., 2011) and insulin receptors (García-Cáceres et al., 2016). García-Cáceres et al. found a pathway that leads hypothalamic astrocytes to trigger pro-opiomelanocortin (POMC) neurons via insulin signaling. They reported that the activation of POMC neurons is responsible for reducing food intake and achieving satiety. Astrocytes participate in this pathway, thus maintaining internal homeostasis, by the regulation of feeding behavior, energetic costs, and glucose metabolism. Thus, during a meal, astrocytes orchestrate a response that guarantees energy balance and body weight regulation.

Mediobasal hypothalamus astrocytes may alter neural activity in the bidirectional regulation of leptin- and ghrelin-mediated feeding circuits, via the release of adenosine and activation of adenosine A1 receptors (A1Rs) (Yang, Qi, & Yang, 2015). Thus, by modulating the activity of leptin and insulin receptors, astrocytes may act on the internal regulation of food intake (García-Cáceres et al., 2016; Kim et al., 2014).

In hypoglycaemia, glucose sensors located in the hypothalamus and dorsal brainstem restore blood and brain levels of glucose. Sensing of decreased glycemic levels decrease can induce the activation of the autonomic nervous response, stimulating pancreatic α-cells to secret glucagon, thereby supporting hepatic glucose production and release (Teschemacher et al., 2015). Experiments performed on mice lacking glucose transporter type 2 (GLUT2) showed glucagon insensitivity to systemic and central hypoglycaemia. Interestingly, targeted re-expression of GLUT2 in brainstem astrocytes re-established glucagon responses to hypoglycaemia (Burcelin & Thorens, 2001; Marty et al., 2005). Indeed, central glucose sensing mechanisms are found dependent on astrocyte GLUT2 and on functional coupling between glial and neuronal cells to regulate glucagon secretion. Particularly, it was demonstrated that in the dorsal medullary NTS, which integrates visceral, respiratory, cardiovascular, gustatory, and orotactile information, astrocytes are glucosensitive (McDougal, Hermann, & Rogers, 2013). Another study found that astrocytes inactivation by fluorocitrate interfered with neural activity in the NTS and in the dorsal motor nucleus of the vagus nerve blocking the glucose recovery that normally follows glucose deprivation (Hermann, Viard, & Rogers, 2014). These findings indicate that local glucose sensing by astrocytes represents a sensory input able to modify interoceptive signal.

Several studies highlight the potential role of L-lactate as a gliotransmitter in the communication between astrocytes and neurons (Teschemacher et al., 2015). According to the lactate shuttle hypothesis (Magistretti, 2006), when the brain is subjected to intense activity, astrocytes produce and export lactate to support the activity of neurons. This pathway is probably activated under conditions of oxygen

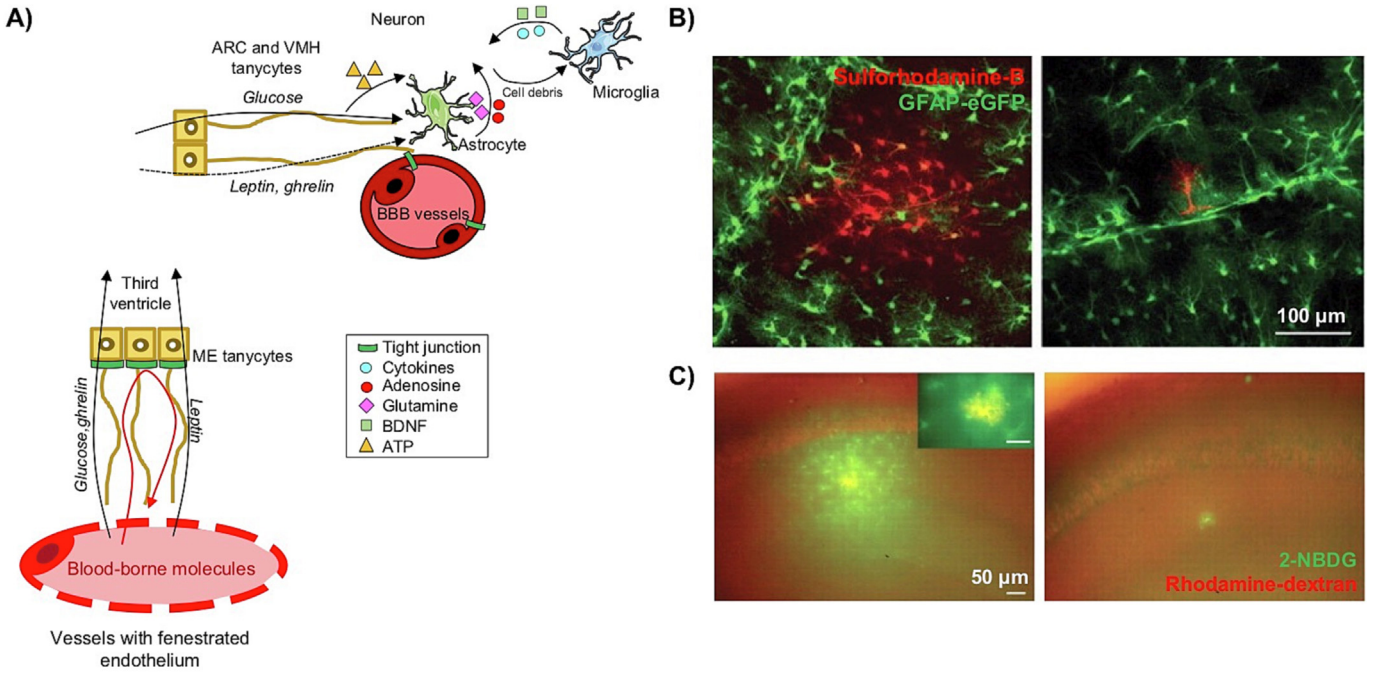

Fig. 7. Metabolic regulation by glia. A) The cellular functional heterogeneity of hypothalamic glial cells in metabolic sensing and systemic metabolism. Tanycytes located in the third ventricle enable the exchange of leptin, ghrelin and glucose 1) from the general circulation, thought tight junctions, (ME, tanycytes in the hypothalamic median eminence) or 2) to the parenchymal area (ARC and VMH, tanycytes in the arcuate and ventromedial nuclei of the hypothalamus). Astrocytes participate in metabolic sensing, by transporting energy substances and metabolic factors, while microglia contribute to immune regulation by secreting inflammatory cytokines and neurotrophic factors and phagocytosis of cell debris. Created by smart.servier.com, adapted from García-Cáceres et al., 2019. B) Functional coupling of perivascular astrocytes in hippocampal slices from GFAP-eGFP mice visualized by diffusion of gap-junction-permeable dye sulforhodamine-B to astrocytes surrounding blood vessels (left panel). This intercellular diffusion is abolished by the gap-junction blocker carbenoxolone (right panel). C) Measurement of glucose trafficking by fluorescent glucose derivative 2-NBDG imaging, through the astroglial network (left panel); simultaneously the gap-junction impermeable dye dextran tetramethylrhodamine is dialyzed to localize the recorded astrocyte (inset). 2-NBDG inter-astrocytic trafficking is mediated by gap junctions because it is abolished by CBX (right panel). Adapted with permission from Rouach et al., 2008, Copyright © 2008, The American Association for the Advancement of Science.

deprivation, where glycolysis is favored. Furthermore, following noradrenergic stimulation, astrocytes split glycogen into glucose, which is taken up by neurons to produce energy (Teschemacher et al., 2015). Thus, astrocytes contribute to the energy metabolism of the brain by drawing from their stable stores of glucose and its metabolites such as lactate. However, positron emission tomography imaging studies show that there are brain areas that differ in the rate of lactate production and its fate (Vaishnavi et al., 2010). Hypothalamic orexin neurons, that are involved in nutrient control, are depolarized by lactate release from astrocytes (González, Jensen, Fugger, & Burdakov, 2008). Parsons et al. suggest that lactate could reduce ATP-sensitive K^+ (KATP) channel activity (Parsons and Hirasawa, 2010). However, lactate could also inhibit neuronal activity through its own G-protein coupled receptors. This mechanism is activated in conditions such as tissue hypoxia or seizures. Recently it was discovered that astrocytes drive the response of locus coeruleus (LC) to release norepinephrine via lactate-mediated signaling (Tang et al., 2014). We can conclude that the use of lactate by astrocytes plays a significant role in the brain's interoceptive mechanisms, integrating and detecting various metabolic signals and coordinating neuronal circuits in accordance with the body needs, in both physiological and pathological states.

Collectively, these studies underline the strong impact of diverse astrocyte signaling pathways on the modulation of food intake and energy balance, connected to gastro-intestinal physiology and pathology (García-Cáceres et al., 2019). However, the molecular mechanisms behind "gastrocyte" functions in many feeding behaviors remain partly unknown (Ellacott, 2023; MacDonald & Ellacott, 2020). Notably, a recent comprehensive study from Clyburn and coworkers provided insight into the homeostatic mechanisms of astrocytes in caloric regulation (Clyburn, Carson, Smith, Travagli, & Browning, 2023). They demonstrated that, after high-fat diet exposure, brainstem astrocytes can trigger a cascade of signaling events by the glutamatergic modulation of information transmission to dorsal motor nucleus of the vagus neurons, thereby regulating the gastric activity and food intake.

4.1.1. Role of the panglial syncytium in metabolite delivery throughout the interoceptive network

One of the functions first demonstrated for gap junctions between cells was sharing metabolites, referred to as the "kiss of life" when rescuing cells deficient in enzymatic substrates (Pitts, 1998) or in bystander cell killing when delivering toxic molecules (Spray, Hanstein, Stout Jr., Suadicani, & Thi, 2013). Regarding energy-providing molecules, glucose-6-phosphate is not highly gap junction permeable (Gandhi, Cruz, Ball, Theus, & Dienel, 2009), whereas lactate rapidly diffuses throughout the astrocyte syncytium, with a rate estimated to be 3–5 times as high as for diffusion from astrocytes to neurons (Hertz, Gibbs, & Dienel, 2014).

Delivery of energy on demand from the coupled astrocyte network at large to loci adjacent to active neurons was shown through imaging studies using the fluorescent glucose analogue 2-NDBG (Rouach, Koulakoff, Abudara, Willecke, & Giaume, 2008). In this study, the number of astrocytes to which 2NDBG spread depended on synaptic activity, with Tetrodotoxin (TTX) the size of the metabolic network was decreased by about 30%, and the blocking of glutamate decreased it by 25%. By contrast, spread was increased by stimulation of Schaffer collaterals. Critically, the movement of inert tracers (sulforhodamine and neurobiotin) was found to not be affected by neuronal activity, from which the authors concluded that energetic requirements of neurons altered the extent and distribution of energetic supply rather than causing anisotropic changes in gap junction-mediated coupling.

The functionality of hypothalamic astrocytes is influenced by adjacent neurons and the local microenvironment (García-Cáceres et al., 2019).

Stimulation of the paraventricular nucleus (PVN) of the hypothalamus with norepinephrine or glutamate activates astroglial ATP release, leading to a potentiation of glutamatergic synapses (Gordon et al., 2009).

An example of the role of the coupled astrocyte network in interoception has come from studies examining the impact of stress on metabolite availability at synapses (Murphy-Royal et al., 2020). This study showed that stress reduced the effective size of the metabolically coupled astrocyte network in the mouse brain, thereby restricting neuronal access to glucose and lactate at the synapse, compromising long-term potentiation. Decreasing gap junction expression or reducing lactate release similarly compromised synaptic plasticity, which was restored by lactate loading of the astrocytes. This modulation illustrates the degree to which interoceptive circuits encompass glial cells and the system-wide plasticity that they control.

Importantly, oligodendrocytes also contribute to the metabolic support of neuronal cells. They deliver energy metabolites by cytoplasmic "myelinic" channels and monocarboxylate transporters. Energy substrates, such as pyruvate and lactate, are transferred from oligodendrocytes to neurons, to be metabolized and contribute to ATP synthesis (Kuhn et al., 2019; Philips & Rothstein, 2017). Delivery of the energetic substrates to the neurons is in part due to the panglial gap junction syncytium that connects oligodendrocytes to astrocytes.

Transfer of energetic substrates between astrocytes and both oligodendrocytes and OPCs was analyzed using 2-NBDG, as a probe for glucose (Niu et al., 2016). Glucose transfer was detected between astrocytes and oligodendrocytes, but not between astrocytes and OPCs. CBX-sensitive uptake of ethidium bromide (EtBr) and 2-NBDG from extracellular space was observed in OPCs in the presence of GLUT1 inhibitor and was enhanced by Ca^{2+} elevation and reduced by chelation, interpreted as evidence for Cx mediated hemichannels. This uptake was absent in astrocytes but still present in OPCs from Cx43 deficient mice, implying that different connexins or other large channels such as Panx1 may be involved, although gap junctions are not normally present between OPCs or between OPCs and other cell types. The authors thus speculated that glucose uptake through hemichannels plays a critical role in OPC development whereas gap junction-mediated exchange between astrocytes and oligodendrocytes may be more important at later stages of oligodendrocyte differentiation. Among the surprising aspects of this study were uptake at normal Ca^{2+} levels (a condition under which most authors have reported that hemichannel openings are rare) and the argument that passive diffusion through hemichannels driven by a small concentration gradient may be more efficient than uptake mediated by a specialized glucose transporter.

The microglial ability to sense local damage and phagocytose is critical to internal metabolic stress. Microglia are metabolically flexible and can promptly adapt to glutamine consuming in the absence of glucose. In vivo, ex vivo and in vitro investigations on brain slices and cell cultures demonstrated that, when faced with decreased environmental glucose, microglia switch their energy reliance to glutaminolysis. This metabolic flexibility supports their motility and immune surveillance capability for long-term periods, even after brain neuroenergetic homeostasis is compromised (Bernier et al., 2020; García-Cáceres et al., 2019; Kettenmann, Kirchhoff, & Verkhratsky, 2013; Teschemacher et al., 2015).

4.2. Regulation of gastro-intestinal functions

Emerging evidence highlights the association between interoception and gastrointestinal functions and eating-related sensations (Khalsa, Berner, & Anderson, 2022). Indeed, altered interoception has been consistently observed across eating disorders (Jacquemot & Park, 2020; Klabunde, Collado, & Bohon, 2017) or gastrointestinal symptoms (Frank, Golden, & Murray, 2021).

Enteric glia are actively involved in the control of gastrointestinal functions since they have been recognized as critical intermediaries in neurotransmission, neuroinflammation and information processing in the enteric circuits (Fig. 8). Indeed, they express neurotransmitter receptors and are equipped with the necessary machinery for the uptake and degradation of neuroligands in the enteric nervous system. Enteric glial cells regulate gut innervation by secreting neurotrophic factors (such as GDNF, TGF-β1, 15dPGJ2, GSNO) and protect the gut mucosal barrier against intestinal bacteria and inflammatory insults through the synthesis of a variety of chemokines and cytokines (Yu & Li, 2014). Moreover, enteric glia can promote the integrity of the intestinal barrier by increasing the expression of tight junction proteins for epithelial repair after injury (Savidge et al., 2007). A recent study has revealed important differences in the temporal development and gene expression of mucosal enteric glial cells, finding that these cells play even more critical roles in humans than in mice. In contrast to mice, enteric glial populations already appear in the fetal stage of the human gut and maintain the homeostasis of the intestinal environment, independently from microbiota colonization (Inlender et al., 2021).

It has been shown that enteric glia are involved in the pathogenesis of diverse disease processes in the gut (Rühl, 2005; Yu & Li, 2014), including bowel inflammation. The over-secretion of S100B protein, a neurotrophic factor able to trigger chronic inflammatory changes in gut mucosa, has been associated with the activity of enteric glia (Capoccia et al., 2015).

The ability of enteric glia to modulate gut inflammation is further emphasized by the evidence that genetic ablation of enteric glial cells causes inflammatory reaction and necrosis of the gut in rodents (Bush et al., 1998). Increasing glial fibrillary acidic protein (GFAP) levels in response to proinflammatory cytokines, both in vitro and in situ, confirm that intestinal inflammation activates the enteric glia (von Boyen et al., 2004). Additionally, recent evidence indicates that inflammatory bowel disease (such as ulcerative colitis and Crohn's disease) and irritable bowel syndrome, related to regional gastro-intestinal disorders, may concurrently impair other visceral and somatic organs, inducing urinary bladder hyperactivity, leg pain, and skin hypersensitivity. Among the explanations for this "cross-organ sensitization" is that gap junction coupling between SGs in sensory ganglia and among astrocytes in the spinal cord may form excitability bridges between the neurons, effectively coactivating them (Qiao & Tiwari, 2020). Considering these findings, the participation of glia in interoceptive regulation of gastrointestinal function appears plausible and deserves to be more thoroughly investigated.

4.3. Regulation of sleep and rhythmic behavior

Sleep is determined by circadian oscillations and sleep homeostasis processes. Sleep onset is also dependent on sensory gating signals mediated by interoceptors. Several studies support the dynamic connection between sleep and interoceptive modalities including thermoception, nociception, visceral sensations, and correlated subjective feelings (Wei & Van Someren, 2020). Sleep propensity is correlated to thermal sensations, as it depends on both amplitude and temporal features of external thermal stimuli (Harding, Franks, & Wisden, 2019; Wei & Van Someren, 2020;Te Lindert and Van Someren, 2018). Even gastrointestinal stimulation has been found to reduce sleep onset latency (Orr and Chen, 2005;Wei & Van Someren, 2020). Sleep deprivation causes elevation in blood pressure and distal skin temperature. These perturbations can be sensed by carotid baroreceptors and skin thermoreceptors, originating glia-mediated feedback signals that lead to sleepiness. Similarly, the circadian rhythmicity might contribute to interoceptive mechanisms of sleep, for example by the regulatory action of melatonin, a neurohormone that is secreted by the pineal gland to regulate the internal biological clock depending on the external light-dark cycles. Given the expression of melatonin receptors in diencephalic and telencephalic astrocytes in vitro from different species, and the surprising discovery of modulatory effect of melatonin on glial intercellular Ca^{2+} waves (Peters, Earnest, Tjalkens, Cassone, & Zoran, 2005), a possible

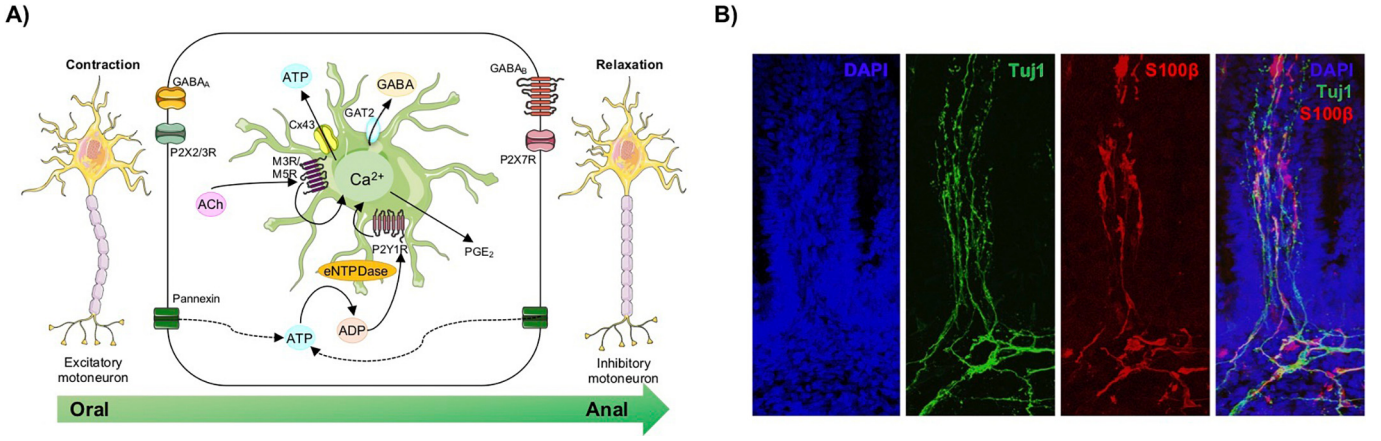

Fig. 8. Gastro-intestinal regulation. A) Ca^{2+} signals coming from Glial cells are elicited in the myenteric plexus by neurotransmitters, mainly acetylcholine (ACh) and ATP, which induce the release of gliotransmitters such as ATP and GABA through membrane channels, like connexin 43 (Cx43) and through the reversal of neurotransmitter transporters (such as GABA transporter 2, GAT2). The gliotransmitters act on excitatory and inhibitory neuron receptors having reciprocal effects on enteric neural circuits modulating the intestinal motility. Created by smart.servier.com, adapted from Seguella and Gulbransen, 2021. B) Immunofluorescence of mucosal enteric glial cell network from cryosections of human fetal intestine. From left to right: DAPI, anti Tuj1 and anti S100β staining individual channel and merging of the three channels. Adapted from Inlender et al., 2021, under Creative Commons CC BY license, Copyright © 2021, The Author(s).

glioceptive modulation might be considered in the organism regulation of sleep and rhythmic behavior. Indeed, studies in vertebrate and invertebrate models, more specifically in mice and Drosophila, have revealed the implication of glial cells in the neural circuits regulating sleep (Fig. 9). Furthermore, the cellular correlation between sleep/wake behavior and circadian rhythms is now evident in glial networks (Artiushin & Sehgal, 2020; Jackson, Ng, Sengupta, You, & Huang, 2015).

In particular, astrocytes participate in homeostatic sleep responses following sleep deprivation (Halassa et al., 2009; Seugnet, Suzuki, Donlea, Gottschalk, & Shaw, 2011; Weiss & Donlea, 2022), as well as in baseline sleep. The modulation of sleep homeostasis might be attributable to the astrocytic functions of signaling and neurotransmitter recycling. Astrocytes release adenosine which acts like a somnogen. Adenosine binds A1Rs on pre-synaptic neurons to inhibit the excitatory pathway mediated by glutamate release (Bjorness & Greene, 2009). This inhibition decreases neural activity and promotes sleep initiation (Porkka-Heiskanen, Zitting, & Wigren, 2013; Sims, Wu, & Dale, 2013).

Interestingly, astrocytes are also responsible for *"cleaning the brain"* during sleep. As noted in preceding section on glial mechanosensitivity, a "glymphatic" perivascular circulation system powered by astrocytic AQP4 is able to drain solutes from the brain, and dysfunctions in this pathway may contribute to Alzheimer's disease (Haydon, 2017; Iliff et al., 2013; Mestre, Mori, & Nedergaard, 2020). Brain clearance is increased during sleep (Xie et al., 2013), coinciding with dilation in extracellular space (Nicholson & Hrabetova, 2017).

The impact of circadian properties of astrocytes on neuronal clocks and rhythms of locomotor behavior has been evaluated. Several studies document the rhythmic expression of clock proteins and other neural proteins (e.g., PER, TIM, Ebony, CREB2, Na^+ /K^+ -ATPase) in glial cells of the adult Drosophila brain (Ng et al., 2016; Suh & Jackson, 2007; Zerr, Hall, Rosbash, & Siwicki, 1990). The presence of PER-based molecular oscillators acting as internal circadian clocks has been described in mammalian astrocytes (Prolo, Takahashi, & Herzog, 2005) and microglia (Hayashi et al., 2013).

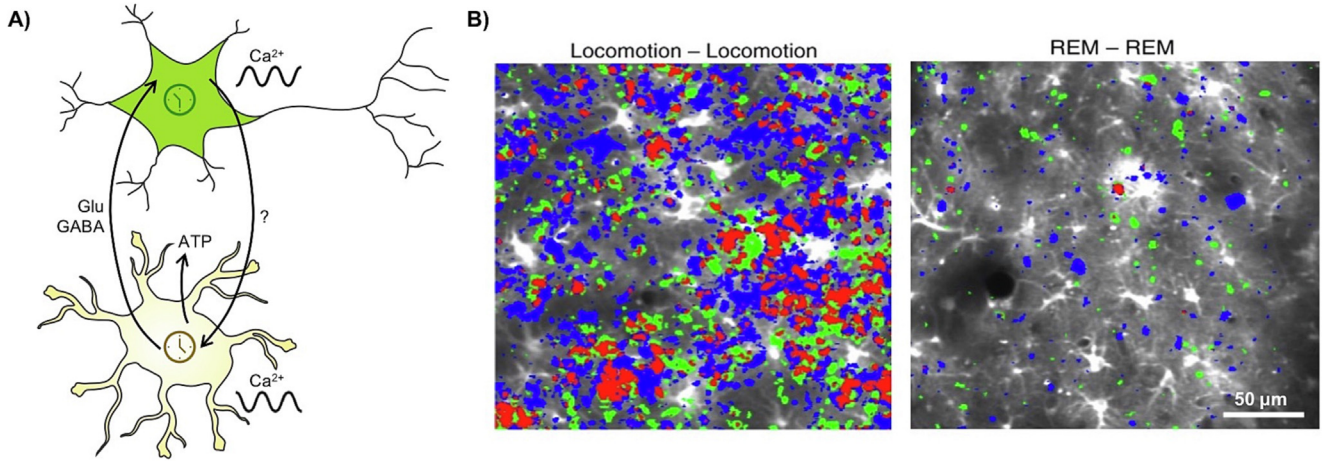

Fig. 9. Glioception in Sleep regulation. A) Astrocytic clocks (lower figure, pale yellow) of the suprachiasmatic nucleus (SCN) influence neuronal clocks (upper figure, green) via GABA release in vitro and glutamate release in vivo. Both cell types display rhythmic Ca^{2+} dynamics, which are antiphasic to each other throughout the day. Other signals such as extracellular ATP, which depends on astrocytic Ca^{2+}, might also modulate neuronal clocks. Drawing created by smart.servier.com, adapted from Artiushin & Sehgal, 2020. B) Representative astrocytic Ca^{2+} activity maps outlining areas active during different episodes (green and blue) of the same sleep-wake state (locomotion-locomotion, REM-REM), and the overlap between the active areas (red). Note dramatically lower individual and coactive neural areas during REM sleep. Adapted from Bojarskaite et al., 2020, under the Creative Commons CC BY license, Copyright © 2020, The Author(s). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

More recently, astrocytic Ca^{2+} signaling in the neocortex of awake and naturally sleeping mice has been studied by the group of Bojarskaite and coworkers. They reported that astrocytic Ca^{2+} signals exhibit distinct features across the sleep-wake cycle and are decreased during sleep compared to wakefulness. Furthermore, astrocytic Ca^{2+} signaling appears increased before transitions from slow-wave sleep to wakefulness, with stronger oscillations upon awakening compared to locomotion. Finally, genetic ablation of an important mediator of astrocytic Ca^{2+} signaling, the IP_3 receptor, impairs slow-wave sleep and resulting in abnormal brain oscillations, elevated number of microarousals, and higher frequency of slow waves and sleep spindles. Interestingly, ER-mediated Ca^{2+}-release via Sarco-Endoplasmic Reticulum Calcium ATP-ase (SERCA) leads to arrhythmic behavior, indicating that intracellular Ca^{2+} stores are important for physiological behavioral rhythmicity (Bojarskaite et al., 2020).

These findings clearly denote the essential role of astrocytes in sleep-related Ca^{2+} signaling pathways and shed light on their function as glioregulators of slow-wave sleep and modulators of interior rhythms and behaviors (Clasadonte, Scemes, Wang, Boison, & Haydon, 2017). In addition, this work adds the concept that it is the coupled glial network that mediates interoception, achieved through metabolic synchrony.

5. Glial signaling in cognition and self-perception

The term cognition encompasses the mental functions through which knowledge is acquired, retained, and used: perception, attention, learning, memory, and thinking (Kihlstrom, 2018).

Interoception, referring to the perception of internal body states, is the intersection between cognition and the body. Numerous studies have shown that interoception performs a significant role in memory processes and intuitive decision-making (Dunn et al., 2010; Werner, Peres, Duschek, & Schandry, 2010). The term “Sense of Embodiment” describes the senses of self-location, agency, and body ownership. This sense of embodiment seems to be vital for self-recognition and awareness (Carruthers, 2008; Kilteni, Groten, & Slater, 2012).

Interoceptive dysfunctions are recognized as key components of several mental health conditions and disorders including schizophrenia. In patients suffering from schizophrenia, there has been detected severe loss of the ability of detecting internal bodily signals and attributing them to themselves (Ardizzi et al., 2016).

Vostrikov and collegues studied postmortem brains of schizophrenic patients, some of whom had had anosognosia-a condition in which a person is unaware of their condition/disease or they cannot perceive their condition/disease accurately. The results of the study showed a reduction in glial cells (more specifically oligodendroglia) in the inferior parietal lobule (Vostrikov, Kolomeets, & Uranova, 2013) of individuals with anosognosia. Anosognosia, also defined as reduced self-awareness and metacognition, is present in patients with AD and corresponds with failure of the autonomic nervous system to regulate the interoceptive network (Sun, Ueno, & Narumoto, 2022).

The cellular mechanisms behind cognition remain obscure even though they are some of the most studied nervous system processes. One of the reasons may lie in the inadequate exploration of the role of the non-neuronal brain cells in these processes. Electrical signaling is indeed the backbone of brain function but neurons working by themselves can only explain part of the complexity of the cognitive processes. Glial cells have been found to participate in complex cognitive functions that require broad spatial integration and long-term temporal regulation (Fig. 10) (Fields et al., 2014). Among their various roles in healthy adult brain function, astrocytes affect the cognitive processes of memory and learning as they are closely involved with regulation of the synaptic activity (Panatier et al., 2011), energy supply in neuronal support (Bélanger, Allaman, & Magistretti, 2011), adult neurogenesis (Ashton et al., 2012) and maintenance of homeostasis (Benarroch, 2016). In astrocytes, intracellular Ca^{2+} signaling activation can either elevate or suppress both excitatory and inhibitory synaptic transmission and thus affect state-dependent changes in cortical activity during e.g. sleep and working memory. Studies by Halassa' group demonstrated that astrocytes modulate behavior and highlighted the importance of A1Rs in the regulation of sleep homeostasis as well as the cognitive decline associated with sleep deprivation (Halassa et al., 2009). Nedergaard's lab proposed and demonstrated that altering the local ion composition can drive extracellular space volume changes and consequently compromise, alter or evoke brain rhythms associated with sleep/awake transition (Ding et al., 2016).

Koeppen and collaborators demonstrated that the astrocytic ephrin-B1 regulates long-term contextual memory by restricting new synapse formation in the adult hippocampus (Koeppen et al., 2018).

Oligodendrocytes are also important players in cognitive processes. Plasticity at the synaptic level, affecting oligodendrocytes and the myelin sheaths they produce, plays a key role in memory and learning (Xin & Chan, 2020). It has been demonstrated that oligodendrocytes are required for motor-skill learning (Xiao et al., 2016). Motor learning promotes myelin plasticity in humans which reflects learning-related increases in myelination (Hofstetter, Tavor, Moryosef, & Assaf, 2013; Lakhani et al., 2016; Sampaio-Baptista et al., 2013). A recent study showed that disruption of oligodendrogenesis impairs memory consolidation in adult mice (Steadman et al., 2020).

The contribution of microglia to cognition, learning and behavior has become clearer in studies using microglial depletion assays and conditional mutants. Studies have demonstrated that the absence of microglia leads to cognitive and learning deficits in rodents, especially during development (Augusto-Oliveira et al., 2019). Elmore's group showed that the replacement of microglia in aged brains resulted in the reversion of cognitive, synaptic, and neuronal deficits in mice (Elmore et al., 2018). Microglia exhibit phagocytic behavior in aged animals where deficits in auditory function are associated with containing axon-like or dendritic inclusions (Tremblay, Zettel, Ison, Allen, & Majewska, 2012). Microglial brain-derived neurotrophic factor (BDNF) signaling has been shown to play an important role in learning and memory formation via the tropomyosin-related kinase receptor B signaling pathway (Parkhurst et al., 2013). There is evidence that children with autism spectrum disorder (ASD), which affects cognitive function, exhibit an ongoing neuroinflammatory process in different brain regions involving microglial activation. Microglial activation can lead to loss of synaptic connections or underconnectivity with the latter being reported in several studies in autism (Rodriguez & Kern, 2011). Numerous studies have demonstrated that GFAP levels are elevated in autism, indicating activation of astrocytes (Bailey et al., 1998; Rosengren et al., 1992). Moreover, Fatemi et al. reported significant changes in the astrocyte proteins AQP4 and Cx43 in Brodmann's Area 40 (BA40, parietal cortex), BA9 (superior frontal cortex) and the cerebella of brains of subjects with autism in comparison to matched controls. More specifically, in individuals with autism, AQP4 expression was decreased in the cerebellum and Cx43 expression was increased in BA9. These findings appeared to be specific since the levels of β-actin did not significantly vary between groups (Fatemi, Folsom, Reutiman, & Lee, 2008). Regarding cell communication, Antonucci and coworkers identified microglia-derived microvesicles as a new mechanism through which microglia influence synaptic activity through enhanced sphingolipid metabolism (Antonucci et al., 2012). Considering their association with cognition, exploring the glial pathways in interoception might help to deepen our understanding of how we can sense and perceive ourselves and, thus, might offer a novel target for the development of technologies and therapeutics devoted to the study of cognitive functions and dysfunctions as well as their treatment.

6. Glia in pain

Deficits and alterations in interoceptive processes are strongly associated with the genesis and manifestation of several chronic pain-

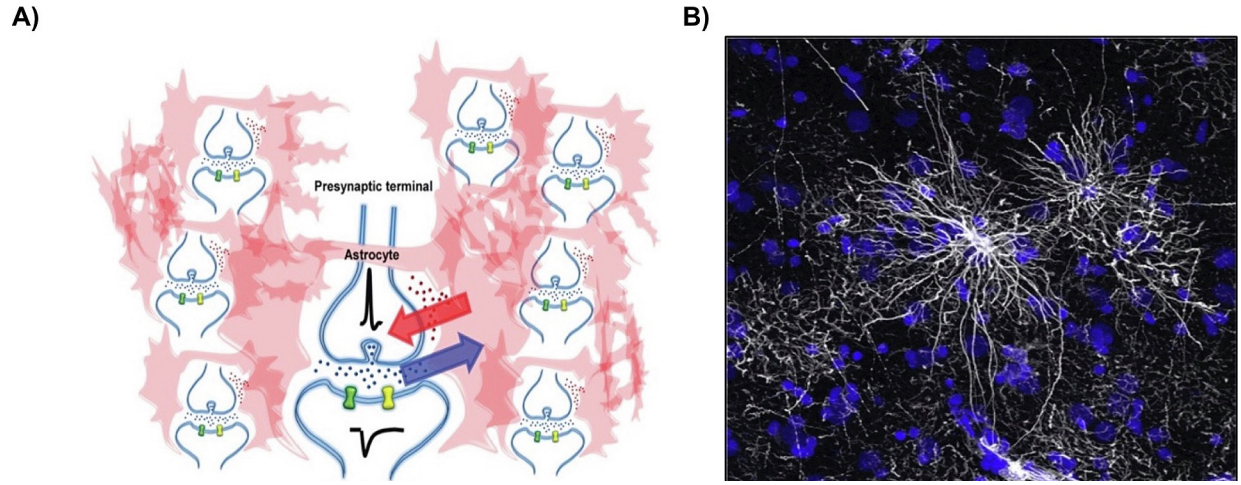

Fig. 10. Glioception in cognition and awareness. A) Representation of one astrocyte (pink) ensheathing multiple synapses. Astrocytes can modulate synaptic transmission by the release (red arrow) and uptake (blue arrow) of neurotransmitters, and by controlling ion levels and blood flow locally. Coupling of neurons into functional assemblies by astrocytes could improve information processing and implicates astroglia in complex cognitive function, such as perception and memory. B) Astrocytes from human cerebral cortex (shown here after GFAP/DAPI staining) can be distinguished from the mice counterpart by the more elaborated complexity, that enables human astrocytes to interact with up to 2 million synapses across the cortical layers. Reproduced from Fields et al., 2014, under the Creative Commons CC-BY-NC license, Copyright © 2014, © SAGE Publications. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

related conditions, such as inflammatory pain, neuropathic pain, and cancer pain (Di Lernia, Serino, & Riva, 2016). Chronic visceral pain originates from nociceptor activation or nerve injury in thoracic, abdominal, or pelvic internal organs. The sensation of pain can be elicited by the stimulation of nociceptive endings in the skin or by injury to the sensory neurons. Peripheral states of damage and inflammation are transmitted to the CNS via interoceptive pathways. CNS contributes to the processing and integration of pain information and inflammation events or responds to these insults by the activation of cardiovascular and gastrointestinal reflexes, as well as the regulation of immune reactions. Beyond the progress in the study of the underlying neuronal mechanisms in pain circuits, lies the emerging importance of glial cells in the initiation and maintenance of pain injuries. Activated glia could modulate or enhance pain by releasing various neuroactive molecules, that, in turn, trigger a cascade of events that lead to excitation, sensitization, or potentiation of neurons in the pain pathway (Watkins & Maier, 2003).

Accumulating evidence reports the involvement of microglia and astrocytes of the CNS, and macrophages and SGCs of dorsal root, nodose and trigeminal ganglia, as critical regulators of pain pathways (Fig. 11) (Hanani & Spray, 2020; Long et al., 2021).

Under physiological conditions, both astrocytes and SGCs support neurons with trophic substances while maintaining the homeostasis of K^+, glutamate, and H_2O of the microenvironment in the CNS and PNS. Both astrocytes and SGCs are interconnected by gap junctions that provide a pathway for the diffusion of ions and small molecules between cells and mediate the electrical coupling to enable signaling processes through networks. Astrocytes respond to neuronal activity with variations in their internal Ca^{2+} concentration and trigger the release of glial transmitters causing the feedback regulation of synapses. In contrast to sensory ganglia, neurons in autonomic ganglia are connected by synapses, and SGCs form a layer over the synapses, enabling them to control synaptic transmission. Healthy microglia are not quiescent, but they actively sense changes in the environment with their ramified processes and dynamically interact with synapses to modulate their structures and functions and to maintain the internal homeostasis of the CNS (Colonna & Butovsky, 2017).

It is widely accepted that pathological conditions such as chronic pain are associated not only with neuropathy but also with "gliopathy" (Ji, Berta, & Nedergaard, 2013). Painful injuries evoke rapid activation of SGCs, and microglial and astrocytic reactions, leading to central and peripheral pain sensitization.

As a result of gliopathy, glia can no longer "insulate" the pain circuit, while they act as an amplifier of pain, through releasing proinflammatory and pronociceptive mediators to enhance pain states, by activating key signaling pathways.

Upon painful stimuli, glia demonstrate variable alterations in functions and morphologies, associated with different activation states, including:

1) morphological changes such as hypertrophy and proliferation, and upregulation of glial markers such as GFAP in astrocytes and ionized Ca^{2+} — binding adaptor molecule-1 (IBA1) in microglia;
2) ionic perturbations, such as intracellular Ca^{2+} elevations, especially in astrocytes;
3) phosphorylation of mitogen-activated protein kinases (MAPK) and Steroid Receptor Coactivator (Src);
4) regulation of receptors, channels, and transporters, including the upregulation of gap junctions and hemichannels (Cx43, Panx1), resulting in increased gap junction communication in the ganglia and the release of ATP and glutamate and the activation of P2X7 and other receptors;
5) synthesis and release of pro- and anti-inflammatory glial mediators, including cytokines, chemokines, growth factors, and proteases, to the extracellular space (eg, ATP, BDNF, CCL2, TNF-α, IL-1β, IL-6, CCL2, IFN-γ, bFGF, MMP-2) (Ji et al., 2013).

Astrocytes and microglia are established as active contributors in the genesis and maintenance of pain induced by inflammation and damage to peripheral tissues and nerves, spinal nerves and spinal cord. On activation, astrocytes release various neuroexcitatory substances that potentiate pain transmission by neurons. Among these glial products, pro-inflammatory cytokines appear to be common spinal mediators of allodynia and hyperalgesia. Dysregulation of K^+ channels (Kir 4.1) and glutamate transporters (GLT1, GLAST) may result in elevations in spinal extracellular K^+ and glutamate concentrations leading to spontaneous pain (Sung, Lim, & Mao, 2003). It was also demonstrated that the AQP4 levels increased in spinal cord astrocytes after spinal cord injury (Nesic et al., 2005) and mice lacking AQP4 displayed decreased pain sensitivity (Bao, Chen, Zhang, & Zhao, 2010; Guanyi, Chong, Ying, Ning, & Jin, 2020).

Notably, many studies show that enhanced expression of gap junctions in astrocytes is associated with mechanisms of pain sensitization

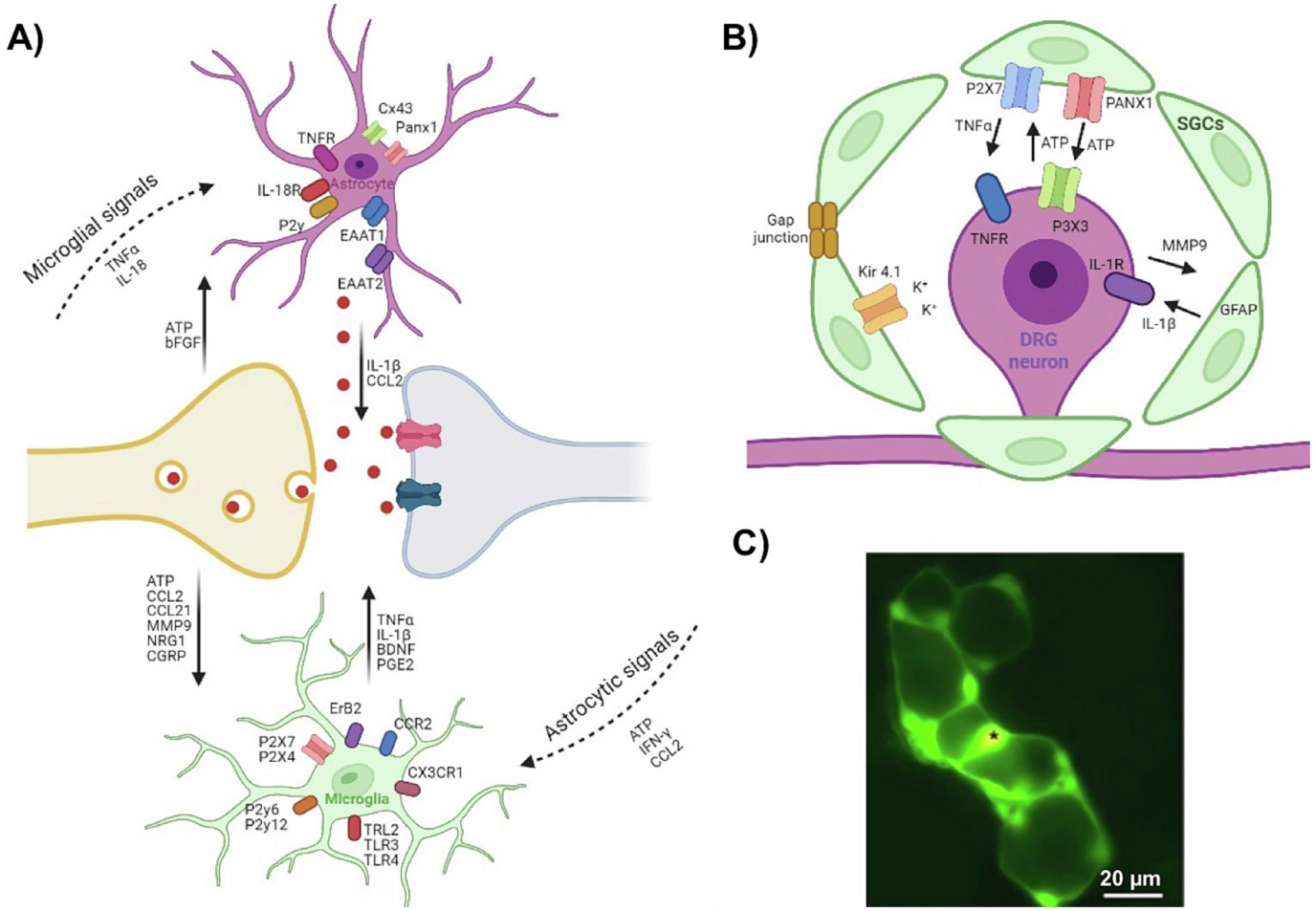

Fig. 11. Glial cells and pain modulation. A) Schematic representation of neuronal-glial and glial-glial interactions in the spinal cord in persistent pain. Following a painful insult a spontaneous discharge occurs, leading to the release of ATP, MMP-9, NRG1, chemokines and CRGP from the afferent central terminals, resulting on dorsal horn microglia activation. The activation of ATP, chemokines, and NRG1 receptors on spinal microglia induces the p38 and ERK phosphorylation which results in the production and release of proinflammatory cytokines and BDNF. Astrocytes are modulated by microglial mediators such as TNF-α and IL-18 and astrocytes mediators such as MMP-2 and bFGF. JNK and P-ERK phosphorylation occurring in astrocytes leads to the production and release of different cytokines and chemokines. The activation of Cx43 and PNX1 can results in the production of ATP and glutamate from astrocytes. Following the nerve injury, the down regulation of glutamate receptor GLT1 leads to a decrease of glutamate uptake from astrocytes. The release of CCL1, IL-1β and glutamate can modulate NMDAR-mediated sensitization. ATP and CCL2 astrocytic release could further keep microglia activation. B) Schematic representation of neuronal-glial interactions in dorsal root and trigeminal ganglia of the peripheral nervous system. Satellite glial cells (SGCs, green) are connected by gap junctions and express Kir4.1 channels and P2X7 receptors and Panx1 channels, though which they release ATP. They also secrete cytokines and growth factors, including TNFa. ATP and released cytokines/growth factors act on sensory neurons (red) to maintain activation following injury. Drawing created by Biorender.com, adapted from Ji et al., 2013. C) Fluorescence image of dorsal root ganglion from a mouse treated with a chemotherapeutic drug, which causes neuropathic pain and increases the extent of coupling, here demonstrated by diffusion of Lucifer Yellow from its injection into a satellite glial cell (SGC, indicated by asterisk) to other SGCs surrounding non fluorescent neurons. Adapted with permission from Warwick & Hanani, 2013, Copyright © 2012 European Federation of International Association for the Study of Pain Chapters. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

in both the CNS and PNS. Cronin et al. demonstrated that Cx43 is upregulated in astrocytes after nerve lesions, spinal cord injuries, and inflammation. Spinal cord injury-induced ATP release in the spinal cord is diminished after Cx43 blockade (Cronin, Anderson, Cook, Green, & Becker, 2008). In double-knockout mice lacking Cx30/Cx43, the development of neuropathic pain following spinal cord injury is prevented, and spinal astroglial reaction is reduced (Chen et al., 2012). Interestingly, CBX which as previously mentioned blocks gap junctions, also inhibits Panx1, which is expressed in astrocytes and SGCs and provides a conduit for ATP release (Garré et al., 2010; Hanstein, Hanani, Scemes, & Spray, 2016; Ji et al., 2013).

Emerging evidence suggests that SGCs in sensory ganglia are activated after painful injuries while playing an active role in the development of persistent pain (Spray & Hanani, 2019; Warwick & Hanani, 2013). Changes in SGCs, such as increased sensitivity to ATP, increased cytokine release and downregulation of Kir4.1 potassium channels, contribute to pain hypersensitivity by increasing neuronal activity. These changes have been consistently observed in various rodent pain models and likely also occur in human pain states. Importantly, SGCs exhibit enhanced gap junction-mediated coupling in rodent models of persistent inflammatory and neuropathic pain. Nerve injury has been shown to upregulate Cx43 in SGCs of trigeminal ganglia. Interestingly, reducing the expression of Cx43 in SGCs via RNAi, reduced neuropathic pain in nerve-injured rats but induced pain-like behaviors in healthy rats, suggesting different roles of SGCs-Cx43 in pain modulation in non-injured versus injured animals (Ohara, Vit, Bhargava, & Jasmin, 2008).

Microglia are also activated after various insults and pain states, displaying morphological changes, such as a change from ramified to amoeboid shape and upregulating microglial markers (CCR3/CD11b, MHC II, IBA1). Microglia sense changes in their immediate environment and react to pain injury by clearing cellular debris and secreting neurotrophins (Colonna & Butovsky, 2017). Visceral damage or persistent inflammation lead to the release of a variety of neurotransmitters, such as ATP, substance P (SP), glutamate, ATP, and calcitonin gene-related peptide (CGRP), from the Aδ-fiber and C-fiber endings of primary sensory neurons in the spinal dorsal horn. Reactive microglia

can release various proinflammatory cytokines, including IL-1β and TNF-α (Chu, Zhang, & Zhao, 2012). Additionally, TNF-α released by microglia is a key component of the neuroinflammatory response, which plays a major role in pain genesis and maintenance (Ji et al., 2013).

TRP ion channels, that are widely expressed in neuronal and glial cells, have been proposed as the most important ion channel family for the detection and transmission of pain stimuli. Many TRP channels, such as TRPV1, TRPV4, TRPM8 and TRPA1 have been associated with neuropathic pain conditions especially in animal models (González-Ramírez, Chen, Liedtke, & Morales-Lázaro, 2017).

The role of oligodendrocytes in chronic pain has not been thoroughly investigated. Some studies, however, have demonstrated the importance of oligodendrocytes as pain modulators. An upregulation of markers of oligodendrocyte precursors (NG2 and Olig2) and mature cells (PDGFRa and MBP) has been reported in post-mortem tissue of spinal dorsal horn of patients with HIV-associated peripheral neuropathy (Shi, Shu, Liang, Yuan, & Tang, 2016). Moreover, antibodies against myelin oligodendrocyte glycoprotein have been found in patients affected by neuromyelitis optica (NMO), which is a painful demyelinating disorder (Asseyer et al., 2018), characterized by the production of autoantibodies against AQP4 (Nicchia et al., 2016; Rosito et al., 2018). Besides the absence of AQP4 due to immune reaction in the CNS, evidence indicates that the supramolecular structure of AQP4 is different between the brain and skeletal muscles, which likely cause differences in tissues susceptibility to the NMO disease and could explain why patients affected by NMO do not suffer of muscular diseases. Finally, a recent discovery indicates the specific role of extended isoforms (AQP4ex) in perivascular arrangement of AQP4 into large orthogonal array of particles (OAPs) and confinement to the endfoot domain and reveals AQP4ex as a new and important player in NMO (Palazzo et al., 2019).

Additionally in patients with Multiple Sclerosis, the most common demyelinating disorder, the presence of chronic pain has been suggested to be a consequence of the massive destruction of oligodendrocytes (Urits et al., 2019). Adult mice lacking oligodendrocytes displayed neuropathic pain for several weeks, independently of adaptive immune cells or reactive microglia and astrocytes, suggesting a role of oligodendrocytes in pain maintenance. Another study in mice showed an increase of IL-33 expression by oligodendrocytes in sciatic nerve injury, while mice lacking the IL-33 receptor ST2 experienced a reduction of pain. In the same study, intrathecal injection of IL-33 induced hypersensitivity and potentiated mechanical allodynia in mice following nerve injury, dependent on TNF-α and IL-1β (Zarpelon et al., 2016). This result suggests that the role of oligodendrocytes in chronic pain is somehow connected with the pain modulation activity of astrocytes and microglia.

Moreover, recent evidence reveals that specialized nociceptive sensory Schwann glia are tightly connected to unmyelinated C-fiber endings within mechanosensory end-organs and can be activated by pain mechanical stimuli. Thus, SCs act as sensors for mechanical nociception and are part of a nociceptive glio-neural complex formed by two types of receptors, the glia and the nerve, both modulators of the pain sensation (Ojeda-Alonso et al., 2022).

Despite some perspectives targeting the control of interoception (Di Lernia et al., 2016; Schaefer, Egloff, Gerlach, & Witthöft, 2014), the field of clinical treatments for chronic pain disorders targeting glia in interoceptive dysfunctions remains unknown. Therefore, there is need for further studies which should focus on the understanding of selective glioceptive signals and channels to promote more comprehensive management of pain-related conditions.

7. Therapeutic potential of glioception

The brain maintains physiological integrity through processing and responding to interoceptive signals. Interoception is strictly associated with the prediction of signals coming from the inner body to ensure homeostasis. When the system fails to keep the organism stable, the body can be afflicted by dysfunctions and diseases. In the preceding sections, we have discussed the role that glia play in modulating interoceptive pathways and the importance of studying interoception to better understand internal body signals that maintain physical and mental well-being (Lu et al., 2013).

Abnormal processing of interoceptive signs can be involved in psychiatric disorder pathophysiology and the symptomatic expression of developmental and neurodegenerative disorders. Moreover, dysfunctional interoception could explain somatic disorders of brain-body interactions, such as chronic pain and digestive disorders (Bonaz et al., 2021).

Microglial cells respond to internal stimuli by changing morphology and behavior. In this context, microglial cells signaling pathways underpinning their modification in morphology and behavior could be the sentinel of brain interoceptive mechanisms that sense the danger-associated homeostatic changes. Microglial cells respond to interoceptive pathways involving the release of various cytokines (e.g. TNF, IL-1, IL-6), prostaglandin E2 and the infiltration of stress-sensitive monocytes in the CNS (Laflamme & Rivest, 2001). Glioceptive pathway disruption can result in disturbances in neuronal metabolism, psychopathology, and anomalous neurotransmitter release (Savitz & Harrison, 2018). Studying the role of glia in interoception and identifying the underlying molecular and cellular mechanisms will likely reveal novel glial cell-based therapy to treat the dysfunctions and diseases resulting from disruptions affecting interoceptive biological pathways. For example, in depressive disorders, anti-cytokine therapies have been administered to block interoceptive signaling pathways, showing anti-depressant effects exclusively in individuals with increased inflammatory markers (Raison et al., 2013). Vagus-nerve stimulation (VNS) has been shown to have strong anti-depressant properties (Aaronson et al., 2017). The mechanism is still to be clarified, even though there is evidence of the VNS ability to inhibit the production of TNF, IL-1 and IL-6 in humans (Koopman et al., 2016). Targeting microglia directly might be an effective therapeutic approach for mental disorders. Minocycline, which inhibits microglial activation, has been shown to have anti-depressant properties in rodent models (Moller et al., 2016). The inhibition of the microglial receptor P2X7 (implicated in the modulation of IL-1 release) showed a protective effect in animal models of depression (Chrovian, Rech, Bhattacharya, & Letavic, 2014).

As noted above, chronic pain is one of the most devastating pathological conditions provoked by defective decoding of inner body signs. Due to its complex pathophysiology, the treatment for visceral hyperalgesia is currently still limited to reducing pain transduction and transmission in neurons, and no pharmacological strategies are currently available for the effective management of pain related to visceral disorders (Ji et al., 2013; Watkins & Maier, 2003). Glial cell activation, with neuroinflammation and inflammatory mediator production, plays an important role in chronic pain. Therefore, understanding and manipulating the interactions of glial cells with sensory neurons could provide a potential approach that might be exploited therapeutically in alleviation and prevention of pain. Glia have been recognized as critical modulators of nociception. As discussed previously, pain could be a result of "gliopathy" and deficits in glioceptive processes, suggesting that glial cells could represent a key target for developing new types of therapies (Ji et al., 2013).

There is vast literature demonstrating unequivocally that if certain populations of nociceptive neurons are absent or inactivated in mice and people, then pain sensation is gone and/or (depending on the disease and/or gene deleted) severely reduced (Bartesaghi et al., 2019; MacDonald et al., 2021; Ren et al., 2014). This clearly establishes nociceptive neurons as the detectors of the noxious stimulus, which is then relayed to the CNS and perceived as "pain". As an example, among TRP channels, the capsaicin receptor TRPV1 is largely expressed by primary sensory neurons and cooperates with TRPA1 to mediate pain sensation (Caterina et al., 2000).

However, the discovery of nociceptive glial cells able to sense and transduce a broad spectrum of mechanical, thermal or chemical stimuli into electrical or chemical signals that result in pain-like sensation is consistent with the emerging idea of considering glia as a complementary partner of sensory neurons in pain genesis and perception (Ojeda-Alonso et al., 2022). Neuroinflammation drives chronic pain through glia-neuron interaction, and mounting evidence demonstrates that chemokines (CXCL1, CCL2, and CX3CL1) and proteases (MMP-9, cathepsin S and caspase-6) facilitate chronic pain sensitization, modulating the interaction between neuronal and glial cells, suggesting neuron-glia interaction as a potential target for the development of new therapeutic strategies for the treatment of pain (Ji, Xu, & Gao, 2014). However, it is important to mention that failures have been reported in 2 clinical trials: propentofylline, a CNS glial modulator, did not show efficacy in reducing pain in patients following herpetic neuralgia (Landry, Jacobs, Romero-Sandoval, & DeLeo, 2012). The other unsuccessful trial was performed using a CCR2 antagonist, showing no effects in treated patients compared to the placebo group in post-traumatic neuralgia patients (Ji et al., 2013).

Recent studies revealing the involvement of TRP channels in chronic pain have indicated that these TRP channels may be potential drug targets for pain. The TRPV1 agonist capsaicin has been used as chronic neuropathic pain therapy in clinical trials. However, the use of TRPV1 modulators was shown to have important side effects such as body temperature dysregulation and burn injuries due to compromised temperature sensitivity (Derry, Rice, Cole, Tan, & Moore, 2017; Kiani, Sajedi, Nasrollahi, & Esna-Ashari, 2015). TRPA1 deletion or inhibition in animal models demonstrated a reduction of pain and inflammation while targeting TRPM8, TRPV2, TRVP3 and TRPV4 has generated various conflicting results (Duitama et al., 2020).

Vagal afferent neurons can sense nutrients and send signaling information to the brain to control the organism energy balance. Inhibition of the vagal afferent pathway has been shown to enhance the long-term control of food intake and body weight (de Lartigue & Diepenbroek, 2016). In this context, considering the ability of glial cells, especially astrocytes, to sense the metabolite levels and regulate energy homeostasis, we can broaden our view of glioception to include the participation of these cells in the modulation of feeding circuits. This might provide a novel useful context to understand and manage different aspects of feeding behaviors and eating disorders, in nutritional medicine. Additionally, enteric glial signaling along the "gut-brain axis" can influence the interaction between the CNS and the enteric nervous system, connecting the emotional and cognitive functions of the brain to the peripheral gastrointestinal activity. The importance of targeting glial cells in the gut-brain pathway might have a substantial impact on the comprehension and modulation of mechanisms involved in gastro-intestinal injuries, most of which are chronic and incurable.

As shown by recent studies, stimulation of the vagus nerve can activate the enteric glia, improving the integrity of intestinal epithelial barrier. New insights into the enteric glia-mediated repair mechanisms after intestinal injury shed light on the possibility of targeting enteric glioceptive paths to re-establish the physiological functioning of the gut and to correct the gut-brain interplay when this is compromised (Capoccia et al., 2015; Cirillo et al., 2022; Costantini et al., 2010; de Lartigue & Diepenbroek, 2016).

8. Technological and computational perspective of glioception

Pharmacological approaches targeting the treatment of clinical nervous diseases have limitations in providing localized, fast and precise dynamics due to issues such as the need to penetrate the BBB and the lack of precise spatiotemporal control of the targeted cells/mechanism. Achieve.

Novel technologies with future therapeutic potential are being developed to address pitfalls, to exploit the tight spatial and temporal delivery that is achievable with these methods to target therapeutics. Yu et al. demonstrated the potential of magneto-mechanical stimulation (MMS) in enabling remote and selective control of astrocytes without genetic modification (Yu et al., 2021). Innovative approaches have already employed the potential of advanced materials interfaces and devices, to facilitate selective and diverse modalities to trigger responses in astrocytes by mechanical, electrical, photonic, and topographical stimuli and to attain unprecedented recording of astrocyte bioelectrical oscillations (Borrachero-Conejo et al., 2020, 2019; Maiolo et al., 2021; Saracino et al., 2021, 2020).

Several studies have been performed on biocompatible implantable devices with promising therapeutic potential as they induce limited inflammatory responses (Salatino, Ludwig, Kozai, & Purcell, 2017). Saracino et al. demonstrated the advantages of gold-coated Silicon Nanowires as a glial interface able to promote adhesion, growth and differentiation of astrocytes providing promising data for the development of bioelectronic devices that can record and modulate astrocyte function in pathological situations (Saracino et al., 2020).

Advances in glial interfaces and glial electronics can add to our technological and therapeutic arsenal, multiscale biomaterials and electronic devices for the stimulation and recording of astrocyte response dynamics. Still, at a developing stage, there is the field of gliophotonics which mainly uses optogenetic and chemogenetic methods. Moreover, promising studies are using organic optoelectronics and infrared photostimulation (Borrachero-Conejo et al., 2020, 2019; Maiolo et al., 2021).

Another rising field of the last decade is that of computational glioscience which is devoted to decoding, interpreting, and predicting glial dynamics and neuro-glial interactions in the function and dysfunction of the organism (Chander & Chakravarthy, 2012; De Pittà & Berry, 2019; Manninen, Havela, & Linne, 2019).

Mathematical modelling can be used to investigate the contribution of diverse signaling pathways occurring at the neuron-glial interface and to analyze the underlying cellular mechanisms. Recent literature reports the emerging implementation of in silico models of the astrocyte-neuron unit, that aim at describing the homeostasis of ions and neurotransmitters by modelling and reconstructing the ion flow through channels, pumps, and receptors at the neuron-glial interface (De Pittà & Berry, 2019; De Pittà, Goldberg, Volman, Berry, & Ben-Jacob, 2009).

Multi-compartmental mathematical models have been developed to describe the neuron-glial interface as a single synapse surrounded by an astrocytic perisynaptic cradle and to simulate the dynamics of membrane potential and ion transport of K^+, Na^+, Ca^{2+}, Cl^-, neurotransmitter release, including Glutamate concentration, and ion exchangers, such as Na^+/Ca^{2+} exchanger (NCX), between neuronal and glial compartments (Breslin et al., 2018; Kenny, Plank, & David, 2018; Wade et al., 2019).

At a more macroscopic level, interoception can be modelled as the bidirectional flow between the brain and the body, with feedback and feedforward loops that recursively update an internal model in order to predict and regulate future body states. As reported in the literature, interoception can be mathematically approximated by Active Inference modelling approaches of "prediction-action", which constantly include afferent sensory inputs by which the brain can decode the estimate of an internal state and infer and predict actions. Active Inference mainly uses Bayesian inference modelling, which aims at reducing the prediction error, or the discrepancy between sensations and their predictions, by changing predictions and shaping individual expectations. Also, by employing Predictive Coding methods, an organism can select actions that fulfill the predictions to reach the desired internal state (Barrett & Simmons, 2015; Petzschner, Garfinkel, Paulus, Koch, & Khalsa, 2021; Pezzulo, Rigoli, & Friston, 2015; Seth, Suzuki, & Critchley, 2012).

Despite these theoretical advances, it should be considered that also interoceptive regulation involves the complex glia-mediated autonomic signals that control body parameters such as heart rate, blood pressure and peristalsis. Moreover, glioceptive modulation of cognitive and

emotional behaviors could be integrated. Notably, the role of astrocytes in the response observed to Deep brain stimulation (DBS) (Fenoy, Goetz, Chabardès, & Xia, 2014) and Transcranial direct cranial stimulation (tDCS) has been clearly demonstrated in vivo (Tsui, Lal, Fox, Churchward, & Todd, 2022). Specifically, both types of stimulation evoke intracellular Ca^{2+} signaling in astrocytes that is mediated through the IP_3 receptor pathway (Monai et al., 2016; Monai and Hirase, 2018). Similarly, optogenetic stimulation revealed the possibility to modulate GABAergic circuitry linked to anxiety and social behavior (Allsop, Vander Weele, Wichmann, & Tye, 2014). These results are paving the way to the use of technologies targeting astrocyte GABA transmission to manipulate homeostasis. It can be envisaged that modulation of interoceptive signals perceived by astrocytes might help in alleviating "bad feelings" associated with tissue implants and reducing inflammatory reaction due to brain interaction with foreign body materials and devices (Maiolo et al., 2021). However, further studies are needed to elucidate if the direct and potentially selective activation of astrocytes can be achieved by electronic, optogenetic, and magnetic photonic technologies, thus exploiting their potential in therapeutics. In this sense, currently available interoceptive in silico technologies could be paired with emerging computational modelling of glia-glia and glia-neuron interaction to achieve new insights into the prediction, decoding and modulation of physiological and pathological internal states of the organism (De Pittà & Berry, 2019; Hayati, Nouri, Haghiri, & Abbott, 2016; Khalsa et al., 2022).

9. Conclusions

Given the recent knowledge on the contribution of non-neuronal cells in sensing, transduction and integrating processes within the nervous system, a complete understanding of the interoceptive mechanisms must incorporate the roles of glia, as active and central players of the interoceptive circuits. Here, we provide a new concept of interoception, called "Glioception", by integrating recent advances in glial research and glial pathology (Bazargani & Attwell, 2016; Borrachero-Conejo et al., 2020, 2019; Dossi et al., 2018; Fabbri et al., 2021; Maiolo et al., 2021; Navarrete et al., 2013; Posati et al., 2016). Our revised definition differs from the current literature visions since it significantly expands the framework of the signal processing between the brain and the internal organs, by including and re-evaluating the interoceptive functions of glial cells of both central and peripheral nervous systems in generating a representation of the internal state of the organism.

The increasing investigation on the active roles of glial cells in brain functions and the growing interest in interoceptive pathways as essential to maintaining the body homeostasis, has led us to explore the connection between interoception and glial cells, proposing the exciting potential of glioception. Here, we collected evidence that sheds light on the participation of glial cells as critical modulators of interoceptive pathways linked to the physiological maintenance of homeostasis, as well as in pain and other glioceptive dysfunctions. The importance of glioception investigation lies in the current lack of effective treatments and management of interoceptive dysfunction such as visceral pain. Understanding and manipulating the interactions of glial cells with interoceptive circuits could provide a potential approach that might be exploited therapeutically in the alleviation and prevention of these pathologies of the organism's inner state. By providing this advanced and novel concept of glioception, we hope to encourage innovative future research on this important topic.

Using technology to target glioceptive pathways may be useful to uncover the mechanisms underlying the coordination between internal organs and the brain and define a new "language" by which cells communicate throughout the whole body. The development and validation of interfaces, devices and theoretical approaches to probe, sense and record glial dynamics with high spatiotemporal resolution, might have clinical relevance in providing novel sensing technologies and data monitoring applications targeting the study and modulation of the brain-organs interplay. Nonetheless, glioception pathways could be investigated in the future to better understand the response of patients to implants in terms of self-perception of the implanted device and/or pain and emotional feeling related to living social life with embedded technologies. Advanced multi-system and multi-scale technologies, such as future innovative organ-on-chip models, and novel modelling and machine learning approaches that predict or describe the mechanism beyond glial function, open novel paths for uncovering the role of "non-excitable" cells in the nervous system and possibly serve as blueprint knowledge on the glioceptive processes occurring not only in the brain but also in other apparatus of our body.

Financial support

This work was supported by US Air Force Office of Scientific Research-AFOSR-Biophysics Program ASTROLIGHT FA9550-20-1-0386, European Union ITN-MSCA-Horizon-2020-ASTROTECH (GA, 956325) Army Research Office -W911NF-21-2-0074-ASTROGOLD; National Institutes of Health (NIH) NS092466.

Declaration of Competing Interest

The authors declare no conflict of interest.

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