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Sodium-calcium exchangers of the SLC8 family in oligodendrocytes: Functional properties in health and disease.

Samantha A. Spencer[1,*], **Edna Suárez-Pozos**[1,*], **Miguel Escalante**[1,2], **Yu Par Myo**[1], **Babette Fuss**[1,#]

[1]Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, Richmond Virginia, USA,

[2]Departamento de Toxicología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Ciudad de México, Mexico

Abstract

The solute carrier 8 (SLC8) family of sodium-calcium exchangers (NCXs) functions as an essential regulatory system that couples opposite fluxes of sodium and calcium ions across plasmalemmal membranes. NCXs, thereby, play key roles in maintaining an ion homeostasis that preserves cellular integrity. Hence, alterations in NCX expression and regulation have been found to lead to ionic imbalances that are often associated with intracellular calcium overload and cell death. On the other hand, intracellular calcium has been identified as a key driver for a multitude of downstream signaling events that are crucial for proper functioning of biological systems, thus highlighting the need for a tightly controlled balance. In the CNS, NCXs have been primarily characterized in the context of synaptic transmission and ischemic brain damage. However, a much broader picture is emerging. NCXs are expressed by virtually all cells of the CNS including oligodendrocytes (OLGs), the cells that generate the myelin sheath. With a growing appreciation of dynamic calcium signals in OLGs, NCXs are becoming increasingly recognized for their crucial roles in shaping OLG function under both physiological and pathophysiological conditions. In order to provide a current update, this review focuses on the importance of NCXs in cells of the OLG lineage. More specifically, it provides a brief introduction into plasmalemmal NCXs and their modes of activity, and it discusses the roles of OLG expressed NCXs in regulating CNS myelination and in contributing to CNS pathologies associated with detrimental effects on OLG lineage cells.

[#]**Correspondence to:** Babette Fuss, Ph.D. Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, PO BOX 980709, Richmond, VA 23298, Phone: 804 827 0826, Babette.Fuss@vcuhealth.org.

[*]Both authors contributed equally to this manuscript

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Introduction

Signaling mediated by the divalent cation calcium is of critical importance for proper functioning of the central nervous system (CNS) [1]. More precisely, spatially and temporally well-coordinated dynamics of intracellular calcium signals act on diverse downstream targets, They, thereby, engage in a multitude of functions ranging from cellular metabolism and gene expression to cell migration and differentiation in both CNS neurons [2–4] and CNS glial cells, i.e. astrocytes [5, 6], microglia [7, 8], and oligodendrocytes (OLGs) [9–13]. On the other hand, abnormalities in calcium signaling are thought to underlie many different neurological and neurodegenerative diseases [14–19]. Thus, there is a critical need for maintaining a well-balanced calcium homeostasis to ensure faultless CNS function. This need is addressed by molecular players that control the movement of calcium ions across membranes and are represented by numerous types of calcium channels and transporters, including the solute carrier 8 (SLC8) family of sodium-calcium exchangers (NCXs).

Historically, the phenomenon of sodium-calcium exchange across the plasma membrane was first described to occur in squid axons and the mammalian heart but it has since been recognized to apply to most mammalian cell types [20–24]. In the CNS, the activity of NCXs has probably been best characterized as a counter transport system that is present in astrocytes and neurons, where it plays important physiological roles by regulating synaptic transmission and plasticity [6, 25–29]. Under pathophysiological conditions, changes in the expression and function of NCXs in astrocytes, neurons and microglia have been associated with neurodegeneration and neuroinflammation [30–36]. Thus, NCXs are increasingly recognized as a critical regulatory system controlling CNS function. Despite a growing knowledge base, however, the roles of NCXs in glial cells belonging to the OLG lineage are only starting to emerge.

This review is focused on providing an update on the current knowledge on plasmalemmal NCXs in OLGs, the myelinating cells of the CNS. In more detail, it presents a brief overview on the role of plasmalemmal NCXs in maintaining calcium and sodium homeostasis. In addition, it provides a detailed discussion on the functional involvement of OLG expressed NCXs in regulating OLG differentiation and myelination, and in contributing to the pathophysiology in a variety of CNS diseases affecting cells of the OLG lineage.

Sodium-calcium exchangers of the SLC8 family: a brief overview

The SLC8 family of NCXs represents one branch of the much larger calcium-cation antiporter (CaCA) superfamily. Collectively, CaCA family members play critical roles in regulating cellular calcium homeostasis by facilitating the efflux of calcium against its electrochemical gradient and in counter exchange for other cations. In the case of NCXs, one

calcium ion is counter exchanged by three sodium ions [37–40]. In mammals, NCXs are encoded by three *SLC8* genes: *SLC8A1* (NCX1) [41], *SLC8A2* (NCX2) [42], and *SLC8A3* (NCX3) [43]. Interestingly, a fourth family member, NCX4 encoded by *SLC8A4*, has been found present in teleost, amphibian, and reptilian species; in mammals and birds, however, it has secondarily and independently been lost [44–46]. Recent evidence further suggests that the long-wanted mitochondrial sodium-calcium exchanger is encoded by the *SLC8B1* gene giving rise to the protein product NCLX [47–49]. This review is focused on the three mammalian *SLC8A*-derived NCXs, for which in the following the NCX nomenclature will be used for both genes and proteins, and uppercase letters will be used independent of the referenced species.

The three distinct mammalian NCXs share a highly conserved overall structure and characteristic transport functions [50]. More specifically, current structural models predict that mammalian NCXs are composed of ten transmembrane helices (TM1–10) and a long cytosolic f-loop positioned between TM5 and TM6 (Fig. 1) [51]. The transmembrane helices are arranged in two pseudo-symmetrical halves (TM1–5 and TM6–10), which form a tightly packed core domain. Notably, TM2–3 and TM7–8 contain two highly conserved homologous sequence motifs, the α1 and α2-repeat; these α repeats form a pocket, including twelve ion-coordinating residues (four in TM2 and TM7, and two in TM3 and TM8) and four ion binding sites, that is responsible for ion recognition and translocation [51–54]. This structure and the presence of two distinct passageways for separate access of sodium and calcium ions to their respective central binding sites [51–54] allows an alternating-access model of secondary active transport; in other words, they allow consecutive exposure of ligand binding domains at opposite sides of the membrane and, upon each ion-binding event, a conversion between two major conformational states, an inward-facing and an outward-facing state [55, 56]. The directionality of NCX-mediated ion exchange is reversible and depends on the relative concentrations of calcium and sodium ions as well as the membrane potential. Thus, NCXs can operate in a forward (calcium efflux) and reverse (calcium influx) mode both of which are thought to exert important physiological functions [20, 57]. NCX activity is regulated through a tandem of calcium-binding domains, CBD1 and CBD2, which are located within the cytosolic f-loop [58–62]. The CBD1 domain functions as the primary high-affinity allosteric calcium sensor [63, 64], while the CBD2 domain of NCX1 and NCX3 (but not NCX2) is subject to alternative splicing, thereby conferring different kinetic properties to individual NCX splice variants [61, 65–69]. Based on these features, increased intracellular calcium levels activate the forward mode, while the reverse mode is favored in the presence of increased intracellular sodium concentrations and a positive membrane potential [20]. In addition, increased cytosolic sodium levels have been shown to transiently inactivate NCX1 and NCX3 (but not NCX2) via interaction of sodium with a site that is located outside of the CBD domains and has been referred to as the eXchanger Inhibitory Peptide (XIP) autoinhibitory region [47, 63, 66, 70, 71]. Such inactivation can prevent entry of a toxic amount of calcium through reverse mode operation. Interestingly, sodium-mediated inactivation can be relieved by calcium-binding to CBD2 splice variants containing one of the mutually exclusive alternatively spliced exons, namely exon A in NCX1 and exon B in NCX3; these splice variants are expressed preferentially in excitable cells [44, 61, 66, 70, 72–74]. From a functional point of

view, it is notable that isoforms and splice variants such as NCX2 and NCX3-AC, which exhibit low sensitivity to sodium-dependent inactivation, are capable to retain forward mode activity even during high amplitude and prolonged sodium transients [75, 76]. Apart from calcium and sodium, NCX activity has been found to be regulated allosterically by non-transported ion species (protons and other monovalent cations), phosphatidylinositol bisphosphate and other acidic phospholipids, and an interacting fatty-acid binding protein referred to as soluble cytosolic regulatory protein (SCRP) or regulatory protein of the squid nerve sodium calcium exchanger (ReP1-NCXSQ) [77–79].

Due to their different regulatory properties, one mechanism of tissue- and/or cell type-specific calcium homeostasis can be achieved by the differential expression of specific *NCX* genes and, in the case of NCX1 and NCX3, their individual splice variants [57, 75, 80–82]. In this context, NCX2 and NCX3 are present primarily in brain and skeletal muscle, whereas NCX1 is found more universally distributed [41–43, 83, 84]. Cardiac and skeletal muscle cells express predominantly one NCX isoform/splice variant while several isoform/splice variants coexist in neurons and glial cells, possibly allowing, especially in the latter, a parallel increase in both calcium and sodium ions [75, 83]. Hence, calcium and sodium signaling can be tightly linked through the activities of NCXs, a phenomenon that has been best characterized for astrocytes and their regulatory roles in synaptic transmission [6, 26, 75, 85]. Furthermore, different tissues, i.e. heart, kidney and brain, have been found to express *NCX1* via three alternate promoters, resulting in independent transcriptional regulation in the absence of changes in protein structure or function [86–89]. In this context, the brain *NCX1* promoter represents a ubiquitous GC-rich TATA-less promoter that gives rise to the majority of the *NCX1* transcripts found in the brain, possibly through binding at its AP-2 binding site, but it is also active elsewhere [86].

Taken together, plasmalemmal NCXs function as unique transporter systems that control intracellular calcium homeostasis and that can directly couple the transfer of calcium and sodium ions across membranes. Cell- and tissue-specific characteristics of calcium-sodium exchange are achieved through the different regulatory properties of the individual NCXs and their alternatively spliced variants as well as through specific *NCX1* promoter use. Hence, NCXs critically contribute to the tight control of calcium and sodium signaling events that is necessary to maintain physiological conditions within the CNS [6, 75, 90].

Sodium-calcium exchangers in oligodendrocytes

Oligodendrocytes (OLGs) are specialized cells of the CNS that generate the axon enwrapping myelin sheath, which enables rapid and efficient saltatory conduction and provides metabolic axonal support [91]. During development, cells of the OLG lineage originate as bipolar and migratory OLG progenitor cells (OPCs), which undergo a stepwise lineage progression by maturing first into premyelinating immature OLGs that extend a complex process network and then into mature OLGs that produce and maintain the myelin sheath [92, 93]. Next to extensive alterations in morphology, precisely regulated changes in gene expression patterns mark each of the individual stages of the OLG lineage [94–97].

The first characterization of NCXs in cells of the OLG lineage dates back to a study published by Quednau et al. [83], which revealed, using reverse transcriptase-polymerase chain reaction (RT-PCR), that all three mammalian genes are expressed in primary cultures of differentiating OLGs. Regarding the presence of alternatively spliced variants, both exon A and B containing mRNA transcripts were detected for *NCX1* but only exon B containing ones were found for *NCX3*. Subsequent investigations confirmed these results but they also suggested that while *NCX2* is the most highly expressed *NCX* gene in the brain (except the brain stem), its levels may be relatively low in OLGs [98, 99]. When assessing the distribution of NCX1 on myelinated axons *in vivo* in the adult rodent CNS, positive results were obtained for the optic nerve and spinal cord but not the corpus callosum, hence indicating regional heterogeneity pertaining the expression of the different *NCX* genes in mature OLGs [100]. Markedly, a developmental switch in *NCX* gene expression was observed in primary cultures of cortical OLG lineage cells in which *NCX1* was found to be expressed predominantly at the progenitor stage while *NCX3* expression was seen upregulated once cells started to differentiate [101, 102]. Consistent with the view that NCX3 represents the main contributor to sodium-calcium exchange in cortical OLGs, *NCX3*-targeted gene silencing was found to reduce overall NCX activity (forward and reverse mode) by about 80% [101]. Given the expression of *NCX1* in the adult optic nerve and spinal cord, it appears, however, that the developmental downregulation of *NCX1* may be specific to cortical OLG lineage cells and aimed at generating regional differences in the characteristics of sodium-calcium exchange within differentiating and mature OLGs.

Functionally, it has been proposed that NCX1 activity in OPCs contributes to the regulation of OPC migration, possibly via a mechanism that is induced by signaling through gamma-aminobutyric acid (GABA) receptors and subsequent elevation in intracellular sodium levels triggering calcium influx (and compensatory sodium efflux) through reverse operation of the exchanger (Fig. 3A) [99]. This pathway has been characterized in OPCs using hippocampal slices [99], and calcium signaling has been shown to contribute to the regulation of OPC migration [9, 11, 103, 104]. However, GABA-stimulated OPC migration events have not yet been assessed in detail *in vivo* [105], and they may be specific to OPCs leaving the postnatal subventricular zone (SVZ) [99].

In differentiating and myelinating OLGs, NCX3 activity has been implicated in promoting OLG maturation [101, 102] and the onset of local synthesis of *myelin basic protein* (*MBP*) [106]. As an underlying mechanism for the latter, it has been proposed that neuronal activity, presumably through an increase in extracellular potassium concentration, leads to local increases in intracellular sodium levels and changes in membrane potential; these changes drive an influx of calcium via reverse mode NCX3 activity, thereby triggering the onset local *MBP* translation in the vicinity of electrically active axons [106, 107]. Consistent with a prominent role of NCX3 in regulating the appearance of myelin proteins, protein levels for MBP and 2’,3’-cyclic-nucleotide 3’-phosphodiesterase (CNP) were found to be reduced in the spinal cords of *NCX3* knockout mice [101]. It is of note that the CNS myelin mRNA pool has recently been found to be much larger than previously recognized [108]. Specifically, it was found to include mRNAs, such as *PLP1* and *CNP*, which have traditionally been associated with a localization solely to the OLG soma. These findings suggest that locally regulated translation may affect a broader range of myelin-related

transcripts, thus providing a new level of complexity to the regulation of myelination in general and via the activity of NCXs.

In our own studies, we identified a signaling mechanism that promotes the morphological maturation of OLGs, i.e. process outgrowth and branching, via activation of OLG expressed sodium-dependent glutamate transporters and subsequent increase in intracellular calcium concentrations [109, 110]. Based on studies done in astrocytes, the observed influx in calcium was proposed to be mediated by reverse mode NCX activity [109, 111]. To address this hypothesis experimentally, primary cultures of differentiating OLGs were treated, prior to stimulating sodium-dependent glutamate transporters via application of D-aspartate (D-Asp), with the selective NCX inhibitor SN6 that blocks preferentially reverse mode operation [112, 113]. D-Asp was used in these experiments as glutamate-equivalent transporter substrate since it has been described to not stimulate non-NMDA ionotropic and metabotropic glutamate receptors [114, 115] and to not be metabolized by glutamine synthetase [116]. As shown in Fig. 2, D-Asp treatment increased process outgrowth and the OLG's process network area to an extent similar to the one reported previously [109]. Importantly, this effect could be effectively blocked by pre-incubation with SN6, thus demonstrating an activation of NCX reverse mode activity downstream of glutamate transporter activation. In support of *in vivo* relevance of this pathway, recent studies demonstrated that D-Asp treatment can stimulate *in vivo* remyelination by promoting OLG maturation via a pathway that involves, among others, the activation of glutamate transporters and the sodium-calcium exchanger NCX3 [117]. Considering that glutamate is released along at least a subset of unmyelinated and electrically active axons [118–120], the glutamate transporter-NCX pathway may, similar to the extracellular potassium-OLG membrane depolarization pathway [106, 107], contribute to the adaptive program of electrical activity-dependent myelination (Fig. 3B) [121–124]. Future studies are, however, needed to determine the *in vivo* contribution of either pathway to developmental myelination and myelin repair and to establish the extent of crosstalk and interaction, beyond an involvement of NCX reverse mode activity, between these two pathways.

Collectively, it becomes apparent that sodium-calcium exchange is critically involved in the regulation of various physiological processes related to CNS myelination. In OPCs, it is primarily NCX1 that is involved in controlling cell migration *in vitro* and possibly from the postnatal SVZ into the brain parenchyma. At more mature stages of the OLG lineage, NCX3 emerges as the primary *NCX* gene in OLGs in which sodium-calcium exchange has been implicated in signaling pathways promoting maturation. Remarkably, all these physiological roles have been shown mediated by well-controlled reverse mode NCX activities leading to calcium influx.

Potential contributions of oligodendrocyte-expressed sodium-calcium exchangers to CNS disease

Premyelinating OLGs have been shown to be particularly vulnerable to hypoxic-ischemic injury, a process that has been implicated in brain injury in premature infants [125]. Interestingly, oxygen-glucose deprivation (OGD) as a model of ischemic damage was found

to lead to a downregulation of *NCX3* expression in premyelinating OLGs; attenuation of this downregulation was shown to prevent calcium overload, an effect that was attributed to NCX3 forward mode operation (Fig. 4B), thereby improving OLG viability and maturation [126]. Similar observations were made under conditions of lead (Pb) poisoning, whereby Pb is thought to enhance the generation of reactive oxygen species, to reduce the antioxidant defense system of cells and to decrease the expression of calcium extrusion proteins [127, 128]. Thus, under conditions of hypoxic-ischemic injury and oxidative stress, NCX3 activity appears to exert protective functions by ameliorating injury to premyelinating OLGs. Such a beneficial role for NCX3 is supported by studies investigating ischemic preconditioning as a mechanism by which a brief non-injurious episode of ischemia protects the brain from a subsequent lethal insult. This protective effect has, at least in part, been attributed to an upregulation of NCX1 and NCX3 [30, 129, 130]. Interestingly, in addition to beneficial forward mode NCX avtivity, reverse mode operation has been implicated in counteracting ischemia-induced injury processes by dampeming intracellular sodium overload and promoting calcium refilling into the endoplasmic reticulum (Fig. 4B) [129, 131]. Undoubtedly, further research will be neceesary to more precisely define the contribtions of NCX activities to the pathology seen upon hypoxic-ischemic injury to the brain.

Somewhat different from the above proposed protective roles, reverse mode NCX activity has, during glutamate-mediated excitotoxicity, been proposed to trigger calcium overload and to thereby compromise mitochondrial function and OLG viability [132]. In OPCs, such pathological reverse mode NCX activity has been shown to be triggered by activation of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and subsequent sodium influx via the sodium-potassium-chloride co-transporter 1 (NKCC1) (Fig. 4A) [132]. Increased levels of glutamate, possibly triggering pathways of glutamate-mediated excitotoxicity, have been associated with OLG and myelin damage in a number of human CNS pathologies and their rodent animal models; these include the major demyelinating disease in human, Multiple Sclerosis (MS) [133–135], hypoxia/ischemia-mediated neonatal and adult white matter damage [136, 137], and spinal cord injury [75, 138, 139]. For human adult OLGs, however, it has been reported that the expression of AMPA receptor subunits is low and that they are resistant to excitotoxic injury [140]. On the other hand, AMPA receptor-mediated calcium signaling in rodents has been described to be transiently enhanced in perinatally-derived OPCs and immature OLGs [141, 142], thus pointing toward a developmental window of vulnerability in both rodents and humans that may be altered under inflammatory conditions associated with CNS injury.

The origin of cells for glioblastoma multiforme (GBM), the most lethal primary neoplasm in the CNS, has been proposed to be represented, next to neural stem cells, by OPCs [143]. Given the vulnerability of OPCs to reverse mode NCX activity-induced cell death (see above) and evidence for NCX expression by glioma cells [144, 145], selective blockade of the forward mode of NCX activity has, in analogy to studies done in other cancer cell types [146], been explored as a strategy to suppress GBM growth [147]. Remarkably, inhibition of forward mode NCX activity was found to suppress tumor growth of established glioma cell lines both *in vitro* and *in vivo*. Treatment of astrocytes under the same conditions was found to not affect cell viability, possibly due to differences in NCX gene expression patterns.

Effects on other CNS cells, importantly neurons and cells of the OLG lineage, however, were not assessed in these studies.

In summary, alterations in NCX expression and/or activity in both the forward and reverse mode have been implicated in contributing to a variety of CNS pathologies. Currently, however, knowledge about the exact contributions of either mode of activity, individual NCX genes or alternatively spliced variants is limited, thus complicating the design of well-targeted therapeutic approaches.

Conclusions

Cells of the OLG lineage have been reported to express all three of the mammalian NCX genes. However, NCX3 is beginning to emerge as the most prominent NCX gene in differentiating and mature OLGs, where it has been identified to play crucial roles in regulating OLG maturation and myelin sheath formation [101, 106, 107, 148]. NCX1, on the other hand, appears to be primarily operative during OPC migration [99]. Despite an increasing awareness of NCX function in OLGs, knowledge still remains limited. For example, increasing evidence has revealed diversity and potential heterogeneity within the OLG lineage [149–152]. In this regard, NCX2 may be enriched in a subtype of mature OLGs possibly involved in synaptic activity [149]. Such potential regional differences, however, have not been investigated in detail. In addition, potential diversity in sodium-calcium exchanger kinetics, due to the expression of different *NCX* genes and/or splice variants, has not been fully explored. Notably, most of the functional roles of NCXs in OLGs have been associated with changes in intracellular calcium concentrations. In contrast, little is known about potential roles of intracellular sodium transients in OLGs, despite the known coupling of calcium and sodium ion fluxes and crosslinking between calcium and sodium signaling [75].

In addition, to their involvement in developmental processes, NCXs expressed by OLG lineage cells have been implicated in contributing to pathophysiological mechanisms under a number of neurological disorder conditions. Thus, characterizing NCX activity may provide insight into novel therapeutic approaches. Thus far, therapeutically targeting NCX activity has shown promise in patients with coronary heart disease [153]. In addition, NCXs have been proposed as druggable targets for the treatment of cerebral ischemia [31, 154] and brain tumors [147]. However, it is becoming increasingly clear that NCXs play diverse roles under various pathological conditions and compared to physiological processes. Thus, a deeper understanding of the functional roles of NCXs under both physiological and pathophysiological conditions as well as within the diverse cell types of the CNS, including OLGs, is needed to be able to specifically target individual CNS disease promoting processes involving NCXs.

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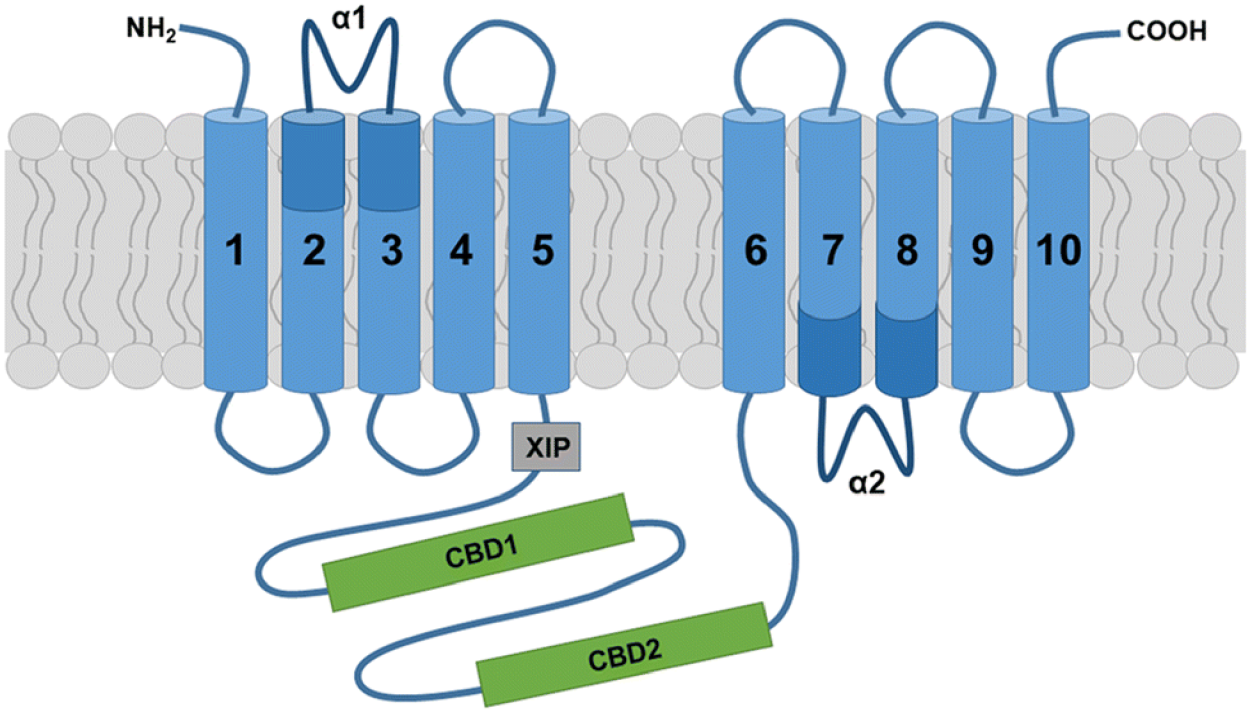

Fig. 1. Topology model for sodium calcium exchangers of the SLCA8 family.

The current model for NCX topology proposes five transmembrane helices in both the first and second hydrophobic cluster. The two conserved α-repeats (α1 and α2) contain ion-coordinating amino acid residues that are involved in ion transport activities. The cytosolic f-loop encompasses the two calcium binding domains CBD1 and CBD2, and the exchanger inhibitory peptide (XIP) site, which is present in NCX1 and NCX3 and has been implicated in sodium-dependent inactivation.

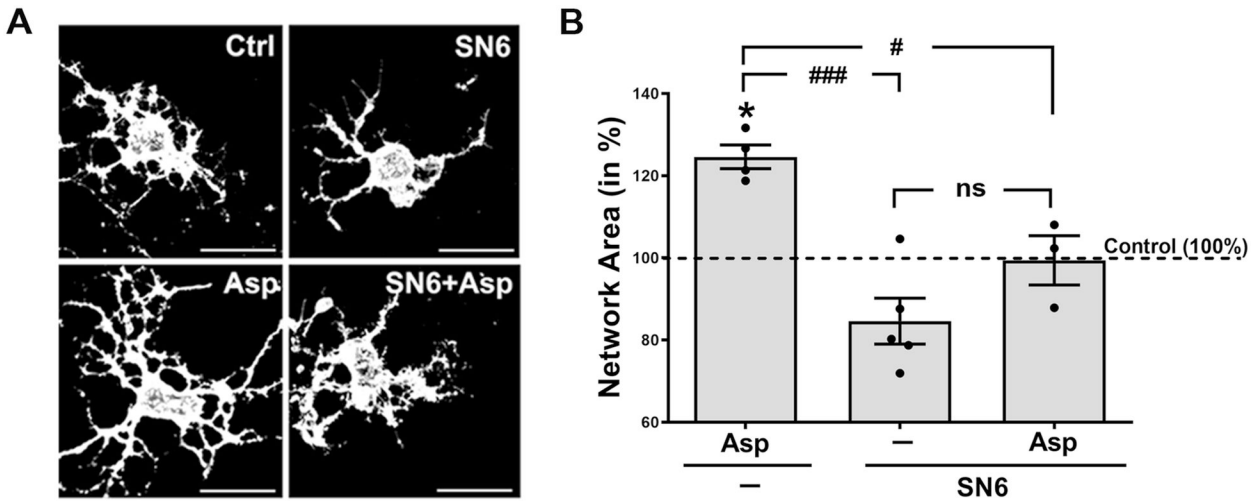

Fig. 2. Inhibition of the reverse mode of Na^+/Ca^{2+} exchange attenuates glutamate transporter stimulated morphological maturation of oligodendrocytes.

Cells were treated for 6h as indicated. Asp (D-Asp, 100 μM), SN6 (a selective inhibitor of Na^+/Ca^{2+} exchange (reverse mode), 10 μM). **A:** Representative images of differentiating oligodendrocytes after immunostaining with O4 hybridoma supernatants. Scale bars: 20 μm. **B:** Graph depicting network areas. The mean values for control (non-treated) cells were set to 100% (dotted horizonal line) and experimental values were calculated accordingly. Dots represent individual experiments, horizontal lines indicate means, error bars are depicted as SEM. *$p \leq 0.05$ (compared to control; one sample *t*-test); $^{\#}p \leq 0.05$, $^{\#\#\#}p \leq 0.001$, ^{ns}not significant (ANOVA, Tukey's multiple comparison test)

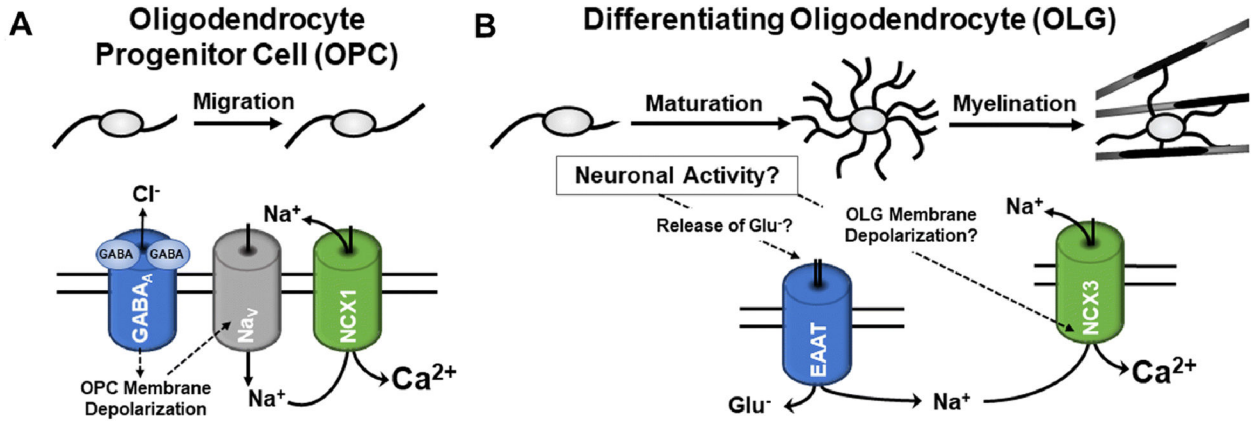

Fig. 3. Proposed physiological roles of NCX activities in cells of the OLG lineage.

A: For OPCs located in the postnatal subventricular zone (SVZ), activation of $GABA_A$ receptors has been reported to induce a chemotactic migration response that is mediated by calcium influx via reverse mode NCX1 activity triggered by sodium influx through non-inactivating sodium channels (Na_V) after GABA-induced membrane depolarization [99]. **B:** For differentiating and myelinating OLGs, a differentiation promoting role emerges for NCX3 [101, 102]. Thus far, two neuronal activity-induced pathways have been proposed. First, OLG membrane depolarization-induced reverse mode NCX activity has been implicated in promoting the syntheses of the myelin protein myelin basic protein (MBP) and the processes of active myelination [106, 107]. Second, activation of sodium-dependent glutamate transporters (EAAT), presumably through glutamate release from electrically active axons, was found to promote the morphological maturation of differentiating OLGs by a molecular mechanism involving reverse mode NCX activity and an increase in intracellular calcium concentration (Fig. 2) [109, 110].

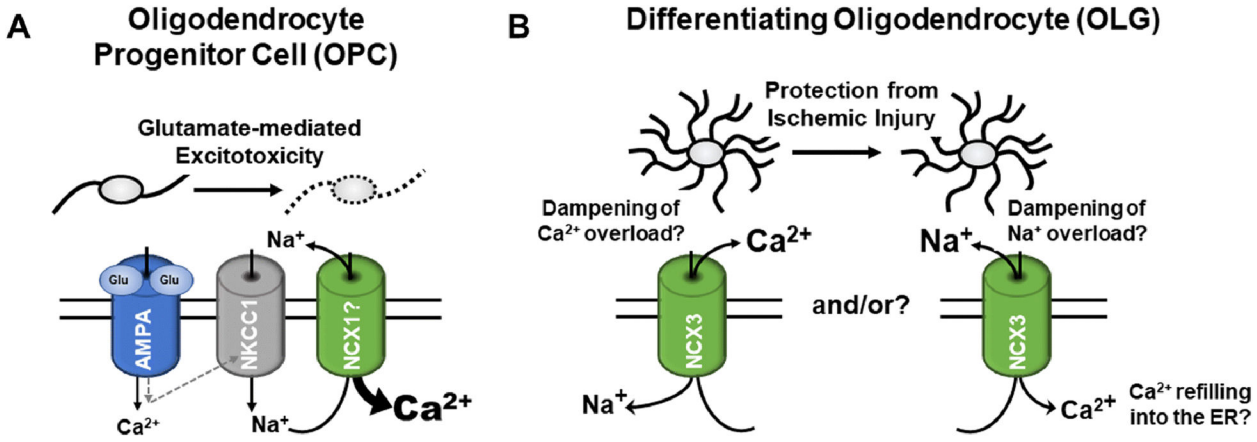

Fig. 4. Proposed pathophysiological roles of NCX activities in cells of the OLG lineage.

A: For OPCs, overactivation of AMPA receptors has been associated with glutamate-mediated excitotoxic injury; more specifically, a pathway involving the sodium-potassium-chloride co-transporter 1 (NKCC1) and the reverse mode of NCX activity has recently been described to lead to calcium overload and OPC injury upon prolonged AMPA receptor activation [132]. **B:** For differentiating OLGs a protective role of NCX3 activity is emerging in the context of ischemic-hypoxic injury and oxidative stress; possible beneficial effects of both forward (left) [126] and reverse mode activity have been proposed [129, 131].