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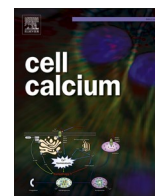
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## Neurophysiological functions and pharmacological tools of acidic and non-acidic $\text{Ca}^{2+}$ stores

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### ABSTRACT

$\text{Ca}^{2+}$  signalling is of prime importance in controlling numerous cell functions in the brain. Endolysosomes are acidic organelles currently emerging as important  $\text{Ca}^{2+}$  stores in astrocytes, microglia, endothelial cells, and neurons. In neurons, these acidic  $\text{Ca}^{2+}$  stores are found in axons, soma, dendrites, and axon endings and could provide local sources of  $\text{Ca}^{2+}$  to control synaptic transmission, neuronal plasticity, and autophagy to name a few. This review will address how acidic  $\text{Ca}^{2+}$  stores are recruited in response to cell stimulation. We will focus on the role of the endolysosomal two-pore channels (TPCs) and their physiological agonist nicotinic acid adenine dinucleotide phosphate (NAADP) and how they interact with cyclic ADP-ribose and ryanodine receptors from the endoplasmic reticulum. Finally, this review will describe new pharmacological tools and animal mutant models now available to explore acidic  $\text{Ca}^{2+}$  stores as key elements in brain function and dysfunction.

### Abbreviations

TPC	Two-pore channel
NAADP	Nicotinic acid adenine dinucleotide phosphate
NAAD	Nicotinic acid adenine dinucleotide
$\text{NAD}^+$	Nicotinamide adenine dinucleotide
$\text{NADP}^+$	Nicotinamide adenine dinucleotide phosphate
cADPR	cyclic ADP-Ribose
RyR	Ryanodine receptor
CICR	$\text{Ca}^{2+}$ -induced $\text{Ca}^{2+}$ release
GPCR	G-protein coupled receptor
S/ER	(sarco-)endoplasmic reticulum
VGC	Voltage-gated channel
CNS	Central nervous system

In the central nervous system (CNS), the  $\text{Ca}^{2+}$  ion occupies a place of primary importance.  $\text{Ca}^{2+}$  is involved in numerous functions such as in neurotransmitter and neuropeptide release, signal transduction, neuronal excitability, synaptic plasticity, gene transcription, cell metabolism and cerebral blood flow to cite a few (for review, [1–5]). Such essential roles highlight the need for a better understanding of specific  $\text{Ca}^{2+}$  signalling pathways, channels and receptors involved in these disparate processes. Cytosolic  $\text{Ca}^{2+}$  changes occur following  $\text{Ca}^{2+}$  influx from the extracellular space via the opening of plasma membrane channels and through the release of  $\text{Ca}^{2+}$  from intracellular stores such as the (sarco-)endoplasmic reticulum (S/ER) and endolysosomes. In this review, we will focus on the recruitment of intracellular acidic  $\text{Ca}^{2+}$

stores in brain cells and not discuss the pathways for extracellular  $\text{Ca}^{2+}$  entry that have been well described elsewhere (for review, [3,6]). Although considerable advances have been made to understand the  $\text{Ca}^{2+}$  signalling pathways in neurons, many questions remain to be answered, in particular concerning the role of intracellular  $\text{Ca}^{2+}$  stores such as the acidic stores and how they often interact with other organelles to control so many cellular processes.

### 1. A brief history of intracellular $\text{Ca}^{2+}$ signalling

Intracellular  $\text{Ca}^{2+}$  stores came to the fore since the 1960s when researchers discovered that the S/ER was replete with  $\text{Ca}^{2+}$  [7–11]. In skeletal and cardiac muscles, it was then shown that ryanodine, a plant alkaloid, inhibits a “ $\text{Ca}^{2+}$  channel located on the sarcoplasmic reticulum” [12–14] later named as the ryanodine receptor (RyR). RyRs were then eventually purified by two teams and identified as the main  $\text{Ca}^{2+}$  release channel of the SR [15–19]. In parallel, the  $\text{Ca}^{2+}$  mobilizing messenger inositol-1, 4, 5-trisphosphate ( $\text{IP}_3$ ) targeting the ER store was discovered [20,21] and its receptor ( $\text{IP}_3$ R) was then purified from rat cerebellum [22–24].

These two  $\text{Ca}^{2+}$  channels of the S/ER became widely accepted as the principal channels controlling the intracellular  $\text{Ca}^{2+}$  stores and have been well-characterized (for review, [25,26]). Still, additional  $\text{Ca}^{2+}$ -releasing molecules were discovered during the 1980s. In a seminal study, Hon-Cheung Lee and colleagues showed that two pyridine nucleotides evoked  $\text{Ca}^{2+}$  release by  $\text{IP}_3$ -independent mechanisms in

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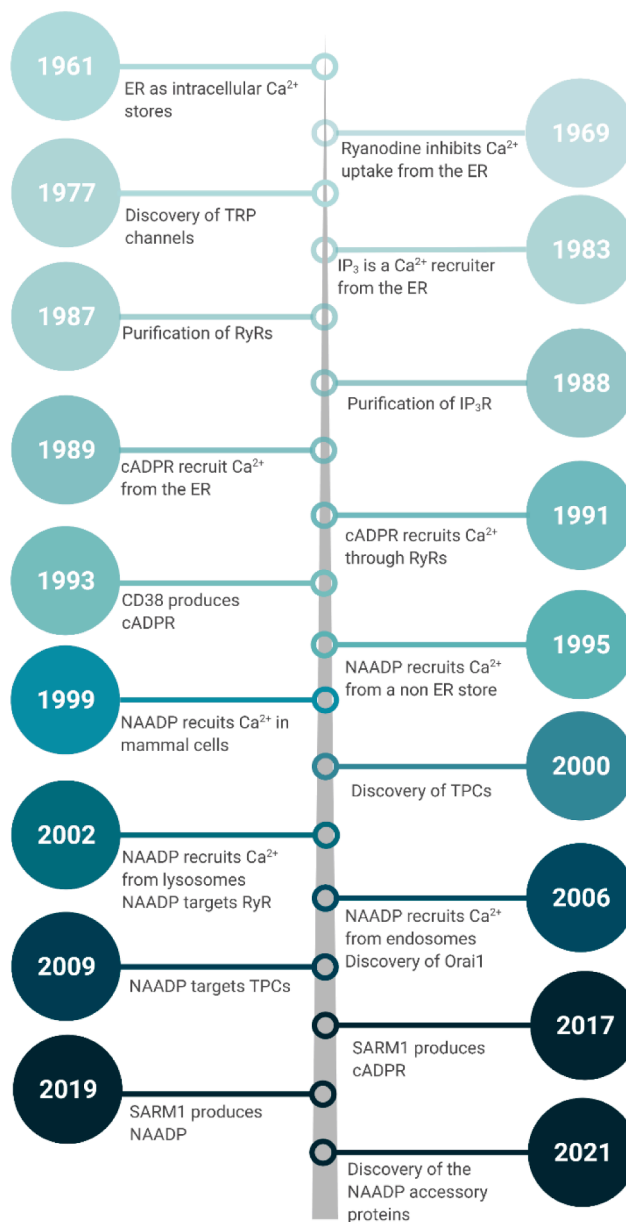
*Lytechinus pictus* (sea urchin) microsomes [27]. They discovered that the addition of NADP<sup>+</sup> (nicotinamide adenine dinucleotide phosphate) triggered rapid Ca<sup>2+</sup> release and that NAD<sup>+</sup> (nicotinamide adenine dinucleotide) was metabolized by an unknown enzyme to form an active Ca<sup>2+</sup>-releasing messenger, later identified by x-ray crystallography as a novel cyclic nucleotide, namely cyclic ADP-ribose (cADPR) [27–29]. Soon after, the principal target channel of cADPR was established as being the well-known RyR [30]. In mammals, one of the enzymes producing cADPR was then identified by Hon-Cheung Lee's team as being the ubiquitous CD38 molecule [31–33]. A few years later, Lee and Aarhus demonstrated that, as they already suspected in their first publication, NADP<sup>+</sup> was not the molecule releasing Ca<sup>2+</sup> from intracellular stores but it was instead NAADP (nicotinic acid adenine dinucleotide phosphate) [34] present as a contaminant in commercial NADP<sup>+</sup> [27, 35]. Indeed, they showed that NAADP triggered Ca<sup>2+</sup> release from a separate store from the ER [35,36]. *In vitro*, NAADP could be synthesized by *L. pictus* and *Aplysia* ADP-ribosyl cyclase [37,38] and the mammalian CD38 [38]. Importantly, NAADP and cADPR both act at lower concentrations than IP<sub>3</sub> to release Ca<sup>2+</sup> [35,39]. The first experiments were conducted in *L. pictus* and *Aplysia californica* and soon thereafter researchers demonstrated the Ca<sup>2+</sup> releasing property of NAADP in various invertebrate models such as in *Phallusia mammillata* (ascidia) oocytes [40], *Chaetopterus pergamentaceus* (parchment worm) eggs [41] and *Asterina pectinifera* (starfish) oocytes [42]. In mammals, it was known that NAADP was effectively synthesized by mammalian cells [34, 36,43] but the first studies failed to detect any cytosolic Ca<sup>2+</sup> elevation by directly injecting NAADP into mammalian intact cells [44,45]. In 1999, Cancela *et al.*, finally demonstrated that NAADP evoked Ca<sup>2+</sup> release in mouse pancreatic acinar cells [46]. They proposed that the primary released Ca<sup>2+</sup> from the unidentified store/receptor could be amplified by further Ca<sup>2+</sup> release from the ER through the recruitment of both RyR and IP<sub>3</sub>R by a mechanism called Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release (CICR). They also obtained the first evidence for a second messenger role of NAADP in hormone signalling [46]. These studies were the starting point for hunting for the NAADP target and the 21st-century studies have been full of astonishing accomplishments about NAADP signalling as depicted in Fig. 1.

NAADP releases Ca<sup>2+</sup> in various cell types from plants to mammals [46–53] but the subcellular compartment from which this Ca<sup>2+</sup> is released was debated for some time. For instance, it has been proposed that NAADP was directly targeting the ER Ca<sup>2+</sup> stores and in particular RyR1 and 2 [53–59]. Understanding of NAADP's mechanism of action reached a higher level when it was discovered that the stores from which NAADP triggers Ca<sup>2+</sup> release were lysosomal-related organelles [60]. What a surprise to discover that NAADP targets lysosomes, a completely ignored Ca<sup>2+</sup> store compared to the well-recognised ER! A few years later, it was also shown that endosomes, which are acidic organelles related to lysosomes were also a source of Ca<sup>2+</sup> mobilized by NAADP [61]. From 1999 to 2009, multiple NAADP molecular targets were proposed including RyR1 [54,55], TRPM2 [62] but see [63] and TRPML1 [64] but see [65]), and a newly discovered protein called Two-Pore Channel, TPC [66–68]. So far, RyR1 and TPCs are the most widely accepted targets for NAADP. In support of this view, two accessory proteins have been recently identified; the Jupiter microtubule-associated homolog 2 (JPT2) [69,70] that allows NAADP to act on TPC1 and RyR1 [70]; and Lsm12 (Like-sm protein) that links NAADP to both TPC1 and TPC2 [71].

## 2. Nucleotide-producing enzymes

### 2.1. CD38

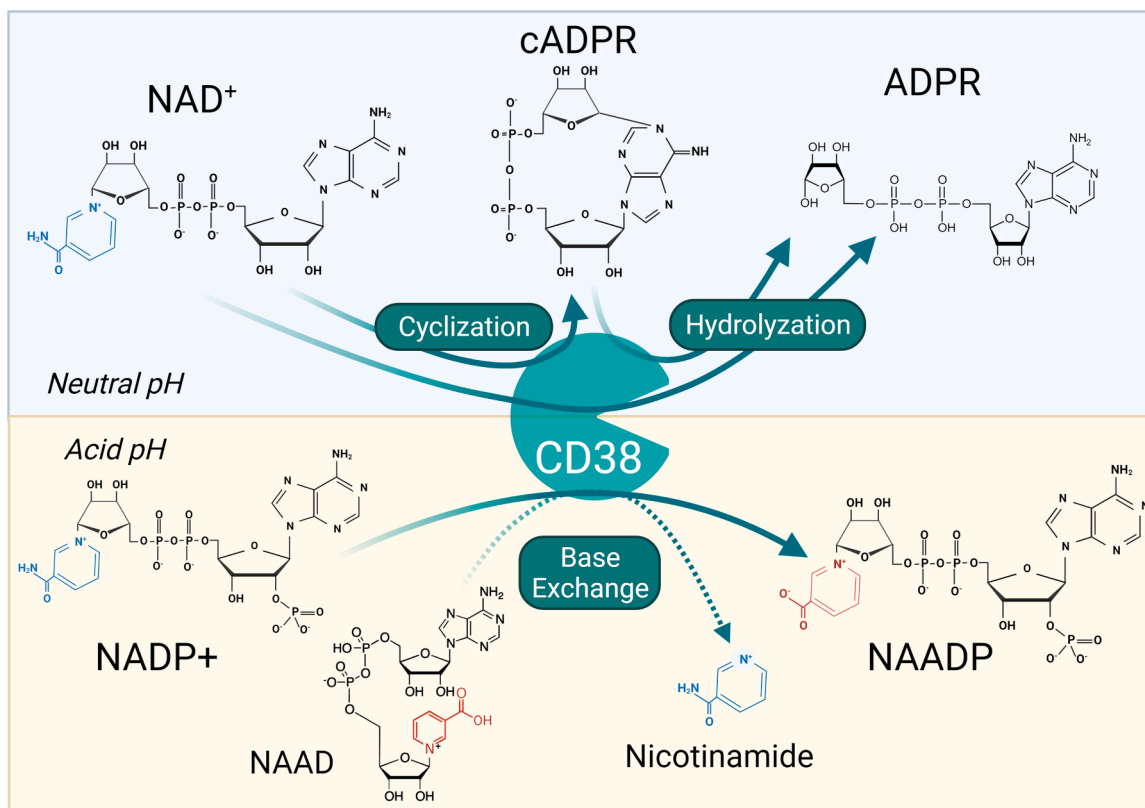
During the 1980s, a large-scale project aiming to identify human surface molecules of the immune system was undertaken. These molecules were designated as “CD” for “Cluster of Differentiation” followed by a number incremented by each new molecule discovered. This led to



**Fig. 1. Chronology of the main discoveries about intracellular Ca<sup>2+</sup> signalling.** The timeline begins at the top thin line in 1961 and run until 2021 at the bottom.

the discovery of CD38, identified as a marker of T lymphocyte activation [72–74].

CD38 is a transmembrane enzyme composed of a single chain of ~45 kDa [74,75] that has been described *in vitro* for its ability to produce cADPR from NAD<sup>+</sup> [31,76,77]. Strikingly, CD38 catalyses many different enzymatic reactions and the three most studied are described in Fig. 2: the cyclization of NAD<sup>+</sup> into cADPR, the hydrolyzation of NAD<sup>+</sup> into ADPR and, the base-exchange reaction to produce NAADP [31,35, 37,38,76,78–82]. As illustrated in Fig. 2, the production of NAADP *in vitro* is optimal in acidic conditions in contrast to cADPR production that preferentially occurs at neutral pH. For many years, it was proposed that the base-exchange reaction for the NAADP synthesis occurs by exchanging the co-substrate nicotinic acid with the nicotinamide group of NADP<sup>+</sup> (nicotinic adenine dinucleotide phosphate) [38,83]. Intriguingly, no study so far has shown that endogenous nicotinic acid levels can change in response to cell stimulation and recently, Kim's group proposed that the base rather comes from the nicotinic acid adenine



**Fig. 2.** Drawing showing that CD38 is a multifunctional enzyme. The cyclase and hydrolase reaction occur preferentially at neutral pH (top) and the base-exchange (bottom) reaction occurs under acidic conditions. Of note, until very recently the candidate substrate for the base exchange reaction was nicotinic acid. Now, a new report has proposed that NAAD is the nicotinic acid donor [84]. Abbreviations: NAD<sup>+</sup>, nicotinamide adenine dinucleotide; cADPR, cyclic adenosine diphosphate ribose; ADPR, adenosine diphosphate ribose; NADP<sup>+</sup>, nicotinamide adenine dinucleotide phosphate; NAAD, nicotinic acid adenine dinucleotide; NAADP, nicotinic acid adenine dinucleotide phosphate.

dinucleotide (NAAD) which accumulates in the acidic endolysosomal lumen [84].

Structurally, CD38 is predicted to be a type-II transmembrane protein with its catalytic site exposed to the extracellular space [31,74, 85–87]. Under such an orientation, the endocytosed CD38 has its catalytic site within the vesicular lumen (Fig. 3), providing the acidic environment required for NAADP synthesis [81,82,84,88]. CD38 has also a type-III orientation coexpressed with the type-II [89], exposing the catalytic site in the cytosol where it could have direct access to its intracellular substrate NAD<sup>+</sup> to produce cADPR under neutral pH [52, 90,91].

CD38 has virtually ubiquitous expression but a few number of studies have looked at its role in the brain [93,94]. Brain expression of CD38 has been demonstrated in mice [95], rats [96,97], and humans [98], and its expression has been shown in neurons [96,98], astrocytes [96,99–102], and microglia [102–104]. In the brain, as for the periphery, CD38 appears highly involved in inflammation processes [100,102–107].

## 2.2. Other nucleotide-producing enzymes

If CD38 is now widely accepted as a cADPR- and NAADP-synthesizing enzyme, several studies have shown that other enzymes may also synthesize cADPR and/or NAADP. It appears that the mammalian CD38 shares 68% homology with the *Aplysia* cyclase, the first ADP-ribosyl cyclase identified from *A. californica*. The enzyme shares with CD38 its ability to produce cADPR [31,77,108–111] and NAADP through the base-exchange reaction [38,112]. In other invertebrates, an ADP-ribosyl cyclase has also been purified from *L. pictus* [113] and *Schistosoma mansoni* (trematode) [114]. In mammal neural cells, a CD38-independent ADP-ribosyl cyclase activity was also

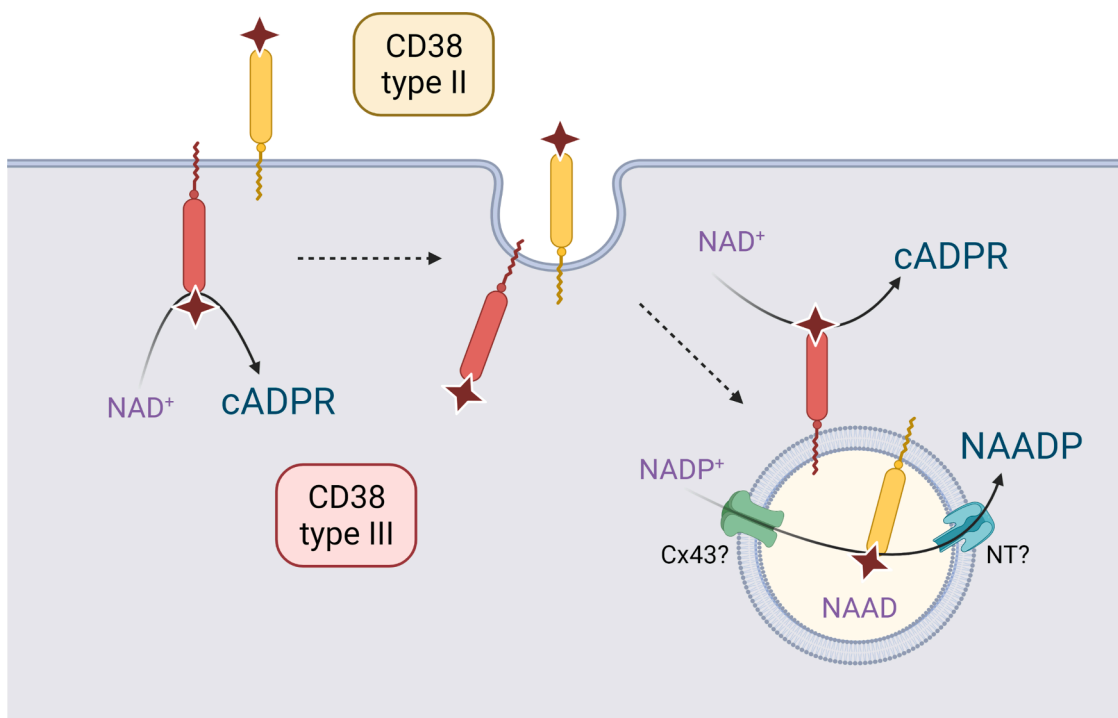
detected [95] which efficiently produced cADPR despite a low basal activity [115]. Since the discovery of the *A. californica* cyclase, other ADP-ribosyl cyclases have been identified in many species, including marine invertebrates, amphibians, birds, and zebrafish [116–118].

Another enzyme called CD157 (or BST-1 for bone marrow stromal cell antigen 1) also shares high homology with CD38 as it results from a duplication of the ancestor gene located on chromosome 4 in humans [119,120]. CD157 exhibits both the cyclase and hydrolase activity but not the base-exchange activity and appears to be several hundred-fold less efficient than CD38 at producing cADPR [121–126]. CD157 is highly expressed in the brain throughout the neonatal period and its expression notably decreases in adulthood [127–129].

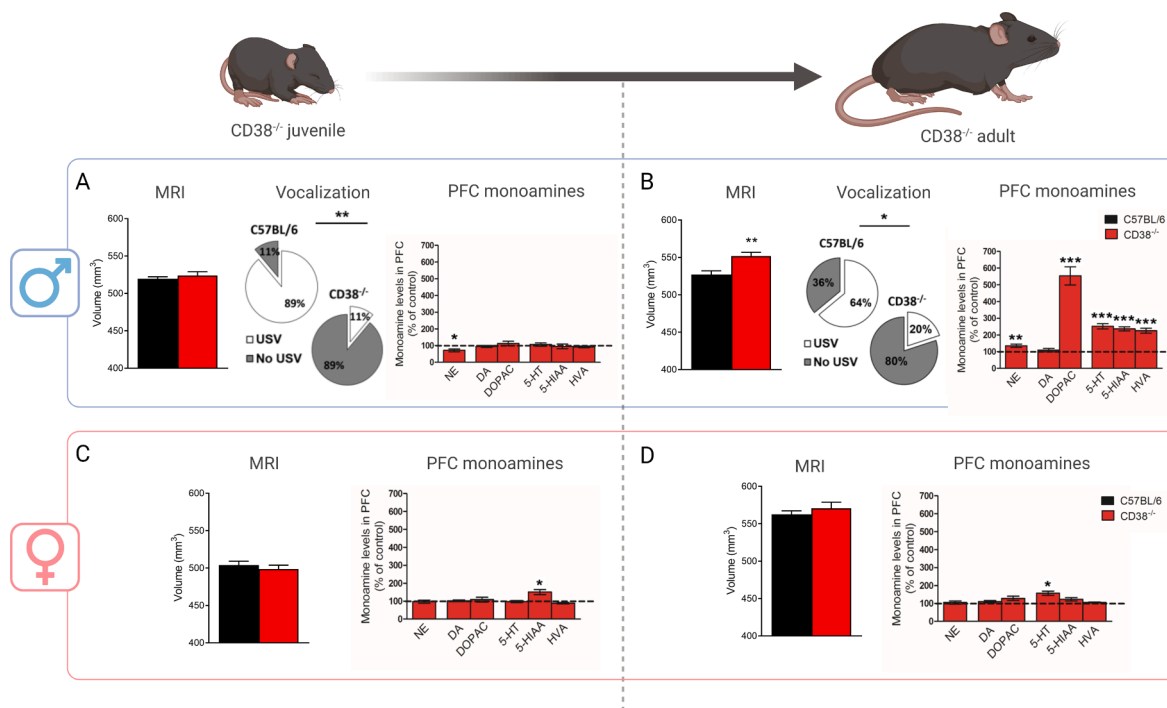
The enzyme SARM1 has been identified and shown to use NAD<sup>+</sup> as a substrate to produce ADPR and cADPR [130–132] and strikingly, could also produce NAADP from NADP<sup>+</sup> [133]. SARM1 is highly expressed in neurons and, so far, has been mostly studied in pathological conditions where deletion of SARM1 has proven to be beneficial for neuron survival [134,135]. Additionally, in lymphocytes T-cells, it has recently been proposed that the enzyme DUOX could also produce NAADP [136]. It is now of importance to better characterize these nucleotides producing enzymes, their regulation, and their cell-specific expression.

## 3. The cADPR-RyR signalling pathway

The messenger cADPR is known to release Ca<sup>2+</sup> from the ER by activating RyRs [30,49,137]. cADPR production in the brain occurs following the activation of G-protein coupled receptors (GPCR) such as the glutamatergic metabotropic receptor (mGluR) and the oxytocinergic receptor (OTR) [106,138].



**Fig. 3.** Scheme showing the co-expression of type II and type III CD38. The star-shaped symbol represents the catalytic site of the CD38 enzyme. Type II (in yellow) is internalized to provide the acidic conditions to produce NAADP [81,88]. Connexin 43 (Cx43) has been proposed to transport NAD<sup>+</sup>/NADP<sup>+</sup> into the endosomes [84,92]. The co-substrate NAAD is present in the acidic lumen of the endolysosomes [84]. In this model, the product NAADP is released into the cytosol by an unidentified nucleotidic transporter (NT).



**Fig. 4.** Gender- and age-specific effect of CD38 deletion on brain function. The left panel depicts results obtained in juvenile mice while the right panels depict results from adult mice. (B) Magnetic Resonance Imaging (MRI) reveals that adult male mice exhibit a macrocephaly compared with male juvenile (A) and female mice (C, D). During a free social interaction, ultrasonic vocalizations (USV) were recorded, in CD38<sup>-/-</sup> male mice (A, B) that emitted significantly fewer USVs compared with WT mice (A, B). The monoamine content of the prefrontal cortex (PFC) was measured and appears dramatically altered in adult male mice (B) compared with the limited changes observed in juvenile mice (A, C) and adult females (D). Abbreviations: NE, norepinephrine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid. (from [93]).

### 3.1. Neurons

As early as 1998, it was demonstrated that presynaptic injection of cADPR into neurons of the buccal ganglion of *A. californica* induces a presynaptic  $\text{Ca}^{2+}$  elevation that modulates acetylcholine release [139, 140]. In addition to its role in neurotransmitter release, cADPR also stimulates secretion of neuropeptides such as oxytocin and adrenocorticotropin [141, 142]. Using acute brain slice preparation, it has been shown that cADPR participates in both rat hippocampal neuronal long-term depression (LTD) induction [143], and the regulation of the neuronal firing activity of the rat dorsolateral geniculate nucleus [144]. Interestingly, a recent study has also shown a cADPR-dependent activation of TRPM2 that led to stellar neuron depolarisation and increased firing rate [145]. Finally, it appears that the cADPR pathway can form a positive feedback loop since it is also recruited during neuron depolarization through the opening of L-Type  $\text{Ca}^{2+}$  channels as proposed in *A. californica* buccal ganglion neurons [146]. In contrast, in rats, an inverse relationship was observed between cADPR brain levels and spatial learning ability assessed in the Morris water maze [147]. This effect could be related to the role of cADPR in LTD [143, 148] that is known to modulate learning ability (for review, [149]). cADPR has also been shown to be involved in the glutamatergic regulation of the circadian clock [150] and in the regulation of social behaviours by modulating the release of the prosocial neurohormone oxytocin [138, 142]. Finally, it has been proposed that CD38, through cADPR production, regulates neural proliferation and differentiation during development [151, 152] and modulates the dendritic organization in hippocampal neurons [153].

In line with the role of CD38 in development [107, 151–153] and the report of CD38 single nucleotide polymorphisms (SNPs) found in autistic patients [154], we recently demonstrated that CD38 deletion in mice led to neurodevelopmental alterations such as macrocephaly observed by magnetic resonance imaging (Fig. 4, [93]). Knowing that CD38 is involved in neural differentiation and microglial activation [103, 104, 107, 152, 155], we postulated that CD38 deletion may lead to impaired processes such as pruning or neuronal apoptosis. Interestingly, these features are found in autistic patients who typically exhibit a higher number of neurons [156] or spine density that could be due to pruning deficits [157–159] as well as modification in the size of brain structures [160–165]. We also described a progressive phenotype since the macrocephaly was not present in juvenile CD38<sup>-/-</sup> mice (Fig. 4). The first behavioural alterations observed were fewer vocalizations during an interaction in juvenile male CD38<sup>-/-</sup> mice, preceding the appearance of a more severe phenotype in adult male mice (Fig. 4, [93]). The adult phenotype is characterized by impaired social interactions and aggressiveness [93] as well as defects in maternal behaviour, social memory [142] and learning and spatial memory [166]. It has been proposed that such behavioural alterations are due to the lack of the prosocial hormone oxytocin in these mice [93, 142] but we further demonstrated that CD38 deletion also led to dramatic changes in monoamine levels in the prefrontal cortex (Fig. 4, [93]) which is a key structure for regulating social behaviours. The prefrontal cortex is regulated by both oxytocin and monoamine neurotransmitters such as 5-HT, dopamine and norepinephrine that modulate behavioural flexibility [167–172] as well as anxiety and aggressiveness [173–176]. Thus, the lack of oxytocin from the CD38<sup>-/-</sup> mice is not the sole neuromodulator that account for the behavioural alterations observed in these mice. We also demonstrated a role for CD38 in regulating the excitation/inhibition balance and the long-term potentiation (LTP) in the prefrontal cortex [93].

### 3.2. Glial cells

Astrocytes also have ADP ribosyl cyclase activity and highly express CD38 [107, 177]. In these cells, the addition of cADPR induces a cytosolic  $\text{Ca}^{2+}$  elevation that leads to the release of glutamate and GABA [99, 106]. It has also been shown that CD38, through its ability to produce

cADPR, regulates oligodendrocyte development [107]. Importantly, the role of cADPR in astrocytes has also been investigated in pathological contexts. In response to transient neuroinflammation, astrocytes are recruited and proliferate, to release numerous inflammatory components in concert with microglia, the immune cells of the CNS [178–183]. These astrocyte and microglial activations could then lead to neurotoxicity and neurodegeneration [184–186]. The microglial activation has been shown to depend on both CD38 and cADPR [103, 187] and the so-called “activated microglia” can enter the cell death program, a process also relying on CD38 and cADPR upregulation induced by lipopolysaccharides and interferon- $\gamma$  [103, 187, 188]. In activated astrocytes, CD38 is upregulated by interleukins and TNF $\alpha$  [100] and the resulting  $\text{Ca}^{2+}$  signalling generated is dependent on cADPR [189]. Similarly, it has been reported that the increase in the cytosolic  $\text{Ca}^{2+}$  concentration observed under hypoxia conditions in cultured astrocytes, is dependent on cADPR-evoked  $\text{Ca}^{2+}$  release from RyRs [190]. Finally, studies have recently demonstrated an intriguing role for CD38 and cADPR in enabling the transfer of functional mitochondria from astrocytes to neurons and back [191–193]. Such mitochondrial transfer has been suggested to be part of a protective mechanism promoting neuronal survival after a transient focal cerebral ischaemia [191].

## 4. NAADP-TPC signaling pathways molecule

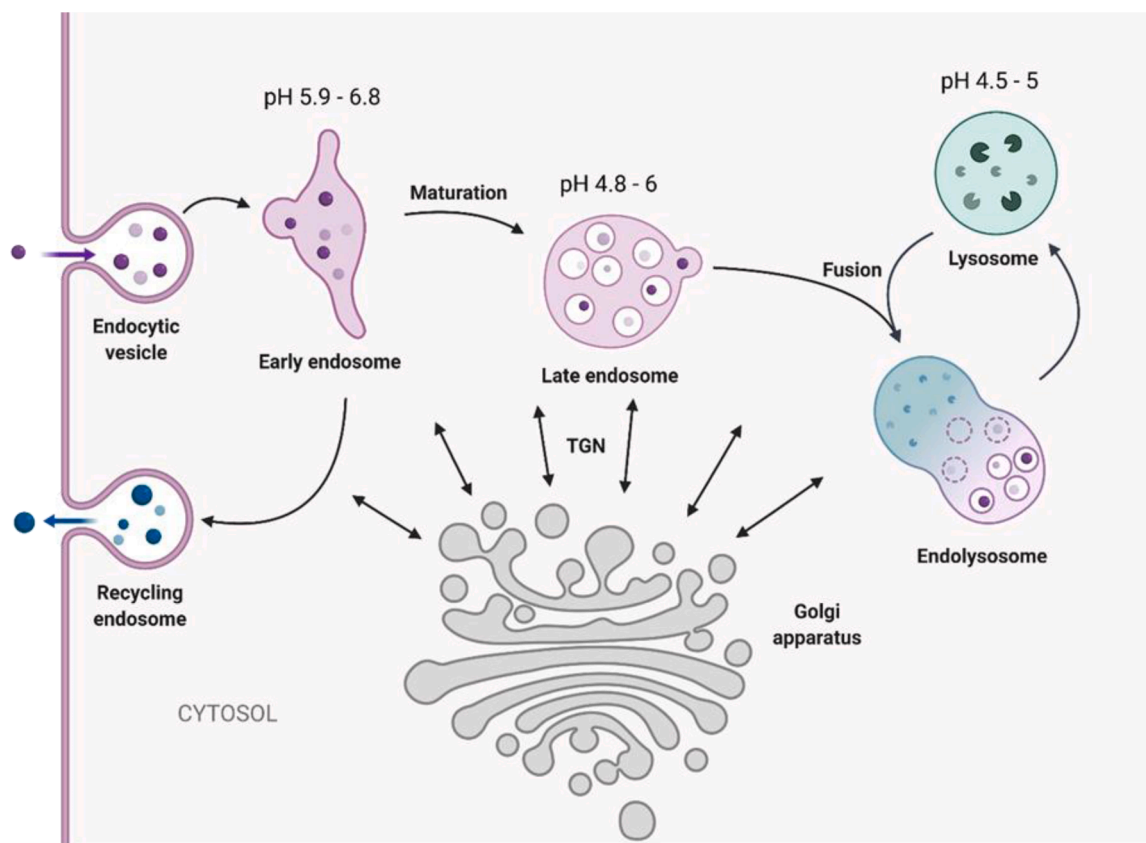
NAADP differs from cADPR by its ability to release  $\text{Ca}^{2+}$  not only from the ER but also from endosomes, lysosomes and other acidic organelles [46, 53, 60, 61, 194–199]. Notably, NAADP is now essentially described to mobilize  $\text{Ca}^{2+}$  through the opening of the endolysosomal TPCs, but it may also release  $\text{Ca}^{2+}$  from the ER and/or the nucleus by activating RyR and IP<sub>3</sub>R (for review [49, 53, 200, 201]). Of note, NAADP does not bind directly to TPCs or RyR, but it needs an accessory protein that has been sought for many years [202–207]. NAADP requires JPT2 to bind to TPC1 and RyR1 [69, 70] and it requires Lsm12 to bind to TPC1 and TPC2 [71]. So far, the physiological role of these two binding proteins in the brain is poorly understood.

### 4.1. Lysosomal $\text{Ca}^{2+}$ and organelle interactions

Since their discovery by de Duve [208], lysosomes have been viewed as degradative organelles containing proteases and other enzymes. And of course, this is true. Yet, it is quite reductive as we will see here. Lysosomes have long been known to be in every cell type of the brain such as neurons, astrocytes, or microglia [209–212]. In neurons, lysosomes are localized in axons [213–215], dendrites [216–218] and in the soma [213, 219, 220]. These strategic locations sustain the lysosomal-dependent cellular functions as described thereafter. The last years have seen a growing interest in lysosomal  $\text{Ca}^{2+}$  signalling especially in the brain where lysosomal dysfunctions are linked with numerous psychiatric and neurological diseases [221–228]. For instance, it has been shown that the endolysosomal LRRK2 kinase mutation involved in a familial form of Parkinson disease leads to TPC2 overactivation and lysosomal morphological defect [228, 229]. Another example of lysosomal disease is the mucopolisidosis IV associated with a mutation in the lysosomal TRPML channels that leads to severe psychomotor deficiency [230–233].

Endosomes are organelles formed both by the *trans*-Golgi budding and endocytosis of the plasma membrane (Fig. 5). They can mature to sort recycling proteins [234] and eventually fuse with the lysosome (Fig. 5) to degrade their non-recycling endocytic content [235, 236]. Both endosomes and lysosomes (here called endolysosomes) are acidic organelles (pH 4.8–6 and 4.5–5 respectively) that acidify due to the presence of an H<sup>+</sup>-ATPase pump on their membrane [237, 238].

Lysosomes are complex organelles containing a large variety of enzymes, ion channels and transporters and ions (H<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>) that sustain various intracellular signalling functions [238, 240]. The lysosomal luminal  $\text{Ca}^{2+}$  concentration is high (~500  $\mu\text{M}$ ) and comparable



**Fig. 5. Schematic drawing of endolysosomal traffic and maturation.** Early endosomes are formed by endocytosis of the plasma membrane or by budding from the Golgi apparatus. Endosomes could either be recycled to the plasma membrane or mature into late endosomes that aim to fuse with lysosomes. Abbreviations: TGN, Trans Golgi network (Adapted from [239]).

with the ER  $\text{Ca}^{2+}$  content [225,241–244]. However, the  $\text{Ca}^{2+}$  refilling mechanisms that maintain such luminal concentration remain to be identified. Luminal  $\text{Ca}^{2+}$  is regulated in lysosomes, either through an ion transporter or an ion exchanger. Indeed, CAX, a  $\text{Ca}^{2+}/\text{H}^{+}$  exchanger that uses the high  $\text{H}^{+}$  gradient to counter transport  $\text{Ca}^{2+}$  in acidic organelles has been identified in yeast and plant cells [245] and some animal cells of lower vertebrates such as *Xenopus* neural crest cells [246]. It has also been shown that lysosomes express the S/ER  $\text{Ca}^{2+}$ -ATPase 3 (SERCA3) but, until now, this has only been observed in human platelets [247, 248]. Additionally,  $\text{Ca}^{2+}$  refilling of lysosomes may also require interaction with various cell compartments. Notably, some studies suggest that lysosomes require the ER  $\text{Ca}^{2+}$  store to refill. For example, studies have shown that lysosomes sequester the  $\text{Ca}^{2+}$  released by the  $\text{IP}_3\text{R}$  opening which requires an intact ER  $\text{Ca}^{2+}$  pool [223,249–253] and recently, it has been proposed that the  $\text{Ca}^{2+}$  sensor STIM1 (stromal interaction molecule) regulates lysosomal-ER coupling in cortical neurons [223,254]. Lysosomes form contact sites with other organelles by close apposition ( $\sim 30$  nm) and it has been reported that 50% of early endosome and 95% of lysosomes are in contact with the ER [255–258]. However, these values are not set in stone as lysosomes are highly mobile in the cell [259–263]. These studies demonstrate that lysosomes may interact with the ER, either to reuptake  $\text{Ca}^{2+}$  or to fulfil more complex functions. Remarkably, physical [258,264] and functional contacts between lysosomes and mitochondria have also been described and notably a  $\text{Ca}^{2+}$  flux exchange has been shown between these two organelles [265]. These interactions appear to be crucial, for instance, for regulating energy metabolism [266–268]. Disruption in mitochondrial-lysosomal interactions may also be involved in diseases such as Niemann-Pick disease [269] or Parkinson's disease [270–272]. Finally, contact sites between lysosomes and the plasma membrane have also been described [273] and seem important in membrane repair

processes [274–278] and for regulation of spine morphology in neurons [217]. Additionally, it has been proposed that lysosomal  $\text{Ca}^{2+}$  facilitates  $\text{Ca}^{2+}$  influx through the opening of several plasma membrane channels such as N-type  $\text{Ca}^{2+}$  channels in the hippocampus [279] and Orai1 in various cell lines [280–283].

How lysosomal  $\text{Ca}^{2+}$  is mobilized is currently an active field of research and numerous channels and enzymes have been identified and described elsewhere [284]. Most studies aiming to understand the role of TPCs were conducted in peripheral cells of mice and zebrafish, such as in smooth muscle myocytes [285], ventricular myocardium [286], superficial slow muscle cells in the trunk of zebrafish [287,288], T-cell [289], embryonic stem cells [290] or platelets [291] to cite a few (for review, [201,292]). It was only in 2018 that the first study on TPCs was conducted in neurons [293]. The next section will describe some aspects of the lysosomal channel TPC, its structure and properties, what we know about the cellular roles of NAADP and TPCs, and which lessons could be drawn for brain studies.

#### 4.2. TPC structure & biochemical properties

Three isoforms of TPCs have been characterized: TPC1, TPC2, and TPC3 (*Tpcn* for gene name) and exhibit different distribution patterns based on a dileucine motif at their N-terminal end [294]. TPC1 and TPC3 are mainly expressed on endosomes (recycling endosome, early endosome, and late endosome) while TPC2 is preferentially expressed on late endosomal- and lysosomal membranes [66–68,200,295]. The gene encoding TPC3 (*Tpcn3*) is absent or incomplete (pseudogene) in mice, rats, primates, and humans [296]. The two genes *Tpcn1* and *Tpcn2* are encoded on distinct chromosomes: in the region 12q24.13 for human *Tpcn1* and 11q13.3 for human *Tpcn2*.

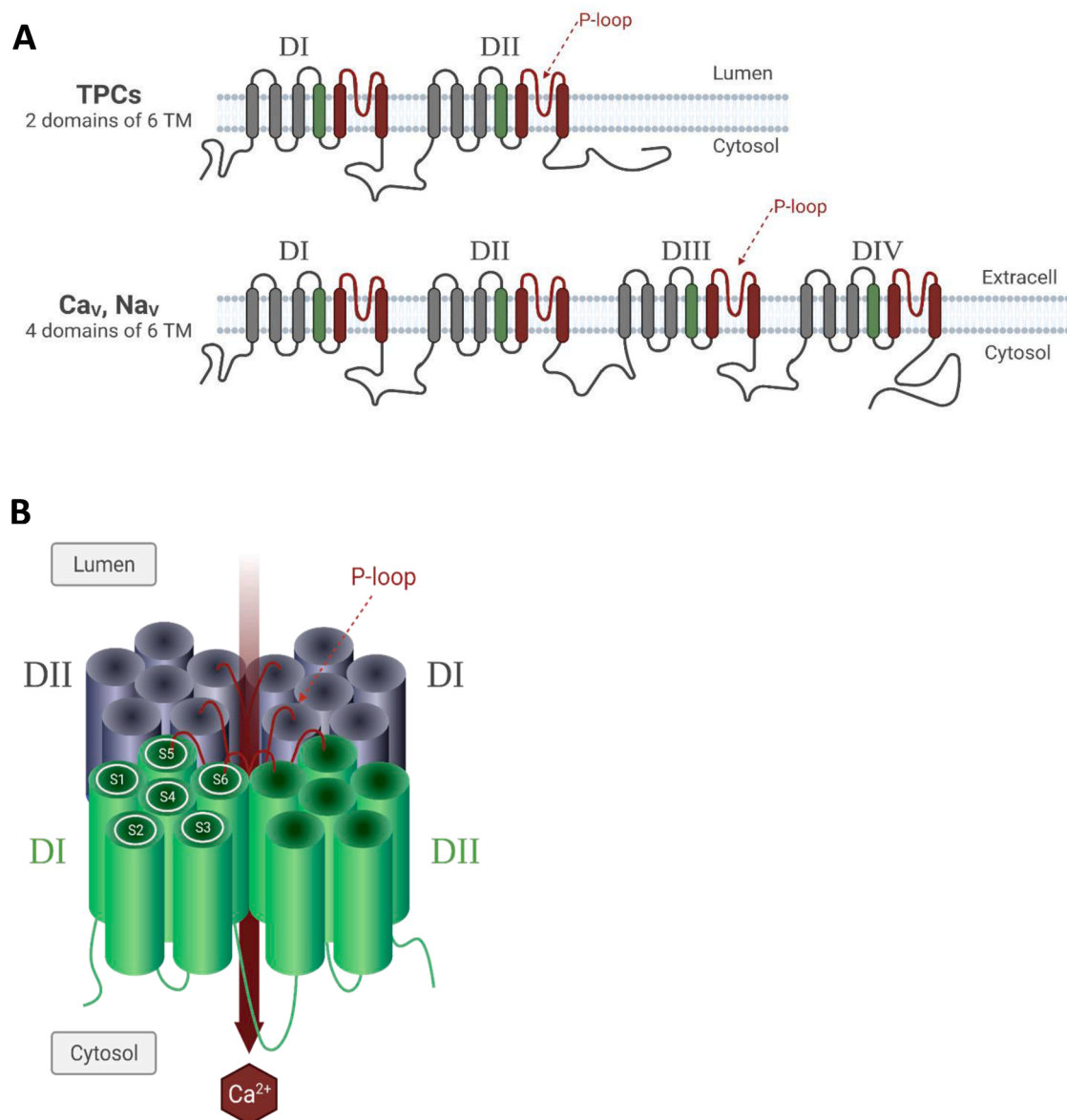
TPCs are ancient ion channels found in very different species from

plants to mammals and have been proposed to have a common ancestor with  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  channels [297–301]. Like voltage-gated cation channels ( $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  VGCs), TPCs are composed of six transmembrane segments forming a domain. But, instead of being assembled as four domains like VGCs, only two domains are linked in TPCs (Fig. 6) [297]. The name “two-pore” channel comes from their structure. In each domain, between the transmembrane segment 5 and 6, there is a “P-loop” (Fig. 6) that could also be called a “pore domain” even if a single p-loop is not sufficient to form the ion-permeant pore in a membrane. To form such a pore, two subunits of TPCs need to assemble as a dimer leading to a four-domain structure (Fig. 6). In accordance with the similarity with  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  VGCs, TPCs are also voltage-sensitive [300,302]. This voltage sensitivity is provided by the transmembrane segments 4 and 10 but is not required for channel opening [303]. TPC1 and TPC3 are particularly sensitive to the voltage which may modulate the affinity for NAADP but, surprisingly, TPC2 appears to be mostly

voltage-insensitive [304,305]. Of note, TPCs are nonselective cation channels for which the ion preference conductance have been long debated [268,302,304,306–310]. If the ion selectivity of TPC1 and TPC2 may vary depending on experimental conditions, nowadays, it is quite well accepted that TPC1 is rather  $\text{H}^{+}$  selective ( $\text{H}^{+} \gg \text{K}^{+} > \text{Na}^{+} > \text{Ca}^{2+}$ ) whereas TPC2 is rather  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  selective [50,305,307,308, 310–313]. Discrepancies about the ion selectivity of TPC2 (for review [314]) lasted for a decade and can now be explained by a peculiarity of TPCs. They can be activated by two different agonists, namely  $\text{PI}(3, 5)\text{P}_2$  and NAADP that respectively leads to  $\text{Na}^{+}$ - or  $\text{Ca}^{2+}$ -current activation [310]. This interesting property will be further described in the following section about pharmacological tools.

#### 4.3. Pharmacological tools

To target the NAADP pathway, diverse strategies are available. We



**Fig. 6.** TPCs and voltage-gated cation channels structures. A) High structural similarity between voltage-sensitive ion channels since TPCs are composed of 2 domains (DI and DII) containing 6 transmembrane segments (TM) and  $\text{Ca}^{2+}$ - and  $\text{Na}^{+}$  voltage-gated channels are formed by 4 domains of 6-TM. The 4th segment (in green) is charged and confers the ionic selectivity. Between the 5th and 6th segments (in red), the P-loops form the pore of the channel. B) 3-dimensional structure of TPCs assembled in dimer (one in green and the other in grey). Such dimer forms the functional 4-domain channel. In dark red, the p-loops between each transmembrane segments 5 and 6 form the pore of the channel.



could either target the receptor (i.e., the channel), the producing enzyme or the  $\text{Ca}^{2+}$  stores recruited. Interestingly, activation of GPCR by diverse agonists such as cholecystokinin [81,315], histamine [316], interleukin 8 [82], thrombin [317],  $\beta$ -adrenergic stimulation [318], and metabotropic glutamatergic receptors (mGluR) [198,293,319] induces NAADP production. Besides measuring the changes in endogenous levels of NAADP following cell activation by extracellular hormones or neurotransmitters, the role of NAADP in agonist-evoked  $\text{Ca}^{2+}$  response has been also investigated. These investigations took advantage of the biphasic property of NAADP which releases  $\text{Ca}^{2+}$  at low nanomolar range concentrations (5–100 nM) whereas, at a high micromolar range (10–100  $\mu\text{M}$ ), NAADP shows a self-desensitization property [46,47,194,293]. More recently various studies used Ned-19, a permeant NAADP antagonist, in addition to NAADP [293,320–325]. Most of the reports also concomitantly used pharmacological tools to disrupt the lysosomal  $\text{Ca}^{2+}$  store either with the lysosomotropic agent, GPN (glycyl-L-phenylalanine-beta-naphthylamide) that disrupts the lysosome or with the  $\text{H}^{+}$ -ATPase inhibitor, bafilomycin A1 [60,61,81,194,293,318,321,324–328] (Fig. 7). Alternatively, researchers have also used mutant mice such as  $\text{CD38}^{-/-}$  [93,94] or  $\text{TPC1/2}^{-/-}$  mice [293,329] as well as mutant zebrafish [330,331] for studying the role of this pathway in neural cells.

However, NAADP has been shown to target not only TPCs but also RyR and therefore to further investigate the role of the NAADP/TPC pathway, selective agonists and antagonists of TPCs are crucially needed. Many years before the discovery of TPCs as being an NAADP target, Genazzani *et al.* discovered that a high concentration of L-type  $\text{Ca}^{2+}$  blockers completely abolishes NAADP-evoked  $\text{Ca}^{2+}$  release, thus suggesting that the NAADP sensitive  $\text{Ca}^{2+}$ -channel could be related to L-type  $\text{Ca}^{2+}$  channels [332]. The discovery of TPCs' structure has proven that the presumption of Genazzani *et al.*, was correct (see "TPC structure and biochemical properties"). The structural homology between TPCs and voltage-gated channels (Fig. 6) is the basis of their common sensitivity to VGCs blockers as summarized in Table 1. Recent years have seen the description of a growing number of various blockers targeting TPCs, such as tricyclic antidepressants, anaesthetics or dihydropyridines (Table 1). Due to their poor selectivity, such molecules should be used with caution to study TPCs' functions. However, it is of crucial

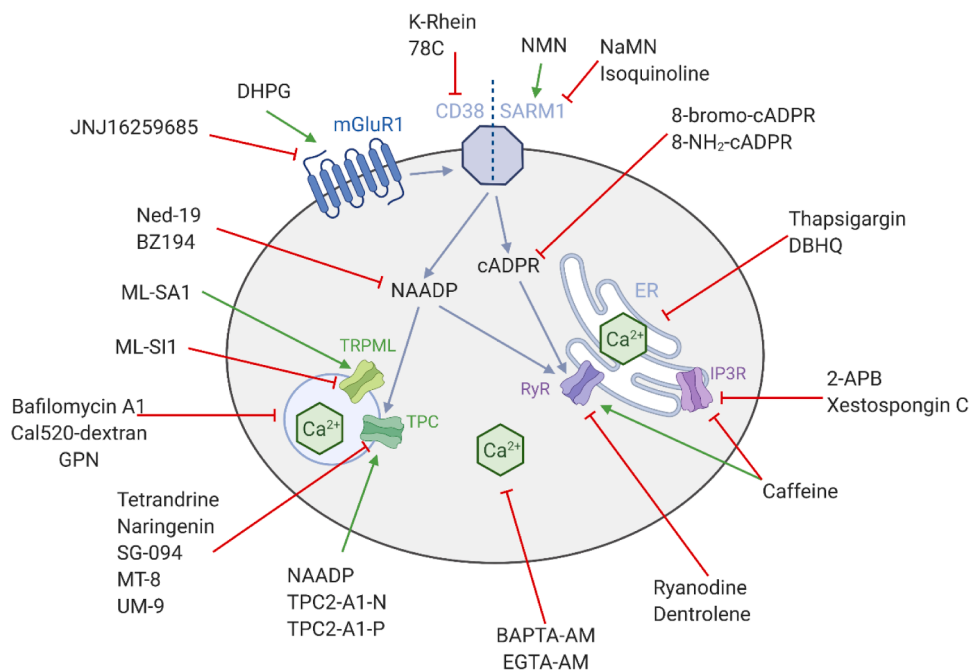
importance that studies using these drugs for other purposes consider the possibility of off-target effects on TPCs to fully interpret the data. To facilitate TPC research, selective pharmacological tools need to be developed. In this respect, a recent study has described new promising inhibitors that preferentially target TPC2 such as SG-094 [333,334] that could be a highly valuable addition to the mostly commonly used non-selective TPC inhibitors such as tetrandrine [335] and naringenin [336]. Not only is it important to block TPCs, but it is also important to selectively activate TPCs to elucidate their functions, and lately, Gerndt *et al.* successfully identified two TPC2 agonists: TPC2-A1-N and TPC2-A1-P [310]. In the meantime, the study revealed that TPC2-A1-N and TPC2-A1-P likely bind to different sites on TPC2 and control the ion selectivity of this channel. The authors demonstrated that TPC2-A1-N mimicking NAADP favoured the  $\text{Ca}^{2+}$  conductance by inducing  $\text{Ca}^{2+}$  release from endolysosomes whereas TPC2-A1-P mimicking  $\text{PI}(3, 5)\text{P}_2$  preferentially activates the  $\text{Na}^{+}$  conductance of TPC2 [310]. These TPC2 agonists (Fig. 7) were identified very recently and should greatly facilitate the study of TPCs in the field for the coming years [310].

#### 4.4. Lysosome and TPC, the local $\text{Ca}^{2+}$ signal trigger

Using various pharmacological tools and genetic deletion of TPCs, several studies have begun to unravel the cellular functions of the TPCs. As previously mentioned in the "Lysosomal  $\text{Ca}^{2+}$ " section, lysosomes often couple to the ER to generate a  $\text{Ca}^{2+}$  signal in response to physiological agonists. During lysosome-ER coupling, the ER  $\text{Ca}^{2+}$  is released by CICR following a primary lysosomal  $\text{Ca}^{2+}$  release called a trigger [49,50,370] as illustrated in Fig. 8.

Of note, similarly to  $\text{IP}_3\text{R}$  and  $\text{RyR}$ , TPCs could be directly activated by  $\text{Ca}^{2+}$  [302–304,312,372]. Thus, NAADP may be a modulator of a positive  $\text{Ca}^{2+}$  feedback loop by activating both TPCs and  $\text{RyR}$  (Fig. 9), a mechanism relying on  $\text{Ca}^{2+}$  microdomains. Indeed, several studies have shown that NAADP-evoked  $\text{Ca}^{2+}$  signalling occurred at "discrete trigger areas" [46,60,196,256,257,373–377,417]. The role of TPCs in these  $\text{Ca}^{2+}$  microdomains has been subsequently demonstrated [66,256,370] and these microdomains represent a trigger for CICR to induce a larger  $\text{Ca}^{2+}$  response from the ER [51,66,378,379].

The interaction between lysosomal TPCs and the ER controls



**Fig. 7. Pharmacology of TPC signalling pathway and affiliated pathways.** Red lines represent an inhibitory effect. Green arrows represent agonistic effect. Abbreviations and references are in table 1.

**Table 1**  
Pharmacological components of the intracellular Ca<sup>2+</sup> signalling components.

Target	Component	Action	Notes	Ref
mGluR1	DHPG ((S)-3,5-Dihydroxyphenylglycine)	+		[337]
	JNJ16259685	-		[338]
CD38	IL-8 (interleukin-8)	+		[339]
	ATRA ( <i>all-trans</i> retinoic acid)	+	Active metabolite of vitamin A - Induce CD38 expression	[340, 341]
	K-Rhein	-		[342]
	78C	-		[343]
SARM1	NAD <sup>+</sup>	-	Substrate and self-inhibitory binding site of SAMR1.	[344]
	NMN (nicotinamide mononucleotide)	+		[345, 346]
	CZ-48	+	NMN mimetic.	[133]
	NaMN (Nicotinic acid mononucleotide)	-		[347]
	Isoquinoline	-		[348]
cADPR	8-bromo-cADPR	-	Membrane permeant.	[349]
	8-NH <sub>2</sub> -cADPR	-	Membrane non-permeant.	[349, 350]
ER	Thapsigargin	-	Inhibit SERCA pump leading to Ca <sup>2+</sup> leak and ultimately to empty the ER store.	[351]
	DBHQ (2,5-Di( <i>tert</i> -butyl)-1,4-benzohydroquinone)	-	Inhibit SERCA pump leading to Ca <sup>2+</sup> leak and ultimately to empty the ER store.	[352]
	Cyclopiiazonic acid	-	Inhibit SERCA pump pump leading to Ca <sup>2+</sup> leak and ultimately to empty the ER store.	[353, 354]
IP <sub>3</sub> R	2-APB (2-aminoethoxydiphenyl borate)	-	Inhibit TRP channels too.	[355]
	Xestospongins C	-		[356]
	Caffeine	-		[357]
RyR	Caffeine	+		[358]
	Ryanodine	-		[12]
	Dantrolene	-		[359]
Free Ca <sup>2+</sup>	BAPTA	-	Fast chelator	[360, 361]
	EGTA	-	Slow chelator	[362, 363]
NAADP	Ned-19	-		[320]
	BZ194	-	Inhibit NAADP action on RyR1	[59]
	NAADP	-	Self-inhibition at high concentration (10–100 μM)	[46]
TRPML	ML-SA1	+		[364]
	ML-SI1	-		[365]
Lysosome	Bafilomycin A1	-	Inhibitor of the H <sup>+</sup> -ATPase leading to a leak in lysosomal Ca <sup>2+</sup>	[366]
	Cal-520-dextran	-	Ca <sup>2+</sup> chelator of the lysosomal lumen	[367]
	GPN (Glycyl-L-phenylalanine 2-naphthylamide)	-	Causes osmotic change leading to the rupture of the	[368]

**Table 1 (continued)**

Target	Component	Action	Notes	Ref
			lysosomal membrane	
TPC1 & TPC2	Tetrandrine	-	Clinically used as anti-inflammatory and anti-fibrogenic. Also used to block the entry of the Ebola virus in the cell	[335]
	SG-005	-	Derived from tetrandrine – As potent as tetrandrine to inhibit TPC2.	[334]
	NAADP	+	Inhibit TRPML1 and TPC1 too. Preferentially trigger Ca <sup>2+</sup> release under 5–100nM	[66–68]
	PI(3, 5)P2	+	Preferentially conducts Na <sup>+</sup> current	[308]
TPC2	TPC2-A1-N	+	Drives Ca <sup>2+</sup> current	[310]
	TPC2-A1-P	+	Drives Na <sup>+</sup> current	[310]
	Riluzole	+	Clinically used to treat amyotrophic lateral sclerosis	[305]
	Naringenin	-		[336]
	SG-094	-	Derived from tetrandrine – More potent than tetrandrine - No considerable inhibitory effect on TRPML1	[334]
	Pratensein (MT-08)	-	O-methylated isoflavone extract from <i>Dalbergia parviflora</i> (Akar Laka). Suggested anti-cancer effect	[333]
	Duartin (UM-09)	-	Tri-O-methylated isoflavan extract from <i>Kaempferia parviflora</i> (Thai ginseng). Suggested anti-cancer effect	[333]
	Raloxifene	-	Selective estrogen receptor modulators	[369]
	Clomiphene	-	Selective estrogen receptor modulators. Only partially blocks NAADP Ca <sup>2+</sup> response	[369]
	Fluphenazine	-	Dopamine receptor antagonist	[369]
	Pimozide	-	Dopamine receptor antagonist	[369]
	Tricyclic antidepressant (amitriptyline, clomipramine, chlorpromazine, desipramine, imipramine, nortriptyline, triflupromazine)	+	Clinically used as an antidepressant. Believed to act on neurotransmitter transporters or voltage-gated Na <sup>+</sup> channels	[305]
TPC1		-	Clinically used as an antidepressant.	[305]

(continued on next page)

Table 1 (continued)

Target	Component	Action	Notes	Ref
	Tricyclic antidepressant (clomipramine, chlorpromazine)		Believed to act on neurotransmitter transporters or voltage-gated Na <sup>+</sup> channels	
Ca <sub>L</sub> & TPC	Dihydropyridines (Felodipine, Amlodipine, Isradipine, Nifedipine, Nimodipine, Nitrendipine, Oxodipine)	-	Clinically used against hypertension	[300, 332]
	BayK 8644	+		[332]
	Bepridil	-	Once used to treat angina	[369]
	Verapamil	-	Clinically used to treat high blood pressure, angina and tachycardia	[300, 332]
Ca <sub>V</sub> & TPC	Diltiazem	-	Clinically used to treat high blood pressure, angina and tachycardia	[300, 332]
Na <sub>V</sub> & TPC	Veratridine	-	An alkaloid that simultaneously opens voltage dependant Na <sup>+</sup> channels, blocks Na <sup>+</sup> channel activation and induces Ca <sup>2+</sup> influx	[300]
	Amide (benzocaine, bupivacaine, dibucaine, etidocaine, lidocaine, mepivacaine, prilocaine, procaine, tetracaine, trimecaine)	-	Commonly used as local anaesthetics	[300]

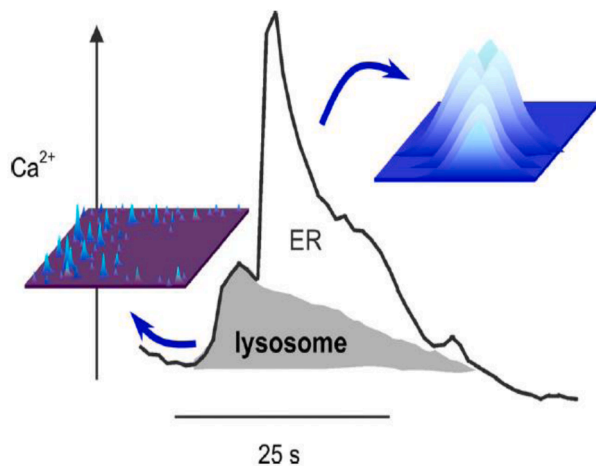


Fig. 8. Diagram showing the local lysosomal Ca<sup>2+</sup> amplified by the ER into a global Ca<sup>2+</sup> signal. The primary Ca<sup>2+</sup> release from lysosomes (in grey) triggers a subsequent release of Ca<sup>2+</sup> from the ER (from [371]).

secretion events such as the hormonal pancreatic release [66,380], cytotoxic T lymphocyte granule exocytosis [289] and mast cell histamine release [381]. The lysosomal TPC-ER interactions are also important regulators of endolysosomal trafficking, maturation, and fusion events [295,382–384] and have also been described to regulate smooth muscle contraction and  $\beta$ -adrenergic modulation of cardiomyocyte contractility [323,376] and in endothelial-colony forming cells [385].

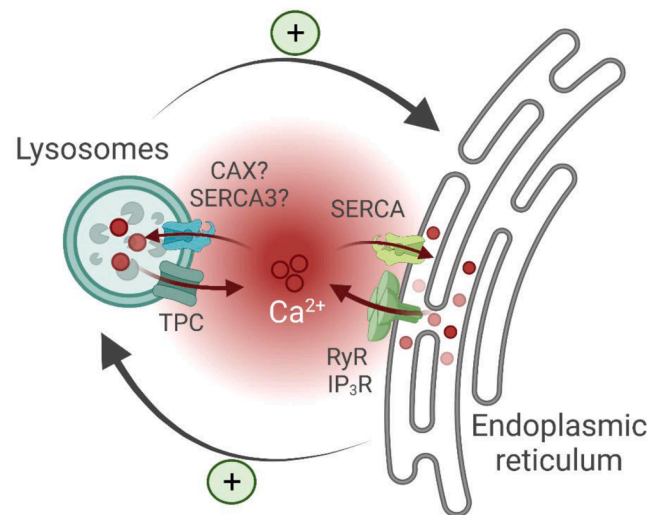


Fig. 9. Representation of endolysosomal traffic and interactions with the ER. Endolysosomes closely interact with RyR and IP<sub>3</sub>R where Ca<sup>2+</sup> release from TPCs triggers Ca<sup>2+</sup> mobilization from the ER. Such lysosome-ER interaction is also required to replenish the Ca<sup>2+</sup> stores. The Ca<sup>2+</sup>/H<sup>+</sup> exchanger (CAX) that pumps the Ca<sup>2+</sup> back into the lysosomal lumen has not been clearly identified yet in mammals. Similarly, the lysosomal SERCA3 pump has been only observed in human platelets.

#### 4.5. Neuronal roles

Limited information exists about the role of NAADP and TPCs in the brain. An important study has described NAADP binding sites in rat whole brain regions, suggesting a prominent role of NAADP in the nervous system [386]. It is well known that mammalian neurons express both CD38 and SARM1, two enzymes that likely produce NAADP in neurons [27,38,133], and the endogenous cellular content of NAADP can be modulated by various physiological agonists such as glutamate [198,293,387]. Because glutamate is one of the most abundant neurotransmitters in the brain, the role of mGluR activation in NAADP production [198,387] has been further investigated and it appears that mGluR1 preferentially triggers the synthesis of NAADP in hippocampal neurons of mice [293]. In peripheral organs, hormones shown to stimulate NAADP synthesis include cholecystokinin [81] and oxytocin [388], two hormones showing receptors in the brain. For example, in the rat uterus, the binding of oxytocin to its receptor (OTR) induces an increase in endogenous NAADP levels and releases lysosomal Ca<sup>2+</sup> to induce myometrial contraction [388]. Interestingly, OTR is widely expressed in the brain, but whether oxytocin induces NAADP production in the central nervous system has not yet been investigated. In the hypothalamus and pituitary gland, it has been suggested that OTR activation recruits CD38 and increases cADPR synthesis [138]. Interestingly, in these hypothalamic neurons, a positive autocrine feedback loop has been proposed in which cADPR produced in response to OTR activation is involved in additional oxytocin release from oxytocinergic neurons [138,142]. Intriguingly, exogenous addition of NAADP does not stimulate oxytocin secretion by itself in permeabilized neurons [142] whereas in other cell systems such as in the pancreas, NAADP and cADPR combine to control hormone and enzyme secretion [194,373,389]. So far, whether OTR signalling requires NAADP synthesis and lysosomal Ca<sup>2+</sup> in hypothalamic neurons remain to be investigated.

Regarding NAADP action in neurons, several studies have injected NAADP and showed that in *A. californica* neurons [140] and neuromuscular junctions in frogs [390,391], NAADP induces cytosolic Ca<sup>2+</sup> elevation and controls the secretion of acetylcholine. To sustain this neurotransmitter release, it was proposed that NAADP triggers Ca<sup>2+</sup>

from an unidentified store interacting with the ER [49,140,390,391]. The presynaptic effect of NAADP could be due to the presence of both ER and lysosomes in presynaptic terminals [392]. At a post-synaptic level, lysosomes are also present and could be exocytosed to release cathepsin and activate metalloprotease 9 (MMP9) which regulates structural plasticity of the dendritic spines in hippocampal neurons [217]. In this study, the authors demonstrated that the  $\text{Ca}^{2+}$  response evoked by back-propagating action potentials not only requires extracellular  $\text{Ca}^{2+}$  influx but also involves the lysosomal  $\text{Ca}^{2+}$  stores and NAADP [217]. These results suggest a role for lysosomes and NAADP signalling in long-term plasticity [217]. Exogenous addition of NAADP-containing liposomes have been shown to depolarize medullary neurons [67] and recently, a study proposed that TPCs play a key role in neuronal depolarization [293]. The authors recorded hippocampal neurons and showed that NAADP intracellular injection evoked depolarization of hippocampal neurons. Using a pharmacological approach, they showed that NAADP recruits both lysosomes and ER to generate this depolarizing effect. Importantly, the study elucidated the long-sought mechanism of mGluR1-induced neuronal depolarization. Indeed, they demonstrated that inhibition of NAADP signalling with either NAADP inhibitors or lysosomal disruptors abolished the mGluR1-induced cell depolarization [293]. The authors further proposed that the mGluR1-induced depolarization is mediated through the sequential activation of TPC2 and RyRs [293]. The  $\text{Ca}^{2+}$  released then inhibits the  $\text{Ca}^{2+}$ -sensitive SK channels in the plasma membrane, probably by activating the  $\text{Ca}^{2+}$ -dependent protein phosphatase 2A [293] that forms a macromolecular complex with SK channels [393,394]. The authors proposed that this mechanism might help to understand how mGluR1 can produce both synaptic potentiation and synaptic depression.

In addition to the effects of NAADP on adult neurons, CD38 is also greatly expressed at early developmental stages [95] suggesting a potential role for NAADP in neuronal development. Indeed, the addition of NAADP-containing liposomes induces neuronal differentiation in PC12 cell lines [395] and neurite outgrowth in cultures of rat cortical neurons [195]. Furthermore, using both exogenous cell-permeant NAADP-AM, and TPC2<sup>-/-</sup> mice, a study has shown that the neuronal differentiation of mouse embryonic stem cells occurs through TPC2 [290]. Recently, *in vivo* evidence has been reported for a neurodevelopmental role of NAADP and TPCs in the CNS development. Indeed, in zebrafishes, TPC2 are required for  $\text{Ca}^{2+}$  transients frequency involved in normal spinal circuitry maturation and in particular in the regulation of primary motor neuron innervation of the skeletal musculature by regulating the establishment of synchronized activity once innervation has taken place [330,331] (for review [292]).

#### 4.6. Glial roles

In glial cells, a few studies are available relating to the role of NAADP and TPCs. It has been reported that CD38 [96,99–102,326], lysosomes [209,210] and TPCs are present [324] in astrocytes. With regard to NAADP, it appears that intracellular NAADP mobilizes  $\text{Ca}^{2+}$  from lysosomes in astrocytes [324,326,327] whereas extracellular addition of NAADP can mobilize  $\text{Ca}^{2+}$  in rat astrocytes through activation of plasma membrane purinergic P2Y receptors [326,396]. On the other hand, it has been proposed that the astrocytic endogenous NAADP level is regulated by purinergic receptors activated by ATP as well as endothelin-1 [327]. This NAADP releases  $\text{Ca}^{2+}$  from “lysosome-related  $\text{Ca}^{2+}$  stores” [327], raising the potential of a role for TPCs such as demonstrated by Pereira *et al.* in astrocytic autophagy [324,387]. The authors demonstrated that intracellular microinjection of NAADP in cultured astrocytes evoked the release of lysosomal  $\text{Ca}^{2+}$  that subsequently stimulated autophagic vacuole formation. Using either overexpression of TPC2 or a dead-pore mutated TPC2, they further demonstrated that the NAADP-induced  $\text{Ca}^{2+}$  response relies on TPC2 [324]. The role of TPCs in autophagy has been also shown in peripheral cells [397–399] and cultured cells [400,401]. Overall, it has been

proposed that TPCs could be an ATP-sensor [268] and are inhibited by both ATP, and mTOR, an autophagic regulator [202,268,398,399]. Interestingly, mTOR is tethered to lysosomal membranes [402–404] and could inhibit both the  $\text{PI}(3, 5)\text{P}_2\text{-Na}^+$  [268] and the NAADP- $\text{Ca}^{2+}$  currents of TPCs [399]. The role of TPCs in autophagy in astrocytes and neurons is poorly understood and requires further study.

#### 4.7. Endothelial roles

Regional brain blood supply matches local metabolic demand and requires local vasodilation in active region [405–407]. These processes depend on interactions between endothelial cells and neurons. Endothelial cells have lysosomes [408] and their role in agonist-evoked  $\text{Ca}^{2+}$  signalling has been well-studied. One of the first study was published by Brailoiu's group which demonstrated that in endothelial cells, NAADP evokes  $\text{Ca}^{2+}$  release from lysosomes and also stimulates nitric oxide (NO) production to control blood pressure [409]. Filippini's group in a seminal study has demonstrated the role of NAADP and TPC2 in VEGF2-evoked  $\text{Ca}^{2+}$  release, NO production and neoangiogenesis [321]. Regarding brain endothelial cells, it has been shown that glutamate is one of the signalling molecules that acts on N-methyl-D-aspartate receptors (NMDARs) and mGluR located at the surface of endothelial cells [406,410]. Glutamate triggers the production of NO in a  $\text{Ca}^{2+}$ -dependent manner and NO eventually acts as a vasodilator agent. However, by which mechanism glutamate activation led to intracellular  $\text{Ca}^{2+}$  signals is poorly understood. Using various pharmacological tools in human and rodent brain microvascular endothelial cell lines, recent studies have proposed that glutamate, recruits  $\text{IP}_3$  and NAADP signalling pathways as well as the lysosomal  $\text{Ca}^{2+}$  stores to evoke  $\text{Ca}^{2+}$  release and NO production [411–413]. Similarly, NAADP and lysosomal  $\text{Ca}^{2+}$  are recruited by acetylcholine and histamine to stimulate endothelial NO production [410,414]. At this point, it would be valuable to now explore the role of TPCs in brain microvascular endothelial cells as well as to identify the enzyme that may produce NAADP in response to physiological stimulation.

### 5. Unanswered questions

Lysosomes have emerged in the last decade as an important hub between metabolism and  $\text{Ca}^{2+}$  signalling. Indeed, lysosomes have been mostly studied in regard to their degradative property and their involvement in numerous diseases link to cell degeneration. Most recently studies of  $\text{Ca}^{2+}$  signalling have demonstrated that lysosomes and the related acidic organelles are important sources of intracellular  $\text{Ca}^{2+}$  involved in cell proliferation, autophagy and secretion to name a few. Questioning how the lysosomal  $\text{Ca}^{2+}$  could be mobilized, researchers have discovered numerous endolysosomal  $\text{Ca}^{2+}$  channels, such as TRPML, TPCs and P2 $\times$ 4, for instance. How these channels are recruited and interact to control so many  $\text{Ca}^{2+}$ -dependent processes remain to be further investigated.

Only a limited number of studies have investigated the role of NAADP and the endolysosomal TPCs in the brain. NAADP-dependent lysosomal  $\text{Ca}^{2+}$  signalling has been described as modulating neurotransmitter release, neuronal differentiation, neuronal plasticity and astroglial autophagy. However, whether NAADP recruiting TPCs is a general mechanism remains to be shown since in the periphery NAADP has multiple targets that are also expressed in the brain. Additionally, NAADP acts on RyR and two accessory proteins have been discovered that link either to TPCs (Lsm12, [711]) or couple RyR and TPC1 (JPT2, [69]). Additionally, several enzymes can produce NAADP such as CD38 [27,38] and SARM1 [133] but so far, no report exists describing a neuronal function linking either CD38 or SARM1 to TPC activity. For their part, TPCs could also be recruited independently of NAADP. Undeniably, evidence exists for higher complexity. Indeed, it has been reported that TPCs could also be recruited by either change in the cytosolic  $\text{Ca}^{2+}$  concentration [252,303,312,415] or by small molecules such as P

(3,5)IP<sub>2</sub> [308]. Neurons, astrocytes and endothelial cells integrate exceptional amounts of extracellular stimuli and generate adapted cellular responses. These adaptive responses greatly rely on intracellular machinery. In the brain, we know that mGluR1 activation recruits TPCs [293] but many other RCPGs may also have this property. Although some evidence exists that CD38 and mGluR signalling are linked, a demonstration that CD38 activation leads to NAADP-activated TPC signalling remains to be performed. It is early days and our knowledge about the intracellular pathways recruiting TPCs is at a nascent stage. Most of the studies have so far shown that lysosomal Ca<sup>2+</sup> and TPCs act by interacting with the ER and whether a cellular response will be modulated by pure lysosomal Ca<sup>2+</sup> signal remains to be shown (see “Lysosome and TPCs, the local Ca<sup>2+</sup> signal trigger”).

A precise characterization of endolysosomal Ca<sup>2+</sup> signalling is now crucial in the CNS. This leads us to the last point. The last decade has seen the development of numerous pharmacological tools that makes it possible to interfere with lysosomes, TPCs and the Ca<sup>2+</sup>-releasing messenger synthesizing enzymes CD38 and SARM1 (see “Pharmacological tools”). These pharmacological approaches have made it possible to outline the *in vitro* role of the lysosomal Ca<sup>2+</sup> and TPCs in secretion and autophagy for instance. It is important to note that mouse, pig, and zebrafish mutants are now available which make *in vivo* study possible and thus firmly establish the importance of lysosomal Ca<sup>2+</sup> signalling in brain functions. So far, the CD38<sup>-/-</sup> mouse has been the most studied model revealing the importance of CD38 in brain development, inflammation, plasticity and social behaviour (for review, [94,105]). The SARM1<sup>-/-</sup> mouse has been mostly studied in neuronal degeneration and whether SARM1 and CD38 are complementary or have a selective role in brain functions remained to be discovered. Finally, TPC mutant mice have been barely studied in the context of brain function, revealing so far, a role in plasticity and learning [293,329] and using TPC mutant zebrafish revealed their role in the regulation of primary motor neuron innervation of the skeletal musculature [330]. Recently, TPC mutant pigs have been developed that would permit to investigate higher brain function [416].

Future discoveries will rely on investigating the lysosomal Ca<sup>2+</sup> signalling in animal mutant models for studying brain function and dysfunction. This approach has been already valuable for CD38 which has been associated with a familial form of autism [154]. Finally, looking at polymorphisms of TPC and other endolysosomal proteins in humans would be a very promising avenue to understand the role of such proteins in normal brain function and also in pathological brain such as in social behaviour deficits and neurodegenerative diseases.

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