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The Plasma Membrane Ca^{2+}-ATPase, a Molecular Target for Tau-induced Cytosolic Calcium Dysregulation

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Abstract—Disruption of calcium (Ca^{2+}) homeostasis is emerging as a prevalent feature of aging and aging-associated neurodegenerative diseases, including Alzheimer's disease (AD), the most common type of tauopathy. This disease is characterized by the combined presence of extracellular neuritic plaques composed by amyloid β-peptides (Aβ) and neurofibrillary tangles of tau. The association of calcium dyshomeostasis with Aβ has been extensively studied, however its link with tau has been less investigated. Thus, this review will concentrate on the functional link between tau and the plasma membrane Ca^{2+} pump (PMCA) and other membrane proteins involved in the regulation of intracellular calcium and/or its association with neurodegeneration.

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Key words: PMCA, tau, Alzheimer's disease, calmodulin, methylene blue, sorcin.

INTRODUCTION

Transient increase in intracellular Ca^{2+} concentration is a major signaling event leading to the activation of many cellular processes (Berridge, 2013). But, in the non-activated state, the levels of cytosolic Ca^{2+} must be kept low (nM range) to preserve the cell function, and this is performed by the cell trough several mechanisms. Among them, Ca^{2+} transport ATPases located in the plasma membrane (PMCAs) and in the sarco/endoplasmic reticulum (SERCAs) and secretory pathway (SPCAs) play a major role in controlling the concentration of free Ca^{2+} in the cytosol. Disruption of neuronal Ca^{2+} homeostasis involves deregulation of these pumps and other Ca^{2+}-transporters and channels, and Ca^{2+} binding proteins.

Dysregulation of intracellular calcium (Ca^{2+}) is a common feature of many neurodegenerative pathologies and is one of the main sources of neuronal dysfunction in Alzheimer's disease (AD) (Magi et al., 2016). AD is characterized by the presence of aberrant aggregates of the amyloid-β peptide (Aβ) and phosphorylated tau. It is the most common tauopathy and more precisely it can be considered as a secondary tauopathy because the primary driver of the disease is the Aβ peptide (Selkoe and Hardy, 2016; Chung et al., 2021). Several reviews highlight the involvement of PMCA and other proteins associated to Ca^{2+} signaling (such as the Na^{+}/Ca^{2+} exchanger, plasma membrane Ca^{2+} channels, plasma membrane and endoplasmic reticulum receptors, Ca^{2+} buffers and Ca^{2+} sensors) in AD and other diseases associated to neuronal degeneration (Brini et al., 2014; Brini et al., 2017; Stafford et al., 2017; Hajieva et al., 2018; Mata, 2018; Strehler and Thayer, 2018; O'Day, 2020; Boczek et al., 2021; Hwang et al., 2021).

Although tau is mostly a cytoplasmic protein bound to microtubules, it can also be localized at the cell membrane in pheochromocytoma (Brandt et al., 1995) and neuroblastoma cells (Arrasate et al., 2000), and in cerebral cortex affected by AD (Gray et al., 1987). Besides, Arrasate et al. (2000) reported that in neuroblastoma cells this localization is facilitated by dephosphorylation of tau in its proline-rich region, and suggested that this can be important in tauopathies, such as AD.

It has been widely reported that tau interacts with the cell membrane through its binding to lipids or/and membrane proteins, causing cellular dysfunctions and propagation of tauopathies. The N-terminal acidic projection domain and the C-terminal microtubule-binding domain of tau seem to play a key role in its interaction with the membrane and with membrane proteins (Brandt et al., 1995; Arrasate et al., 2000). Extensive reviews describe in full detail these interactions (Brandt et al., 2020; Brunello et al., 2020; Bok et al. 2021; Sallaberry et al., 2021). However, there are not many evidences about the interaction of tau with proteins involving alteration of their roles as modulators of Ca^{2+}

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Abbreviations: AD, Alzheimer's disease; CaM, calmodulin; MB, methylene blue; PMCA, plasma membrane Ca^{2+}-ATPase.

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homeostasis. This review provides an overview of the relationship between tau and Ca^{2+}, focusing on the interaction of tau with several proteins. First, we summarize and discuss the main findings of our laboratory regarding the inhibitory effects of tau on the functioning of plasma membrane Ca^{2+}-ATPase (PMCA), which plays a major role in the fine tuning of intracellular Ca^{2+}, and the modulation of this inhibition, which may contribute to restoration of intracellular Ca^{2+} levels. In the second part we provide a brief review of tau binding with other major membrane-associated proteins, linked to tau pathologies.

FUNCTIONAL IMPAIRMENT OF PMCA BY TAU

A recent work by Shrivastava et al. (2019) pointed out the interaction of exogenous fibrillar tau with the neuron plasma membrane. In fact, they show that fibrillar tau clamps at the plasma membrane following lateral diffusion. By proteomic screening, using liquid chromatography and tandem mass spectrometry, these authors identified the interaction of exogenous tau with 29 membrane proteins. Among those interacting proteins they revealed the interaction of tau with plasma membrane Ca^{2+}-ATPase isoforms PMCA1 and PMCA4. Other authors (Drummond et al., 2020) also used affinity purification mass-spectrometry to identify a great number of membrane proteins that interact with tau. Seventy five proteins were associated to phosphorylated tau and 34 proteins were associated with total tau, including plasma membrane and intracellular Ca^{2+}-ATPases isoforms PMCA1 and SERCA2, respectively, and other ATPases such as the vacuolar ATPase, ATP synthase alpha/beta family proteins, V-type proton ATPase subunits D1, B2 and H and the Na^{+}-K^{+}-ATPase (subunits α1, α2 and β1).

In line with Ca^{2+} dysregulation linked to neurodegeneration and specifically to AD, we have shown that among the three types of Ca^{2+}-ATPases, only PMCA is functionally affected by two main components of the histopathological marks of AD, the Aβ peptide (Berrocal et al., 2009) and tau (Berrocal et al., 2015). The peptide binds to a calmodulin (CaM) binding site which is present in the PMCA (Berrocal et al., 2012), but neither in SERCA nor in SPCA. Interestingly, the inhibitory effect of tau on PMCA was only seen when the pump was reconstituted with acidic phospholipids, while neutral lipids protected the protein from its inhibition by tau (Berrocal et al., 2017), suggesting that tau effects are highly dependent on the ionic nature of the phospholipids surrounding the protein.

Taking into consideration that both, the N- and the C-terminal regions of tau are involved in its interaction with the membrane and membrane proteins, and that the N terminus is negatively charged whereas the C terminal tail is mainly positively charged (Rosenberg et al., 2008), and also the charge of the substrates of PMCA (Ca^{2+}, H^{+}, Mg^{2+} and ATP), we suggested that tau-PMCA binding is supported by electrostatic interactions, and that tau may use its N-terminus to interact trough the plasma membrane with positively charged residues of PMCA. Activity assays performed at increasing concentrations of KCl showed a reversion of the inhibitory effect of tau on PMCA activity (Berrocal et al., 2015). Salts may affect the interaction between water and protein side chains or backbone by masking charged residues which are important for PMCA binding to tau. Therefore, we can consider that ionic interactions play an important role in tau-PMCA binding. Furthermore, overlay assays led us to suggest that PMCA binding sites for tau should be located somewhere at its C-terminal cytosolic tail, and that it may involve the calmodulin binding site, or another region close to it. This was supported by further studies showing that tau impaired to some extent the binding of CaM to PMCA (Berrocal et al., 2017). In addition, we must consider membrane lipids as another factor that could contribute to the inhibitory effect of tau on PMCA.

The affinity of tau for lipids is dependent on its electrostatic interactions with phospholipids headgroup (Künze et al., 2012). In fact, tau binds preferentially to acidic phospholipids (Yamauchi et al., 1997; Jones et al., 2012; Majewski et al., 2020) and other charged lipid membranes (Jones et al., 2012), with dissociation constant values up to about 250 lower than for neutral lipid membranes (Künze et al., 2012). Therefore, the ionic nature of membrane lipids is relevant for the effects of tau on membrane proteins. It has been extensively reported that PMCA can be activated by acidic phospholipids such as PS, reaching the maximal activity (Brodin et al., 1992; Salvador and Mata, 1996). Then, it is possible that the interaction of tau with acidic lipids could counteract the activating effect of these lipids on PMCA. Our studies corroborated this possibility as part of the mechanisms involved in the inhibition of PMCA by tau (Berrocal et al., 2017).

The works reviewed here have led us to propose that the failure of PMCA function by tau points out the involvement of PMCA in pathologies such as AD and related tauopathies.

COUNTERACTING THE EFFECTS OF TAU ON PMCA BY CALMODULIN, SORCIN AND METHYLENE BLUE

We focused our interest to identify compounds that could block or prevent the negative effects of tau on PMCA functioning. Up to now we have found beneficial effects with two proteins, calmodulin (CaM) and sorcin, and with the methylene blue (MB) dye. Fig. 1 summarize the strategies followed by those compounds to counteract the inhibitory effect of tau on PMCA activity.

Calmodulin and PMCA

CaM is the main endogenous activator of PMCA. In the presence of Ca^{2+}, CaM binds to the CaM binding site of the pump, which also serves as an autoinhibitor, and releases the protein from the autoinhibition (Carafoli, 1997). As a result, the PMCA became fully activated and then is able to pump the excess of cytosolic Ca^{2+} out of the cell, thus maintaining the optimum low intracellular Ca^{2+} levels. We have already reported that CaM decreases and even prevents the inhibition of PMCA activity by tau (Berrocal et al., 2017). Although the inhibitory effect of tau does not interfere with the activating effect of CaM on PMCA, tau reduced slightly the binding

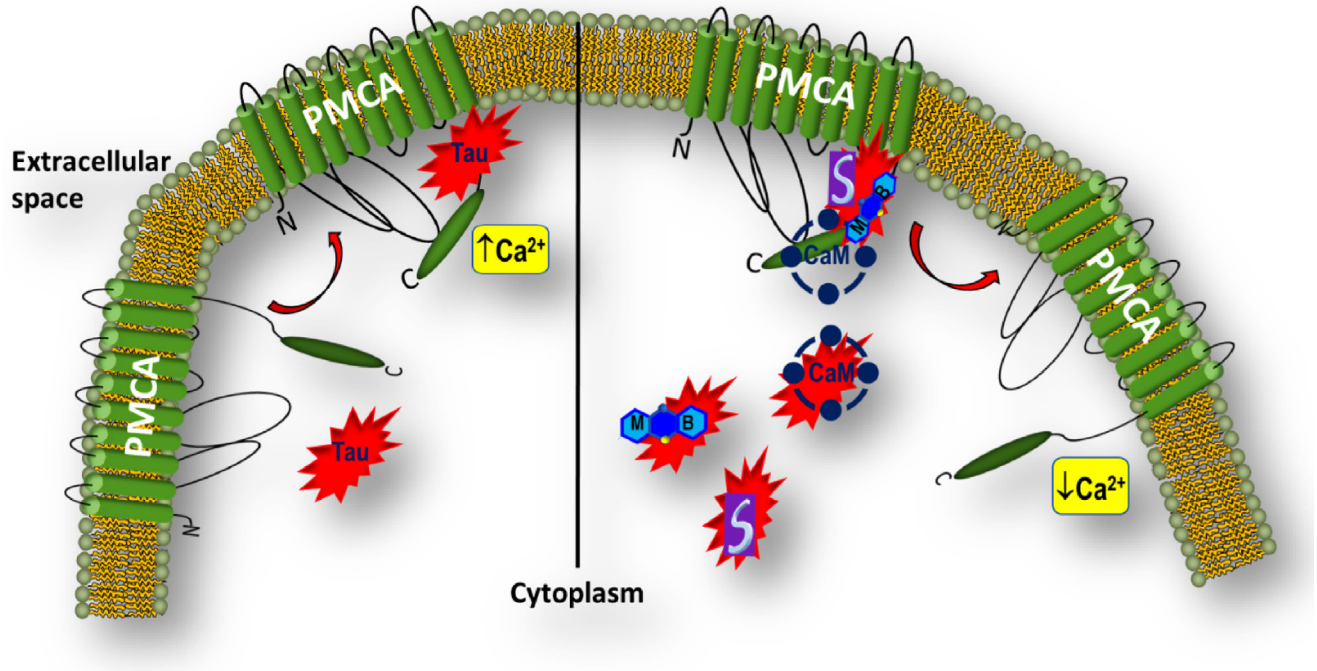

Fig. 1. Summary of the effects of tau and blocking agents on PMCA activity. The left side of the figure shows the inhibition of PMCA by tau binding, leading to cytosolic Ca^{2+} increase. The right side of the figure shows that calmodulin (CaM), sorcin (S) and methylene blue (MB) interact with both PMCA and tau, reversing or blocking its toxic effect, and then restoring PMCA activity.

of CaM to PMCA, showing a 30% increase in the Kd. We also found competition between inhibitory and protective effects produced by tau and CaM, respectively, on Ca^{2+}-ATPase activity. But an equimolar tau/CaM ratio was enough to prevent the inhibitory action of tau (Berrocal et al., 2015; Berrocal et al., 2017). Besides, overlay interaction assays showed that tau not only bind to PMCA but also to CaM. Therefore, an increase in CaM concentration results in a decrease of free tau to inhibit PMCA (Berrocal et al., 2017).

Sorcin and PMCA

The soluble resistance-related Ca^{2+}-binding protein (sorcin) has also been described by our group as a blocking agent of the inhibitor effect of tau on PMCA. Data bank report that sorcin is highly expressed in brain (Andreev et al., 2012; Hondius et al., 2018; Sathe et al., 2021). Further studies have shown a molecular interaction of sorcin with tau in cell cultures overexpressing both proteins (Kim et al., 2016), with presenilin-2 (which is involved in the onset of familial AD) in cell cultures and human brain tissues (Pack-Chung et al., 2000), and also with synuclein and synphilin-1 (involved in Parkinson's disease and other Lewy body diseases) using phage display (Woods et al., 2007) and gene co-expression analysis (George et al., 2019). Besides, this protein activates the cardiac SERCA pump (Matsumoto et al., 2005). Those finding lead us to investigate the association of sorcin with PMCA. By using kinetic approaches we found that sorcin was able to activate all SERCA isoforms, and also the PMCA pump in purified preparations of pig brain, in human brain membranes and in COS cell membranes overexpressing each of the four main PMCA isoforms (Berrocal et al., 2021). Besides, it could block the inhibitory effects of tau in all preparations. Sorcin was also able to prevent the toxicity of tau in human SH-SY5Y cells, as showed by cell viability, ROS production and apoptosis assays. Additional binding assays were carried out to demonstrate that functional effects were associated to molecular interactions of sorcin, not only with the PMCA but also with tau. In addition, sorcin was able to activate the truncated variant hPMCA4b-R1052* lacking the whole C-terminal tail, that resembles the structure of SERCA, suggesting that sorcin may bind to a similar region or pocket in both calcium pumps. Thus, the interaction of sorcin with tau could be a significant mechanism to avoid the partial or total loss of PMCA function by tau. Similar effects were also reported for sorcin and Aβ (Berrocal et al., 2021).

Methylene blue and PMCA

The phenothiazine MB is a dye which has been widely used in several fields including chemistry, medicine or as a photosensitizing agent to treat bacterial and fungal infections. MB attracted our attention because a growing number of evidence have shown neuroprotective roles of MB against brain damage in mice and rats (Mori et al., 2014; Huang et al., 2018; Cheng et al., 2021), and also in patients with mild AD (Wilcock et al., 2018). In fact, a stable reduced form of the MB (leucomethylene blue), acts as a selective inhibitor of tau aggregation, both in vitro and in transgenic mouse models, and it has been used in clinical trials in patients with mild to moderate AD (Wilcock et al., 2018; Schelter et al., 2019). As pointed out

above, the general idea is that the beneficial effect of tau is due to inhibition of tau aggregation, preventing the toxic effects of tau. However, it has been shown that the monomeric form of tau is sufficient to initiate the spread of tau pathology (Michel et al., 2014), and dimers and trimers could also induce toxicity (Cowan and Mudher, 2013). We then, performed functional studies with tau and PMCA in the presence of MB to see if this phenothiazine could exert a protective effect against tau toxicity through its interaction with PMCA. By using purified PMCA and crude membranes from human tissues affected by AD and control subjects and from neuroblastoma cells, MB could block and even reverse the inhibitory effect of tau on PMCA activity (Berrocal et al., 2019). Besides, MB was able to protect neuroblastoma cell cultures against DNA damage due to loss of cell viability and increase of ROS production, due from exogenous tau. Fluorescence experiments allow us to propose that MB interacts and binds to PMCA at micromolar concentrations, and that this interaction was modulated by tau. In fact, the quenching of intrinsic fluorescence of PMCA by MB was largely increased in the presence of tau, suggesting that tau significantly increases the affinity of MB for PMCA, in such way that just micromolar MB concentrations will be needed to bind the brain PMCA in cells. We then proposed that this drug may have beneficial effects in AD by preventing and blocking the toxic effects of tau on PMCA function associated to the maintenance of cellular Ca^{2+} homeostasis (Berrocal et al., 2019).

INTERACTION OF TAU WITH OTHER MEMBRANE PROTEINS RELATED TO CA^{2+} DYSREGULATION AND/OR TAUOPATHIES

The relationship between tau and Ca^{2+} dysregulation has been revealed in cell cultures and in transgenic tauopathy mice models. It has been reported that extracellular tau induces an increase of intracellular Ca^{2+} concentrations in SH-SY5Y neuroblastoma cells and in COS-7 non-neuronal cells, leading to toxic effects (Gomez-Ramos et al., 2006; Gómez-Ramos et al., 2008). This increase has been attributed to its selective interaction with **M1 and M3 muscarinic receptors**, that promote the release of Ca^{2+} from intracellular compartments. By performing fluorescence assays in Fura-2 loaded cells transfected with M1 and M3 cDNAs in the presence of tau, acetylcholine and atropine, as agonist and antagonist of muscarinic receptors, respectively, they found that the increase of cytosolic Ca^{2+} induced by acetylcholine was suppressed by atropine, indicating that muscarinic receptors were the main cholinergic receptors in that cell line. Besides, extracellular tau induced the same effect as acetylcholine, suggesting that tau mediates the increase in Ca^{2+} concentration through its interaction with muscarinic receptors. The Ca^{2+} concentration increase was not seen after addition of atropine (Gómez-Ramos et al., 2008). Both muscarinic receptors are highly expressed in the hippocampus and entorhinal cortex of mice, two areas involved in tau pathology at the early stages of the AD. Besides, other proteins related to neurodegeneration also produce dysregulation of Ca^{2+} homeostasis in neuronal cell cultures (Demuro et al., 2005; Danzer et al., 2007).

Other studies (Smith et al., 1995; Giaccone et al., 1996; Islam and Levy, 1997), have highlighted the interaction of tau with the **amyloid precursor protein** (APP), which plays a key role in AD pathogenesis, because it is the precursor of toxic Aβ peptides, and its mutations are linked to familial AD. However, the amino acid residues of APP involved in its binding with tau are under controversy (Maron et al., 2020; Britton et al., 2021). It has also been shown (Piacentini et al., 2017) that APP may act as a receptor of extracellular tau in astrocytes, inducing its internalization and subsequent impairment of intracellular Ca^{2+} signaling that is essential for gliotransmitter release.

The **apoE4** is the strongest genetic risk factor for late-onset AD. It has been shown that APOE4 produces a considerable reduction of protein synthesis in neurons and a continuous increase in Ca^{2+} levels by activating both NMDARs and L-type voltage-gated calcium channels. Thus, disruption of Ca^{2+} homeostasis by APOE4 leads to a defective protein synthesis. These observations could explain the APOE4-mediated predisposition to AD and involve Ca^{2+} dyshomeostasis in the molecular events associated to ApoE4 and AD (Ramakrishna et al., 2021). Other studies have reported that this isoform aggravates Aβ-mediated neurodegeneration by its interaction with the neuronal low-density lipoprotein receptor-related protein 1 (**LRP1**) (Tachibana et al., 2019). Recently, LRP1, has been identified as an endocytic receptor for extracellular tau (Rauch et al., 2020). Other authors have reported that LRP1 binds with lower affinity to phosphorylated tau and then is less efficiently internalized by LRP1 (Cooper et al., 2021). Besides, the LRP1-mediated uptake of tau is inhibited by apoE4. It has also been reported that ApoE4 affects tau pathogenesis, tau-mediated neurodegeneration and neuroinflammation independently of Aβ pathology (Shi et al., 2017). Thus, the authors propose ApoE4 as a potential therapeutic approach in reducing tau-mediated neurodegeneration and suggest a re-evaluation of the role of ApoE in AD and other tauopathies.

The interaction of tau with these proteins may lead to several effects, depending on the proteins and tau species, and on the cell type. It is widely known that aggregates of hyperphosphorylated tau in the AD brain are a characteristic hallmark of AD. However, it has also been shown that soluble monomers and dimers of extracellular tau are highly toxic to hippocampal granule neurons (Bolós et al., 2017; Bengoa-Vergniory et al., 2021). Wu et al. (2021), have also reported that Ca^{2+} dyshomeostasis correlates better with soluble than insoluble pathological tau in mouse models of tauopathy. Besides, Perea et al. (2018) have shown that dephosphorylated rather than hyperphosphorylated tau generates a pro-inflammatory response in microglia through the activation of p38 mitogen-activated protein kinase **(MAPK)** pathway. And more recently, the same group have reported that this toxic effect of tau can be reversed by pharmacological inhibition of P38 (Perea et al., 2022). As a result, they suggest that P38 inhibition can be a potential therapeutic strategy for tauopathies.

In summary, Ca^{2+} dysregulation associated to tauopathies such as AD, could be mediated by the interaction of tau with membrane proteins such as the PMCA and other key proteins involved in neurodegeneration.

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