

# A 3R-Tau-mediated mechanism in oligodendrocytes: could it be the key for neuroprotection after stroke?

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## An overview of cerebral ischemia:

Cerebrovascular accident or stroke have a high global incidence. The most common types of stroke are ischemic, accounting for 87% of the total number, and they are triggered by a reduction or interruption of blood flow to the central nervous system, usually caused by a thrombus, embolus or atherosclerotic plaque. The severity of brain damage caused by this kind of stroke is directly related to the size of the vessel that is occluded and the duration of occlusion. Stroke is currently the leading cause of long-term disability worldwide and as such it has an enormous socioeconomic impact (Benjamin et al., 2019). In fact, between 30–50% of stroke patients do not recover functional independence and need personal assistance to carry out normal everyday activities. Also, according to statistics issued by the World Health Organization (WHO), ischemic stroke is the second cause of death worldwide. This year (2020) has witnessed a new cause of stroke related to coronavirus disease 2019 (COVID-19), with devastating consequences for the prognosis of this disease across all ages (García-Monco et al., 2020). Given that the incidence of stroke increases with age and life expectancy is rising worldwide, the WHO predicts an increase in the prevalence and incidence of this condition in the coming years (Benjamin et al., 2019). The only therapeutic strategy currently used to reduce ischemic brain damage is early reperfusion using surgical methods (mechanical thrombectomy), or more frequently, the administration of a thrombolytic agent, namely the recombinant tissue plasminogen activator. However, the last approach has a therapeutic window limited to 4.5 hours after the first symptoms appear (Biggs et al., 2019). This temporal restriction implies that reperfusion is not a suitable strategy for a significant number of stroke patients due to the high risk of cerebral hemorrhage. Statistics in different countries reflect that only 10–20% of patients in acute phase of stroke, receive thrombolysis treatment (Lees et al., 2010). The remaining patients do not receive any pharmacological therapy, thus precluding the opportunity to reduce the disability and cognitive dysfunction caused by ischemia. An extension of the time window up to 24 hours has been reported for mechanical thrombectomy in certain patients (Dmytriw et al., 2019). Although reperfusion enhances the prognosis of stroke, it does not prevent the neurodegenerative processes that occur after damage. Therefore, to improve the beneficial effects of reperfusion and to enable pharmacological intervention in patients for whom this approach is not suitable, it is critical to explore alternative therapeutic strategies.

In this regard, there is a need to understand not only the pathophysiological mechanisms that trigger cerebral ischemia and end in death or neuronal damage but also the response mechanisms of the central nervous system. With this knowledge in hand, strategies could be devised to reduce damage and maintain certain brain functions. Indeed, humans and experimental models have provided evidence that the adult brain can self-repair, which is reflected in a spontaneous

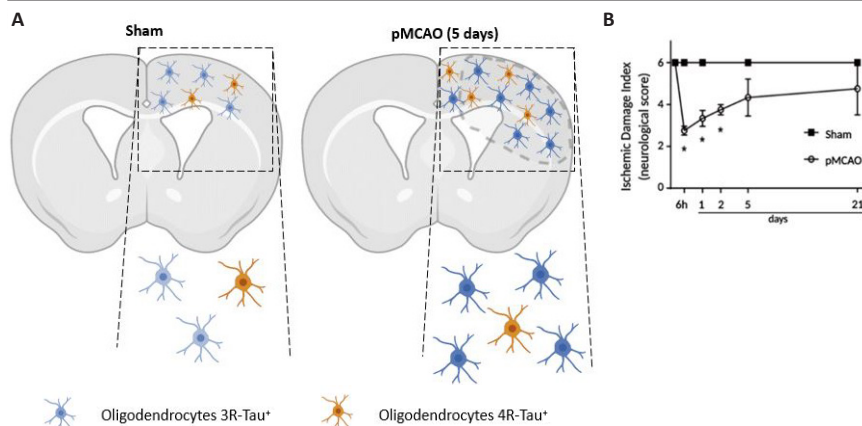
improvement of motor and sensory capacities (Pallast et al., 2020; Villa González et al., 2020).

**“In vivo” models for cerebral ischemia:** Animal models are a good approximation to understand cerebral ischemia and test potential treatments. These models allow us to analyze the effect of cerebral ischemia simultaneously on all cell types and their complex interactions, which may be the key to understanding the brain response, which is aimed at maintaining certain functions. The most widely used model is middle cerebral artery occlusion (MCAO), which reliably mimics the pathology in humans. Transient MCAO (tMCAO) simulates a therapeutic intervention in stroke patients, the occlusion of the artery is maintained for a short period (between 30–120 minutes) and injured tissue reperfusion is allowed. Permanent MCAO (pMCAO) consists of maintaining arterial occlusion until animal sacrifice (from hours to days) and therefore mimics non-therapeutic interventions in humans. In the latter model, we have observed spontaneous recovery of neurologic status in ischemic rats from 5 to 21 days after ischemia induction (Villa González et al., 2020). This recovery is significant, with animals showing improved neurological symptoms. However, tissue neurodegeneration persists, in a similar manner as to what occurs in humans. Most of the studies in this field have focused on the tMCAO model and have thus overlooked a very important aspect of the pathology, namely the long-term brain response to permanent ischemic damage, which, according to the statistical data, is the most common feature in stroke patients.

*In vivo* models have allowed us to understand the sequence of pathophysiological events, called the “ischemic cascade,” triggered in the damaged area after arterial blood flow to the brain is blocked. The major pathophysiological events include early processes that occur between minutes to hours, namely excitotoxicity and perinfarct depolarization, and delayed processes that occur between hours and days, such as inflammation and apoptotic cell death (Perez-Alvarez et al., 2018). All these events result in neuronal death, with the consequent loss of brain functions, which can be evaluated using appropriate neurological tests. It is important to highlight that brain ischemia is a highly dynamic process that evolves over time, thereby making its study difficult. Most research carried out in this field has focused on the analysis of the effects of drugs or potential therapeutic targets in the short-term after ischemia induction. Consequently, there is little information available about the long-term effects of the insult. Furthermore, most of the articles on cerebral ischemia have addressed its effect on neurons or gray matter, omitting glial cells and the role of this cell population in this pathology. In fact, 75% of the articles related to cerebral ischemia found in PubMed are devoted to the study of neurons, while 25% are focused on glial cells. Evidence of the effects of ischemia on oligodendrocytes or white matter is scarce (4% of total).

**Oligodendrocytes and ischemia:** Brain ischemia causes severe damage to white matter in the ischemic core (the most affected area), which accounts for almost half of the infarct volume. On the other hand, preserving the integrity of white matter reduces neuronal injury and ameliorates neurological function (Dai et al., 2019). Disruption of white matter integrity is characterized by damage or death of oligodendrocytes. However, we have limited knowledge of the direct effect of ischemic stroke on these glial cells. Oligodendrocytes are not only responsible for the correct conduction of action potential but are also crucial for the maintenance of axonal integrity. Thus, loss of myelin or oligodendrocytes contributes to axonal injury and weakening of the neurological functions after injury. Oligodendrocytes are highly sensitive to ischemia, being a target of damage in the early short-term. However, some studies highlight that cerebral ischemia induces an increase in the oligodendrocyte population of the ischemic region in the long-term (Zhang et al., 2013; Villa González et al., 2020) (Figure 1A). Nevertheless, the responsible mechanism and the origin of these new oligodendrocytes are poorly understood. These new oligodendrocytes could derive from two distinct sources, namely newly generated precursors (OPCs) in the subventricular zone, or differentiation of pre-existing NG2 cells in the brain parenchyma. Some authors suggest that these newly generated oligodendrocytes never reach maturity and remain in an immature state with an unknown function (Kishida et al., 2019). Of note, it has been proposed that this phenomenon could be a self-repair response triggered by the brain after ischemic insult in an attempt to myelinate injured axons or promote an optimal environment for neuronal survival. Recent data indicate that a subpopulation of OPCs newly generated after ischemia, called perivascular OPCs, facilitates post-stroke angiogenesis, thereby improving functional disabilities (Kishida et al., 2019). Further in-depth studies are required to decipher the exact role of these newly generated oligodendrocytes.

**Tau and oligodendrocytes:** The myelination is a complex process that requires some important properties of oligodendrocyte cytoskeleton. Microtubule network must be dynamic, since it is the pathway for mRNA and myelin proteins trafficking through the cell. It must also allow the oligodendrocyte extensions to wrap properly around the axon. Moreover, during maturation, oligodendrocytes undergo profound morphological changes that require cytoskeleton reorganization. Some microtubule network properties are regulated by microtubule-associated proteins, Tau being such a protein. Tau has been extensively studied in neurons where it plays a pivotal role in the stabilization of the microtubule network. However, much less is known about the role of this protein in oligodendrocytes. The distribution of Tau in oligodendrocytic processes and process tips is essential for functional myelin. It has been reported that disrupted Tau distribution causes axonal degeneration and incorrect myelination (LoPresti, 2018). Tau comprises distinct isoforms that arise from alternative splicing of a single gene; some of them are virtually exclusive to the embryo. Isoform 4R-Tau, which contains exon 10, is abundant in the mature central nervous system, where it is found mainly in neurons but also in oligodendrocytes. Furthermore, having four microtubule-binding domains, 4R-Tau plays a key role in microtubule stability. This property confers this Tau isoform the ability to bind to microtubules with high affinity and efficacy. 3R-Tau, which has lost exon 10, has three microtubule-binding



**Figure 1 | Long-term response of oligodendrocytes to cerebral ischemia.**

(A) Schematic representation of the effect of pMCAO on the number of oligodendrocytes in the damaged area. pMCAO induces an increase in the number of 3R-Tau<sup>+</sup> oligodendrocytes but not in 4R-Tau. There is also an increase in intracellular levels of 3R-Tau in damage area. (B) As the same time, the ischemic damage index (measured as neurological score) of ischemic animals improves. pMCAO: Permanent middle cerebral artery occlusion. Figure 1B was adapted from Villa-Gonzalez et al. (2020).

domains, thus making its binding to microtubules more labile and conferring greater dynamism to the cytoskeleton network (Goedert and Jakes, 1990). At the mRNA level, it has been shown that 3R-Tau is abundant in the neonatal brain and in immature oligodendrocyte cultures. However, the levels of this isoform are decreased in the adult brain and in mature oligodendrocytes. In contrast, like in neurons, 4R-Tau levels are higher in the adult brain and in mature oligodendrocyte cultures (Goedert and Jakes, 1990). Nevertheless, some recent studies have reported that the splicing of Tau mRNA in oligodendrocytes is highly regulated and that it shows a specific pattern. In contrast to neurons, oligodendrocytes of the adult brain hold a small number of isoforms of Tau mRNA that are abundant in embryo neurons, although the function of each splicing of Tau isoforms is unknown (LoPresti, 2002). This persistent expression of “embryonic” isoforms of Tau in oligodendrocytes of the adult brain suggests that some of them conserve certain embryonic properties that could confer capacity to adapt myelin to brain plasticity conditions. We have recently demonstrated, at the protein level, that 3R-Tau and 4R-Tau show a similar pattern of distribution in interfascicular oligodendrocytes of the corpus callosum in the adult brain. Furthermore, in the cerebral cortex of healthy animals, we found that 3R-Tau is also present in the processes of some oligodendrocytes (Villa González et al., 2020).

After ischemia induction, 3R-Tau levels in oligodendrocytes of the damaged area increase, while 4R-Tau does not, remaining at the same levels as in sham animals (Figure 1A). Simultaneously, 3R-Tau in oligodendrocytes undergoes redistribution towards cellular processes. These changes occur in parallel with an improvement in the neurological status of ischemic animals (Figure 1B), although cresyl violet staining of brain sections of pMCAO animals, shows that the size of damage area increases over time (Villa González et al., 2020). These interesting results lead to the proposal that, after cerebral ischemia, the microtubule network of oligodendrocytes becomes a more dynamic, depending on the increase in 3R-Tau levels. This gain in dynamics may allow not only the migration of oligodendrocytes to ischemic damaged areas but also the myelination of injured axons.

**Future outlooks:** Most pharmacological strategies to reduce the deleterious effects of cerebral

ischemia have been based on neurons, with the main objective to prevent their death and reduce the loss of brain function. While various neuron-focused approaches have been used, most have been devoted to the short-term analysis of the mechanisms triggered after ischemia. In recent years, none of the pharmacological approaches based on neurons that have shown neuroprotection *in vitro* or in *in vivo* models have been transferred to the clinic, because of their limited effects in humans. This scenario has given rise to several scientific publications questioning the validity of *in vivo* animal models of cerebral ischemia. However, given the short-term nature of most studies to date, the lack of understanding of the exact onset of ischemia in humans (to translate the results properly), and the lack of in-depth research into the glial cell response, new strategies should be pursued to study this pathology. For instance, glial cells could offer an interesting approach or target to reduce the deleterious effects of ischemia.

Therefore, a greater understanding of the mechanisms of glial response could be a very useful alternative tool to diminish the deleterious effects of ischemia. Among them, research efforts should be channeled into the oligodendrocytes response, the less known. Understand the mechanisms triggered by cerebral ischemia that induce an increase in the levels of 3R-Tau versus 4R-Tau in oligodendrocytes and identify of the origin of the oligodendrocytes generated in ischemic area it is a promising topic.

*This work was supported by grants from Spanish Ministry of Economy and Competitiveness (BFU-2008-03980, BFU2016-77885-P), from Comunidad de Madrid (S2017/BMD-3700) and from Departamento de Biología, Facultad de Ciencias-UAM (BIOUAM03-2020).*

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**Date of submission:** October 8, 2020  
**Date of decision:** November 21, 2020  
**Date of acceptance:** March 3, 2021  
**Date of web publication:** April 23, 2021

<https://doi.org/10.4103/1673-5374.313027>

**How to cite this article:** Villa Gonzalez M, Pérez-Álvarez MJ (2021) A 3R-Tau-mediated mechanism in oligodendrocytes: could it be the key for neuroprotection after stroke? *Neural Regen Res* 16(12):2401-2402.

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C-Editors: Zhao M, Liu WJ, Wang L; T-Editor: Jia Y