GSK3β and Tau Protein in Alzheimer’s Disease and Epilepsy

Danira Toral-Rios¹, Pavel S. Pichardo-Rojas², Mario Alonso-Vanegas³ and Victoria Campos-Peña⁴*

¹Departamento de Fisiología Biofísica y Neurociencias, Centro de Investigación y de Estudios Avanzados del IPN, Mexico City, Mexico, ²Facultad de Ciencias de la Salud, Universidad Autónoma de Baja California, Ensenada, Mexico, ³Centro Internacional de Cirugía de Epilepsia, Instituto Nacional de Neurología y Neurocirugía, HMG, Hospital Coyoacán, Mexico City, Mexico, ⁴Laboratorio Experimental de Enfermedades Neurodegenerativas, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

Alzheimer’s disease (AD) is the most common form of dementia present in older adults; its etiology involves genetic and environmental factors. In recent years, epidemiological studies have shown a correlation between AD and chronic epilepsy since a considerable number of patients with AD may present seizures later on. Although the pathophysiology of seizures in AD is not completely understood, it could represent the result of several molecular mechanisms linked to amyloid beta-peptide (Aβ) accumulation and the hyperphosphorylation of tau protein, which may induce an imbalance in the release and recapture of excitatory and inhibitory neurotransmitters, structural alterations of the neuronal cytoskeleton, synaptic loss, and neuroinflammation. These changes could favor the recurrent development of hypersynchronous discharges and epileptogenesis, which, in a chronic state, favor the neurodegenerative process and influence the cognitive decline observed in AD. Supporting this correlation, histopathological studies in the brain tissue of temporal lobe epilepsy (TLE) patients have revealed the presence of Aβ deposits and the accumulation of tau protein in the neurofibrillary tangles (NFTs), accompanied by an increase of glycogen synthase kinase-3 beta (GSK3β) activity that may lead to an imminent alteration in posttranslational modifications of some microtubule-associated proteins (MAPs), mainly tau. The present review is focused on understanding the pathological aspects of GSK3β and tau in the development of TLE and AD.

Keywords: tau protein, GSK3β, epilepsy, neurodegeneration, hippocampal sclerosis

INTRODUCTION

Alzheimer’s disease (AD) is characterized by progressive memory loss, behavioral changes, and cognitive decline. Histopathologically, it is defined by the presence of neuritic plaques (NPs) composed of fibrillar accumulation of amyloid beta-peptide (Aβ) and neurofibrillary tangles (NFTs) formed by the microtubule-associated protein (MAP) tau. These lesion products produce microglial and astrocyte activation, leading to synaptic loss and neuronal death (Meraz-Ríos et al., 2013). It has been proposed that Aβ can interact with Frizzled receptors, impairing the
Wnt/β-catenin signaling pathway conducting to increased activity of the main tau protein kinase, glycogen synthase kinase-3 beta (GSK3β). Tau hyperphosphorylation promotes the destabilization of cytoskeleton microtubules (MTs), leading to axonal transport abnormalities and neuronal death (Inestrosa and Toledo, 2008). Aβ and tau protein have been linked to excitotoxicity and hyperexcitability (Holth et al., 2013). The relationship of tau and excitability is important in view of the increased incidence of unprovoked seizures observed in AD patients, which may result from alterations in neural circuits and neurodegenerative processes (Pandis and Scarmeas, 2012). In this way, seizures and hyperexcitability of the network could contribute to accelerating the development of cognitive impairment. In addition, the neuronal circuits affected in AD involve brain areas that have been shown to be highly epileptogenic and are strongly related to temporal lobe epilepsy (TLE), the most common type of epilepsy. Histopathological studies in TLE patients have shown the presence of hyperphosphorylated tau protein aggregates (Sen et al., 2007; Thom et al., 2011; Tai et al., 2016). The present review aims at assessing the role of tau and GSK3β proteins in the development of AD and TLE.

TAU PROTEIN

Tau is a type II MAP, mainly located in axons. It is a heat-stable protein that prevents MT assembly and stabilization in the central nervous system (CNS). Human tau is encoded by the MAPT gene located on chromosome 17q21 and consists of 16 exons (Andreadis et al., 1992; Andreadis, 2005; Figure 1A). Six different isoforms of the protein are expressed in the adult human brain. Each isoform contains three or four microtubule binding repeats (3R/4R) and the presence or absence of one or two N-terminal inserts (Buée et al., 2000; Martin et al., 2011; Figure 1B).

Under normal conditions, tau interacts with motor proteins such as dynein and kinesin, participating in retrograde and anterograde transport (Dixit et al., 2008), in embryonic development, long-term potentiation (LTP; Ahmed et al., 2014), and long-term depression (LTD; Kimura et al., 2014; Regan et al., 2015). Under pathological conditions, it self-assembles into insoluble structures, known as paired helical filaments (PHFs; Goedert, 1999). Two tau posttranslational modifications are present in PHFs: hyperphosphorylation and truncation (Flament et al., 1990; Alonso et al., 1996; Hasegawa et al., 1998).

Hyperphosphorylation prevents tau microtubule binding, resulting in an altered cytoskeletal stability (Evans et al., 2000), a subsequent loss of axonal transport, and other signaling-related functions (Mandelkow et al., 1995); it has also been considered the primary event that triggers the tau pathological aggregation in filaments (Grundke-Iqbal et al., 1986; Wood et al., 1986; Alonso et al., 1996).

TAU AND EPILEPSY

In recent years, tau protein has been implicated in the disruption of neuronal synchronization and hyperexcitability; in this way, it could also be linked to epilepsy. Even though the specific pathologic mechanisms are yet to be clarified, there are different reports supporting these claims.

Some models of tau pathology have been shown to induce drastic changes in connectivity and strong uncoupling of the gamma–theta oscillations. However, no signs of epileptiform activity were registered (Ahnaou et al., 2017). Challenging this idea, a transgenic mouse model of human amyloid precursor protein (hAPP) presented an overproduction of Aβ and consequent development of spontaneous seizures. Adding a tau gene knockout to this model revealed that tau reduced levels, prevented N-methyl-D-aspartate receptor (NMDAR) dysfunction, impaired LTP, ameliorated cognitive decline, and reduced epileptiform activity in the hippocampus (Roberson et al., 2007, 2011).

Another interesting study which evaluated the relationship of tau with hyperexcitability is the Kcnal−/− mouse, a TLE model. These mice have a null allele for the alpha subunit of Kv1.1, a voltage-gated potassium channel that conditions the development of spontaneous seizures in the third week of life. The tau gene knockout in this model reduced the occurrence and frequency of spontaneous seizures and promoted survival, specifically in the CA3 pyramidal region of the hippocampus (Holth et al., 2013). Another similar model demonstrated that Aβ-induced hyperexcitability was associated with a reduction in the levels of Kv4.2, a dendritic potassium channel important in regulating dendritic excitability and synaptic plasticity. Interestingly, enough of both of these phenomena were dramatically reduced in tau knockout mice, suggesting that tau may have a direct role in modulating neuronal excitability (Hall et al., 2015). Similar results were observed in a Tau−/− mouse model treated with Pentylentetrazole (PTZ). In this case, it was observed that a reduction in tau expression protects against seizure severity (DeVos et al., 2013). This is interesting considering that it is possible that endogenous tau levels in AD patients may influence the risk of developing seizures.

Although having higher basal levels of tau in the cerebrospinal fluid does not cause seizures in itself, these patients are more likely to develop seizures after an injury, for example, after an ischemic stroke or traumatic brain injury (Camilo and Goldstein, 2004; Kwan, 2010). For this reason, in the future, it could be important to identify high-risk patients through genetic analysis, maybe by identifying polymorphisms in the tau gene (Myers et al., 2007; Kauwe et al., 2008) or levels of tau in the cerebrospinal fluid (Cruchaga et al., 2013), to determine whether, in this population, it may be useful to provide prophylactic antiepileptic therapy.

Hyperphosphorylated tau aggregates and NFTs have been observed in several patients with epilepsy (Sen et al., 2007; Thom et al., 2011; Tai et al., 2016). Moreover, a study on temporal lobe resections in patients with refractory epilepsy demonstrated that the presence of hyperphosphorylated tau and its accumulation in pre-tangles and NFTs seem to correlate with cognitive decline (Tai et al., 2016). Evidence suggests that prolonged or recurrent seizures in epilepsy patients can cause or exacerbate cognitive impairment (Holmes, 2015; Kneynsberg et al., 2017). Pathologic tau has been correlated...
FIGURE 1 | Tau protein. (A) Tau gene. Exons 2, 3, and 10 are alternatively spliced in the central nervous system (CNS). Exons 9–12 each contain the microtubule-binding domain (MBD). Exons 4a and 6 have been expressed in isoforms of the peripheral nervous system, whereas exon 8 has not been reported in any isoform. (B) Different isoforms of tau protein are expressed in the CNS. The expression of different isoforms is regulated by development. Isoforms with three repeated domains are expressed preferentially in fetal stages, whereas in the adult stages they are characterized by the presence of the six isoforms. The repeated domains that bind to microtubules (MTs) are designated as R1, R2, R3, and R4. Another characteristic is the presence or absence (0N) of one (1N) or two (2N) inserts located in the amino terminus of the protein.

GSK3

GSK3 is a proline-directed kinase; there are two isoforms, glycogen synthase kinase-3 alpha (GSK3β) and beta (GSK3β) encoded by chromosomes 19 and 3, respectively. GSK3β is mainly expressed in the CNS, normally located in axons, and is the main kinase that phosphorylates tau protein (Muylaert et al., 2008). GSK3β could be inactivated through phosphorylation in serine 9 and activated by phosphorylation in tyrosine 216. GSK3β inactivation is regulated by the PI3K/Akt and Wnt/β-catenin pathways. In AD, both are altered and favor an increased activity of GSK3β (Hooper et al., 2008).

Overexpression or overactivity of GSK3β increases tau phosphorylation, allowing it to disassemble from MTs, leading to axonal transport alterations, hippocampal neurodegeneration (Avila et al., 2006; Muylaert et al., 2008), and learning impairment (Gómez De Barreda et al., 2010). GSK3 is able to phosphorylate tau at 42 sites (Figure 2; Hanger et al., 2009; Martin et al., 2013). Also, GSK3 activity correlates with the amount of NFTs in AD brains (Leroy et al., 2002). Another implication of the kinase in AD is the modulation of the intrinsic pathways of cellular apoptosis which could be favored by the Aβ peptide (Takashima et al., 1996). GSK3β promotes Bax activity,
FIGURE 2 | Putative phosphorylation sites on tau protein. The native tau protein is phosphorylated in serine or threonine residues and contains 85 putative phosphorylation sites. Several amino acids are phosphorylated in Alzheimer’s disease (AD) brain (red boxes) and both normal and AD brains (green boxes). The localization of antibody epitopes is indicated (purple circles).

GSK3β AND EPILEPSY

GSK3β could be linked to hyperexcitability and epileptogenesis due to its physiological roles in synaptic plasticity modulation and the control of neuron cytoskeleton dynamic. In a rat model, seizures and hippocampal neuronal damage induced with kainic acid (KA) could stimulate GSK3β activity, inhibiting the Wnt/β-catenin pathway. Administration of lithium, a GSK3β inhibitor, in these rats prevented hippocampal neuronal damage, but not KA-induced seizures (Busceti et al., 2007). Dysfunctional neurogenesis is frequently observed in the latter stages of TLE and has been associated with Wnt/β-catenin pathway inhibition. GSK3β inhibitors restore the pathway and recover neurogenesis (Huang et al., 2015); furthermore, GSK3β activity is also regulated by the PI3k/Akt pathway. This pathway resulted as impaired in KA and electroconvulsive epilepsy models and also could promote GSK3β activation, neuronal damage, and tau phosphorylation before seizures (Crespo-Biel et al., 2007; Gangarossa et al., 2015).

In line with the above information, other studies evidenced a pro-apoptotic trend in Bcl2/Bax expression in a Western blot assay 48 h after KA injection; Bcl2 family proteins seem to be an important downstream target of GSK3β (Linseman et al., 2004). In this regard, decreased Bcl2 expression may be another consequence of the neurodegenerative process (Bhowmik et al., 2015). All of these findings suggest that alterations of GSK3β after an excitotoxic insult play a key role not only in neurodegeneration but also in the disruption of the normal neuronal survival signaling pathways.

Even though GSK3β has not been demonstrated to produce epilepsy in itself, there is evidence showing that GSK3β inhibition does result in anticonvulsant activity, even after brain excitability has been altered from normal, healthy conditions into a “pro-epileptic” state (Aourz et al., 2019). Furthermore, GSK3β alterations do increase seizure susceptibility, and increased GSK3β activity has been evidenced in other epilepsy models (Lohi et al., 2005; Tripathi et al., 2010; Lee et al., 2012).

Despite the increased GSK3β activity having been probed in other epilepsy models (Lohi et al., 2005; Tripathi et al., 2010; Lee et al., 2012), the addition of KA into hippocampal slices of mice that overexpressed a constitutively active form of GSK3β produced a decreased progression of induced epileptogenesis,
Glycogen synthase kinase-3 beta (GSK3β) and epilepsy. Impaired PI3K/Akt and Wnt/β-catenin signaling pathways can induce GSK3β increased activity, which could promote N-methyl-D-aspartate receptor (NMDAR) overstimulation, leading to hyperexcitability and synaptic plasticity alterations. Probably, this mechanism represents the major link between GSK3β and seizures in the hippocampus, although some studies have proposed that GSK3β increased activity confers protection. In another way, GSK3β could favor tau hyperphosphorylation, promoting axonal transport impairment and hippocampal neuronal death. Hyperphosphorylated tau actively participates in hyperexcitability and neurodegeneration. GSK3β also promotes a mitochondrial pro-apoptotic profile (high BAX/Bcl2 ratio). In this sense, GSK3β also could trigger dysfunctional neurogenesis, which prevents recovery of the synaptic equilibrium of the hippocampus, one neurogenic structure.

probably mediated by the reduced phosphorylation of the GluA1 subunit of the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Urbanska et al., 2019). This result seems contradictory because of the beneficial effects attributed to GSK3β inhibition, but a recent study exposed that the brain has limited tolerance for the modulation of GSK3β activity on hippocampal damage related to the severity of status epilepticus (Engel et al., 2018).

Another strong hypothesis of GSK3β and its role in epileptogenesis favoring TLE is the close relation with NMDAR and its stimulation, which may induce excitability in the acute stages of the disease (Liu et al., 2017).

All the evidence mentioned above remark on the importance of GSK3β homeostasis in preventing epilepsy. Even though an excitotoxic insult may initially disrupt GSK3β, once this happens, GSK3β actively plays a role in increasing seizure susceptibility (Figure 3). There is no doubt that GSK3β alterations promote the disruption of normal survival signaling pathways and hyperexcitability, which, together, could produce epileptogenesis and neurodegeneration.

THERAPEUTICS

As previously mentioned, tau and GSK3β have been associated with several neurological disorders, including AD and TLE; therefore, both represent potential therapeutic targets.

Interestingly, the efficacy of various antiepileptic drugs (AEDs) has been tested in epilepsy experimental models and in AD patients, showing a promising function in cognitive impairment prevention (Sánchez et al., 2018). Since tau hyperphosphorylation is the main mechanism responsible for NFT formation, it has been suggested that inhibiting different tau kinases such as CDK5 and GSK3β, involved in tau hyperphosphorylation, could reduce their aggregation (Xie et al., 2017; Holzer et al., 2018), observed in AD (Morris et al., 2011) and epilepsy (Sen et al., 2007; Thom et al., 2011; Tai et al., 2016).

When AEDs are used in healthy volunteers and different neuropsychological variables are measured, researchers have found that, in general, AEDs like carbamazepine, phenytoin, and valproate have mild cognitive effects (Meador et al., 1995; Martin et al., 2001; Salinsky et al., 2002). In contrast,
GSK3β in AD and Epilepsy

The cognitive effects of oxcarbazepine, gabapentin, and carbamazepine were evaluated in healthy volunteers, the results showed that individuals presented a better performance in the focused attention task and manual writing speed, without any effect on long-term memory (Curran and Java, 1993; Meador et al., 1999). It is worth mentioning that older patients are generally more sensitive to the negative cognitive effects of some AEDs due to the complex interactions among several factors (neuropathologies, genetics, the effects of seizures, psychosocial background, etc.; Kwan and Brodie, 2001).

The efficacy of AEDs in preventing seizures in AD patients has been tested. However, reports regarding their cognitive effects in the elderly are relatively limited, specifically in the elderly with AD. Most of the old AEDs exert negative effects on mood, behavior, and cognitive functions, such as memory (Craig and Tallis, 1994; Meinhold et al., 2005). In contrast, newer AEDs appear to be less harmful and may even produce a slight cognitive benefit, even though some of these newer drugs like topiramate appear to impair language and verbal memory (Fritz et al., 2005). Other various new AEDs like lamotrigine and gabapentin do not impair memory and may have slight beneficial effects on memory, and even mood (Tekin et al., 1998; Meador et al., 1999). Levetiracetam has demonstrated cognitive benefits, which can be measured in routine clinical practice, particularly in attention and oral fluency (Cumbo and Ligori, 2010).

The main objective of AED therapy is to improve the patient’s quality of life, and even though the main aim is to reduce the quantity of seizures, the current review may provide additional information, which may aid physicians and their patients in making treatment decisions when considering other therapeutic variables like cognition.

The most advanced protein kinase inhibition strategy in the clinic so far has been aimed at GSK3β, leading to the development of novel drugs such as Tideglusib (Hooper et al., 2008; Medina, 2018). Treatment with this thiadiazolidinone (TDZD) compound resulted in decreased amyloid deposition, lower levels of tau phosphorylation, and prevention of memory deficits in a transgenic mouse model (APPsw-tauYw; Serénó et al., 2009). Lithium and valproic acid have been used in epilepsy for their anticonvulsant activity and in other psychiatric disorders (Jope and Roh, 2006). Moreover, these inhibitors and TDZD-8, a selective inhibitor of GSK3β, promote the phosphorylation of serine 9, which conducts to GSK3β inactivation (Zhang et al., 2003). The inhibition strategy reduces tau hyperphosphorylation, prevents neuronal death, and inhibits the alteration of neurogenesis processes in the hippocampus in the setting of status epilepticus (Busceti et al., 2007; Bhowmik et al., 2015; Huang et al., 2015; Urbanska et al., 2019). Memantine and ifendropil are NMDAR antagonists and have been demonstrated to conduct to GSK3β inactivation and reduction of tau phosphorylation (Liu et al., 2017). Recently, the use of potent and selective GSK3β inhibitors such as indirubin and BIO-acetoxime showed anticonvulsant properties (Aourz et al., 2019). In this report, PTZ-treated zebrafish larvae were treated with both compounds, which exhibited anticonvulsant activity, with a reduction of epileptiform discharges. In the same way, indirubin and BIO-acetoxime showed anticonvulsant activity in the 6-Hz refractory seizure mouse model (Aourz et al., 2019).

Acetylation is another posttranslational modification that leads to impaired tau function and promotes its pathological aggregation; hence, tau acetylation inhibitors are proposed as a potential therapeutic strategy for AD and other tauopathies (Medina et al., 2016). Salsalate is a nonsteroidal anti-inflammatory drug which inhibits acetyltransferase p300-induced tau acetylation; this drug has been shown to rescue tau-induced memory deficits and prevent hippocampal atrophy in a mouse model of frontotemporal dementia (FTD; Min et al., 2015). Leuco-methylthioninium bis-hydromethanesulfonate (LMTM) is currently in phase III clinical trials and has shown efficacy in inhibiting tau aggregation (Bulic et al., 2013). Passive and active tau immunotherapy is a promising strategy which has been designed for clearing toxic tau species such as monomers, oligomers, prefilaments, granules, fibrils, or insoluble aggregates present in tauopathies and related disorders. The main objectives of immunotherapy are to reduce tau aggregation, prevent neurodegeneration, and improve cognitive functions (Bittar et al., 2018; Medina, 2018; Novak et al., 2018).

![Schematic representation of the roles of tau and GSK3β in the neurodegeneration process.](https://frontiersin.org)
Even though all of these therapeutic strategies mainly target AD, it is clear that, in the future, they may well serve for the treatment of other tauopathies, including TLE. Hence, it is important to procure and encourage the potential therapeutic efficacy of tau and GSK3β-based strategies in the future of these diseases.

CONCLUSIONS

TLE is a common disorder characterized by hippocampal sclerosis and chronic seizures that are frequently resistant to pharmacological treatment and are associated with disabling comorbidities and cognitive decline. Epidemiological studies have shown an increased prevalence of several dementias, including AD, in chronic epilepsy. These pathologies converge in the hyperphosphorylation of tau protein, apparently mediated by an increased activity of GSK3β that can promote apoptosis, aberrant neurogenesis, impaired synaptic plasticity, and hyperexcitability in the hippocampus. These alterations have been well described in AD, but are not yet completely understood in TLE (Figure 4). For this reason, further studies are necessary to clarify the roles of tau and GSK3β in physiopathology and structural abnormalities and to probe the effectiveness of novel tau immunotherapies. Also, considering that AD and TLE are sporadic and multifactorial diseases, it would be interesting to study different alterations in the GSK3β and the tau (MAPT) encoding genes that could represent genetic risk factors for the development of TLE and AD.

AUTHOR CONTRIBUTIONS

DT-R, PP-R, MA-V, and VC-P drafted the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by a grant from CONACYT S0008-2016-1, no. 273182.

REFERENCES

Ahmed, T., Van Der Jeugd, A., Blum, D., Galas, M. C., D’Hooge, R., Buee, L., et al. (2014). Cognition and hippocampal synaptic plasticity in mice with a homozygous tau deletion. Neurobiol. Aging 35, 2474–2478. doi: 10.1016/j.neurobiolaging.2014.05.005

Ahnaou, A., Moechars, D., Raeymaekers, L., Biermans, R., Manyakov, N. V., Bottelbergs, A., et al. (2017). Emergence of early alterations in network oscillations and functional connectivity in a tau seed mouse model of Alzheimer’s disease pathology. Sci. Rep. 7:14189. doi: 10.1038/s41598-017-13839-6

Alonso, A. C., Grundke-Iqbal, I., and Iqbal, K. (1996). Alzheimer’s disease hyperphosphorylated tau sequesters normal tau into tangles of filaments and disassembles microtubules. Nat. Med. 2, 783–787. doi: 10.1038/nm0796-783

Andreadis, A., Brown, W. M., and Kosik, K. S. (1992). Structure and novel exons of the human tau gene. Biochim. Biophys. Acta 1173, 91–103. doi: 10.1016/0005-2728(92)90173-N

Andreasen, A. (2005). Tau gene alternative splicing: expression patterns, regulation and modulation of function in normal brain and neurodegenerative diseases. Biochim. Biophys. Acta 1739, 1–8. doi: 10.1016/j.bbadis.2004.08.010

Bottelbergs, A., et al. (2017). Emergence of early alterations in network oscillations and functional connectivity in a tau seed mouse model of Alzheimer’s disease pathology. Sci. Rep. 7:14189. doi: 10.1038/s41598-017-13839-6

Bulic, B., Pickhardt, M., and Mandelkow, E. (2013). Progress and developments in GSK3β in AD and Epilepsy. Front. Cell. Neurosci. 7:18. doi: 10.3389/fncel.2013.00017

Bottelbergs, A., et al. (2017). Emergence of early alterations in network oscillations and functional connectivity in a tau seed mouse model of Alzheimer’s disease pathology. Sci. Rep. 7:14189. doi: 10.1038/s41598-017-13839-6

Camilo, O., and Goldstein, L. B. (2004). Seizures and epilepsy after ischemic stroke. Stroke 35, 1769–1775. doi: 10.1161/01.STR.0000130989.17100.96

Craig, I., and Tallis, R. (1994). Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study. Epilepsia 35, 381–390. doi: 10.1111/j.1528-1157.1994.tb02448.x

Crespo-Biel, N., Canudas, A. M., Camins, A., and Pallas, M. (2007). Kainate induces AKT, ERK and cdk5/GSK3β pathway deregulation, phosphorylates tau protein in mouse hippocampus. Neurochem. Int. 50, 435–442. doi: 10.1016/j.neuint.2006.10.002

Cruchaga, C., Kauwe, J. S., Harari, O., Jin, S. C., Cai, Y., Karch, C. M., et al. (2013). GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer’s disease. Neuropathol. 78, 256–268. doi: 10.1016/j.neuro.2013.02.026

Cumbo, E., and Ligori, L. D. (2010). Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer’s disease. Epilepsy Behav. 17, 461–466. doi: 10.1016/j.yebeh.2010.01.015

Curran, H. V., and Java, R. (1993). Memory and psychomotor effects of oxcarbazepine in healthy human volunteers. Eur. J. Clin. Pharmacol. 44, 529–533. doi: 10.1007/bf02440853

DeVos, S. L., Goncharoff, D. K., Chen, G., Kebodeaux, C. S., Yamada, K., Stewart, F. R., et al. (2013). Antisense reduction of tau in adult mice protects against seizures. J. Neurosci. 33, 12887–12897. doi: 10.1523/jneurosci.2107-13.2013

Dixit, R., Ross, J. L., Goldman, Y. E., and Holzbaur, E. L. (2008). Differential regulation of dynein and kinesin motor proteins by tau. Science 319, 1086–1089. doi: 10.1126/science.1152993

Engel, T., Gomez-Sintes, R., Alves, M., Jimenez-Mateos, E. M., Fernandez-Mateos, M., Sanchez-Rodriguez, A., et al. (2018). Bi-directional genetic modulation of GSK-3β exacerbates hippocampal neuropathology in experimental status epilepticus. Cell Death Dis. 9:969. doi: 10.1038/s41419-018-0963-5

Evans, D. B., Rank, K. B., Bhattacharya, K., Thomsen, D. R., Gurney, M. E., and Sharma, S. K. (2000). Tau phosphorylation at serine 396 and serine 404 by human recombinant tau protein kinase II inhibits tau’s ability to promote microtubule assembly. J. Biol. Chem. 275, 24977–24983. doi: 10.1074/jbc.M000880200

Flemant, S., Delacourte, A., and Mann, D. M. (1990). Phosphorylation of Tau proteins: a major event during the process of neurofibrillary degeneration. J. Neurosci. 10, 435–442. doi: 10.1016/00146226(90)91274-7

Fritz, N., Glogau, S., Hoffmann, J., Rademacher, M., Elger, C. E., and Helmstaedter, C. (2005). Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy. Epilepsy Behav. 6, 373–381. doi: 10.1016/j.yebeh.2005.01.002
Gangarossa, G., Sakkaki, S., Lory, P., and Valjent, E. (2015). Mouse hippocampal phosphorylation footprint induced by generalized seizures: focus on ERK, mTORC1 and Akt/GSK-3 pathways. Neuroscience 311, 471–483. doi: 10.1016/j.neuroscience.2015.10.051

Goedert, M. (1999). Filamentous nerve cell inclusions in neurodegenerative diseases: tauopathies and α-synucleinopathies. Philos. Trans. R. Soc. Lond. B Biol. Sci. 354, 1101–1118. doi: 10.1098/rspb.1999.0466

Gómez De Barreda, E., Perez, M., Gomez Ramos, P., De Cristobal, J., Martin-Maestro, P., Moran, A., et al. (2010). Tau-knockout mice show reduced GSK3-induced hippocampal degeneration and learning deficits. Neurobiol. Dis. 37, 622–629. doi: 10.1016/j.nbd.2010.11.017

Grundke-Iqbal, I., Iqbal, K., Quinlan, M., Tung, Y. C., Zaidi, M. S., and Goedert, M. (1998). Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. J. Biol. Chem. 273, 38336–38343. doi: 10.1074/jbc.273.58.38336

Hanger, D. P., Anderton, B. H., and Noble, W. (2009). Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. Trends Mol. Med. 15, 112–119. doi: 10.1016/j.molmed.2009.01.003

Hasegawa, M., Smith, M. J., and Goedert, M. (1996). Mutations in the tau gene of familial dementia cause paroxysmal kinesigenic dyskinesia. FEBS Lett. 397, 207–210. doi: 10.1016/0014-5793(96)02174-7

Holms, G. L. (2015). Cognitive impairment in epilepsy: the role of network abnormalities. Epileptic Disord. 17, 101–116. doi: 10.1684/epid.2015.0739

Holth, J. K., Bomberg, V. C., Reed, J. G., Inoue, T., Younkin, L., Younkin, S. G., et al. (2013). Tau loss attenuates neuronal network hyperexcitability in mouse and Drosophila genetic models of epilepsy. J. Neurosci. 33, 1651–1659. doi: 10.1523/jneurosci.3191-12.2013

Holzer, M., Schade, N., Opitz, A., Hilbrich, I., Stiebler, J., Vogel, T., et al. (2018). Novel protein kinase inhibitors related to tau pathology modulate tau protein-self interaction using a luciferase complementation assay. Molecules 23:E2335. doi: 10.3390/molecules23092335

Huang, C., Fu, X. H., Zhou, D., and Li, J. M. (2015). The role of Wnt/jp-catenin signaling pathway in disrupted hippocampal neurogenesis of temporal lobe epilepsy: a potential therapeutic target? Neurochem. Res. 40, 1319–1332. doi: 10.1007/s11064-015-1614-1

Inestrosa, N. C., and Toledo, E. M. (2008). The role of Wnt signaling in neuronal dysfunction in Alzheimer’s disease. Mol. Neurodegener. 3:9. doi: 10.1186/1750-1232-3-9

Iope, R. S., and Rob, M. S. (2006). Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. Curr. Drug Targets 7, 1421–1434. doi: 10.2174/138945010607011421

Kauwe, J. S., Cruchaga, C., Mayo, K., Fenoglio, C., Markwardt, S. J., Peng, Y., Wang, Q., et al. (2015). Tau-dependent Kv2.2 depletion and dendritic hyperexcitability in a mouse model of Alzheimer’s disease. J. Neurosci. 35, 6221–6230. doi: 10.1523/jneurosci.2552-14.2015

Kwiat, J., Latty, X. Z., and Bar, R. (2011). Post-translational modifications of tau protein: implications for Alzheimer’s disease. Nutr. Neurosci. 15, 21–30. doi: 10.1179/147398911X124884

Linseman, D. A., Butts, B. D., Precht, T. A., Phelp’s, R. A., Le, S. S., Laasig, T. A., et al. (2004). Glycogen synthase kinase-3β phosphorylates Bax and promotes its mitochondrial localization during neuronal apoptosis. J. Neurosci. 24, 10366–10374. doi: 10.1523/jneurosci.2057-04.2004

Liu, X., Ou, S., Yin, M., Xu, T., Wang, T., Liu, Y., et al. (2017). N-methyl-D-aspartate receptors mediate epilepsy-axedonal impairment and tau phosphorylation via activating glycogen synthase kinase-3β and cyclin-dependent kinase 5. Discov. Med. 23, 221–234.

Lohi, H., Ianzano, L., Zhao, X. C., Chan, E. M., Turnbull, J., Scherer, S. W., et al. (2005). Novel glycogen synthase kinase 3 and ubiquitination pathways in progressive myoclonic epilepsy. Hum. Mol. Genet. 14, 2727–2736. doi: 10.1093/hmg/ddl306

Mandal, K. S., Bhattacharya, D., and Mandal, E. (1999). Tau domains, phosphorylation, and interactions with microtubules. Neurobiol. Aging 16, 355–362; discussion 362–363. doi: 10.1016/0197-4580(95)00025-a

Mills, A. R., and Proud, G. W. (2011). GSK3α and GSK3β: a plethora of kinases, substrates and functions. Biochem. J. 434, 1–25. doi: 10.1042/BJ20120018

Mistry, K. R., and Iqbal, K. (2015). GSK3 and tau: two proteins that can cross-talk to promote neuronal degeneration. Front. Neurol. 6, 192. doi: 10.3389/fneur.2015.0192

Muyllaert, D., Kremer, A., Jaworski, T., Borghgraef, P., Devijver, H., Croes, S., et al. (2011). Regulation of cell survival and cytokinesis by glycogen synthase kinase 3. J. Biol. Chem. 286, 4580–4587. doi: 10.1074/jbc.M110.156874

Muyllaert, D., Kremer, A., Jaworski, T., Borghgraef, P., Devijver, H., Croes, S., et al. (2011). Regulation of cell survival and cytokinesis by glycogen synthase kinase 3. J. Biol. Chem. 286, 4580–4587. doi: 10.1074/jbc.M110.156874

Muyllaert, D., Kremer, A., Jaworski, T., Borghgraef, P., Devijver, H., Croes, S., et al. (2011). Regulation of cell survival and cytokinesis by glycogen synthase kinase 3. J. Biol. Chem. 286, 4580–4587. doi: 10.1074/jbc.M110.156874

Nichols, M. E., et al. (1999). Differential cognitive effects of carbamazepine and gabapentin. Neurology 52, 1494–1499. doi: 10.1212/wnl.52.10.1494

Nichols, M. E., et al. (1999). Differential cognitive effects of carbamazepine and gabapentin. Neurology 52, 1494–1499. doi: 10.1212/wnl.52.10.1494
Novak, P., Kontsekova, E., Zilka, N., and Novak, M. (2018). Ten years of tau-targeted immunotherapy: the path walked and the roads ahead. Front. Neurosci. 12:798. doi: 10.3389/fnins.2018.00798

Pandis, D., and Scarmeas, N. (2012). Seizures in Alzheimer disease: clinical and epidemiological data. Epilepsy Curr. 12, 184–187. doi: 10.5698/1555-7511-12.5.184

Peineau, S., Taghibiglou, C., Bradley, C., Wong, T. P., Liu, L., Lu, J., et al. (2007). LTP inhibits LTD in the hippocampus via regulation of GSK3β. Neuron 53, 703–717. doi: 10.1016/j.neuron.2007.01.029

Regan, P., Piers, T., Yi, J. H., Kim, D. H., Huh, S., Park, S. J., et al. (2015). Tau phosphorylation at serine 396 residue is required for hippocampal LTD. J. Neurosci. 35, 4804–4812. doi: 10.1523/jneurosci.2842-14.2015

Roberson, E. D., Halabisky, B., Yoo, J. W., Yao, J., Chin, J., Yan, F., et al. (2011). Tau phosphorylation at serine 396 residue is required for hippocampal LTD. J. Neurosci. 31, 700–711. doi: 10.1523/jneurosci.4152-10.2011

Roberson, E. D., Searce-Levie, K., Palop, J. J., Yan, F., Cheng, I. H., Wu, T., et al. (2007). Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer’s disease mouse model. Science 316, 750–754. doi: 10.1126/science.1141736

Salcedo–Tello, P., Ortiz-Matamoros, A., and Arias, C. (2011). GSK3 function in the brain during development, neuronal plasticity and neurodegeneration. Int. J. Alzheimers Dis. 2011:189728. doi: 10.4061/2011/189728

Salinsky, M. C., Binder, L. M., Oken, B. S., Storzbach, D., Aron, C. R., and Dodrill, C. B. (2002). Effects of gabapentin and carbamazepine on the EEG and cognition in healthy volunteers. Epilepsia 43, 482–490. doi: 10.1046/j.1528-1157.2002.22501.x

Sánchez, M. P., García-Cabrero, A. M., Sanchez-Elexpuru, G., Burgos, D. F., and Serratos, J. M. (2018). Tau-induced pathology in epilepsy and dementia: notions from patients and animal models. Int. J. Mol. Sci. 19:E1092. doi: 10.3390/ijms19041092

Sen, A., Thom, M., Martinian, L., Harding, B., Cross, J. H., Nikolic, M., et al. (2007). Pathological tau tangles localize to focal cortical dysplasia in older patients. Epilepsia 48, 1447–1454. doi: 10.1111/j.1528-1167.2007.01107.x

Serenó, L., Coma, M., Rodriguez, M., Sánchez-Ferrer, P., Sánchez, M. B., Gich, I., et al. (2009). A novel GSK-3β inhibitor reduces Alzheimer’s pathology and rescues neuronal loss in vivo. Neurobiol. Dis. 35, 359–367. doi: 10.1016/j.nbd.2009.05.025

Tai, Y. X., Koepp, M., Duncan, J. S., Fox, N., Thompson, P., Baxendale, S., et al. (2016). Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain 139, 2441–2455. doi: 10.1093/brain/aww187

Takashima, A., Noguchi, K., Michél, G., Mercken, M., Hoshi, M., Ishiguro, K., et al. (1996). Exposure of rat hippocampal neurons to amyloid β peptide (25–35) induces the inactivation of phosphatidylinositol-3 kinase and the activation of tau protein kinase I/glycogen synthase kinase-3 β. Neurosci. Lett. 203, 33–36. doi: 10.1016/0304-3908(95)22527-5

Tan, W. F., Cao, X. Z., Wang, J. K., Lv, H. W., Wu, B. Y., and Ma, H. (2010). Protective effects of lithium treatment for spatial memory deficits induced by tau hyperphosphorylation in splenectomized rats. Clin. Exp. Pharmacol. Physiol. 37, 1010–1015. doi: 10.1111/j.1440-1681.2010.05433.x

Takin, S., Aiyuk-Bingol, C., Tanridag, T., and Aktan, S. (1998). Antiglutamatergic therapy in Alzheimer’s disease—effects of lamotrigine. Short communication. J. Neural Transm. 105, 295–303. doi: 10.1007/s007020050059

Thom, M., Liu, J. Y., Thompson, P., Phadke, R., Narkiewicz, M., Martinian, L., et al. (2011). Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study. Brain 134, 2969–2981. doi: 10.1093/brain/awr209

Tripathi, P. P., Santorofo, G., Brilli, E., Borrelli, E., and Bozzi, Y. (2010). Kinase- and sodium channel inhibitors reduces amyloid-β-induced seizures in mice. Epilepsia 51, 846–850. doi: 10.1111/j.1528-1167.2010.06891.x

Urbanska, M., Kazmierska-Grebowska, P., Kowalczyk, T., Caban, B., Nader, K., Pijet, B., et al. (2019). GSK3β activity alleviates epileptogenesis and limits GluA1 phosphorylation. EBioMedicine 39, 377–387. doi: 10.1016/j.ebiom.2018.11.040

Wood, J. G., Mirra, S. S., Pollock, N. J., and Binder, L. I. (1986). Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc. Natl. Acad. Sci. U S A 83, 4040–4043. doi: 10.1073/pnas.83.11.4040

Xie, H., Wen, H., Zhang, D., Liu, L., Liu, B., Liu, Q., et al. (2017). Designing of dual inhibitors for GSK-3β and CDK5: virtual screening and in vitro biological activities study. Oncotarget 8, 18118–18128. doi: 10.18632/oncotarget.15085

Zhang, F., Phiel, C. J., Specie, L., Gurvich, N., and Klein, P. S. (2003). Inhibitory phosphorylation of glycogen synthase kinase-3 (GSK-3) in response to lithium. Evidence for autoregulation of GSK-3. J. Biol. Chem. 278, 33067–33077. doi: 10.1074/jbc.m121635200

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Toral-Rios, Pichardo-Rojas, Alonso-Vanegas and Campos-Peña. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.