Is riluzole a new drug for Alzheimer's disease?

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Both experimental and clinical studies indicate that impaired excitatory synaptic transmission, which ultimately culminates in hypoactivity, is a hallmark feature of Alzheimer's disease (AD) pathology. Intriguingly, studies also find that AD patients have a propensity for epileptic seizures, and various *in vitro* cellular models of AD pathology display hyperactive and dyssynchronous network function (Palop and Mucke 2010). Taken together, this suggests the coexistence of hyper- and hypoactivity, which perhaps varies by brain region, neuronal subtype and/or stage of disease (Busche and Konnerth 2015). Glutamate is the major excitatory neurotransmitter in the brain, and so its production, secretion, and clearance are all tightly regulated cellular processes. Dysregulation of glutamate could be critical in the expression of aberrant network activity in AD (Rudy *et al.* 2015). However, the underlying mechanisms have not yet been established.

A key component of AD pathology is a change to the microtubule-associated protein tau. The protein, which canonically functions to stabilize microtubules, becomes hyperphosphorylated in the disease, leading to formation of aggregates termed paired-helical filaments, which are considered neurotoxic. Though first thought of as a predominantly neuronal axon protein, growing evidence now suggests that tau is also present in other subcellular compartments, such as dendritic spines (Kimura *et al.* 2014), as well as in glial cells. Under pathological conditions tau seems to accumulate in astrocytes (Berry *et al.* 2001). However, the physiological role for tau in glial cells is yet to be fully characterized.

A number of mutations to the tau gene have been identified as risk factors for hereditary tauopathy (Wolfe 2009). One such is the P301L mutation, which has been explored in detail following the generation of a doxycycline-suppressed transgenic mutant mouse (SantaCruz *et al.* 2005). The exact toxicity of this tau mutation may be due to the reduced binding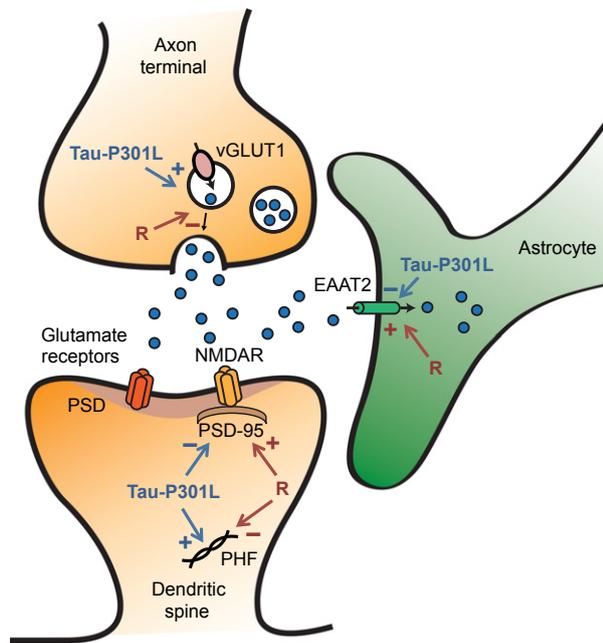 affinity with microtubules and a propensity for aggregation (Hong *et al.* 1998). One of the clear advantages of this model is the delayed onset of tauopathy, avoiding potential confounding factors that may arise if pathological tau were to be expressed during development, and perhaps more closely following the late-onset nature of tauopathy in human AD. However, it is important to acknowledge that the P301L model, focusing on tau expression, does not consider any significant contribution from amyloid beta, widely considered to partner hyperphosphorylated tau in driving AD pathogenesis. Thus, as is the case with many transgenic models, findings and interpretations must be caveated.

Riluzole [2-amino-6-(trifluoromethoxy) benzothiazole] functions as a sodium channel blocker, and is a US Food and Drug Administration-approved disease-modifying drug for amyotrophic lateral sclerosis. A number of studies have now established that riluzole exerts anti-glutamatergic effects, through the inhibition of presynaptic glutamate release and enhancement of glutamate transporter activity (Fumagalli *et al.* 2008; Grant *et al.* 2010). Adverse side effects associated with the drug are generally considered relatively mild. One of the more frequently reported effects is an increase in levels of transaminases. However, given that most clinical data have come from studies with amyotrophic lateral sclerosis patients, and the condition itself is generally fatal, there is currently limited understanding of what the

Fig. 1 Schematic representation of riluzole effects on tau-induced changes at hippocampal glutamatergic synapses. Riluzole (R) counteracts the tau-P301L expression (Tau-P301L)-induced increase in glutamate release, decrease in glutamate uptake and reduction in PSD-95 levels at hippocampal synapses (based on Hunsberger *et al.* 2015). EAAT2, excitatory amino acid transporter 2; NMDAR, *N*-methyl-D-aspartate-type ionotropic glutamate receptor; PHF, paired-helical filaments; PSD, postsynaptic density; PSD-95, postsynaptic density protein 95; vGLUT1, vesicular glutamate transporter 1. See text for details.

possible implications of long-term use of the drug are (Grant *et al.* 2010).

In this issue, Hunsberger *et al.* (2015) explore the effects of riluzole treatment on tau-P301L transgenic mice (Fig. 1). The authors employed a comprehensive analysis of possible restorative effects of the drug by examining: (i) glutamate levels in subregions of the hippocampus, (ii) expression of tau and its hyper-phosphorylated forms, and (iii) memory function using behavioral tests. The authors report a simultaneous reduction in glutamate reuptake and an increase in glutamate release in the tau-P301L model, both of which are ameliorated with riluzole treatment (Fig. 1). It remains to be explored whether one of these functions is more important than the other in contributing to the pathology of the disease. Interestingly, whilst the authors observed an increase in tonic and KCl-induced glutamate levels in the P301L mice, this was only present in the CA3 and CA1 regions of the hippocampus, not the dentate gyrus, indicative of some regional differences in vulnerability to a presumably tau-mediated dysregulation of glutamate processing. Such differences in propensity for succumbing to pathological dysregulation have been explored in previous studies (Small *et al.* 2011). Histological studies indicate that the entorhinal cortex is severely affected in AD, with similar pervasive cell death noted in the CA1 and subicular regions of the hippocampus. However, the CA3 remains relatively unaffected by comparison (Small *et al.* 2011). Relevant to the present study, there is tentative evidence (both in animal models and postmortem studies in human patients), for dentate gyrus-specific resistance to AD-related changes (Small 2014), though more work is required to substantiate this further.

The postsynaptic density protein 95 (PSD-95) forms a multimeric scaffold for the clustering of receptors, ion channels and signaling proteins at the postsynaptic density of excitatory synapses (Fig. 1). Changes in PSD-95 expression can alter the ratio of excitatory to inhibitory synapses. Furthermore, PSD-95 interacts with *N*-methyl-D-aspartate (NMDA) receptors and is required for *N*-methyl-D-aspartate-type ionotropic glutamate receptor-mediated synaptic plasticity. The authors report that reductions in PSD-95 expression in P301L tau transgenic mouse brains are prevented by riluzole treatment (Fig. 1). Whilst the normalization of PSD-95 levels is certainly indicative of restoration of excitatory synapses, such an assertion cannot really be made until further examination of more discrete components of the synapse under these conditions has been performed. Changes in, for example, glutamate receptor expression or subunit composition have significant impact on synaptic function, and so the capacity for riluzole to regulate these will also be of critical importance to consider in the future.

The authors note that trying to understand the mechanisms that mediate the increase in tonic and KCl-induced levels of glutamate in the tau-P301L transgenic mice will be carried out in future studies. The outstanding question here is a fundamental one; why does the expression of a mutant form of tau lead to impaired glutamate processing? Answering this question could well be pivotal in our understanding of the links between a developing AD pathology and hyperexcitabilty in the brain. Growing evidence is beginning to outline novel physiological roles for tau in neurons, particularly in the regulation of excitatory synaptic transmission (Kimura *et al.* 2014; Regan *et al.* 2015). Perhaps in addition to these, tau also forms part of the glia-based mechanism responsible for glutamate processing, for example regulating the expression and/or function of glutamate transporters. Indeed, there is some tentative evidence to suggest that tau interacts with excitatory amino acid transporter 2 in human AD brain tissue (Sasaki *et al.* 2009). Further work will now be required to assess the components of the glutamate regulating system that tau interacts with, both physiologically and pathologically.

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