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Exploring the Therapeutic Potential of Protein Tyrosine Phosphatase 1B in hAPP-J20 Mouse Model of Alzheimer's Disease

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Review of Ricke et al.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which no cure is available. It is estimated that, by 2050, 1 in every 85 people worldwide will be living with AD, emphasizing a dire need for an effective treatment (Brookmeyer et al., 2007). AD is characterized by amyloid plaques and neurofibrillary tangles, composed of aggregates of extracellular ß-amyloid (Aβ) peptides and intracellular hyperphosphorylated tau proteins, respectively (Holtzman et al., 2011). A long-standing hypothesis is that Aβ initiates AD pathology. Specifically, an increase in longer, more toxic forms of Aβ is proposed to lead to amyloid plaque formation and to formation of neurofibrillary tangles, which disrupt microtubules and impair axoplasmic flow, resulting in neuronal cell loss (Sadigh-Eteghad et al., 2015). Despite evidence from preclinical studies, however, support for this hypothesis has been challenged in recent years by the fact that many therapeutics developed to target either Aβ or tau failed to show efficacy at later stages of clinical trials (Huang et al., 2020). Therefore, many researchers have shifted their focus away from Aβ and toward other AD pathologies, such as neuroinflammation and metabolic dysfunction. One potential player in this pathology is the phosphatase protein-tyrosine phosphatase 1B (PTP1B).

PTP1B regulates several processes in the CNS, including metabolism-related signaling pathways, such as insulin and leptin signaling, synaptic plasticity, endoplasmic reticulum stress, and microglia-mediated neuroinflammation (Fuentes et al., 2012; Tsou and Bence, 2013; Song et al., 2016; Vieira et al., 2017). Given its integral role in these pathways that are disrupted in AD, PTP1B appears to hold great potential as a candidate for therapeutic development. Therefore, Ricke et al. (2020) explored the effects of PTP1B inhibition in a mouse model of AD, hAPP-J20. These mice overexpress human amyloid precursor protein (APP) with AD-linked mutations that result in high Aβ expression levels and amyloid plaque formation. Consequently, these mice display deficits in spatial memory and learning, changes in synaptic plasticity, and elevated neuroinflammation.

To determine whether targeting PTP1B can ameliorate AD phenotypes, Ricke et al. (2020) evaluated the effects of treating hAPP-J20 mice with trodusquemine, a PTP1B-specific inhibitor, for 1 month starting at 4.5 months of age. After repeated administration of trosdusquemine, hAPP-J20-treated mice performed as well as control WT mice in the Morris water maze test, suggesting a complete rescue in spatial learning and memory. Moreover, PTP1B inhibition was sufficient to rescue neurodegeneration. This was determined by quantifying NeuN-positive cells in the pyramidal cell layer of hippocampus.

Ricke et al. (2020) next examined the effects of PTP1B inhibition on downstream signaling pathways. As mentioned previously, PTP1B is a key regulator of insulin signaling. When insulin binds to the insulin receptor (IR), the receptor becomes autophosphorylated at tyrosine residues, then recruits and activates (by tyrosine phosphorylation) its intracellular effectors, IRS1 and IRS2. PTP1B dephosphorylates tyrosine residues in IR and IRS1, reducing insulin sensitivity and inhibiting signaling (Goldstein et al., 2000). In neurons exposed to Aβ, tyrosine phosphorylation of IRS1 is reduced, reducing the neurons' sensitivity to insulin (Bomfim et al., 2012; Talbot et al., 2012). Ricke et al. (2020) found that inhibition of PTP1B restored insulin signaling by increasing levels of phosphorylated IRS1 in acutely cultured brain slices from hAPP-J20.

Similar results were presented for the kinase GSK3β, an indirect target of PTP1B implicated in AD. GSK3β is a ubiquitously expressed and constitutively active multifunctional serine/threonine kinase involved in a number of cellular functions, including glycogen metabolism, gene expression,

Received Apr. 12, 2020; revised June 10, 2020; accepted June 20, 2020.
The author declares no competing financial interests.
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https://doi.org/10.1523/JNEUROSCI.0852-20.2020

apoptosis, and microtubule stability. It acts as a downstream regulatory switch for several signaling pathways, including insulin (Doble and Woodgett, 2003). Trosdusquemine treatment increased levels of phosphorylated GSK3β and restored the pGSK3β-to-GSK3β ratio in hAPP-20 mice to WT levels. Therefore, PTP1B inhibition was sufficient to revert signaling pathways disrupted in AD back to normal.

In addition, Ricke et al. (2020) examined the effects of PTP1B inhibition on inflammation in hAPP-J20 mice. These mice have elevated levels of neuroinflammation as indicated by an increase in activated microglia (IBA-1-positive cells) in the hippocampus CA3 region. Previous reports demonstrated that PTP1B functions as a positive regulator of neuroinflammation in microglia. Specifically, PTP1B activates Src kinase via dephosphorylation at a negative regulatory site, allowing Src to activate NF-κB, a transcriptional regulator of proinflammatory cytokines and chemokines (Song et al., 2016). Consistent with this, trosdusquemine treatment reduced the total area of IBA-1-positive staining measured in the hippocampus CA3 region to levels comparable with WT, suggesting that PTP1B inhibition reduced inflammation in hAPP-J20 mice.

Given that PTP1B possesses a highly conserved active site shared among many protein tyrosine phosphatases (Tonks, 2013), Ricke et al. (2020) examined PTP1B-deficient mice to verify that the effects of trosdusquemine was not attributable to effects of other phosphatases. hAPP-J20 mice with PTP1B selectively ablated in glutamatergic neurons (hAPP-J20-PTP1B-KO mice) were compared with hAPP-J20 mice. Similar to what was found with trosdusquemine treatment, hAPP-J20-PTP1B-KO mice performed better in the water maze test and had less neurodegeneration than hAPP-J20 mice. Moreover, the ratio of pGSK3β-to-GSK3β in hAPP-J20-PTP1B-KO mice was comparable with that in WT mice. However, neuron-selective ablation of PTP1B did not reduce neuroinflammation. hAPP-J20-PTP1B-KO and hAPP-J20 mice had comparable numbers of activated microglia (IBA-1-positive cells) in hippocampal CA3. This is consistent with previous studies showing distinct roles for PTP1B in microglia and neurons (Vieira et al., 2017).

The study by Ricke et al. (2020) provides novel insights into the role of PTP1B in AD. Behavioral data revealed PTP1B as a key contributor to memory deficits and neurodegeneration in hAPP-J20 mice. Yet the mechanisms remain to be fully resolved. Exploring the role of PTP1B in BDNF signaling may highlight some of these underlying mechanisms. BDNF signaling through its receptor TrkB is a key regulator of synaptic plasticity, including LTP, a form of activity-dependent synaptic plasticity believed to underlie learning and memory. In addition, BDNF signaling through TrkB has been shown to promote neuronal survival (Fumagalli et al., 2006). PTP1B inhibits BDNF signaling by dephosphorylating the TrkB receptor, rendering it inactive (Ozek et al., 2014). Notably, clinical studies and animal studies have shown that BDNF signaling is significantly reduced in AD (Fumagalli et al., 2006). Because PTP1B functions as an inhibitor of BDNF signaling via TrkB (Ozek et al., 2014), it is possible that PTP1B inhibition enhances BDNF signaling to increase cognition and reduce neuronal death in hAPP-J20 mice. Indeed, Nagahara et al. (2009) demonstrated neuroprotective roles for BDNF in several AD animal models, including hAPP-J20 mice.

GSK3β signaling may also contribute to neuronal and memory loss present in hAPP-J20 mice. GSK3β has been strongly linked to AD pathogenesis: its increased levels and activity are commonly identified in AD patients and animal models, and these changes associate closely with synaptic dysregulation, memory impairment, and apoptosis (DaRocha-Souto et al., 2012). Interestingly, BDNF signaling has been shown to inhibit GSK3β by inducing phosphorylation through a PI3K-activated Akt/PKB kinase signaling cascade (Smillie et al., 2013). GSK3β is also regulated by insulin signaling through the activation of PI3K by IR (Albeely et al., 2018). Ricke et al. (2020) showed that PTP1B inhibition was sufficient to restore insulin signaling and the ratio pGSK3β-to-GSK3β in hAPP-J20 mice. Whether PTP1B functions through BDNF signaling and/or insulin signaling in these mice to regulate pGSK3β levels, cognitive deficits, and neurodegeneration remains to be determined.

Finally, Ricke et al. (2020) provide insightful data on the role of inflammation in AD. They demonstrate that neuronal ablation of PTP1B did not reduce inflammation in hAPP-J20-PTP1B-KO mice but was nonetheless sufficient to rescue cognition and neuronal loss at 6 months of age. These results suggest that inflammation does not contribute to the pathogenesis of the disease at this stage but appears to be a byproduct of it. Whether this remains to be true in older mice remains to be studied.

In conclusion, Ricke et al. (2020) have demonstrated that inhibition of PTP1B either by trosdusquemine or neuronal ablation was sufficient to rescue cognitive deficits and neurodegeneration present in hAPP-J20 mice independent of neuroinflammation. This supports the therapeutic potential of targeting PTP1B in AD. However, more work is required to determine the underlying mechanisms for the beneficial effects presented in this study and whether these findings can be replicated in other models of AD, including tau-based models.

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