Mini-review: Role of the PI3K/Akt pathway and tyrosine phosphatases in Alzheimer's disease susceptibility

Running title: **PI3K/Akt and tyrosine phosphatases in Alzheimer's disease**

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Summary

A variety of findings from *in vitro* experiments and animal models support the hypothesis that one contribution to pathogenesis in Alzheimer's disease (AD) is enhanced phosphorylation of tau protein which may be triggered by amyloid β (Aβ) and mediated by impaired activity of the PI3K/Akt signalling pathway. A number of tyrosine phosphatases act to reduce PI3K/Akt activity and inhibition of tyrosine phosphatases is protective against Aβ toxicity in cell cultures and whole animals. Results from analysis of exome sequenced late onset AD cases and controls similarly show that rare coding variants predicted to damage PI3K functioning increase AD risk whereas those which are predicted to damage genes for tyrosine phosphatase genes are protective. Taken together, these results support the proposition that tyrosine phosphatase antagonists might be trialled as therapeutic agents to protect against the development of AD.

Keywords

Alzheimer's disease; PI3K; Akt; tyrosine phosphatase; tau protein.

Background

Alzheimer's disease (AD) is a common cause of dementia characterised by deposition of amyloid β (Aβ), derived from amyloid precursor protein (APP) and formation of neurofibrillary tangles consisting of hyperphosphorylated tau protein (Kanno et al., 2016). Variants in the genes for APP and other proteins which process it can act in a mendelian fashion and cause early onset forms of AD, demonstrating that abnormal handling of APP can be causative. However, the density of Aβ deposits correlates poorly with clinical severity and it is thought that tau phosphorylation may be a key contributor to neuronal damage and loss of function. Here we bring together evidence from experiments and genetic studies in human subjects to highlight a possible role for the PI3K/Akt signalling pathway in AD pathogenesis and to suggest that tyrosine phosphatases, which modify its activity, may be potential targets for the prevention of AD progression.

Tyrosine phosphatases and the PI3K/Akt pathway

One mechanism whereby cells can moderate the activity of proteins is by phosphorylating or dephosphorylating specific amino acid residues using kinases or phosphatases. Phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB, also known as Akt) are kinases which are elements of a number of different signalling pathways and disruption of their function is thought to be a key feature of many disease processes, including cancer and diabetes (Sugiyama et al., 2019). Lately, evidence has grown for their potential importance in the development of AD. A key step in the pathogenesis of AD is the phosphorylation of tau protein by glycogen synthase kinase 3 beta (GSK-3β), with the accumulation of phosphorylated tau in neurons causing cell damage and reduced survival (Balaraman et al., 2006; Kanno et al., 2016). GSK-3β is maintained in an inactive state by phosphorylation and this is achieved by Akt. Akt is in turn activated by PI3K, both directly and indirectly via phosphoinositide-dependent kinase-1 (PDK1). Thus, increased activity of PI3K is associated with reduced GSK-3β activity and reduction of tau phosphorylation. PI3K/AKT signalling is subject to many complex control mechanisms but one which is of potential relevance is that the activity of PI3K can be stimulated by receptor tyrosine kinases (RTKs), including the insulin receptor (IR), which phosphorylate insulin receptor substrate 1 (IRS-1) and which in turn phosphorylates PI3K. Additionally, an isoenzyme of protein kinase C, PKCε, has been shown to activate Akt and deactivate GSK-3β (Kanno et al., 2006).

The activation of PI3K and Akt through phosphorylation by tyrosine kinases can be opposed by tyrosine phosphatases. Although the relevant processes are yet to be fully elucidated, one example is protein tyrosine phosphatase 1B (PTP1B), which dephosphorylates RTKs and IRS-1 (Stuible and Tremblay, 2010). Another is that receptor-type tyrosine-protein phosphatase S (PTPRS) has been shown to directly interact with epidermal growth factor receptor (EGFR), a RTK, and that in its presence the activity of EGFR is reduced, accompanied by reduced phosphorylation of Akt (Morris et al., 2011; Suárez Pestana et al., 1999; Vijayvargia et al., 2004). Likewise, receptor-type tyrosine-protein phosphatase T (PTPRT) indirectly reduces the activity of PI3K and Akt while phosphatase and tensin homolog (PTEN) is a phosphatase for IRS1 and also reduces PI3K/Alt activity (Shi et al., 2014; Zhao et al., 2017).

Although there are many complex and sometimes contradictory findings, it has been proposed that in AD there is an increase in production of Aβ and that this can suppress the activity of RTKs and may also inhibit PDK1, thus leading to increased activity of GSK-3β and tau phosphorylation, leading to neuronal cell loss (Gabbouj et al., 2019; Jimenez et al., 2011; Kanno et al., 2016; Lee et al., 2009; Townsend et al., 2007; Zhao et al., 2008). In post mortem studies of AD cases there is reduced responsiveness of the IR/IRS-1/PI3K/Akt signalling pathway to insulin stimulation, especially in the hippocampus, potentially triggered by Aβ oligomers (Talbot et al., 2012). These relationships are summarised in Figure 1.

Role of PI3K/Akt and tyrosine phosphatases in models of AD pathology

Results from a number of *in vitro* experiments and with animal models support the notion that increased activation of the PI3K/Akt pathway may tend to be preventive against AD pathogenic mechanisms. One way to accomplish this is to antagonise the activity of tyrosine phosphatases which inhibit the pathway.

In cultures of neuronally differentiated PC12 cells, Aβ was shown to cause decreased phosphorylation of Akt and GSK-3β, increased phosphorylation of tau and reduced cell viability

(Cheng et al., 2018). These effects of Aβ could be prevented by asiatic acid, a natural pentacyclic triterpene derived from the medicinal herb *Centella asiatica*. These actions of asiatic acid were blocked by LY294002, a specific inhibitor of PI3K, suggesting that they relied on PI3K activation.

PTEN is a target of the microRNA miR-193a-3p and suppression of *PTEN* using miR-193a-3p, which is predicted to lead to increased PI3K/Akt activity, protected against Aβ-induced impairment of cell viability inhibition and apoptosis in PC12 and SH-SY5Y cell cultures (Cao et al., 2020). Additionally, Aβ treatment led to reduced expression of miR-193a-3p in cell cultures, while in patients with late onset AD (LOAD) serum levels and expression in white blood cells of miR-193a-3p were both lower than in controls.

In a 5xFAD transgenic mouse model of AD, inhibition of PTP1B in combination with activation of PKCε suppressed Aβ-induced tau phosphorylation and ameliorated spatial learning and memory impairment (Kanno et al., 2016). This could be accomplished using DCP-LA, a linoleic acid derivative which simultaneously inhibits PTP1B and activates PKCε (Kanno et al., 2006; Nishizaki, 2017; Shimizu et al., 2011; Tsuchiya et al., 2014).

Another inhibitor of PTP1B is bergenin (Li et al., 2005). Using the intracerebroventricular streptozotocin model of AD in rats, oral bergenin was able to ameliorate cognitive deficits, prevent hippocampal neuronal loss and reduce levels of Aβ and phosphorylated tau (Barai et al., 2019). However, bergenin has a range of other actions. It is a β-secretase antagonist and was also shown to inhibit acetyl and butyryl cholinesterases as well as reversing NMDA-induced cell loss and cognitive deficits produced by scopolamine (Barai et al., 2019; Kashima and Miyazawa, 2013). Therefore it is not clear whether the observed effects on cognition were due to PTP1B inhibition or other mechanisms.

Although the above studies suggest that inhibition of PTP1B in animal models of AD can counteract processes which involve Aβ toxicity and tau phosphorylation, accompanied by improvements in cognitive functioning, further experiments suggest that PTP1B inhibition produces other effects which are also neuroprotective. Vanadium compounds act as inhibitors of tyrosine phosphatases, including PTP1B (Irving and Stoker, 2017). A mouse model of vascular dementia can be produced by administering methionine to induce hyperhomocystinaemia and in this model administration of sodium orthovanadate attenuated impairments in learning and memory (Kumar et al., 2019). In treated mice there were reductions in vascular permeability and acetyl cholinesterase activity as well as in levels of two indicators of oxidative stress, thiobarbituric acid reactive substances and glutathione. These benefits are presumably not consequences of reduced tau phosphorylation but may reflect more general vascular, anti-inflammatory and neuroprotective effects of PTP1B inhibition.

A more recent study used sodium orthovanadate in the intracerebroventricular-streptozotocin rat model of Alzheimer's disease and demonstrated that this led to reduced cognitive impairments, increased expression of genes in the PI3K/AKT pathway, improved mitochondrial activity and reduced tau pathology (Akhtar et al., 2020).

Another recent study has demonstrated that selective pharmacological inhibition of PTP1B with trodusquemine or genetic ablation of PTP1B specifically in neurons prevented hippocampal neuron loss and spatial memory deficits in a hAPP-J20 transgenic AD mouse model (Ricke et al., 2020). This

occurred without a change in cerebral amyloid levels or plaque numbers, although there was a reduction in average Aβ plaque size. This seems to provide compelling evidence that reduction in PTP1B function within neurons can indeed be protective against Aβ-mediated toxicity.

A summary of these compounds which experimentally seem to have effects on the PI3K/Akt pathway which might moderate the pathogenesis of AD is shown in Table 1.

Findings in humans

There seems to be a fairly consistent picture derived from *in vitro* and animal studies for a role for PI3K/Akt mechanisms in AD disease mechanisms and it has been proposed that this pathway could have relevance for the development of AD in humans (Gabbouj et al., 2019). Post-mortem AD brain samples show inactivation of IRS1 and decreased levels of PI3K but it is difficult to distinguish aetiological factors from secondary manifestations of the disease process (Bomfim et al., 2012; Moloney et al., 2010; Steen et al., 2005; Talbot et al., 2012). Additionally, a rare variant in the *TREM2* gene is associated with increased risk for LOAD and *TREM2* knockdown does lead to reduced phosphorylation of Akt and GSK-3β suggesting a possible mechanism, although TREM2 has many additional actions (Guerreiro et al., 2013; Jonsson et al., 2013; Zheng et al., 2017). One activator of the PI3K/Akt pathway is insulin, which acts via neuronal insulin receptors, and clinical trials of intranasal insulin for AD have produced some promising results (Chapman et al., 2018). As mentioned above, serum levels of miR-193a-3p, which in vitro protects against Aβ toxicity, are reduced in LOAD patients and as miR-193a-3p suppresses *PTEN* it is expected to enhance PI3K/Akt activity (Cao et al., 2020).

Genome wide association studies have not implicated common variants in genes related to PI3K/Akt activation (Kunkle et al., 2019; Marioni et al., 2018). However in our own study of exome-sequenced samples of 4,600 subjects with LOAD and 6,199 controls it was found that there was an excess of rare, damaging coding variants in the *PIK3R1* gene ($p = 0.0001$) among cases (Curtis et al., 2019). This gene codes for the phosphoinositide-3-kinase regulatory subunit 1 of PI3K. Additional analyses were carried out using sets of genes as defined in the Molecular Signatures Database (Subramanian et al., 2005). In the set of genes defined as those having protein tyrosine phosphatase activity there was an excess of rare, damaging coding variants among controls compared to cases with overall significance of $p = 5 \times 10^{-6}$. 9 of these genes were individually significant at $p < 0.05$, consisting of *PTPN1*, which codes for PTP1B, as well as *PTPRS*, *PTPRU*, *PTPRR*, *PTPRT*, *PTPN12*, *PTP4A3*, *PTPN22* and *DUSP6*. The variants involved were individually very rare so it was not possible to clearly characterise their effects and there was no obvious pattern as to where they occurred within the genes. Although nonsynonymous variants may result in either loss of function or gain of function, the expectation is that variants annotated as damaging will on average result in reduced function. Therefore these results suggest that coding variants which impair PI3K/Akt functioning increase risk of LOAD whereas variants which impair functioning of tyrosine phosphatases, hence expected to enhance PI3K/Akt functioning, are protective.

Conclusions

There is now a striking concordance between the results from experiments using cell cultures and animal models and the implications of findings from analysis of rare coding variants in human subjects. Overall, there is a strong implication that interventions which enhance PI3K/Akt

functioning might mitigate the downstream effects of Aβ and tend to prevent the development of AD. This could be accomplished by agents which inhibited the action of tyrosine phosphatases. The most strongly implicated specific target is PTP1B but the fact that the result for the set of tyrosine phosphatase genes combined is much more significant than for *PTPN1* alone suggests that variants in other genes might also be protective. Likewise, there is no suggestion that variants in *PTEN* are commoner in controls than LOAD cases but this could reflect the fact that genetic variants damaging *PTEN* cause a variety of severe developmental disorders (Isik et al., 2020). This would preclude them being observed in normal controls. However it remains perfectly possible that a PTEN antagonist might be an effective agent to prevent the development of AD. The evidence to date seems to suggest that tyrosine phosphatases which reduce PI3K/Akt functioning represent a class of proteins which might be targeted individually or collectively.

We suggest that there now seems to be sufficient evidence to consider embarking on clinical trials to discover whether tyrosine phosphatase antagonists might reduce tau phosphorylation, neurodegeneration and clinical deterioration in subjects in preclinical or early stages of AD.

Conflict of interest statement

The authors declare they have no conflict of interest.

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DC conceived the theme and both DC and SB contributed to researching and writing up the manuscript.

Data availability statement

This review did not utilise or generate data and no data is available.

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Table 1 Summary information about compounds with experimental evidence for an effect on the PI3K/Akt pathway relevant to AD pathogenesis.

Pharmaceutical agent	**Observed effects**	**Presumed mechanism of action**	**Known effects in humans**
Asiatic acid	Prevention of the following effects of Aβ in cell cultures: decreased phosphorylation of Akt and GSK-3β; increased phosphorylation of tau; reduced cell viability (Cheng et al., 2018).	Increased PI3K activation.	Used in traditional Indian and Chinese folk medicine with claims that it has many beneficial roles including for depression, dementia, stress, wound healing, heart disease and cancer (Meeran et al., 2018).
DCP-LA	Suppression of Aβ-induced tau phosphorylation and amelioration of spatial learning and memory impairment in mice (Kanno et al., 2016; Nishizaki, 2017).	Inhibition of PTP1B and activation of PKCε.	Not yet trialled.
Bergenin	Amelioration of cognitive deficits, prevention of hippocampal neuronal loss and reduction of levels of Aβ and phosphorylated tau in rats (Barai et al., 2019).	Inhibition of PTP1B, though other actions may also be relevant.	Used in traditional Indian and Chinese folk medicine and claimed to have antiurolithic, antidiabetic, hepatoprotective, antifungal and cardioprotective activities, among others (Gurav and Gurav, 2014).
Sodium orthovanadate	Attenuation of impairments in learning and memory in mice (Kumar et al., 2019). Reduced cognitive impairments and reduced tau pathology in rats (Akhtar et al., 2020).	Inhibition of tyrosine phosphatases, though other actions may also be relevant.	Some preliminary studies of vanadium compounds as potential antidiabetic agents but no phase 2 trials (Rana and Kumar, 2018; Thompson and Orvig, 2006). Vanadium compounds are sold as dietary supplements.
Trodusquemine	Prevention of hippocampal neuron loss and spatial	Inhibition of PTP1B.	Reported to be well-tolerated in Phase 1 trials for diabetes and

	memory deficits in mice.		breast cancer, though these have not been published. In development as a regenerative agent for myocardial infarction.

Figure 1. Illustration of modifying effects of Aβ on the activity of the PI3K/Akt pathway with respect to tau phosphorylation. PI3K activation leads to the phosphorylation of Akt1 at two sites: directly at pS473 and indirectly via PDK1 at pT308 (Kanno et al., 2016; Lee et al., 2009; Shi et al., 2014; Townsend et al., 2007). By inhibiting the pathway, Aβ leads to increased phosphorylation of tau protein.