Published in final edited form as:
Prog Mol Biol Transl Sci. 2012 ; 106: 343–379. doi:10.1016/B978-0-12-396456-4.00012-2.

Protein Phosphatases and Alzheimer's Disease

Steven P. Braithwaite[*], **Jeffry B. Stock**[†], **Paul J. Lombroso**[‡], and **Angus C. Nairn**[§]
[*]Signum Biosciences, Monmouth Junction, New Jersey, USA
[†]Department of Molecular Biology, Princeton University, Princeton, New Jersey, USA
[‡]Child Study Center, Yale University School, of Medicine, New Haven, Connecticut, USA
[§]Department of Psychiatry, Yale University, School of Medicine, New Haven Connecticut, USA

Abstract

Alzheimer's Disease (AD) is characterized by progressive loss of cognitive function, linked to marked neuronal loss. Pathological hallmarks of the disease are the accumulation of the amyloid-β (Aβ) peptide in the form of amyloid plaques and the intracellular formation of neurofibrillary tangles (NFTs). Accumulating evidence supports a key role for protein phosphorylation in both the normal and pathological actions of Aβ as well as the formation of NFTs. NFTs contain hyperphosphorylated forms of the microtubule-binding protein tau, and phosphorylation of tau by several different kinases leads to its aggregation. The protein kinases involved in the generation and/or actions of tau or Aβ are viable drug targets to prevent or alleviate AD pathology. However, it has also been recognized that the protein phosphatases that reverse the actions of these protein kinases are equally important. Here, we review recent advances in our understanding of serine/threonine and tyrosine protein phosphatases in the pathology of AD.

I. Introduction

Alzheimer's Disease (AD), the most common neurodegenerative disorder, is a major and growing public health concern because of increases in both median age and life expectancy.[1] With the enormous economic cost of AD patient care and loss of productivity, its impact as a major clinical, social, and economic issue has been widely acknowledged. AD is characterized by progressive loss of cognitive function, starting with mild cognitive impairment that eventually evolves to include more severe cognitive deficiencies followed by death from secondary complications. At a cellular level, AD is characterized by marked neuronal and neuritic loss.[2]

The major pathological hallmarks of AD are the aberrant accumulation of the amyloid-β peptide (Aβ) in the form of amyloid plaques and the intracellular formation of hyperphosphorylated tau protein inclusions (neurofibrillary tangles, or NFTs).[1] Oligomeric assemblies of Aβ and tau are increasingly recognized as the most pathogenic forms, probably more so than amyloid plaques or NFTs.[3] Aβ peptides are generated by the processing of the amyloid precursor protein (APP). The central role of APP in AD is underscored by the fact that mutations in APP [familial AD (FAD)] cosegregate with an early onset AD pathology.[4,5] Notably, various independent lines of transgenic mice expressing APP with FAD mutations display pathological and cognitive deficits that correlate with those found in human AD.[6]

Formation of Aβ is catalyzed by β- and γ-secretase (γ-secretase/presenilin).[7] The formation and subsequent aggregation of Aβ initiate a complex cascade of molecular and cellular changes that gradually leads to the clinical features of AD. Recent studies have indicated that soluble Aβ oligomers act initially to disrupt synaptic function.[8,9] Thus, Aβ-mediated

synaptopathology represents a critical component in the cognitive decline associated with the disease. Aβ oligomeric preparations inhibit long-term potentiation (LTP) likely through its effects on AMPA and NMDA glutamate receptor trafficking. However, while much has been learned about the role of Aβ in AD, particularly in synaptopathology, it is still unknown what mechanisms are involved in the transition from impaired synaptic function to loss of synapses and to eventual cell death.

Accumulating evidence supports a key role for protein phosphorylation in both the normal and pathological actions of APP, Aβ, and tau. APP itself is phosphorylated at multiple sites by several protein kinases,[10–15] and this may modulate its processing and influence the production of Aβ.[16,17] For example, phosphorylation of APP may influence the ability of β-secretase to cleave APP to produce the most amyloidogenic and toxic peptide $A\beta_{1-42}$.[16,18] Both presenilin (the γ-secretase) and BACE (the β-secretase) responsible for generation of Aβ are regulated by phosphorylation.[19–23]

AD is a member of the family of tauopathies that are characterized by the presence of hyperphosphorylated tau.[24] Up to 50 different sites of phosphorylation are present in tau (out of a total of 85 serine, threonine, and tyrosine residues)[25–27] (Table I), and many of these are found in tau isolated from AD brain. Phosphorylation of tau in AD brain is likely mediated by various protein kinases, including Cdk5, GSK3β, PKA, and MARK, which target serine and threonine residues in proline-rich domains of the protein.[30] Phosphorylation of tau interferes with its ability to interact with microtubules, leading to its aggregation and, ultimately, to the generation of NFTs.

Studies of the protein kinases that phosphorylate APP, tau, and the proteases involved in generation of Aβ are clearly important, as protein kinases are viable drug targets, and inhibitors may prevent or alleviate AD pathology. However, it has also been recognized that the protein phosphatases that reverse the actions of these protein kinases are equally important and warrant detailed analysis. For example, it appears that a major contributor to the hyperphosphorylation of tau at so many sites is that there is a significant decrease in the levels or activity of the protein phosphatase(s) that dephosphorylate tau in AD brain. Protein phosphatases are classified on the basis of their ability to dephosphorylate either serine and threonine residues (PPPs and PPMs) or tyrosine residues (protein tyrosine phosphatase, PTPs or dual-specificity DSPs). The PPP family includes PP1, PP2A, PP2B (also known as calcineurin), PP4, PP5, and PP6, while the PPM family includes various forms of PP2C and mitochondrial PPases. High levels of the serine/threonine PPases are found throughout the brain, with PP1, PP2A, PP2B, and PP5 being abundant and implicated in AD. Recent studies have also begun to reveal roles for PTPases, especially striatal-enriched tyrosine phosphatase (STEP), in AD. Here, we review recent advances in our understanding of the role of these serine/threonine and tyrosine protein phosphatases in the pathology of AD.

II. Protein Phosphatase 2A

A. General Properties

Protein phosphatase 2A (PP2A) is widely expressed throughout the body and plays a predominant role in the dephosphorylation of thousands of different phosphoproteins in vertebrate tissues.[38] PP2A is expressed at high levels in the brain, where it acts on diverse substrates.[39–42] It has been estimated that perhaps more than 50% of all proteins are regulated by one or more of several hundred different protein kinases whose activities are, in turn, regulated by a wide range of signal transduction pathways.[43,44] This regulatory network is highly interconnected, as kinases are invariably subject to cross talk regulation wherein one or more kinase phosphorylate and thereby activate or inhibit one or more other kinase. In this respect, in addition to its general role in the direct dephosphorylation of many

cellular phosphoproteins, PP2A is responsible for the dephosphorylation of many protein kinases.[45] The broad spectrum of PP2A activity means that any dysfunction in PP2A can have profound consequences on diverse cellular processes. In neurodegenerative disorders, exemplified by AD, any PP2A dysfunction would lead to an imbalance in kinase-mediated signaling pathways that contribute to multiple pathologies at the core of the disease process.

The majority of PP2A exists as a functional heterotrimer consisting of a catalytic C subunit, a scaffold-like A subunit, and one of a series of alternative regulatory B subunits.[38] Four structurally unrelated families of B subunits have been identified, termed B, B', B'', and B'''. Splice variants lead to at least 24 alternative forms. Holoenzymes with different B subunits direct PP2A to different spectra of substrates and different subcellular compartments. Additionally, the specificity and subcellular localization of the PP2A catalytic subunit are posttranslationally regulated by a chemistry that appears to be completely specific to PP2A involving the formation and hydrolysis of a leucine carboxyl methyl ester at the carboxyl terminal leucine L309.[46–49] PP2A carboxyl methylation facilitates the assembly and enhances the activity of microtubule-associated PP2A in neuronal cells.[48,49] In addition to carboxyl methylation at L309, the catalytic subunit of PP2A activity is inhibited by tyrosine phosphorylation at Y307.[50] The C subunit can also be phosphorylated at T304.

B. Protein Phosphatase 2A Linkage to Alzheimer's Disease

Postmortem studies have closely linked PP2A at multiple levels with AD. Ultimately, the activity of PP2A is reduced in the disease owing to reduced levels, increased inhibition, and alterations in its specificity and subcellular localization.[51–54] Decreased expression of mRNA encoding the PP2A catalytic subunit has been reported,[55] which may underlie the decreased levels of the protein that are observed.[53] A protein that binds and inhibits PP2A, termed SET or inhibitor 2 (I2), is highly expressed in AD brains.[56] Thus, in AD, increased levels of SET probably contribute to the general downregulation of PP2A associated with disease progression. Note, however, that the level of ARPP-19, which has recently been found to be an inhibitor of PP2A,[57,58] has also been found to be reduced in AD brain.[59] Importantly, a substantial decrease in PP2A methylation has been observed in postmortem brains of AD patients.[52,60] This is associated with decreased levels of a PP2A targeting subunit Bα/PR55, which binds preferentially to the methylated form of the PP2A catalytic core.[52,61]

Other recent studies have identified potential genetic links between AD and PP2A. The number of CAG repeats in the gene encoding the Bβ subunit, which had previously been linked to spinocerebellar ataxia 12, was found to be reduced in a Taiwanese AD cohort, and this might be associated with lower levels of expression of PP2A.[62] A follow-up study of a Japanese AD cohort found a similar result, particularly in a subgroup of samples who expressed the APOE4 allele.[63] Therefore, there are multiple mechanistic links between PP2A and AD.

C. Pathophysiological Roles of Protein Phosphatase 2A in Alzheimer's Disease

Based on a number of biochemical studies, where the ability of different PPase preparations immunoprecipitated from human brain was used to dephosphorylate hyperphosphorylated tau, it appears that PP2A is the major phospho-tau phosphatase[28,30,33,34,64] (Table I). Thus the reduced PP2A activity mentioned above appears likely to be a major factor in increased tau phosphorylation and NFT pathology.[65] As tau is phosphorylated at so many sites, studies have been limited to only a subset of sites where specific phospho-antibodies are available. In addition, only qualitative assessment of the rates of dephosphorylation and affinity for any given site is possible. With these limitations in mind, T205, T212, S262, and S409

appear to be the preferred sites for PP2A, with S262 being the site that is most favored by PP2A compared to other PPases. However, as for other sites, these individual sites can be dephosphorylated by more than one PPase (see Table I).

As mentioned above, PP2A exists as a core enzyme consisting of the AC dimer together with various B subunits that influence substrate specificity. Only the Bα-containing isoform has been demonstrated to effectively bind to and dephosphorylate tau,[53] with the mechanism of selective interaction of the Bα subunit and phospho-tau revealed by X-ray crystallography studies.[66] Thus, although other forms of PP2A may be relevant for additional pathways that contribute to the disease, the data to date suggest that it is the deficiency in methylated ABαC that is the primary PP2A defect in AD pathogenesis.[52,53] Recent studies have also suggested that the ability of PP2A to dephosphorylate tau is regulated by the activity of the peptidyl-prolyl isomerase Pin1.[54,67,68] However, differing roles for Pin1 in promoting or inhibiting the effects of PP2A have been observed.

Regulation of PP2A has also been connected to APP. Phosphorylation of APP influences the ability of β-secretase to cleave APP to produce the most amyloidogenic and toxic peptide $A\beta^{1-42}$.[18] PP2A appears to inhibit the generation of this peptide,[69] presumably by dephosphorylating APP at Thr668 where it is phosphorylated by Cdk5[14] and/or c-jun N-terminal kinase.[70] Interestingly, a recent RNA Seq study using cells expressing the APPswe mutant form of APP showed that the expression levels of the PP2A catalytic subunit as well as several PP2A regulatory subunits were decreased.[71] The mechanism involved was not elucidated, but this preparation might be useful for understanding the effects of mutant APP expression on transcriptional events. The catalytic subunit of PP2A is known to be inhibited by phosphorylation of Y307.[50] Increased levels of Y307 were found in cells expressing the APPswe form of APP and in transgenic mice expressing APPswe and presenilin 1.[72] Increased phosphorylation of Y307 was also observed in sections of hippocampus and entorhinal cortex from human AD patients, especially in neurons containing NFTs. These results suggest that inhibition of PP2A may be caused by Aβ, and that this is linked to hyperphosphorylation of tau.

PP2A is also actively involved in apoptotic cell death and therefore can directly contribute to neurodegeneration, the final hallmark pathology of AD.[73] Generally, PP2A's proapoptotic functions involve dephosphorylation of Bcl family proteins.[74] In the progression of AD, the relevance of PP2A in early apoptotic processes may be relevant, such as in synaptic and axonal pruning, which ultimately lead to the programmed, controlled process of cell death.[75]

PP2A has diverse cellular roles beyond these pathological hallmarks, as it regulates multiple cellular signaling pathways. Neuroinflammatory processes are closely linked to a cascade of serine/threonine phosphorylation events, and the action of PP2A on the kinases in these pathways reduces their activity and can thus decrease inflammation.[76] Neuroinflammation is a key component of AD, with abnormally accumulated peptides such as Aβ being highly immuno-genic.[77] Amyloid plaques are generally surrounded by microglia, and the associated inflammatory responses are thought to play a major role in neuronal cell death.[78] Decreased PP2A levels and activity may therefore be associated with increased inflammation. Anti-inflammatory agents are effective in reducing cognitive deficits in rodent models of AD[78–80] and have potential therapeutic utility in humans.[81,82]

PP2A is also intimately linked with cell cycle progression.[38] In AD, stress-induced re-entry/cell cycle re-entry has been proposed as a key potential initiating event.[83] Normally, quiescent neurons are seen to display markers of cell division,[84] and in an animal model in which cell cycle re-entry is driven by overexpression of the SV40 large T antigen, an

inhibitor of PP2A, AD-like pathology is observed.[85] PP2A controls the G2/M transition,[86] and PP2A demethylation has been associated with cell division.[87] Thus, reduced PP2A methylation may be causally associated with the observed changes in cell cycle status.

D. *In Vivo* Models Linking PP2A to Alzheimer's Disease

The central role that PP2A dysregulation appears to play in most of the pathological hallmarks of AD, and the mounting evidence of significant deficits in PP2A regulation in brains from individuals with AD, has led to the study of this mechanism in animal models. PP2A plays such critical roles in physiological functioning throughout the body that it has not been possible to generate knockout mouse models.[88] Knockdown of PP2A phosphatase activity has been achieved *in vivo* by overexpressing dominant negative forms of the catalytic subunit. This has been shown to lead to the tau hyperphosphorylation characteristic of the human disorder.[89,90] Pharmacological inhibition of PP2A with okadaic acid has yielded similar phenotypes. When okadaic acid was stereotactically injected into the brains of rats, many of the hallmark features of AD were recapitulated including Aβ deposition, tau hyperphosphorylation, and neurodegeneration.[91,92] But note that the effects of PP2A inhibitors such as okadaic acid may not be selective, and other PPases including PP1, PP4–6 may also be inhibited at the concentrations needed in these *in vivo* studies.

A chronic model of PP2A inhibition has been developed using I2 (SET) overexpression.[93] I2 is overexpressed in AD, and in the diseased state, it is cleaved into N- and C-terminal fragments that redistribute from the nucleus to the cytoplasm where they can act upon PP2A. Wang *et al.* have developed a model in which the C-terminal fragment of I2 ($I2_{CTF}$) is delivered to rat brains via adeno-associated virus (AAV), leading to its overexpression in the hippocampus.[93] AAV-$I2_{CTF}$ infected rats display Aβ deposition, tau hyperphosphorylation, neurodegeneration, and cognitive deficits linked to inhibition of PP2A activity. Another approach to test the effects of PP2A dysregulation involves introducing deficiencies in methylation through generation of a transgenic mouse with a mutated PP2A C subunit (L309A) that is unable to undergo C-terminal methylation. This mouse model displays tau hyperphosphorylation and microtubule dysfunction, consistent with the importance of PP2A methylation in tau regulation.[94] Although not directly linked to AD, a recent study has examined the effects of knockout of the B'dsubunit and found that this resulted in spatially restricted tauopathy in the brain stem and spinal cord.[95] There were no obvious cognitive impairments in this mouse model, and the effects of the B'd knockout were likely explained through the ability of this subunit to influence the activities of GSK3 and/or Cdk5, which phosphorylated tau.

Additional models relevant to AD have further linked PP2A to the disorder. For example, anesthesia induces tau hyperphosphorylation,[96] which has been demonstrated to be due to decreases in PP2A activity associated with anesthesia-induced hypothermia. Anesthesia-induced hypothermia differentially affects activity of kinases and phosphatases, although even in normothermic conditions some anesthetics can inhibit PP2A to induce tau hyperphosphorylation.[97]

III. Protein Phosphatase 2B (Calcineurin)

A. General Properties

Protein phosphatase 2B (PP2B or calcineurin) is a Ca^{2+}/calmodulin-dependent protein phosphatase that is highly enriched in the central nervous system where it plays key roles in diverse aspects of signaling.[98] PP2B is comprised of a dimer of the catalytic A subunit and a Ca^{2+}-binding B subunit. Following increased intracellular Ca^{2+}, Ca^{2+}/calmodulin binds to the A subunit, relieving autoinhibition. PP2B is the sole target for the immunosuppressant drugs cyclosporin and FK506 which bind to cyclophilin or FKBP, respectively, and then

bind to and inhibit PP2B activity. PP2B is required for long-term depression (LTD), where it mediates the actions of Ca^{2+} downstream of NMDA glutamate receptors.[99–101] In this respect, it is involved in control of synaptic plasticity and learning and memory. PP2B also plays an important role in the striatum, where it regulates dopaminergic signaling.[42] PP2B acts in different cellular compartments, with substrates located at the pre- and postsynaptic side of the synapse.[102,103] An important family of substrates for PP2B is the NFAT transcription factors, to which PP2B interacts with in the cytosol, leading to dephosphorylation of NFATs at multiple sites allowing the import of NFAT into the nucleus and activation of specific tran-scriptional programs.[104]

B. Protein Phosphatase 2B Linkage to Alzheimer's Disease

Decreases in PP2B levels have been associated with normal aging.[105] While earlier studies found either no change in PP2B protein levels or activity in AD brain[106] or reduction in activity,[107–109] more recent studies have consistently indicated that PP2B activity is increased.[28,110,111] The increase in activity appears to result from the formation of a truncated A subunit.[110,111] The position of the proteolytic cleavage is C-terminal to the autoinhibitory domain, and PP2B remains Ca^{2+}/calmodulin dependent.[110] However, the resulting activity of the truncated PP2B is higher than that of the full-length A subunit form of the enzyme. Proteolysis of the A subunit may be mediated by calpain I, which was also found to be more active in AD brain. Interestingly, proteolysis of PP2B and calpain was also found in hippocampus from subjects with mild cognitive impairment.[112] In this latter study, a shorter active form of the A subunit was detected, and it was also found that oligomeric forms of Aβ could increase PP2B proteolysis in cultured hippocampal neurons. Related to these results, a recent study of the Tg2576-APPswe mouse model of AD that expresses the human APPswe mutant linked to FAD found that caspase-3 activity was enhanced in hippocampus and that this was associated with truncation and activation of PP2B[113] (see further discussion below).

Although PP2B has been found to interact with fewer regulatory proteins compared to PP1 and PP2A, PP2B is known to be inhibited by calcipressin1 (also known as DSCR1, Adapt78, or RCAN1), the product of a gene encoded in the Down's syndrome critical region 1. Both mRNA and protein levels of calcipressin1 were found to be increased in AD brain, and the level of expression of calcipressin1 was correlated with the number of NFTs in the temporal cortex.[114–116]

The catalytic A subunit of PP2B dimerizes with the regulatory B subunit, a Ca^{2+}-binding protein related to calmodulin and other EF-hand Ca^{2+}-binding proteins. A recent genetic study, that aimed to identify associations between single nucleotide polymorphisms (SNPs) in AD subjects and levels of phospho-tau measured in patient CSF samples, has identified an SNP located in intron 5 of the B subunit (PPP3R1) of PP2B.[117] The SNP was associated with the rate of decline in disease progression but was not associated with the risk for AD, or the age of onset. Notably, the B subunit allele was associated with lower levels of PPP3R1 and higher levels of NFT pathology.

There are three genes that encode the catalytic A subunit (PPP3CA–C) and two genes that encode the regulatory B subunit (PPP3R1 and R2). A detailed analysis has identified a variety of novel PPP3CA variants that can generate a number of splicing isoforms of PP2B that exhibit differential expression in brain and nonbrain tissues.[118] The expression of several of these PPP3CA isoforms, but not all, that encode functional phosphatase domains was found to be decreased in the medial temporal gyrus from AD patient brains.

In summary, contradictory results have been obtained from studies of PP2B expression and/or activity. Both decreases and increases have been identified, with the increases being

associated with proteolysis of the regulatory A subunit. Conceivably, proteolysis and increased activity might be related to postmortem conditions and not directly related to AD phenotype. It is notable that some genetic studies have found both decreased expression of A subunit isoforms and decreased levels of the B subunit that are associated with the degree of AD progression. Increased levels of a PP2B inhibitor, namely, calcipressin1, have also been detected. It remains possible that there may be local changes in PP2B subunit expression or expression of calcipressin1 in specific brain regions, or in specific subcellular compartments that lead to restricted inhibition of phosphatase activity which could, in turn, influence the phosphorylation of substrates such as tau (see below for further discussion). In this respect, one study of a double APP/PS1 AD mouse model has reported that there was increased PP2B immunoreactivity found in activated astrocytes, but not neurons, surrounding amyloid deposits.[119]

C. Pathophysiological Roles of Protein Phosphatase 2B in Alzheimer's Disease

PP2B activity has been implicated in the generation of both Aβ and hyperphosphorylated tau, the two hallmarks of AD pathology. Early studies suggested a role for PP2B in the production of Aβ, but the molecular basis for the effects observed using PP2B inhibitors was never identified.[120] Several studies have implicated PP2B in the regulation of tau phosphorylation. As for PP2A (discussed above), PP2B can directly dephosphorylate specific sites in hyperphosphorylated tau (Table I).[28,30,32] These *in vitro* studies suggested that PP2B may not be a very active tau phosphatase, and consistent with this conclusion, other studies in AD brain have indicated that the increased proteolysis and activation of PP2B were not associated with dephosphorylation of tau but was correlated with hyperphosphorylation of tau.[110,111] In contrast, downregulation of PP2B using antisense oligonucleotides or the inhibitors cyclosporin or FK506 resulted in increased phosphorylation of a number of sites in tau that are implicated in formation of NFTs.[35–37] Given that PP2B can directly dephosphorylate some of the same sites *in vitro* that are altered by PP2B inhibitors, the simplest explanation of these results is that PP2B directly can dephosphorylate certain sites in tau *in vivo*. However, PP2B, like other PPases, may also act indirectly to control the activities of the kinases that phosphorylate tau. In this regard, PP2B was shown to dephosphorylate S9 of GSK3β in neuroblastoma cells, leading to activation of GSK3β and phosphorylation of tau.[121]

D. Role of Protein Phosphatase 2B in the Synaptopathology of Alzheimer's Disease

As mentioned above, there is a growing recognition that the earliest cognitive impairments seen in AD may result from loss of functional synaptic transmission. Studies that argued against the original amyloid hypothesis of AD found that the patterns of synapse loss, rather than amyloid deposits, correlated best with the cognitive deficits in affected patients.[122–124] Subsequent studies in AD model mice and through the use of Aβ oligomeric preparations in *in vitro* studies indicated that synaptic plasticity at excitatory synapses was impaired.[125–127] Further studies indicated that application of Aβ to brain slices and into rodent brain induced synaptic loss, blocked LTP, and impaired cognitive function.[8,9,128–135] Aβ is produced in neurons in an activity-dependent manner and may normally be part of a negative feedback process that controls excitatory synaptic transmission.[127] However, higher levels of soluble Aβ oligomers lead to defective AMPA and NMDA glutamate receptor trafficking and ultimately synaptic loss.[133,136–138] The precise mechanisms involved in the actions of Aβ oligomers at the cell surface are not clear but may include both pre- and postsynaptic signaling processes and α7-nicotinic acetylcholine receptors, glutamate receptors, and the cellular prion protein.[133,136,139–141] Glutamate re-uptake at excitatory synapses may also be impaired, leading to altered synaptic and extrasynaptic signaling.[139] There is now a significant body of evidence that supports a key role for PP2B in mediating the disruptive effects of Aβ on synaptic structure and function.

The first suggestion for a role for PP2B in the actions of Aβ came from studies of LTP in dentate gyrus.[142] Both induction and maintenance of early and late phases of NMDA receptor-dependent LTP were found to be inhibited by application of Aβ1–42. Based on previous data which indicated that Aβ could increase intracellular Ca^{2+} levels[143,144] and the knowledge that PP2B plays a key role in regulation of synaptic plasticity,[101] the effects of the immunosuppressant inhibitors of PP2B, namely, cyclosporin A and FK506, were studied. Both cyclosporin A and FK506, but not rapamycin (a control for FK506), prevented the effects of Aβ1–42 on LTP. The mechanism(s) involved in the effects of Aβ were investigated in detail by Snyder *et al.*,[136] who found that application of Aβ to cortical cultures resulted in decreased surface expression of NMDA glutamate receptors at synapses through promotion of endocytosis. Moreover, there was reduced surface expression of NMDA receptors in cultures obtained from the APPswe mouse model of AD. Further work established a role for α-7 nicotine receptor activation by Aβ and a requirement for PP2B, based on the ability of cyclosporin to block the effects of Aβ on NMDA receptor surface expression. As discussed in more detail below, a likely substrate for PP2B is the tyrosine phosphatase, STEP61, which is known to regulate NMDA receptor endocytosis through dephosphorylation of Tyr1472 of NR2B. Aβ was also able to block downstream signaling via NMDA receptors as demonstrated by reduced phosphorylation of the key transcription factor CREB in cultured neurons. Additional studies also showed that Aβ exposure resulted in increased endocytosis of AMPA receptors[137,138,145] and that PP2B was required for the effect of Aβ.[138,145] The effects of Aβ on disruption of synaptic signaling were also accompanied by loss of dendritic spines, and although the precise mechanisms have not been clearly resolved, PP2B has been shown to be required for the effects of Aβ on spine loss.[133,138]

PP2B is required for LTD, and studies of overexpression and inhibition of PP2B in mice show that it plays an important negative role in learning and memory.[101] Consistent with this role, intraperitoneal injection of FK506 was found to rescue deficits in contextual fear conditioning and novel object recognition in relatively young (5-month-old) mice expressing human APPswe (the Tg2576 AD mouse model).[146,147] Taken together, these studies strongly support a role for PP2B in mediating early effects of Aβ on synaptic plasticity and synaptic structure that is likely linked to impairment of learning and memory as well as cognition. Given the similarities observed, it has been suggested that the effects of Aβ on synaptic plasticity share common mechanisms with those involved in LTD.[133,138]

E. Mechanisms of Action of Protein Phosphatase 2B in Mediating the Effects of Aβ

Despite the clear evidence that PP2B is involved in the actions of Aβ on synaptic function, a number of important questions remain to be answered. Several mechanisms may be involved in the activation of PP2B. Consistent with the growing appreciation that soluble oligomeric forms of Aβ are critical for the early synaptic dysfunction, activation of PP2B also requires Aβ oligomers.[133,145,148,149] The target for Aβ oligomers is not, however, clear and several possible binding partners have been suggested.[140,145] Snyder *et al.* implicated α7 nicotinic receptors in the effects of Aβ on NMDA receptor endocytosis,[136] but no role for α7 receptors were found in studies of Aβ on spine loss.[133] Rather, impairment in NMDA receptor-dependent Ca^{2+} influx was suggested. This may seem paradoxical since PP2B requires Ca^{2+} for activation. However, PP2B exhibits high affinity for Ca^{2+}/calmodulin and is preferentially responsive to small increases in Ca^{2+}, which is the basis for its selective activation in LTD.[100] Alternatively, as discussed above, PP2B may be proteolytically cleaved to produce a more active form.[110,111] While most of the studies implicating PP2B in Aβ actions have focused on soluble oligomeric forms, and processes that occur prior to amyloid plaque deposition, a recent study in AD model mice expressing human APP and presenilin 1 shows elevated Ca^{2+} overload in neurites and spines.[150] Notably, the changes in

Ca^{2+} were located in the proximity of amyloid plaques, where it was shown that spino-dendritic Ca^{2+} compartmentalization was perturbed. Intraperitoneal injection of FK506 prevented Ca^{2+} overload and the associated structural changes, further complicating the identification of the source of Ca^{2+} that might activate PP2B.

PP2B is a multifunctional phosphatase that dephosphorylates a wide variety of substrates in different cellular compartments.[101,103,151] Key phosphorylation sites in either NMDA or AMPA receptors that are associated with receptor trafficking may be direct substrates for PP2B.[103,152,153] In support of this, studies of the Tg2576 AD mouse model suggested that S845 of GluR1 was a direct target for PP2B.[113] Alternatively, PP2B may act to control glutamate receptor trafficking indirectly through regulation of substrates that include the tyrosine phosphatase STEP (see further discussion below). PP2B plays an important role in the regulation of transcription, and transcription factors, including NFAT1–4 and MEF2, are important neuronal substrates. MEF2 is activated by PP2B and this is known to be coupled to loss of dendritic spines,[154] although to date there are no studies of MEF2 in AD. NFAT proteins have been studied intensively in immune signaling, and the immunosuppressants cyclosporin A and FK506 work through inhibition of the actions of PP2B dephosphorylation of NFATs and nuclear translocation. Notably, two recent studies have implicated NFAT transcription factors in the actions of PP2B, acting downstream of Aβ.[149,155] While the general conclusions reached by the two studies were similar, the details were distinct. One study found increased nuclear translocation of NFAT1 and NFAT3 which was associated with mild cognitive decline or AD, respectively,[155] while the second study found increased NFAT4 in nuclear fractions from the cortex of AD patients.[149] Oligomeric Aβ was found to stimulate NFAT in astrocyte cultures and to influence glutamate-induced neuronal degeneration.[155] In contrast, in the second study, NFAT signaling was required for dendritic simplification and spine loss in neurons, a process dependent on PP2B.[149] Finally, it has also been suggested that proapoptotic proteins may be activated through their ability to be dephosphorylated and activated by PP2B, and that this is involved in the neurodegenerative actions of Aβ.[156,157]

IV. Protein Phosphatase 1

A. General Properties

PP1 is known to have an important role in several aspects of neuronal function.[100,158] It plays a key role in synaptic signaling, where it is required for LTD.[99,159] Behavioral studies have also elegantly shown that PP1 controls aspects of learning and memory.[160] There are four isoforms of PP1 that are the products of three genes, with PP1α and γ being highly enriched in dendritic spines where they are positioned to regulate early stages of postsynaptic signaling.[158] A notable feature of PP1 is that the catalytic subunits of the phosphatase can interact in a mutually exclusive way, with as many as 200 distinct regulatory proteins that target PP1 to specific subcellular locations where they influence substrate specificity.[161] For example, the F-actin-binding proteins spinophilin and neurabin are localized to actin-rich dendritic spines where they recruit PP1 to selectively dephosphorylate glutamate receptors.[162–164] PP1 also plays an important role in other cellular compartments such as the nucleus where it is a major phosphatase that dephosphorylates S133 in CREB[165,166] and is also targeted to histone modification via interactions with HDACs.[167] Extensive studies have shown that PP1 is a major target for dopamine signaling in striatal neurons where it is regulated by DARPP-32, a protein highly expressed in dopamine-innervated medium spiny neurons.[42]

B. Pathophysiological Roles of Protein Phosphatase 1 in Alzheimer's Disease

Although most of the focus has been on the role of PP2A, PP1 has also been implicated in the regulation of tau dephosphorylation. For example, PP1 prepared from human postmortem brain was found to exhibit some site selectivity toward hyperphosphorylated tau.[28,29] T212, T217, S262, S396, and S422 were found to be preferentially dephosphorylated by the PP1 preparations, while T181, S199, S202, T205, S214, and S404 were not dephosphorylated. Of the selected sites, in one study, it was suggested that T212 might be a specific site for PP1,[29] as this site was apparently not a good substrate for PP2A or PP2B. However, this observation was not confirmed in another study.[28] It was also not clear what the status of the PP1 preparation was in terms of potential PP1 regulatory proteins, which might be expected to significantly influence substrate specificity.

In other recent studies, PP1 and hyperphosphorylated tau have been connected to deficits in axonal transport via a mechanism involving PP1. Using a squid axoplasm preparation, a reduced system in which various aspects of axonal transport can be studied, earlier studies found that filamentous human tau could inhibit fast anterograde axonal transport.[168] The effect of human tau was found to act via a process that involved activation of PP1, dephosphorylation and activation of GSK3, and subsequent phosphorylation of kinesin light chains by GSK3. This process depended on an 18-amno acid domain at the N-terminus of tau, which the authors suggested was a PP1-activating motif. In a follow-up study, it has been shown that pathogenic AD forms of tau enable greater exposure of the PP1-activating motif, which is normally sequestered by protein–protein interactions.[169] Moreover, there is a large increase in the accessibility of the PP1-activating motif in postmortem samples from AD patients. The mechanism by which PP1 might be activated is not known. However, it seems possible that this might involve recruitment of a form of PP1 that is targeted to GSK3 via a specific PP1-targeting protein. Alternatively, the N-terminal region of tau might perturb the interaction of a specific targeting subunit with PP1.

There is no obvious data related directly to studies of PP1 activity or levels in AD brain. However, PP1 activity may be required for mediating the effects of Aβ on synaptic plasticity. In a study that used transgenic mice expressing human APP with both Swedish and Arctic mutations, hippocampal slice LTP was found to be inhibited.[170] A selective PP1 inhibitor blocked the effects of Aβ, and a similar result was found in hippocampal slices isolated from APPswe/ PS1 mice. Notably, the effects on LTP were not observed in mice that overexpressed a PP1 inhibitor, a result that is consistent with the known role for PP1 in LTD. Early studies of LTD in hippocampal neurons indicated that PP1 is required downstream of PP2B,[171] although the targets for PP1 have not been clearly identified. As for PP2B, PP1 may act directly to dephosphorylate NMDA and AMPA glutamate receptors and regulate their trafficking to and from synapses. Alternatively, PP1 may act at the level of regulation of substrates such as CaM kinase II, or transcription factors such as CREB. The tyrosine protein phosphatase, STEP, may also be a target since it can be regulated by PP1 (see below). Interestingly, PP1 has been suggested to be inhibited by Aβ,[172] but it is not clear how this would relate to known synaptic roles of PP1 in LTD where PP1 activity would be required for the disruptive effects of Aβ on synaptic plasticity.

A more indirect role for PP1 in AD has been suggested by studies of the translational control of BACE1 protein levels.[173] The level of BACE1 protein, which is the rate-limiting protease involved in Aβ formation, is known to be upregulated in AD.[174,175] In attempts to address the possible mechanisms involved, studies carried out in HEK cells and primary neuronal cultures indicated that cell stress leads to regulation of the unfolded protein response system and increased phosphorylation of the translational initiation factor eIF2α. Notably, while phosphorylation of eIF2α leads to a general inhibition of translation, certain mRNAs including that for BACE1 can be preferentially translated, leading to increased BACE1

protein synthesis. A large body of work has found that eIF2α dephosphorylation is regulated by PP1 in complexes with the specific PP1 targeting protein GADD34. [176,177] In primary neurons, the small molecule, salubrinal, which specifically inhibits PP1 in this complex,[178] selectively increased eIF2α phosphorylation leading to increased levels of BACE1 and Aβ. In contrast, blocking eIF2α phosphorylation had the opposite effect. Analysis of the 5×FAD AD mouse model found parallel increases in levels of BACE1 and eIF2α phosphorylation, and a similar effect on eIF2α was observed in samples from AD brains. As for PP2A (discussed earlier), these studies highlight the potential importance of studying specific forms of PP1 in complexes with unique targeting subunits that may play important roles in the regulation of neuronal processes related to AD.

V. Protein Phosphatase 5

A. General Properties

Protein phosphatase 5 (PP5) is a serine/threonine PPase related to PP2A, which is ubiquitously expressed but present in high levels in neurons.[179] It is unique in terms of the domain structure of the catalytic subunit, in that it contains three so-called tetratricopeptide repeat domains at the N-terminus which may play a role in autoinhibition of PPase activity. While PP5 is less studied than PP2A, a few reports have suggested a role for PP5 in regulation of tau dephosphorylation and also in the toxic effects of Aβ.

B. Pathophysiological Roles of Protein Phosphatase 5 in Alzheimer's Disease

Using either recombinant PP5[33] or enzyme immunoprecipitated from rat or human brain, [28,34] PP5 has been shown to dephosphorylate a number of sites in hyperphosphorylated tau. T205, T212, and S409 were relatively good substrates for PP5, while S199, T202, S214, S396, and S404 were less efficiently phosphorylated (Table I). Interestingly, while S199 was not the best site for PP5 compared to PP1, PP2A, and PP2B, PP5 was the most effective PPase for this site. Analysis of postmortem samples from human AD brains indicated that PP5 levels and activity were reduced by ~20% compared to control samples, suggesting a contributing role for PP5 in the increased phosphorylation of tau seen in AD brain. [28,34]

PP5 may also be able to play a neuroprotective role to attenuate the effects of Aβ toxicity.[180] Previous studies have indicated that Aβ impairs mitochondrial function and can increase the levels of reactive oxygen species that may be causally involved in neuronal toxicity.[181] In cortical neurons in culture, PP5 downregulation was associated with increased Aβ-induced cell death, while overexpression of PP5 had the opposite effect. PP5 may prevent the actions of Aβ through its ability to suppress MAP kinase pathways involved in apoptosis.

VI. Striatal-Enriched Tyrosine Phosphatase

A. General Properties

STEP is an intracellular tyrosine phosphatase expressed in the striatum, hippocampus, neocortex, and other brain regions that are involved in learning and memory.[182–184] STEP isoforms include a cytosolic STEP46 and a membrane-associated STEP61, the latter being localized, in part, to the postsynaptic density.[185] A large body of work supports a model in which STEP opposes the development of synaptic strengthening through its ability to dephosphorylate various cellular substrates involved in this process (reviewed in Refs.[184,186]). These include key neuronal signaling molecules such as the MAP kinases, ERK1/2, and p38,[187,188] the Src family kinase Fyn,[189] and Pyk2.[190] STEP also regulates NMDA and AMPA receptor trafficking. STEP61 dephosphorylates the NR2B subunit of the

NMDA receptor, leading to internalization of NR1/ NR2B. Increased STEP61 activity was associated with increased internalization of GluR1/GluR2 receptor complexes and STEP KO mice have increased levels of these AMPA receptors on neuronal synaptic membranes, although whether STEP directly dephosphorylates the GluR2 subunit of the AMPA receptor is under investigation.[136,191–194]

STEP is also subject to regulation by various mechanisms that control its level of expression and activity. An important feature of STEP is the presence of a kinase-interacting motif (KIM domain) that is essential for substrate binding.[187,195] Notably, phosphorylation by protein kinase A at a serine residue within the KIM acts to inhibit the interaction of STEP with substrates,[196] and phosphorylation of the KIM domain can be reversed by the actions of either PP1 or PP2B.[188,196,197] The action of PP1 on STEP is subject to regulation in striatal neurons by dopamine through the ability of DARPP-32 to inhibit PP1, a process that contributes to synergistic activation of ERK1/2 by glutamate and dopamine and which plays an important role in the actions of drugs of abuse.[197] In addition to regulation of activity, STEP protein levels can be controlled by local translation in neurons[198] or through degradation by calpain-dependent cleavage or through ubiquitination and targeting to the proteasome.[199–201] Given its critical role in regulation of synaptic function, as well as its regulation by various signaling pathways, it is not surprising that STEP has been implicated in various neuropsychiatric and neurological disorders, including drug addiction, schizophrenia, fragile X syndrome, and stroke. Several recent studies have also revealed a key role for STEP in AD.

B. Pathophysiological Roles of STEP in Alzheimer's Disease

As discussed above, there is a growing appreciation that the effects of Aβ on synaptic plasticity are responsible, at least in part, for the cognitive decline observed in AD. An important series of studies that contributed to this hypothesis has found that Aβ reduces surface expression of both NMDA and AMPA glutamate receptors at synapses through increased endocytosis and that STEP plays a central role in the actions of Aβ.[136,137,194,202] In the case of NMDA receptors, activation of α-7 nicotinic receptors is coupled to activation of PP2B, which promotes dephosphorylation of STEP at the regulatory site within the KIM domain.[136] PP2B may act directly on STEP as a substrate or act via inhibitor-1/DARPP-32 and PP1.[197] In either case, dephosphorylation of STEP would promote its interaction with substrates. As mentioned earlier, STEP is known to regulate NMDA receptor endocytosis through its ability to regulate the dephosphorylation the NR2B subunit[193,193] STEP likely modulates the phosphorylation of the NR2B subunit of the NMDA receptor by two parallel pathways. STEP can directly dephosphorylate Y1472 of the NR2B subunit.[136,201] STEP may also act indirectly via dephosphorylation and inactivation of the Src family kinase Fyn, which is a kinase implicated in phosphorylation of Y1472[189].Phosphorylation of Y1472 resides within a conserved tyrosine-dependent endocytic motif.[203] When dephosphorylated by STEP, the tyrosine residue in this motif binds to clathrin adapter proteins via strong hydrophobic interactions and promotes endocytosis of the NMDA receptor.

Further direct support for a role of STEP in mediating the actions of Aβ on glutamate receptor endocytosis has come from studies of STEP knockout mice.[194] ST EP knockout mice[204] were crossed with 3×Tg-AD mice[205] to produce progeny null for STEP but with elevated Aβ levels (3×Tg-AD/STEP$^{-/-}$; double mutant). Genetic reduction of STEP attenuated the loss of NR1 and NR2B NMDA receptor subunits from synaptosomal membranes observed in the 3×Tg-AD mice. Similar biochemical results were observed in Tg2576 mice in which STEP was knocked out. Importantly, the recovery in levels of NMDA receptors was accompanied by attenuation of the cognitive deficits normally seen in the 3×Tg-AD mice. Specifically, 6-month-old double mutant mice were improved, relative to 3×Tg-AD littermates, when tested for spatial reference memory in the Morris water maze,

spontaneous alteration performance in the Y maze, and nonspatial hippocampus-dependent memory in an object recognition task. Notably, all groups tested displayed similar locomotor activity and exploratory behavior in the open field task. An important aspect of this study was that the attenuation of AD-like cognitive deficits in double mutant mice took place despite unchanged levels of both Aβ and phospho-tau, which are measurable at 6 months of age in 3×Tg-AD mice. These findings suggest that the improved cognitive function was due to the decrease in STEP levels and that these improvements could be achieved without diminishing Aβ and phospho-tau levels at least at the earlier age tested.

STEP is also likely to be involved in regulation of AMPA receptor endocytosis by Aβ Biochemical studies have implicated STEP in regulation of dephosphorylation of the GluR2 AMPA receptor subunit,[192] although the precise mechanism remains to be clearly elucidated. The GluR2 subunit of the AMPA receptor appears to be phosphorylated by Src family kinases.[206] A recent study has found that phosphorylation of Y876 in GluR2 controls its endocytosis via a mechanism involving the guanine-exchange factor BRAG2, the GTPAse Arf6, and the adaptor protein AP2.[207] As for NMDA receptors, STEP may therefore act either directly to dephosphorylate the GluR2 subunit at Y876 or alternatively to regulate the activity of Src family kinases or other tyrosine kinases that phosphorylate this site. In support of a direct role for STEP, recent studies have shown that the decrease in surface expression of GluR1 and GluR2 observed in Tg2576 mice is reversed when STEP is knocked out.[202]

As mentioned above, the Src family kinase Fyn is a substrate for STEP that may be involved in regulation of glutamate receptor endocytosis. For many years, Fyn has been implicated in various aspects of AD. Fyn phosphorylates tau and may be involved in regulation of tau hyperphosphorylation.[209,210] Fyn has also been implicated in the synaptic and cognitive impairments caused by Aβ.[211,212] Interestingly, recent studies suggest that tau may act as a scaffold for Fyn that is needed for the effects of Aβ[213,214] Activation of Fyn is achieved by intermolecular autophosphorylation of Y420 in its catalytic domain, and STEP can inactivate Fyn through dephosphorylation of Y420.[189] It is not clear how the actions of STEP might influence these various effects of active Fyn in terms of mediating the effects of Aβ, but it is possible that activation of Fyn and activation of STEP occur with different kinetics or in different postsynaptic locations in neurons affected by Aβ

C. Levels of STEP Protein Expression Are Elevated in Alzheimer's Disease

In addition to regulation of activity, the levels of expression of STEP protein have been implicated in AD. Elevated levels of the STEP61 isoform are present in Tg2576 [201] and 3×Tg-AD mice.[194] Other studies have found that STEP61 levels are elevated in the J20 AD mouse line.[212] Moreover, elevated levels of STEP61 have been found in prefrontal cortex from AD patients.[201] The mechanism for the increase in STEP61 levels involves Aβ-mediated inhibition of the ubiquitin proteasome system (UPS).[201] Increasing evidence suggests that UPS dysfunction plays an important role in the pathogenesis of AD.[215–217] In human AD brains, ubiquitin immunoreactive inclusion bodies accumulate and proteasomal activity is decreased.[218,219] Proteasomal inhibition results in the accumulation of ubiquitinated proteins, a decrease in free ubiquitin, and increased levels of several proteins involved in AD pathology, including tau and BACE1.[220–225] Notably, proteasome activity decreases with age in the brains of Tg2576 mice,[226] while restoring ubiquitin-recycling enzymes rescues memory deficits and dendritic spine alterations in AD mouse models.[224,227] STEP degradation is controlled by the UPS, and impairment of the UPS seen in response to Aβ in cell-based assays, or in the Tg2576 AD mouse model, has been shown to lead to increased levels of ubiquitinated STEP that remains active.[201] Thus Aβ modulates STEP via two parallel pathways which are not mutually exclusive. Aβ-induced activation of PP2B leads to dephosphorylation of STEP61 and activation, while Aβ-mediated inhibition

of the UPS leads to reduced degradation of STEP61. In either case, elevated levels of Aβ result in upregulation of STEP activity and consequently lead to decreased phosphorylation and surface expression of NMDA and AMPA glutamate receptors, leading to reduced cognitive ability.

VII. Other Protein Phosphatases

A. Role of Additional Protein Phosphatases in the Pathophysiology of Alzheimer's Disease

Given the likely role of diverse signaling pathways being involved in the actions of Aβ in the synaptopathology of AD, and the complexity of the numerous sites being hyperphosphorylated in tau by various kinases, it is to be expected that roles for other serine/threonine and tyrosine protein phosphatases will be elucidated in the near future. In support of this, recent studies have begun to reveal unexpected roles for a number of protein phosphatases in AD-related contexts. For example, a recent study has shown that the leukocyte common antigen CD45, a receptor tyrosine phosphatase that plays an important role in the immune response, contributes to microglial-mediated clearance of Aβ oligomers.[228] Promotion of CD45 action might therefore be of help in treatment of AD. In another recent study, the PTPase PTP1B has been implicated in the susceptibility to diet-induced obesity and glucose intolerance in an APPswe/PSEN1 transgenic mouse line.[229] Increased PTP1B activity is likely associated with insulin resistance, a possible risk factor associated with AD. A number of previous studies in AD mouse models have indicated that there is aberrant upregulation of expression in postmitotic neurons of proteins normally associated with the cell cycle.[230] Included in these cell cycle proteins is the tyrosine phosphatase Cdc25, which plays a critical role at the G2/M transition in the cell cycle through its ability to activate Cdc2/cyclin B.[231,232]

VIII. Protein Phosphatase-Directed Therapeutics for the Prevention and Treatment of Alzheimer's Disease

According to the National Institute on Aging, there are more than 5 million Americans who suffer from AD. Yet, despite a desperate need, development of an effective treatment for AD has been a major challenge. Four drugs are currently approved by the FDA to treat cognitive deficits in AD. Three of them are acetylcholinesterase inhibitors, which combat the loss of acetylcholine caused by the death of cholinergic neurons, while the other is a noncompetitive NMDA receptor antagonist, which inhibits overactivation of NMDA receptors by glutamate.[1] None of these drugs halts progression of the disease. Significant effort has been put into development of inhibitors of Aβ production.[233] However, targeting γ-secretase with nonselective γ-secretase inhibitors has deleterious effects on health, likely because γ-secretase also cleaves other substrates, such as Notch, which are essential for normal biological function.[234] This limitation is highlighted by the recent failure of the γ-secretase inhibitor semagacestat in Phase III clinical trials.[235] Given the lack of available drugs to treat AD, it is imperative to identify novel molecular processes that might be amenable to targeting through new drugs. Protein phosphatases, including PP2A, and STEP may be potential therapeutic targets for AD. It may also be possible to use a strategy that would combine one or more regulator of a protein phosphatase with kinase inhibitors that would provide a complementary approach to control of, for example, hyperphosphorylation of tau.

A. PP2A Regulators

Postmortem analysis and *in vivo* models give strong indications of a central role for PP2A in AD. Understanding neuronal mechanisms of PP2A regulation could therefore provide useful pharmaceutical targets for rational therapeutic interventions to treat or prevent AD.

Convincing data exist that reductions in PP2A activity can contribute to AD progression so that enhanced activity would likely be beneficial. Although generally more difficult to identify than inhibitors, it may be possible to either generate direct PP2A activators or take advantage of the endogenous biochemical regulatory mechanisms to achieve this goal. A number of compounds have been reported that activate PP2A (reviewed in Ref. 236). Sodium selenate has recently been tested in a model of AD.[237,238] This anionic PP2A activator was administered to tau transgenic animals where it was found to reduce tau hyperphosphorylation and enhance cognitive performance. The commonly used AD therapeutic memantine has been demonstrated to inhibit I2's activity toward PP2A, which may explain some of its therapeutic efficacy.[239] Metformin, which enhances PP2A levels by inhibiting its degradation, has been shown to be beneficial in models of AD[240]. Finally it has recently been shown that an inhibitor of PP2A demethylation, namely, eiconsanoyl-5-hydroxytryptamide, provides enhanced PP2A activity, reduced protein phosphorylation, and cognitive benefits in rodent models for neurodegeneration.[241]

The encouraging data from multiple PP2A enhancing strategies suggest efficacy. Questions remain as to whether PP2A can be safely modulated in the therapeutic environment, particularly due to its ubiquitous nature and broad range of substrates. Some of the mechanisms of PP2A activation or stabilization described above may provide a level of selectivity: for example, modulation of only certain regulatory subunits. Given the compelling data linking PP2A to AD and the favorable outcomes from preliminary studies with rodent models, it is apparent that PP2A-targeted therapeutic approaches have significant potential for groundbreaking disease modifying pharmaceutical development.

B. STEP Inhibitors

Based on studies which show that STEP normally acts to oppose synaptic strengthening, that knockout of STEP can attenuate behavioral and biochemical deficits in 3×Tg-AD mice, and that STEP is a tyrosine phosphatase with a known structure and enzymatic mechanism, STEP would appear to be a viable drug target, inhibition of which may potentially alleviate some of the synaptopathology of AD. However, past and current efforts to develop drugs targeting specific PTPs have been plagued by issues related to bioavailability and selectivity. This is due to the fact that the majority of PTP inhibitors carry a tyrosine phosphate-mimicking group that provides most of the binding energy through interaction with a highly conserved phosphate-binding loop in the catalytic center of every PTP. Based on emerging evidence, selectivity of inhibitors may be more readily achieved by targeting and stabilizing an inactive open-state PTP conformation, which dramatically differs from the active closed state. [242–244] In the open state, the flexible WPD-loop, which contains the catalytic acid/base aspartate, is distant from the catalytic center. Interestingly, the 3D structure of STEP exhibits an atypical open conformation that differs from most PTPs.[245] In this conformation, the WPD-loop is farther retracted, resulting in a large binding pocket that is not dominated by the conserved phosphate-binding loop. Hence, small molecules that bind STEP in its open state are likely to be very selective inhibitors. Moreover, STEP has a unique glutamine residue in the flexible WPD-loop, which may be utilized for specific interactions with a small molecule. In studies with the closely related phosphatase HePTP, a selective small-molecule inhibitor was found to interact specifically with the corresponding histidine residue in HePTP.[246] Several pharmaceutical companies have begun drug discovery programs to identify STEP inhibitors that will hopefully be available for preclinical studies in the near future.

C. Other Protein Phosphatase Drug Targets

As for PP2A, PP5 appears to be downregulated in AD, and therefore activators of this enzyme would presumably be desirable. Conceivably, identification of drugs that could

relieve autoinhibition of the enzyme might be useful. With respect to development of drugs that target PP1, a major limitation is the fact that there are potentially 200 or more forms of PP1 in complexes with the large number of regulatory/targeting subunits that have been identified. As discussed above, recent studies have identified the drug salubrinal that targets one specific form of PP1 in a complex with GADD34 and is used to increase the phosphorylation of initiation factor eIF2α.[178] This demonstrates the feasibility of designing selective PP1 drugs. However, the specific example of salubrinal acts to paradoxically increase the synthesis of BACE1, which would not presumably be useful in the treatment of AD. Highly specific inhibitors of PP2B (calcineurin), that act as immunosuppressants, have been identified and used for several decades following transplantation surgery.[98,247,248] While commonly used, long-term cyclosporin and FK506 use is associated with nephrotoxicity, and in some cases, neurotoxicity.[249,250] However, given the recent results indicating that active fragments of PP2B are generated in response to Aβ, and that PP2B mediates many of the effects of Aβ, it may be worth considering the use of these immunosuppressant drugs in AD, or alternatively, using different types of drugs that might inhibit PP2B without unwanted side effects.[251]

References

1. Castellani RJ, Rolston RK, Smith MA. Alzheimer disease. Dis Mon. 2010; 56:484–546. [PubMed: 20831921]
2. Probst A, Langui D, Ulrich J. Alzheimer's disease: a description of the structural lesions. Brain Pathol. 1991; 1:229–239. [PubMed: 1727015]
3. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol. 2007; 8:101–112. [PubMed: 17245412]
4. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991; 349:704–706. [PubMed: 1671712]
5. Pastor P, Goate AM. Molecular genetics of Alzheimer's disease. Curr Psychiatry Rep. 2004; 6:125–133. [PubMed: 15038915]
6. Crews L, Rockenstein E, Masliah E. APP transgenic modeling of Alzheimer's disease: mechanisms of neurodegeneration and aberrant neurogenesis. Brain Struct Funct. 2010; 214:111–126. [PubMed: 20091183]
7. Wolfe MS. Structure, mechanism and inhibition of gamma-secretase and presenilin-like proteases. Biol Chem. 2010; 391:839–847. [PubMed: 20482315]
8. Venkitaramani DV, Chin J, Netzer WJ, Gouras GK, Lesne S, Malinow R, et al. Beta-amyloid modulation of synaptic transmission and plasticity. J Neurosci. 2007; 27:11832–11837. [PubMed: 17978019]
9. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci. 2010; 13:812–818. [PubMed: 20581818]
10. Suzuki T, Oishi M, Marshak DR, Czernik AJ, Nairn AC, Greengard P. Cell cycle-dependent regulation of the phosphorylation and metabolism of the Alzheimer amyloid precursor protein. EMBO J. 1994; 13:1114–1122. [PubMed: 8131745]
11. Suzuki T, Ando K, Isohara T, Oishi M, Lim GS, Satoh Y, et al. Phosphorylation of Alzheimer beta-amyloid precursor-like proteins. Biochemistry. 1997; 36:4643–4649. [PubMed: 9109675]
12. Oishi M, Nairn AC, Czernik AJ, Lim GS, Isohara T, Gandy SE, et al. The cytoplasmic domain of Alzheimer's amyloid precursor protein is phosphorylated at Thr654, Ser655, and Thr668 in adult rat brain and cultured cells. Mol Med. 1997; 3:111–123. [PubMed: 9085254]
13. Isohara T, Horiuchi A, Watanabe T, Ando K, Czernik AJ, Uno I, et al. Phosphorylation of the cytoplasmic domain of Alzheimer's beta-amyloid precursor protein at Ser655 by a novel protein kinase. Biochem Biophys Res Commun. 1999; 258:300–305. [PubMed: 10329382]

14. Iijima K, Ando K, Takeda S, Satoh Y, Seki T, Itohara S, et al. Neuron-specific phosphorylation of Alzheimer's beta-amyloid precursor protein by cyclin-dependent kinase 5. J Neurochem. 2000; 75:1085–1091. [PubMed: 10936190]
15. Suzuki T, Ando K, Iijima K, Oguchi S, Takeda S. Phosphorylation of amyloid precursor protein (APP) family proteins. Methods Mol Med. 2000; 32:271–282. [PubMed: 21318525]
16. Sano Y, Nakaya T, Pedrini S, Takeda S, Iijima-Ando K, Iijima K, et al. Physiological mouse brain Abeta levels are not related to the phosphorylation state of threonine-668 of Alzheimer's APP. PLoS One. 2006; 1:e51. [PubMed: 17183681]
17. da Cruz E, Silva EF, da Cruz E, Silva OA. Protein phosphorylation and APP metabolism. Neurochem Res. 2003; 28:1553–1561. [PubMed: 14570401]
18. Ando K, Iijima KI, Elliott JI, Kirino Y, Suzuki T. Phosphorylation-dependent regulation of the interaction of amyloid precursor protein with Fe65 affects the production of beta-amyloid. J Biol Chem. 2001; 276:40353–40361. [PubMed: 11517218]
19. Seeger M, Nordstedt C, Petanceska S, Kovacs DM, Gouras GK, Hahne S, et al. Evidence for phosphorylation and oligomeric assembly of presenilin 1. Proc Natl Acad Sci USA. 1997; 94:5090–5094. [PubMed: 9144195]
20. Walter J, Schindzielorz A, Grunberg J, Haass C. Phosphorylation of presenilin-2 regulates its cleavage by caspases and retards progression of apoptosis. Proc Natl Acad Sci USA. 1999; 96:1391–1396. [PubMed: 9990034]
21. Fluhrer R, Friedlein A, Haass C, Walter J. Phosphorylation of presenilin 1 at the caspase recognition site regulates its proteolytic processing and the progression of apoptosis. J Biol Chem. 2004; 279:1585–1593. [PubMed: 14576165]
22. Pastorino L, Ikin AF, Nairn AC, Pursnani A, Buxbaum JD. The carboxyl-terminus of BACE contains a sorting signal that regulates BACE trafficking but not the formation of total A(beta). Mol Cell Neurosci. 2002; 19:175–185. [PubMed: 11860271]
23. von Arnim CA, Tangredi MM, Peltan ID, Lee BM, Irizarry MC, Kinoshita A, et al. Demonstration of BACE (beta-secretase) phosphorylation and its interaction with GGA1 in cells by fluorescence-lifetime imaging microscopy. J Cell Sci. 2004; 117:5437–5445. [PubMed: 15466887]
24. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci. 2001; 24:1121–1159. [PubMed: 11520930]
25. Wray S, Saxton M, Anderton BH, Hanger DP. Direct analysis of tau from PSP brain identifies new phosphorylation sites and a major fragment of N-terminally cleaved tau containing four microtubule-binding repeats. J Neurochem. 2008; 105:2343–2352. [PubMed: 18315566]
26. Hanger DP, Anderton BH, Noble W. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. Trends Mol Med. 2009; 15:112–119. [PubMed: 19246243]
27. Chung SH. Aberrant phosphorylation in the pathogenesis of Alzheimer's disease. BMB Rep. 2009; 42:467–474. [PubMed: 19712581]
28. Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Eur J Neurosci. 2005; 22:1942–1950. [PubMed: 16262633]
29. Rahman A, Grundke-Iqbal I, Iqbal K. Phosphothreonine-212 of Alzheimer abnormally hyperphosphorylated tau is a preferred substrate of protein phosphatase-1. Neurochem Res. 2005; 30:277–287. [PubMed: 15895832]
30. Wang JZ, Grundke-Iqbal I, Iqbal K. Kinases and phosphatases and tau sites involved in Alzheimer neurofibrillary degeneration. Eur J Neurosci. 2007; 25:59–68. [PubMed: 17241267]
31. Qian W, Shi J, Yin X, Iqbal K, Grundke-Iqbal I, Gong CX, et al. PP2A regulates tau phosphorylation directly and also indirectly via activating GSK-3beta. J Alzheimers Dis. 2010; 19:1221–1229. [PubMed: 20308788]
32. Rahman A, Grundke-Iqbal I, Iqbal K. PP2B isolated from human brain preferentially dephosphorylates Ser-262 and Ser-396 of the Alzheimer disease abnormally hyperphosphorylated tau. J Neural Transm. 2006; 113:219–230. [PubMed: 15959850]
33. Gong CX, Liu F, Wu G, Rossie S, Wegiel J, Li L, et al. Dephosphorylation of microtubule-associated protein tau by protein phosphatase 5. J Neurochem. 2004; 88:298–310. [PubMed: 14690518]

34. Liu F, Iqbal K, Grundke-Iqbal I, Rossie S, Gong CX. Dephosphorylation of tau by protein phosphatase 5: impairment in Alzheimer's disease. J Biol Chem. 2005; 280:1790–1796. [PubMed: 15546861]
35. Garver TD, Kincaid RL, Conn RA, Billingsley ML. Reduction of calcineurin activity in brain by antisense oligonucleotides leads to persistent phosphorylation of tau protein at Thr181 and Thr231. Mol Pharmacol. 1999; 55:632–641. [PubMed: 10101020]
36. Yu DY, Luo J, Bu F, Song GJ, Zhang LQ, Wei Q. Inhibition of calcineurin by infusion of CsA causes hyperphosphorylation of tau and is accompanied by abnormal behavior in mice. Biol Chem. 2006; 387:977–983. [PubMed: 16913847]
37. Luo J, Ma J, Yu DY, Bu F, Zhang W, Tu LH, et al. Infusion of FK506, a specific inhibitor of calcineurin, induces potent tau hyperphosphorylation in mouse brain. Brain Res Bull. 2008; 76:464–468. [PubMed: 18534252]
38. Janssens V, Goris J. Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. Biochem J. 2001; 353:417–439. [PubMed: 11171037]
39. Strack S, Zaucha JA, Ebner FF, Colbran RJ, Wadzinski BE. Brain protein phosphatase 2A: developmental regulation and distinct cellular and subcellular localization by B subunits. J Comp Neurol. 1998; 392:515–527. [PubMed: 9514514]
40. Saraf A, Virshup DM, Strack S. Differential expression of the B'beta regulatory subunit of protein phosphatase 2A modulates tyrosine hydroxylase phosphorylation and catecholamine synthesis. J Biol Chem. 2007; 282:573–580. [PubMed: 17085438]
41. Van Kanegan MJ, Strack S. The protein phosphatase 2A regulatory subunits B'beta and B'delta mediate sustained TrkA neurotrophin receptor autophosphorylation and neuronal differentiation. Mol Cell Biol. 2009; 29:662–674. [PubMed: 19029245]
42. Walaas SI, Hemmings HC Jr, Greengard P, Nairn AC. Beyond the dopamine receptor: regulation and roles of serine/threonine protein phosphatases. Front Neuroanat. 2011; 5:50. [PubMed: 21904525]
43. Hunter T. The age of crosstalk: phosphorylation, ubiquitination, and beyond. Mol Cell. 2007; 28:730–738. [PubMed: 18082598]
44. Choudhary C, Mann M. Decoding signalling networks by mass spectrometry-based proteomics. Nat Rev Mol Cell Biol. 2010; 11:427–439. [PubMed: 20461098]
45. Zolnierowicz S. Type 2A protein phosphatase, the complex regulator of numerous signaling pathways. Biochem Pharmacol. 2000; 60:1225–1235. [PubMed: 11007961]
46. Lee J, Stock J. Protein phosphatase 2A catalytic subunit is methyl-esterified at its carboxyl terminus by a novel methyltransferase. J Biol Chem. 1993; 268:19192–19195. [PubMed: 8396127]
47. Xie H, Clarke S. An enzymatic activity in bovine brain that catalyzes the reversal of the C-terminal methyl esterification of protein phosphatase 2A. Biochem Biophys Res Commun. 1994; 203:1710–1715. [PubMed: 7945320]
48. Tolstykh T, Lee J, Vafai S, Stock JB. Carboxyl methylation regulates phosphoprotein phosphatase 2A by controlling the association of regulatory B subunits. EMBO J. 2000; 19:5682–5691. [PubMed: 11060019]
49. Wu J, Tolstykh T, Lee J, Boyd K, Stock JB, Broach JR. Carboxyl methylation of the phosphoprotein phosphatase 2A catalytic subunit promotes its functional association with regulatory subunits in vivo. EMBO J. 2000; 19:5672–5681. [PubMed: 11060018]
50. Chen J, Martin BL, Brautigan DL. Regulation of protein serine-threonine phosphatase type-2A by tyrosine phosphorylation. Science. 1992; 257:1261–1264. [PubMed: 1325671]
51. Gong CX, Singh TJ, Grundke-Iqbal I, Iqbal K. Phosphoprotein phosphatase activities in Alzheimer disease brain. J Neurochem. 1993; 61:921–927. [PubMed: 8395566]
52. Sontag E, Hladik C, Montgomery L, Luangpirom A, Mudrak I, Ogris E, et al. Downregulation of protein phosphatase 2A carboxyl methylation and methyltransferase may contribute to Alzheimer disease pathogenesis. J Neuropathol Exp Neurol. 2004; 63:1080–1091. [PubMed: 15535135]
53. Sontag E, Luangpirom A, Hladik C, Mudrak I, Ogris E, Speciale S, et al. Altered expression levels of the protein phosphatase 2A ABalphaC enzyme are associated with Alzheimer disease pathology. J Neuropathol Exp Neurol. 2004; 63:287–301. [PubMed: 15099019]

54. Rudrabhatla P, Pant HC. Role of protein phosphatase 2A in Alzheimer's disease. Curr Alzheimer Res. 2001 [Epub ahead of print].
55. Vogelsberg-Ragaglia V, Schuck T, Trojanowski JQ, Lee VM. PP2A mRNA expression is quantitatively decreased in Alzheimer's disease hippocampus. Exp Neurol. 2001; 168:402–412. [PubMed: 11259128]
56. Tanimukai H, Grundke-Iqbal I, Iqbal K. Up-regulation of inhibitors of protein phosphatase-2A in Alzheimer's disease. Am J Pathol. 2005; 166:1761–1771. [PubMed: 15920161]
57. Gharbi-Ayachi A, Labbe JC, Burgess A, Vigneron S, Strub JM, Brioudes E, et al. The substrate of Greatwall kinase, Arpp 19, controls mitosis by inhibiting protein phosphatase 2A. Science. 2010; 330:1673–1677. [PubMed: 21164014]
58. Mochida S, Maslen SL, Skehel M, Hunt T. Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. Science. 2010; 330:1670–1673. [PubMed: 21164013]
59. Kim SH, Nairn AC, Cairns N, Lubec G. Decreased levels of ARPP-19 and PKA in brains of Down syndrome and Alzheimer's disease. J Neural Transm. 2001; 61(Suppl):263–272.
60. Zhou XW, Gustafsson JA, Tanila H, Bjorkdahl C, Liu R, Winblad B, et al. Tau hyperphosphorylation correlates with reduced methylation of protein phosphatase 2A. Neurobiol Dis. 2008; 31:386–394. [PubMed: 18586097]
61. Bryant JC, Westphal RS, Wadzinski BE. Methylated C-terminal leucine residue of PP2A catalytic subunit is important for binding of regulatory Balpha subunit. Biochem J. 1999; 339(Pt. 2):241–246. [PubMed: 10191253]
62. Chen CM, Hou YT, Liu JY, Wu YR, Lin CH, Fung HC, et al. PPP2R2B CAG repeat length in the Han Chinese in Taiwan: association analyses in neurological and psychiatric disorders and potential functional implications. Am J Med Genet B Neuropsychiatr Genet. 2009; 150B:124–129. [PubMed: 18484086]
63. Kimura R, Morihara T, Kudo T, Kamino K, Takeda M. Association between CAG repeat length in the PPP2R2B gene and Alzheimer disease in the Japanese population. Neurosci Lett. 2011; 487:354–357. [PubMed: 21029765]
64. Liu F, Liang Z, Gong CX. Hyperphosphorylation of tau and protein phosphatases in Alzheimer disease. Panminerva Med. 2006; 48:97–108. [PubMed: 16953147]
65. Iqbal K, Alonso AC, Chen S, Chohan MO, El-Akkad E, Gong CX, et al. Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta. 2005; 1739:198–210. [PubMed: 15615638]
66. Xu Y, Chen Y, Zhang P, Jeffrey PD, Shi Y. Structure of a protein phosphatase 2A holoenzyme: insights into B55-mediated Tau dephosphorylation. Mol Cell. 2008; 31:873–885. [PubMed: 18922469]
67. Bulbarelli A, Lonati E, Cazzaniga E, Gregori M, Masserini M. Pin1 affects Tau phosphorylation in response to Abeta oligomers. Mol Cell Neurosci. 2009; 42:75–80. [PubMed: 19520166]
68. Landrieu I, Smet-Nocca C, Amniai L, Louis JV, Wieruszeski JM, Goris J, et al. Molecular implication of PP2A and Pin1 in the Alzheimer's disease specific hyperphosphorylation of tau. PLoS One. 2011; 6:e21521. [PubMed: 21731772]
69. Sontag E, Nunbhakdi-Craig V, Sontag JM, Diaz-Arrastia R, Ogris E, Dayal S, et al. Protein phosphatase 2A methyltransferase links homocysteine metabolism with tau and amyloid precursor protein regulation. J Neurosci. 2007; 27:2751–2759. [PubMed: 17360897]
70. Colombo A, Bastone A, Ploia C, Sclip A, Salmona M, Forloni G, et al. JNK regulates APP cleavage and degradation in a model of Alzheimer's disease. Neurobiol Dis. 2009; 33:518–525. [PubMed: 19166938]
71. Shin J, Yu SB, Yu UY, Jo SA, Ahn JH. Swedish mutation within amyloid precursor protein modulates global gene expression towards the pathogenesis of Alzheimer's disease. BMB Rep. 2010; 43:704–709. [PubMed: 21034535]
72. Liu R, Zhou XW, Tanila H, Bjorkdahl C, Wang JZ, Guan ZZ, et al. Phosphorylated PP2A (tyrosine 307) is associated with Alzheimer neurofibrillary pathology. J Cell Mol Med. 2008; 12:241–257. [PubMed: 18208556]
73. Klumpp S, Krieglstein J. Serine/threonine protein phosphatases in apoptosis. Curr Opin Pharmacol. 2002; 2:458–462. [PubMed: 12127881]

74. Ruvolo PP, Deng X, Ito T, Carr BK, May WS. Ceramide induces Bcl2 dephosphorylation via a mechanism involving mitochondrial PP2A. J Biol Chem. 1999; 274:20296–20300. [PubMed: 10400650]
75. Culmsee C, Landshamer S. Molecular insights into mechanisms of the cell death program: role in the progression of neurodegenerative disorders. Curr Alzheimer Res. 2006; 3:269–283. [PubMed: 17017859]
76. Shanley TP, Vasi N, Denenberg A, Wong HR. The serine/threonine phosphatase, PP2A: endogenous regulator of inflammatory cell signaling. J Immunol. 2001; 166:966–972. [PubMed: 11145674]
77. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. Int J Biochem Cell Biol. 2005; 37:289–305. [PubMed: 15474976]
78. Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. Arch Pharm Res. 2010; 33:1539–1556. [PubMed: 21052932]
79. Lim GP, Yang F, Chu T, Chen P, Beech W, Teter B, et al. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. J Neurosci. 2000; 20:5709–5714. [PubMed: 10908610]
80. Cole GM, Morihara T, Lim GP, Yang F, Begum A, Frautschy SA. NSAID and antioxidant prevention of Alzheimer's disease: lessons from in vitro and animal models. Ann N Y Acad Sci. 2004; 1035:68–84. [PubMed: 15681801]
81. Breitner JC. The role of anti-inflammatory drugs in the prevention and treatment of Alzheimer's disease. Annu Rev Med. 1996; 47:401–411. [PubMed: 8712791]
82. Szekely CA, Breitner JC, Zandi PP. Prevention of Alzheimer's disease. Int Rev Psychiatry. 2007; 19:693–706. [PubMed: 18092245]
83. Woods J, Snape M, Smith MA. The cell cycle hypothesis of Alzheimer's disease: suggestions for drug development. Biochim Biophys Acta. 2007; 1772:503–508. [PubMed: 17223322]
84. Nagy Z, Esiri MM, Smith AD. Expression of cell division markers in the hippocampus in Alzheimer's disease and other neurodegenerative conditions. Acta Neuropathol. 1997; 93:294–300. [PubMed: 9083562]
85. Park KH, Hallows JL, Chakrabarty P, Davies P, Vincent I. Conditional neuronal simian virus 40 Tantigen expression induces Alzheimer-like tau and amyloid pathology in mice. J Neurosci. 2007; 27:2969–2978. [PubMed: 17360920]
86. Wurzenberger C, Gerlich DW. Phosphatases: providing safe passage through mitotic exit. Nat Rev Mol Cell Biol. 2011; 12:469–482. [PubMed: 21750572]
87. Turowski P, Fernandez A, Favre B, Lamb NJ, Hemmings BA. Differential methylation and altered conformation of cytoplasmic and nuclear forms of protein phosphatase 2A during cell cycle progression. J Cell Biol. 1995; 129:397–410. [PubMed: 7721943]
88. Gotz J, Probst A, Ehler E, Hemmings B, Kues W. Delayed embryonic lethality in mice lacking protein phosphatase 2A catalytic subunit Calpha. Proc Natl Acad Sci USA. 1998; 95:12370–12375. [PubMed: 9770493]
89. Kins S, Crameri A, Evans DR, Hemmings BA, Nitsch RM, Gotz J. Reduced protein phosphatase 2A activity induces hyperphosphorylation and altered compartmentalization of tau in transgenic mice. J Biol Chem. 2001; 276:38193–38200. [PubMed: 11473109]
90. Deters N, Ittner LM, Gotz J. Substrate-specific reduction of PP2A activity exaggerates tau pathology. Biochem Biophys Res Commun. 2009; 379:400–405. [PubMed: 19126401]
91. Arendt T, Holzer M, Fruth R, Bruckner MK, Gartner U. Paired helical filament-like phosphorylation of tau, deposition of beta/A4-amyloid and memory impairment in rat induced by chronic inhibition of phosphatase 1 and 2A. Neuroscience. 1995; 69:691–698. [PubMed: 8596639]
92. Arendt T, Holzer M, Fruth R, Bruckner MK, Gartner U. Phosphorylation of tau, Abeta-formation, and apoptosis after in vivo inhibition of PP-1 and PP-2A. Neurobiol Aging. 1998; 19:3–13. [PubMed: 9562497]
93. Wang X, Blanchard J, Kohlbrenner E, Clement N, Linden RM, Radu A, et al. The carboxy-terminal fragment of inhibitor-2 of protein phosphatase-2A induces Alzheimer disease pathology and cognitive impairment. FASEB J. 2010; 24:4420–4432. [PubMed: 20651003]

94. Schild A, Schmidt K, Lim YA, Ke Y, Ittner LM, Hemmings BA, et al. Altered levels of PP2A regulatory B/PR55 isoforms indicate role in neuronal differentiation. Int J Dev Neurosci. 2006; 24:437–443. [PubMed: 17045446]
95. Louis JV, Martens E, Borghgraef P, Lambrecht C, Sents W, Longin S, et al. Mice lacking phosphatase PP2A subunit PR61/B'delta (Ppp 2r5d) develop spatially restricted tauopathy by deregulation of CDK5 and GSK3beta. Proc Natl Acad Sci USA. 2011; 108:6957–6962. [PubMed: 21482799]
96. Planel E, Richter KE, Nolan CE, Finley JE, Liu L, Wen Y, et al. Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. J Neurosci. 2007; 27:3090–3097. [PubMed: 17376970]
97. Whittington RA, Virag L, Marcouiller F, Papon MA, El Khoury NB, Julien C, et al. Propofol directly increases tau phosphorylation. PLoS One. 2011; 6:e16648. [PubMed: 21304998]
98. Aramburu J, Rao A, Klee CB. Calcineurin: from structure to function. Curr Top Cell Regul. 2000; 36:237–295. [PubMed: 10842755]
99. Mulkey RM, Endo S, Shenolikar S, Malenka RC. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. Nature. 1994; 369:486–488. [PubMed: 7515479]
100. Winder DG, Sweatt JD. Roles of serine/threonine phosphatases in hippocampal synaptic plasticity. Nat Rev Neurosci. 2001; 2:461–474. [PubMed: 11433371]
101. Mansuy IM. Calcineurin in memory and bidirectional plasticity. Biochem Biophys Res Commun. 2003; 311:1195–1208. [PubMed: 14623305]
102. Cousin MA, Robinson PJ. The dephosphins: dephosphorylation by calcineurin triggers synaptic vesicle endocytosis. Trends Neurosci. 2001; 24:659–665. [PubMed: 11672811]
103. Sanderson JL, Dell'Acqua ML. AKAP signaling complexes in regulation of excitatory synaptic plasticity. Neuroscientist. 2011; 17:321–336. [PubMed: 21498812]
104. Oliveira AM, Bading H. Calcium signaling in cognition and aging-dependent cognitive decline. Biofactors. 2011; 37:168–174. [PubMed: 21698696]
105. Agbas A, Zaidi A, Michaelis EK. Decreased activity and increased aggregation of brain calcineurin during aging. Brain Res. 2005; 1059:59–71. [PubMed: 16150427]
106. Billingsley ML, Ellis C, Kincaid RL, Martin J, Schmidt ML, Lee VM, et al. Calcineurin immunoreactivity in Alzheimer's disease. Exp Neurol. 1994; 126:178–184. [PubMed: 7925818]
107. Ladner CJ, Czech J, Maurice J, Lorens SA, Lee JM. Reduction of calcineurin enzymatic activity in Alzheimer's disease: correlation with neuropathologic changes. J Neuropathol Exp Neurol. 1996; 55:924–931. [PubMed: 8759782]
108. Lian Q, Ladner CJ, Magnuson D, Lee JM. Selective changes of calcineurin (protein phosphatase 2B) activity in Alzheimer's disease cerebral cortex. Exp Neurol. 2001; 167:158–165. [PubMed: 11161603]
109. Celsi F, Svedberg M, Unger C, Cotman CW, Carri MT, Ottersen OP, et al. Beta-amyloid causes downregulation of calcineurin in neurons through induction of oxidative stress. Neurobiol Dis. 2007; 26:342–352. [PubMed: 17344052]
110. Liu F, Grundke-Iqbal I, Iqbal K, Oda Y, Tomizawa K, Gong CX. Truncation and activation of calcineurin A by calpain I in Alzheimer disease brain. J Biol Chem. 2005; 280:37755–37762. [PubMed: 16150694]
111. Qian W, Yin X, Hu W, Shi J, Gu J, Grundke-Iqbal I, et al. Activation of protein phosphatase 2B and hyperphosphorylation of Tau in Alzheimer's disease. J Alzheimers Dis. 2011; 23:617–627. [PubMed: 21157033]
112. Mohmmad AH, Baig I, Levine H III, Guttmann RP, Norris CM. Proteolysis of calcineurin is increased in human hippocampus during mild cognitive impairment and is stimulated by oligomeric Abeta in primary cell culture. Aging Cell. 2011; 10:103–113. [PubMed: 20969723]
113. D'Amelio M, Cavallucci V, Middei S, Marchetti C, Pacioni S, Ferri A, et al. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. Nat Neurosci. 2011; 14:69–76. [PubMed: 21151119]

114. Ermak G, Morgan TE, Davies KJ. Chronic overexpression of the calcineurin inhibitory gene DSCR1 (Adapt78) is associated with Alzheimer's disease. J Biol Chem. 2001; 276:38787–38794. [PubMed: 11483593]
115. Ermak G, Davies KJ. Gene expression in Alzheimer's disease. Drugs Today (Barc). 2002; 38:509–516. [PubMed: 12582468]
116. Cook CN, Hejna MJ, Magnuson DJ, Lee JM. Expression of calcipressin1, an inhibitor of the phosphatase calcineurin, is altered with aging and Alzheimer's disease. J Alzheimers Dis. 2005; 8:63–73. [PubMed: 16155351]
117. Cruchaga C, Kauwe JS, Mayo K, Spiegel N, Bertelsen S, Nowotny P, et al. SNPs associated with cerebrospinal fluid phospho-tau levels influence rate of decline in Alzheimer's disease. PLoS Genet. 2010; 6:e1001101. [PubMed: 20862329]
118. Chiocco MJ, Zhu X, Walther D, Pletnikova O, Troncoso JC, Uhl GR, et al. Fine mapping of calcineurin (PPP3CA) gene reveals novel alternative splicing patterns, association of 5'UTR trinucleotide repeat with addiction vulnerability, and differential isoform expression in Alzheimer's disease. Subst Use Misuse. 2010; 45:1809–1826. [PubMed: 20590401]
119. Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, et al. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. J Neurosci. 2005; 25:4649–4658. [PubMed: 15872113]
120. Desdouits F, Buxbaum JD, Desdouits-Magnen J, Nairn AC, Greengard P. Amyloid beta peptide formation in cell-free preparations. Regulation by protein kinase C, calmodulin, and calcineurin. J Biol Chem. 1996; 271:24670–24674. [PubMed: 8798734]
121. Kim Y, Lee YI, Seo M, Kim SY, Lee JE, Youn HD, et al. Calcineurin dephosphorylates glycogen synthase kinase-3 beta at serine-9 in neuroblast-derived cells. J Neurochem. 2009; 111:344–354. [PubMed: 19659461]
122. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. 1988; 23:138–144. [PubMed: 2897823]
123. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Ann Neurol. 1990; 27:457–464. [PubMed: 2360787]
124. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991; 30:572–580. [PubMed: 1789684]
125. Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, et al. Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. Proc Natl Acad Sci USA. 1999; 96:3228–3233. [PubMed: 10077666]
126. Larson J, Lynch G, Games D, Seubert P. Alterations in synaptic transmission and long-term potentiation in hippocampal slices from young and aged PDAPP mice. Brain Res. 1999; 840:23–35. [PubMed: 10517949]
127. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, et al. APP processing and synaptic function. Neuron. 2003; 37:925–937. [PubMed: 12670422]
128. Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, et al. High-level neuronal expression of abeta 1–42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci. 2000; 20:4050–4058. [PubMed: 10818140]
129. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation *in vivo*. Nature. 2002; 416:535–539. [PubMed: 11932745]
130. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, et al. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nat Neurosci. 2005; 8:79–84. [PubMed: 15608634]
131. Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron. 2007; 55:697–711. [PubMed: 17785178]

132. Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, et al. Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J Neurosci. 2007; 27:796–807. [PubMed: 17251419]
133. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci. 2007; 27:2866–2875. [PubMed: 17360908]
134. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002; 298:789–791. [PubMed: 12399581]
135. Selkoe DJ. Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. Behav Brain Res. 2008; 192:106–113. [PubMed: 18359102]
136. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci. 2005; 8:1051–1058. [PubMed: 16025111]
137. Almeida CG, Tampellini D, Takahashi RH, Greengard P, Lin MT, Snyder EM, et al. Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. Neurobiol Dis. 2005; 20:187–198. [PubMed: 16242627]
138. Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, et al. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron. 2006; 52:831–843. [PubMed: 17145504]
139. Li S, Hong S, Shepardson NE, Walsh DM, Shankar GM, Selkoe D. Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. Neuron. 2009; 62:788–801. [PubMed: 19555648]
140. Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature. 2009; 457:1128–1132. [PubMed: 19242475]
141. Gimbel DA, Nygaard HB, Coffey EE, Gunther EC, Lauren J, Gimbel ZA, et al. Memory impairment in transgenic Alzheimer mice requires cellular prion protein. J Neurosci. 2010; 30:6367–6374. [PubMed: 20445063]
142. Chen QS, Wei WZ, Shimahara T, Xie CW. Alzheimer amyloid beta-peptide inhibits the late phase of long-term potentiation through calcineurin-dependent mechanisms in the hippocampal dentate gyrus. Neurobiol Learn Mem. 2002; 77:354–371. [PubMed: 11991763]
143. Mattson MP, Chan SL. Dysregulation of cellular calcium homeostasis in Alzheimer's disease: bad genes and bad habits. J Mol Neurosci. 2001; 17:205–224. [PubMed: 11816794]
144. Camandola S, Mattson MP. Aberrant subcellular neuronal calcium regulation in aging and Alzheimer's disease. Biochim Biophys Acta. 2011; 1813:965–973. [PubMed: 20950656]
145. Zhao WQ, Santini F, Breese R, Ross D, Zhang XD, Stone DJ, et al. Inhibition of calcineurin-mediated endocytosis and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors prevents amyloid beta oligomer-induced synaptic disruption. J Biol Chem. 2010; 285:7619–7632. [PubMed: 20032460]
146. Dineley KT, Hogan D, Zhang WR, Taglialatela G. Acute inhibition of calcineurin restores associative learning and memory in Tg2576 APP transgenic mice. Neurobiol Learn Mem. 2007; 88:217–224. [PubMed: 17521929]
147. Taglialatela G, Hogan D, Zhang WR, Dineley KT. Intermediate- and long-term recognition memory deficits in Tg2576 mice are reversed with acute calcineurin inhibition. Behav Brain Res. 2009; 200:95–99. [PubMed: 19162087]
148. Dineley KT, Kayed R, Neugebauer V, Fu Y, Zhang W, Reese LC, et al. Amyloid-beta oligomers impair fear conditioned memory in a calcineurin-dependent fashion in mice. J Neurosci Res. 2010; 88:2923–2932. [PubMed: 20544830]
149. Wu HY, Hudry E, Hashimoto T, Kuchibhotla K, Rozkalne A, Fan Z, et al. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. J Neurosci. 2010; 30:2636–2649. [PubMed: 20164348]

150. Kuchibhotla KV, Goldman ST, Lattarulo CR, Wu HY, Hyman BT, Bacskai BJ. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron. 2008; 59:214–225. [PubMed: 18667150]
151. Robinson RA, Lange MB, Sultana R, Galvan V, Fombonne J, Gorostiza O, et al. Differential expression and redox proteomics analyses of an Alzheimer disease transgenic mouse model: effects of the amyloid-beta peptide of amyloid precursor protein(Xi). Neuroscience. 2011; 177:207–222. [PubMed: 21223993]
152. Ehlers MD. Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting. Neuron. 2000; 28:511–525. [PubMed: 11144360]
153. Snyder GL, Galdi S, Fienberg AA, Allen P, Nairn AC, Greengard P. Regulation of AMPA receptor dephosphorylation by glutamate receptor agonists. Neuropharmacology. 2003; 45:703–713. [PubMed: 14529709]
154. Flavell SW, Cowan CW, Kim TK, Greer PL, Lin Y, Paradis S, et al. Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. Science. 2006; 311:1008–1012. [PubMed: 16484497]
155. Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, et al. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. J Neurosci. 2009; 29:12957–12969. [PubMed: 19828810]
156. Agostinho P, Lopes JP, Velez Z, Oliveira CR. Overactivation of calcineurin induced by amyloid-beta and prion proteins. Neurochem Int. 2008; 52:1226–1233. [PubMed: 18295934]
157. Reese LC, Zhang W, Dineley KT, Kayed R, Taglialatela G. Selective induction of calcineurin activity and signaling by oligomeric amyloid beta. Aging Cell. 2008; 7:824–835. [PubMed: 18782350]
158. Mansuy IM, Shenolikar S. Protein serine/threonine phosphatases in neuronal plasticity and disorders of learning and memory. Trends Neurosci. 2006; 29:679–686. [PubMed: 17084465]
159. Morishita W, Connor JH, Xia H, Quinlan EM, Shenolikar S, Malenka RC. Regulation of synaptic strength by protein phosphatase 1. Neuron. 2001; 32:1133–1148. [PubMed: 11754843]
160. Genoux D, Haditsch U, Knobloch M, Michalon A, Storm D, Mansuy IM. Protein phosphatase 1 is a molecular constraint on learning and memory. Nature. 2002; 418:970–975. [PubMed: 12198546]
161. Bollen M. Combinatorial control of protein phosphatase-1. Trends Biochem Sci. 2001; 26:426–431. [PubMed: 11440854]
162. Hsieh-Wilson LC, Benfenati F, Snyder GL, Allen PB, Nairn AC, Greengard P. Phosphorylation of spinophilin modulates its interaction with actin filaments. J Biol Chem. 2003; 278:1186–1194. [PubMed: 12417592]
163. Sarrouilhe D, di TA, Metaye T, Ladeveze V. Spinophilin: from partners to functions. Biochimie. 2006; 88:1099–1113. [PubMed: 16737766]
164. Ragusa MJ, Dancheck B, Critton DA, Nairn AC, Page R, Peti W. Spinophilin directs protein phosphatase 1 specificity by blocking substrate binding sites. Nat Struct Mol Biol. 2010; 17:459–464. [PubMed: 20305656]
165. Hagiwara M, Alberts A, Brindle P, Meinkoth J, Feramisco J, Deng T, et al. Transcriptional attenuation following cAMP induction requires PP-1-mediated dephosphorylation of CREB. Cell. 1992; 70:105–113. [PubMed: 1352481]
166. Koshibu K, Graff J, Beullens M, Heitz FD, Berchtold D, Russig H, et al. Protein phosphatase 1 regulates the histone code for long-term memory. J Neurosci. 2009; 29:13079–13089. [PubMed: 19828821]
167. Canettieri G, Morantte I, Guzman E, Asahara H, Herzig S, Anderson SD, et al. Attenuation of a phosphorylation-dependent activator by an HDAC-PP1 complex. Nat Struct Biol. 2003; 10:175–181. [PubMed: 12567184]
168. Lapointe NE, Morfini G, Pigino G, Gaisina IN, Kozikowski AP, Binder LI, et al. The amino terminus of tau inhibits kinesin-dependent axonal transport: implications for filament toxicity. J Neurosci Res. 2009; 87:440–451. [PubMed: 18798283]

169. Kanaan NM, Morfini GA, Lapointe NE, Pigino GF, Patterson KR, Song Y, et al. Pathogenic forms of tau inhibit kinesin-dependent axonal transport through a mechanism involving activation of axonal phosphotransferases. J Neurosci. 2011; 31:9858–9868. [PubMed: 21734277]
170. Knobloch M, Farinelli M, Konietzko U, Nitsch RM, Mansuy IM. Abeta oligomer-mediated long-term potentiation impairment involves protein phosphatase 1-dependent mechanisms. J Neurosci. 2007; 27:7648–7653. [PubMed: 17634359]
171. Mulkey RM, Herron CE, Malenka RC. An essential role for protein phosphatases in hippocampal long-term depression. Science. 1993; 261:1051–1055. [PubMed: 8394601]
172. Vintem AP, Henriques AG, da Cruz E, Silva OA, da Cruz E, Silva EF. PP1 inhibition by Abeta peptide as a potential pathological mechanism in Alzheimer's disease. Neurotoxicol Teratol. 2009; 31:85–88. [PubMed: 19028567]
173. O'Connor T, Sadleir KR, Maus E, Velliquette RA, Zhao J, Cole SL, et al. Phosphorylation of the translation initiation factor eIF2alpha increases BACE1 levels and promotes amyloidogenesis. Neuron. 2008; 60:988–1009. [PubMed: 19109907]
174. Yang LB, Lindholm K, Yan R, Citron M, Xia W, Yang XL, et al. Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease. Nat Med. 2003; 9:3–4. [PubMed: 12514700]
175. Zhao J, Fu Y, Yasvoina M, Shao P, Hitt B, O'Connor T, et al. Beta-site amyloid precursor protein cleaving enzyme 1 levels become elevated in neurons around amyloid plaques: implications for Alzheimer's disease pathogenesis. J Neurosci. 2007; 27:3639–3649. [PubMed: 17409228]
176. Brush MH, Weiser DC, Shenolikar S. Growth arrest and DNA damage-inducible protein GADD34 targets protein phosphatase 1 alpha to the endoplasmic reticulum and promotes dephosphorylation of the alpha subunit of eukaryotic translation initiation factor 2. Mol Cell Biol. 2003; 23:1292–1303. [PubMed: 12556489]
177. Marciniak SJ, Ron D. Endoplasmic reticulum stress signaling in disease. Physiol Rev. 2006; 86:1133–1149. [PubMed: 17015486]
178. Boyce M, Bryant KF, Jousse C, Long K, Harding HP, Scheuner D, et al. A selective inhibitor of eIF2alpha dephosphorylation protects cells from ER stress. Science. 2005; 307:935–939. [PubMed: 15705855]
179. Hinds TD Jr, Sanchez ER. Protein phosphatase 5. Int J Biochem Cell Biol. 2008; 40:2358–2362. [PubMed: 17951098]
180. Sanchez-Ortiz E, Hahm BK, Armstrong DL, Rossie S. Protein phosphatase 5 protects neurons against amyloid-beta toxicity. J Neurochem. 2009; 111:391–402. [PubMed: 19686245]
181. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med. 2008; 14:45–53. [PubMed: 18218341]
182. Lombroso PJ, Naegele JR, Sharma E, Lerner M. A protein tyrosine phosphatase expressed within dopaminoceptive neurons of the basal ganglia and related structures. J Neurosci. 1993; 13:3064–3074. [PubMed: 8331384]
183. Boulanger LM, Lombroso PJ, Raghunathan A, During MJ, Wahle P, Naegele JR. Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. J Neurosci. 1995; 15:1532–1544. [PubMed: 7869116]
184. Braithwaite SP, Paul S, Nairn AC, Lombroso PJ. Synaptic plasticity: one STEP at a time. Trends Neurosci. 2006; 29:452–458. [PubMed: 16806510]
185. Oyama T, Goto S, Nishi T, Sato K, Yamada K, Yoshikawa M, et al. Immunocytochemical localization of the striatal enriched protein tyrosine phosphatase in the rat striatum: a light and electron microscopic study with a complementary DNA-generated polyclonal antibody. Neuroscience. 1995; 69:869–880. [PubMed: 8596655]
186. Goebel-Goody SM, Baum M, Paspalas C, Carty NC, Fernandez S, Kurup P, et al. Therapeutic implications for striatal-enriched protein tyrosine phosphatase (STEP) in neuropsychiatric disorders. Pharmacol Rev. 2011 [Epub ahead of print].
187. Pulido R, Zuniga A, Ullrich A. PTP-SL and STEP protein tyrosine phosphatases regulate the activation of the extracellular signal-regulated kinases ERK1 and ERK2 by association through a kinase interaction motif. EMBO J. 1998; 17:7337–7350. [PubMed: 9857190]

188. Paul S, Nairn AC, Wang P, Lombroso PJ. NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. Nat Neurosci. 2003; 6:34–42. [PubMed: 12483215]

189. Nguyen TH, Liu J, Lombroso PJ. Striatal enriched phosphatase 61 dephosphorylates Fyn at phosphotyrosine 420. J Biol Chem. 2002; 277:24274–24279. [PubMed: 11983687]

190. Venkitaramani DV, Moura PJ, Picciotto MR, Lombroso PJ. Striatal-enriched protein tyrosine phosphatase (STEP) knockout mice have enhanced hippocampal memory. Eur J Neurosci. 2011; 33:2288–2298. [PubMed: 21501258]

191. Pelkey KA, Askalan R, Paul S, Kalia LV, Nguyen TH, Pitcher GM, et al. Tyrosine phosphatase STEP is a tonic brake on induction of long-term potentiation. Neuron. 2002; 34:127–138. [PubMed: 11931747]

192. Zhang Y, Venkitaramani DV, Gladding CM, Zhang Y, Kurup P, Molnar E, et al. The tyrosine phosphatase STEP mediates AMPA receptor endocytosis after metabotropic glutamate receptor stimulation. J Neurosci. 2008; 28:10561–10566. [PubMed: 18923032]

193. Braithwaite SP, Adkisson M, Leung J, Nava A, Masterson B, Urfer R, et al. Regulation of NMDA receptor trafficking and function by striatal-enriched tyrosine phosphatase (STEP). Eur J Neurosci. 2006; 23:2847–2856. [PubMed: 16819973]

194. Zhang Y, Kurup P, Xu J, Carty N, Fernandez SM, Nygaard HB, et al. Genetic reduction of striatal-enriched tyrosine phosphatase (STEP) reverses cognitive and cellular deficits in an Alzheimer's disease mouse model. Proc Natl Acad Sci USA. 2010; 107:19014–19019. [PubMed: 20956308]

195. Munoz JJ, Tarrega C, Blanco-Aparicio C, Pulido R. Differential interaction of the tyrosine phosphatases PTP-SL, STEP and HePTP with the mitogen-activated protein kinases ERK1/ 2 and p38alpha is determined by a kinase specificity sequence and influenced by reducing agents. Biochem J. 2003; 372:193–201. [PubMed: 12583813]

196. Paul S, Snyder GL, Yokakura H, Picciotto MR, Nairn AC, Lombroso PJ. The Dopamine/D1 receptor mediates the phosphorylation and inactivation of the protein tyrosine phosphatase STEP via a PKA-dependent pathway. J Neurosci. 2000; 20:5630–5638. [PubMed: 10908600]

197. Valjent E, Pascoli V, Svenningsson P, Paul S, Enslen H, Corvol JC, et al. From The Cover: regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. Proc Natl Acad Sci USA. 2005; 102:491–496. [PubMed: 15608059]

198. Hu Y, Zhang Y, Venkitaramani DV, Lombroso PJ. Translation of striatal-enriched protein tyrosine phosphatase (STEP) after beta1-adrenergic receptor stimulation. J Neurochem. 2007; 103:531–5341. [PubMed: 17623046]

199. Nguyen TH, Paul S, Xu Y, Gurd JW, Lombroso PJ. Calcium-dependent cleavage of striatal enriched tyrosine phosphatase (STEP). J Neurochem. 1999; 73:1995–2001. [PubMed: 10537058]

200. Xu J, Kurup P, Zhang Y, Goebel-Goody SM, Wu PH, Hawasli AH, et al. Extrasynaptic NMDA receptors couple preferentially to excitotoxicity via calpain-mediated cleavage of STEP. J Neurosci. 2009; 29:9330–9343. [PubMed: 19625523]

201. Kurup P, Zhang Y, Xu J, Venkitaramani DV, Haroutunian V, Greengard P, et al. Abeta-mediated NMDA receptor endocytosis in Alzheimer's disease involves ubiquitination of the tyrosine phosphatase STEP61. J Neurosci. 2010; 30:5948–5957. [PubMed: 20427654]

202. Zhang Y, Kurup P, Xu J, Anderson GM, Greengard P, Nairn AC, et al. Reduced levels of the tyrosine phosphatase STEP block beta amyloid-mediated GluA1/GluA2 receptor internalization. J Neurochem. 2011; 119:664–672. [PubMed: 21883219]

203. Roche KW, Standley S, McCallum J, Dune LC, Ehlers MD, Wenthold RJ. Molecular determinants of NMDA receptor internalization. Nat Neurosci. 2001; 4:794–802. [PubMed: 11477425]

204. Venkitaramani DV, Paul S, Zhang Y, Kurup P, Ding L, Tressler L, et al. Knockout of striatal enriched protein tyrosine phosphatase in mice results in increased ERK1/2 phosphorylation. Synapse. 2009; 63:69–81. [PubMed: 18932218]

205. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003; 39:409–421. [PubMed: 12895417]

206. Hayashi T, Huganir RL. Tyrosine phosphorylation and regulation of the AMPA receptor by SRC family tyrosine kinases. J Neurosci. 2004; 24:6152–6160. [PubMed: 15240807]

207. Scholz R, Berberich S, Rathgeber L, Kolleker A, Kohr G, Kornau HC. AMPA receptor signaling through BRAG2 and Arf6 critical for long-term synaptic depression. Neuron. 2010; 66:768–780. [PubMed: 20547133]

208. Shirazi SK, Wood JG. The protein tyrosine kinase, fyn, in Alzheimer's disease pathology. Neuroreport. 1993; 4:435–437. [PubMed: 8388744]

209. Lee G, Thangavel R, Sharma VM, Litersky JM, Bhaskar K, Fang SM, et al. Phosphorylation of tau by fyn: implications for Alzheimer's disease. J Neurosci. 2004; 24:2304–2312. [PubMed: 14999081]

210. Derkinderen P, Scales TM, Hanger DP, Leung KY, Byers HL, Ward MA, et al. Tyrosine 394 is phosphorylated in Alzheimer's paired helical filament tau and in fetal tau with c-Abl as the candidate tyrosine kinase. J Neurosci. 2005; 25:6584–6593. [PubMed: 16014719]

211. Chin J, Palop JJ, Yu GQ, Kojima N, Masliah E, Mucke L. Fyn kinase modulates synaptotoxicity, but not aberrant sprouting, in human amyloid precursor protein transgenic mice. J Neurosci. 2004; 24:4692–4697. [PubMed: 15140940]

212. Chin J, Palop JJ, Puolivali J, Massaro C, Bien-Ly N, Gerstein H, et al. Fyn kinase induces synaptic and cognitive impairments in a transgenic mouse model of Alzheimer's disease. J Neurosci. 2005; 25:9694–9703. [PubMed: 16237174]

213. Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van EJ, et al. Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell. 2010; 142:387–397. [PubMed: 20655099]

214. Roberson ED, Halabisky B, Yoo JW, Yao J, Chin J, Yan F, et al. Amyloid-beta/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. J Neurosci. 2011; 31:700–711. [PubMed: 21228179]

215. de Vrij FM, Fischer DF, van Leeuwen FW, Hol EM. Protein quality control in Alzheimer's disease by the ubiquitin proteasome system. Prog Neurobiol. 2004; 74:249–270. [PubMed: 15582222]

216. Upadhya SC, Hegde AN. Role of the ubiquitin proteasome system in Alzheimer's disease. BMC Biochem. 2007; 8(Suppl. 1):S12. [PubMed: 18047736]

217. Oddo S. The ubiquitin-proteasome system in Alzheimer's disease. J Cell Mol Med. 2008; 12:363–373. [PubMed: 18266959]

218. Mori H, Kondo J, Ihara Y. Ubiquitin is a component of paired helical filaments in Alzheimer's disease. Science. 1987; 235:1641–1644. [PubMed: 3029875]

219. Lam YA, Pickart CM, Alban A, Landon M, Jamieson C, Ramage R, et al. Inhibition of the ubiquitin-proteasome system in Alzheimer's disease. Proc Natl Acad Sci USA. 2000; 97:9902–9906. [PubMed: 10944193]

220. David DC, Layfield R, Serpell L, Narain Y, Goedert M, Spillantini MG. Proteasomal degradation of tau protein. J Neurochem. 2002; 83:176–185. [PubMed: 12358741]

221. Qing H, Zhou W, Christensen MA, Sun X, Tong Y, Song W. Degradation of BACE by the ubiquitin-proteasome pathway. FASEB J. 2004; 18:1571–1573. [PubMed: 15289451]

222. He G, Qing H, Cai F, Kwok C, Xu H, Yu G, et al. Ubiquitin-proteasome pathway mediates degradation of APH-1. J Neurochem. 2006; 99:1403–1412. [PubMed: 17059559]

223. He G, Qing H, Tong Y, Cai F, Ishiura S, Song W. Degradation of nicastrin involves both proteasome and lysosome. J Neurochem. 2007; 101:982–992. [PubMed: 17326768]

224. Gong B, Cao Z, Zheng P, Vitolo OV, Liu S, Staniszewski A, et al. Ubiquitin hydrolase Uch-L1 rescues beta-amyloid-induced decreases in synaptic function and contextual memory. Cell. 2006; 126:775–788. [PubMed: 16923396]

225. Tseng BP, Green KN, Chan JL, Blurton-Jones M, LaFerla FM. Abeta inhibits the proteasome and enhances amyloid and tau accumulation. Neurobiol Aging. 2008; 29:1607–1618. [PubMed: 17544172]

226. Oh S, Hong HS, Hwang E, Sim HJ, Lee W, Shin SJ, et al. Amyloid peptide attenuates the proteasome activity in neuronal cells. Mech Ageing Dev. 2005; 126:1292–1299. [PubMed: 16153690]
227. Smith DL, Pozueta J, Gong B, Arancio O, Shelanski M. Reversal of long-term dendritic spine alterations in Alzheimer disease models. Proc Natl Acad Sci USA. 2009; 106:16877–16882. [PubMed: 19805389]
228. Zhu Y, Hou H, Rezai-Zadeh K, Giunta B, Ruscin A, Gemma C, et al. CD45 deficiency drives amyloid-beta peptide oligomers and neuronal loss in Alzheimer's disease mice. J Neurosci. 2011; 31:1355–1365. [PubMed: 21273420]
229. Mody N, Agouni A, McIlroy GD, Platt B, Delibegovic M. Susceptibility to diet-induced obesity and glucose intolerance in the APP (SWE)/PSEN1 (A246E) mouse model of Alzheimer's disease is associated with increased brain levels of protein tyrosine phosphatase 1B (PTP1B) and retinol-binding protein 4 (RBP4), and basal phosphorylation of S6 ribosomal protein. Diabetologia. 2011; 54:2143–2151. [PubMed: 21538175]
230. Nagy Z, Esiri MM, Cato AM, Smith AD. Cell cycle markers in the hippocampus in Alzheimer's disease. Acta Neuropathol. 1997; 94:6–15. [PubMed: 9224524]
231. Ding XL, Husseman J, Tomashevski A, Nochlin D, Jin LW, Vincent I. The cell cycle Cdc25A tyrosine phosphatase is activated in degenerating postmitotic neurons in Alzheimer's disease. Am J Pathol. 2000; 157:1983–1990. [PubMed: 11106571]
232. Vincent I, Bu B, Hudson K, Husseman J, Nochlin D, Jin L. Constitutive Cdc25B tyrosine phosphatase activity in adult brain neurons with M phase-type alterations in Alzheimer's disease. Neuroscience. 2001; 105:639–650. [PubMed: 11516829]
233. De SB, Vassar R, Golde T. The secretases: enzymes with therapeutic potential in Alzheimer disease. Nat Rev Neurol. 2010; 6:99–107. [PubMed: 20139999]
234. Cummings J. What can be inferred from the interruption of the semagacestat trial for treatment of Alzheimer's disease? Biol Psychiatry. 2010; 68:876–878. [PubMed: 21035622]
235. Extance A. Alzheimer's failure raises questions about disease-modifying strategies. Nat Rev Drug Discov. 2010; 9:749–751. [PubMed: 20885394]
236. Voronkov M, Braithwaite SP, Stock JB. Phosphoprotein phosphatase 2A: a novel druggable target for Alzheimer's disease. Future Med Chem. 2011; 3:821–833. [PubMed: 21644827]
237. Corcoran NM, Martin D, Hutter-Paier B, Windisch M, Nguyen T, Nheu L, et al. Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer's disease model. J Clin Neurosci. 2010; 17:1025–1033. [PubMed: 20537899]
238. van EJ, Ke YD, Liu X, Delerue F, Kril JJ, Gotz J, et al. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. Proc Natl Acad Sci USA. 2010; 107:13888–13893. [PubMed: 20643941]
239. Chohan MO, Khatoon S, Iqbal IG, Iqbal K. Involvement of I2PP2A in the abnormal hyperphosphorylation of tau and its reversal by Memantine. FEBS Lett. 2006; 580:3973–3979. [PubMed: 16806196]
240. Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, Sharkey J, et al. Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. Proc Natl Acad Sci USA. 2010; 107:21830–21835. [PubMed: 21098287]
241. Lee KW, Chen W, Junn E, Im JY, Grosso H, Sonsalla PK, et al. Enhanced phosphatase activity attenuates alpha-Synucleinopathy in a mouse model. J Neurosci. 2011; 31:6963–6971. [PubMed: 21562258]
242. Liu S, Zeng LF, Wu L, Yu X, Xue T, Gunawan AM, et al. Targeting inactive enzyme conformation: aryl diketoacid derivatives as a new class of PTP1B inhibitors. J Am Chem Soc. 2008; 130:17075–17084. [PubMed: 19012396]
243. Wu S, Bottini M, Rickert RC, Mustelin T, Tautz L. In silico screening for PTPN22 inhibitors: active hits from an inactive phosphatase conformation. ChemMedChem. 2009; 4:440–444. [PubMed: 19177473]
244. Zhang X, He Y, Liu S, Yu Z, Jiang ZX, Yang Z, et al. Salicylic acid based small molecule inhibitor for the oncogenic Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2). J Med Chem. 2010; 53:2482–2493. [PubMed: 20170098]

245. Barr AJ, Ugochukwu E, Lee WH, King ON, Filippakopoulos P, Alfano I, et al. Large-scale structural analysis of the classical human protein tyrosine phosphatome. Cell. 2009; 136:352–363. [PubMed: 19167335]

246. Sergienko E, Xu J, Liu We, Dahl R, Critton DA, Su Y, et al. A specific inhibitor of hematopoietic protein tyrosine phosphatase augments ERK and p38 activation *in vivo* . ACS Chem Biol. 2011 [In press].

247. Borel JF, Feurer C, Gubler HU, Stahelin H. Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions. 1976; 6:468–75. [PubMed: 8969]

248. Calne RY, Rolles K, White DJ, Thiru S, Evans DB, McMaster P, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet. 1979; 2:1033–1036. [PubMed: 91781]

249. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009; 4:481–508. [PubMed: 19218475]

250. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int. 2000; 13:313–226. [PubMed: 11052266]

251. Sieber M, Baumgrass R. Novel inhibitors of the calcineurin/NFATc hub—alternatives to CsA and FK506? Cell Commun Signal. 2009; 7:25. [PubMed: 19860902]

Prog Mol Biol Transl Sci. Author manuscript; available in PMC 2013 August 10.

TABLE I

Assessment of Dephosphorylation of Hyperphosphorylated Tau by Ser/Thr PPases

Site					Site				
Y18					S235				
T39					S237				
S46					S238				
S68					S241				
T69					S258				
T71					S262	PP1	PP2A+++	PP2B +++[2,3]	PP5
S113					S285				
T123					S289				
S137					S305				
T153					S324				
T175					S352				
T181	PP1	PP2A	PP2B[1]		S356		PP2A		
S184					Y294				
S185					S396	PP1	PP2A[*]	PP2B +++[2,3]	PP5
S191					S400				
Y197					T403		PP2A		
S198			PP2B[2,3]		S404	PP1	PP2A	PP2B[2,3]	PP5
S199	PP1	PP2A	PP2B[2,3]	PP5	S409	PP1+++	PP2A+++	PP2B+++	PP5+++
S202	PP1	PP2A	PP2B[2,3]	PP5	S412				
T205	PP1+++	PP2A+++[*]	PP2B	PP5+++	S413				
S208					T414				
S210					S416				
T212	PP1+++	PP2A+++[*]	PP2B	PP5+++	S422	PP1	PP2A	PP2B	
S214	PP1+++	PP2A	PP2B	PP5	T427				
T217	PP1	PP2A[*]	PP2B		S433				
T231		PP2A	PP2B[1]		S435				

More than 50 sites of phosphorylation have been identified in tau.[26] The dephosphorylation of a limited number has been analyzed using available phospho-specific antibodies, and in *in vitro* assays various preparations of PP1,[28,29] PP2A,[28,30,31] PP2B,[28,32] and PP5[28,33,44] exhibit selectivity for different sites (+++ indicates highest activity in *in vitro* assays).

*Note that studies of PP2A came to a different assessment of the dephosphorylation of some sites. Studies of the role of PP2B were also assessed *in vivo*;

*1*PP2B knockdown in rat brain[35]

*2*cyclosporin infusion into mouse left lateral ventricle[36]

*3*FK506 infusion in mouse[37]