Protein phosphatase (PP) 5 is highly expressed in the mammalian brain, but few physiological substrates have yet been identified. Here, we investigated the kinetics of dephosphorylation of phospho-tau by PP5 and found that PP5 had a $K_m$ of 8–13 μM toward tau, which is similar to that of PP2A, the major known tau phosphatase. This $K_m$ value is within the range of intraneuronal tau concentration in human brain, suggesting that tau could be a physiological substrate of both PP5 and PP2A. PP5 dephosphorylated tau at all 12 Alzheimer’s disease (AD)-associated abnormal phosphorylation sites studied, with different efficiency toward each site. Thr$^{205}$, Thr$^{212}$, and Ser$^{409}$ of tau were the most favorable sites; Ser$^{199}$, Ser$^{202}$, Ser$^{214}$, Ser$^{396}$, and Ser$^{404}$ were less favorable sites; and Ser$^{262}$ was the poorest site for PP5. Overexpression of PP5 in PC12 cells resulted in dephosphorylation of tau at multiple phosphorylation sites. The activity but not the protein level of PP5 was found to be decreased by ~20% in AD neocortex. These results suggest that tau is probably a physiological substrate of PP5 and that the abnormal hyperphosphorylation of tau in AD might result in part from the decreased PP5 activity in the diseased brains.

Tau protein is a major microtubule-associated protein in neurons. The known biological function of tau protein is to stimulate and stabilize microtubule formation from tubulin subunits. In human brain, there are six tau isoforms generated by alternative mRNA splicing from a single gene (1, 2).Tau is a phosphoprotein that normally contains 2–3 phosphates/molecule, but it is abnormally hyperphosphorylated with a stoichiometry of 9–10 moles of phosphate per mole of protein in Alzheimer’s disease (AD)$^3$ brain (3, 4). To date, more than 30 phosphorylation sites have been identified in AD hyperphosphorylated tau, some of which are not phosphorylated in normal tau (for review, see Refs. 5 and 6). The abnormally hyperphosphorylated tau is the major component of paired helical filaments (PHFs) (7–10), which form neurofibrillary tangles, a histopathological hallmark brain lesion of AD and several other tauopathies.

The hyperphosphorylation of tau appears to be responsible for the loss of its biological function, gain of its toxicity, and aggregation into PHFs (11–16). However, the molecular mechanism by which tau becomes abnormally hyperphosphorylated in AD brain is not yet well understood. Theoretically, the abnormal hyperphosphorylation of tau could be the result of up-regulation of tau kinases or down-regulation of tau phosphatases. Several studies have shown that there are three major protein phosphatases (PPs), PP1, PP2A, and PP2B, dephosphorylate tau in vitro (17–23). Among these, PP2A appears to be the major phosphatase that regulates tau phosphorylation in the brain (23–28). The activity of PP2A was found to be decreased in AD brain (29–33). Nevertheless, PP2A does not dephosphorylate all the phosphorylation sites of tau, and down-regulation of PP2A in animal brain could not produce PHFs (26, 28). These studies suggest that in addition to PP2A, other phosphatases or factors might also participate in the regulation of tau phosphorylation.

PP5 is a 58-kDa phosphatase that requires phosphorylation by protein phosphatase 2A. It is ubiquitously expressed in all types of mammalian tissue, with a relatively high level in the brain (34, 35). PP5 contains a C-terminal catalytic domain structurally related to the PP1/PP2A/PP2B family and an N-terminal regulatory domain consisting of three tetratricopeptide repeats (TPRs) that usually mediate protein-protein interaction. It has been demonstrated that PP5 interacts with multiple target proteins through the TPR domain (for review, see Ref. 36). In the absence of activators, PP5 exhibits unusually low phosphatase activity in vitro. However, PP5, after removal of its TPR domain or in the presence of long-chain fatty acyl-CoA ester or long-chain fatty acids, effectively dephosphorylates p-nitrophenyl phosphate (pNPP) as well as phosphoproteins such as casein, myelin basic protein, reduced carboxamidomethylated and maleylated lysozyme, and tau (37–40). Although PP5 has been implicated in several signal transduction pathways (36), few physiological substrates and functions for PP5 have thus far been defined.

We recently found (40) that PP5 dephosphorylates tau in vitro and may associate with microtubules, raising the possibility that PP5 may also participate in regulation of tau phosphorylation in the brain. To elucidate the role of PP5 in regulation of tau phosphorylation and in the hyperphosphorylation of tau in AD, we studied the kinetics of tau dephosphorylation by PP5, mapped the sites of tau dephosphorylated by PP5, investigated tau dephosphorylation by PP5 in cultured cells, and measured PP5 activity in AD and control brains. Our
results suggest that PP5 may play a role in regulation of tau phosphorylation and that a reduction of PP5 activity may contribute to hyperphosphorylation of tau in AD.

EXPERIMENTAL PROCEDURES

Materials—Recombinant rat PP5, cyclin-dependent kinase 5 and its activator, p25, and the largest isoform of human tau, tau441, were cloned, expressed, and purified as described previously (14, 38, 41). The catalytic subunit of cAMP-dependent kinase was purchased from Sigma. All phosphorylation-dependent and site-specific tau antibodies were from BioSource (Table 1). Peroxidase-conjugated anti-mouse and anti-rabbit IgG were from Jackson ImmunoResearch Laboratories (West Grove, PA). 32P-labeled anti-mouse and anti-rabbit IgG and ECL kit were from Amersham Biosciences. The phosphorylation-independent tau antibodies 92e and R134d and anti-PP5 antibody were raised in rabbits as described previously (35, 44, 45).

Preparation of Phosphorylated Tau (P-tau) and 32P-labeled Tau—Recombinant tau441 was phosphorylated with cAMP-dependent protein kinase and cyclin-dependent kinase 5/p25 by incubating tau441 (2 mg/ml) with the catalytic subunit of cAMP-dependent protein kinase (10 μmol/l) containing P-tau were pooled and stored at -70 °C until used.

Dephosphorylation of P-tau by PP5—P-tau (0.2 mg/ml) was incubated with 0.5 μmol/l PP5 at 30 °C for 2 h in a reaction mixture containing 50 mm Tris-HCl, pH 7.4, 10 mm β-mercaptoethanol, and 5 μM AA-CoA. The reaction was stopped by adding 0.33 volume of 4-fold concentrated sample buffer for SDS-PAGE. After heating in boiling water for 5 min, the samples were subjected to SDS-PAGE and Western blot analysis using site-specific and phosphorylation-dependent tau antibodies as described previously (41).

For quantitative detection of site-specific dephosphorylation of tau by PP5, the dephosphorylation reaction was carried out by using the same concentration as described above for PP5 activity assay, except that P-tau was used to replace 32P-P-tau. The reaction was stopped by addition of a mixture of phosphatase inhibitors (50 mm sodium sulfate, pH 7.5, 5 μM okadaic acid, 50 mm NaF, 5 mm EDTA, and 5 mm EGTA). The dephosphorylation of P-tau at each specific site was measured by using a dot-blot radioimmunoassay as described previously (47).

Immunoprecipitation of PP5—Rat brain or autopsy human brain tissue was homogenized with 9 volumes of buffer containing 50 mm Tris-HCl, pH 7.4, 150 mm NaCl, 10 mm β-mercaptoethanol, and 2 μg/ml each of aprotinin, leupeptin, and pepstatin. The 16,000 × g extracts were prepared, and the protein concentrations were measured by the Bradford method (48). The diluted extracts were then incubated with anti-PP5 antibody that was pre-bound to protein G-agarose beads (Pierce) for 4 h at 4 °C. The negative control was prepared with protein G-agarose beads without anti-PP5. The immunoprecipitated complex was washed three times with Tris-buffered saline and two times with Tris-HCl buffer and used for Western blots or PP5 activity assay.

Transfection of PC12 Cells and PP5—pCI plasmids encoding full-length rat PP5 (pCI-FLAG-PP5499) or C-terminal truncated, lipid-independent active PP5 (pCI-FLAG-PP5486) were constructed as described previously (38, 50), except that the parent vector was modified to include an N-terminal FLAG epitope tag and a short linker sequence (LGGGATR) immediately preceding the coding sequence for PP5. PC12 cells with stable expression of tau441, which were cloned as described previously (40), were transiently transfected with either pCI-FLAG-PP5499 or pCI-FLAG-PP5486 by using Lipofectamine 2000 Reagent (Invitrogen) according to the manufacturer’s instructions. Forty-eight hours later, the cells were harvested and lysed in SDS-PAGE sample buffer, followed by Western blot analysis as described previously (41).

RESULTS

Kinetics of Tau Dephosphorylation Catalyzed by PP5—PP5 requires free long-chain fatty acids or long-chain fatty acyl-CoA esters for its activity (39). We therefore studied the activation of PP5 using AA-CoA, the most abundant intracellular long-chain fatty acyl-CoA, by using recombinant tau phosphorylated by cAMP-dependent protein kinase and cyclin-dependent kinase 5/p25 as a substrate. We found that AA-CoA caused a concentration-dependent stimulation of PP5 activity toward P-tau. Stimulation was seen with a concentration of AA-CoA as low as 0.3 μM and reached a plateau at ~5 μM AA-CoA (Fig. 4B).
Deamidation of Tau by Protein Phosphatase 5

At 20 μM AA-CoA, PP5 activity toward P-tau was stimulated by 25-fold. The AA-CoA concentration required for half-maximal activation (AC50) was 1.2 μM (Fig. 1A, inset). When pNPP, a commonly used non-protein substrate for phosphatases, was used as substrate, AA-CoA stimulated PP5 activity with a slightly lower AC50 and maximal stimulation (Fig. 1A).

We then measured the K_m value of PP5-catalyzed dephosphorylation of P-tau in the presence of 5 μM AA-CoA. We observed typical Michaelis-Menten kinetics of dephosphorylation of P-tau by PP5 (Fig. 1B). Plot of the data using the Lineweaver-Burk double-reciprocal method demonstrated a very good fit (Fig. 1C). The K_m calculated from the Lineweaver-Burk equation was 7.6 μM. The calculated catalytic efficiency (K_cat/K_m) was 98 × 10^5 s^-1 M^-1. As a reference, we also measured the K_m of PP5-catalyzed dephosphorylation of pNPP and found a K_m of 64 μM, which is in agreement with those reported by Ramsey and Chinkers (39). Because the intraneuronal tau concentration is estimated to be 5–10 μM (49), our results suggest that tau is probably a physiological substrate of PP5.

The above-mentioned kinetic studies were carried out by using recombinant rat PP5 expressed from *Escherichia coli*. To learn whether recombinant PP5 catalyzes dephosphorylation of tau with the same kinetics as brain PP5, we compared the K_m of recombinant PP5 with that of PP5 immuno-affinity-purified from rat brain and human brain extracts. Western blot analyses demonstrated that anti-PP5 successfully immunoprecipitated most of PP5 from brain extract but did not co-precipitate PP1, PP2A, or PP2B, the three major protein phosphatases in mammalian brain (Fig. 2A). Binding of our anti-PP5 to PP5 did not block its phosphatase activity, as demonstrated by dose-dependent phosphatase activity of the immunoprecipitates (Fig. 2B). This is consistent with the fact that the PP5 antiserum recognizes the linker region between the TPR and catalytic domains rather than catalytic domain of PP5 (35). We then studied the kinetics of brain PP5 toward P-tau and found that the K_m values of rat brain PP5 and human brain PP5 were similar to that of recombinant rat PP5 (Fig. 2C and Table II). Therefore, we used recombinant PP5 for the rest of this study. The V_max of brain PP5 calculated from Fig. 2C was not comparable with that of the recombinant PP5 calculated from Fig. 1C because the exact amount of brain PP5 used for these assays was not known.

PP5 Dephosphorylates P-tau at Multiple Sites—Phosphorylation of different sites within tau differentially impacts the biological activity of tau and the polymerization of tau into neurofibrillary tangles.

![Image](http://www.jbc.org)
PHFs. To map to the exact sites that are dephosphorylated by PP5, we used a number of phosphorylation-dependent tau antibodies that recognize tau phosphorylation at individual sites. As shown in Fig. 3, a combination of cAMP-dependent protein kinase and cyclin-dependent kinase 5 phosphorylated recombinant tau at Thr\(^{181}\), Ser\(^{199}\), Ser\(^{202}\), Thr\(^{205}\), Thr\(^{212}\), Ser\(^{214}\), Thr\(^{231}\), Ser\(^{235}\), Ser\(^{236}\), Ser\(^{296}\), Ser\(^{404}\), and Ser\(^{409}\). An up-shift of the gel mobility of tau was also seen after phosphorylation (Fig. 3, A and B, compare lanes 2 with lanes 1). Treatment of P-tau with PP5 abolished the staining of all these phosphorylation-dependent antibodies and changed the gel mobility to the same as that for unphosphorylated tau (Fig. 3, compare lanes 3 with lanes 2). These results indicated that PP5 dephosphorylates tau at all the above-mentioned phosphorylation sites studied.

We further investigated the efficiency of tau dephosphorylation by PP5 at individual phosphorylation sites. The site-specific dephosphorylation of tau was measured by a dot-blot radioimmunoassay developed with the corresponding site-specific tau antibodies. Comparison of the extent of dephosphorylation at specific sites as a function of PP5 concentration indicated that PP5 dephosphorylated tau most efficiently at Thr\(^{205}\), Thr\(^{212}\), and Ser\(^{409}\); moderately at Ser\(^{199}\), Ser\(^{202}\), Ser\(^{214}\), Ser\(^{296}\), and Ser\(^{404}\); and least efficiently at Ser\(^{236}\) (Fig. 4). Similar results were also obtained when the time courses of the dephosphorylation at various sites were studied (data not shown). Because the signal for Thr\(^{181}\), Thr\(^{231}\), and Ser\(^{236}\) of P-tau was 5-fold higher than that of endogenous PP5 as estimated by Western blots developed with the corresponding site-specific and phosphorylation-dependent antibodies (see Fig. 3), the quantitative dephosphorylation of tau at these sites was not measured.

**PP5 Dephosphorylates Tau in Living Cells**—We also investigated whether PP5 dephosphorylates tau in living cells by using PC12 cells that stably expressed human tau\(^{441}\) (40). The cells were transfected with either full-length rat PP5\(^{499}\) or C-terminal truncated PP5\(^{486}\) that is active in the absence of lipid (50). We found that after transfection for 48 h, the expression level of active PP5\(^{486}\) was similar to or slightly lower than that of full-length PP5\(^{499}\) as estimated by Western blots developed with the corresponding site-specific tau antibody R134d and an anti-FLAG antibody (the recombinant tau\(^{441}\) contained a FLAG tag) (Fig. 5, I and J). These results suggested that PP5 regulated phosphorylation of tau in the cell.

**PP5 Activity Is Decreased in AD Brain**—To investigate whether there is a dysregulation of PP5 in AD brain that could theoretically contribute to abnormal hyperphosphorylation of tau, we measured PP5 activity of extracts from AD and age-matched control brains by using P-tau as a substrate. We found an \(-20\%\) reduction of PP5 activity in AD brains as compared with controls (Fig. 6A). To learn whether the reduction of PP5 activity was due to a reduction of the phosphatase protein level, we measured the level of PP5 in the extracts by using quantitative Western blots and found no change in PP5 level in AD brains as compared with controls (Fig. 6B). These results indicate that the activity, but not the level, of PP5 was down-regulated in AD brain.

**DISCUSSION**

We showed previously that PP5 dephosphorylates tau protein and that it is localized in the neuronal cytoplasm in human brain and appears to associate with microtubules (40). These studies suggest that tau might be a physiological substrate of PP5. In the present study, we investigated the kinetics of tau dephosphorylation by PP5 and found that PP5 had a \(K_m\) of 8–13 \(\mu\)M and a catalytic efficiency \((K_{cat}/K_m)\) of \(98 \times 10^3 \text{ s}^{-1} \text{ M}^{-1}\). This \(K_m\) value is similar to that of PP2A, a known tau phosphatase, toward tau (30) and \(-1000\)-fold lower than that of PP5 toward pNPP (38, 39), whereas the \(K_{cat}/K_m\) value of PP5 toward tau was about \(-1000\)-fold higher than that of PP5 toward pNPP, which was reported to be 47–270 \(\text{s}^{-1} \text{ M}^{-1}\) (38). Based on measurements of tau concentration in human brain tissue (49), we estimate that there are 5–10 \(\mu\)M tau in neurons. The \(K_m\) value of PP5 toward tau is at the range of the intraneuronal tau concentration. These data are consistent with the possibility that tau is a physiological substrate of PP5 and that PP5 participates in the regulation of tau phosphorylation.

PP5 has little phosphatase activity \textit{in vitro} in the absence of added lipid or without removal of the TPR domain or C terminus by limited proteolysis (37, 38, 50). Early work showed that unsaturated long-chain fatty acids such as arachidonic acid increased PP5 activity toward both pNPP and artificial protein substrates (37, 38, 50). Ramsey and Chinkers (39) recently found that physiological concentrations of long-chain fatty acyl-
CoA derivatives dramatically activate PP5 toward pNPP. However, this is not true when myelin basic protein is used as a substrate (51), indicating that, as has been seen for other

**Fig. 4.** Quantitation of tau dephosphorylation by PP5 at individual phosphorylation sites. P-tau was incubated with various concentrations of PP5 for 20 min, and the reactions were measured by a dot-blot radioimmunoassay developed with antibodies that only react with tau phosphorylated at the indicated individual sites.

**Fig. 5.** Dephosphorylation of tau by PP5 in PC12 cells. Tau expressing PC12 cells were transfected with empty plasmids as a control (Mock), plasmids of full-length PP5 (pCI-FLAG-PP5_{499}, PP5_{499}), or plasmids of lipid-independent active PP5 (pCI-FLAG-PP5_{486}, PP5_{486}) for 48 h. Then, the cell lysates (5.0 μg/lane) were analyzed by Western blots developed with anti-PP5 to determine PP5 expression levels (A), phosphorylation-dependent and site-specific tau antibodies to determine tau phosphorylation levels at the specific phosphorylation sites (B–H), and R134d and anti-FLAG to determine the levels of tau441 (I and J). Note that due to a FLAG tag of recombinant PP5, full-length PP5_{499} had a slightly larger apparent molecular weight than endogenous PP5, whereas truncated active PP5_{486} migrated to the same position as endogenous PP5 (A). Unlike endogenous PP5, the transfected PP5, for a reason unknown at present, showed as two bands.

**Fig. 6.** Activity and level of PP5 in AD and control brains. A, activities of PP5 immunoprecipitated from equivalent amounts of extracts from temporal cortices of six AD and seven control brains were assayed using ^32P-tau as a substrate. Means ± S.E. are presented. *, p < 0.05 by Student's t test as compared with control group. B, PP5 protein levels of the extracts were analyzed by Western blots developed with anti-PP5 (top panel). The blot was quantitated by densitometry, and the data are presented as mean ± S.E. (bottom panel).
members of this PP family, activation maybe substrate-dependent. In the present study, we found that even 0.625 μM AA-CoA stimulated PP5 activity toward tau and that the activation was maximal at 5–10 μM AA-CoA. This stimulation profile is similar to that seen when pNPP is used as a substrate (39). The intracellular concentration of long-chain fatty acyl-CoA esters has been estimated at 1–4 μM (52). Thus, PP5 might be active toward tau in vivo in the presence of the physiologic levels of fatty acyl-CoA derivatives. Our results showing dephosphorylation of tau in PC12 cells after overexpression of full-length PP5 demonstrated that PP5 can indeed act on tau in living cells.

Dephosphorylation of tau at different sites differentially impacts the biological activity of tau and the polymerization of tau into PHFs (12, 53–55). In the present studies, we used recombinant tau441 as a substrate after phosphorylation with cAMP-dependent protein kinase and cyclin-dependent kinase 5, a non-proline-directed protein kinase and a proline-directed protein kinase, respectively, which are among the most physiologically relevant tau kinases (for review, see Ref. 6). With a combination of these two kinases, tau was phosphorylated at least at 12 phosphorylation sites (Fig. 3), all of which are hyperphosphorylated in AD brain. Hence, this in vitro phosphorylated tau is an ideal tau substrate for studying tau phosphatases. Quantitative analyses of PP5-catalyzed dephosphorylation of tau at each individual site indicated that PP5 dephosphorylates tau most efficiently at Thr212, Thr231, and Ser205 but poorly at Ser262. In contrast, phospho-Ser205 of tau is a favorable substrate for PP2A,2 a major candidate tau phosphatase (21–28). These studies suggest that tau phosphorylation can be regulated by more than one phosphatase and that each phosphatase may regulate tau phosphorylation at different sites with certain preference.

Many studies have demonstrated that abnormal hyperphosphorylation of tau is important in the pathogenesis of AD (for review, see Ref. 6). However, the molecular mechanism by which tau becomes hyperphosphorylated is not well understood. We and others (29–33) have reported previously that the activity of PP2A is decreased in selected areas of AD brain, which suggested that the abnormal hyperphosphorylation of tau might result from the pathological reduction of PP2A activity in AD brain. However, in cultured cells, metabolically active rat brain slices, and in vivo, inhibition of PP2A induces hyperphosphorylation of tau at some, but not all, of the normally hyperphosphorylated sites seen in AD and fails to produce neurofibrillary tangles in the brain (26–28). Hence, the reduction of PP2A activity may only partially account for the abnormal tau hyperphosphorylation in AD brain. In this study, we found that PP5 activity was also decreased in AD brain. Because PP5 and PP2A appear to target differential phosphorylation sites of tau, reduction in the activities of both PP5 and PP2A may contribute to the abnormal hyperphosphorylation of tau in AD brain. It will be interesting to elucidate the relative contributions of PP5 and PP2A to the regulation of tau phosphorylation at each phosphorylation site.

Despite the decreased PP5 activity in AD brain, the protein level of PP5 was found to be the same in AD brain as that of controls. The mechanism leading to a decrease in PP5 activity in AD brain is currently not known. Although free arachidonic acid and its phospholipid forms were found to be decreased in selected regions of AD brain, these decreases do not contribute to the decreased PP5 activity we observed because the immunoprecipitated PP5 was used for the activity assay and the assays were carried out in the presence of 5 μM AA-CoA. One possible mechanism leading to the decreased PP5 activity in AD brain might be some posttranslational or structural modification that may down-regulate PP5 catalytic activity. Another possibility is the presence of a PP5 inhibitor in AD brain that might co-immunoprecipitate with PP5. Because the catalytic domain of PP5 is similar to that of PP2A (56) and PP5 has been shown to interact with certain regulatory subunits of PP2A (57), it is possible that the same inhibitor might underlie the reduction of both PP5 and PP2A activities in AD brain. The mechanism by which PP5 activity is reduced in AD brain requires further investigation.

In summary, we have studied the kinetics of PP5-catalyzed tau dephosphorylation, mapped the tau phosphorylation sites targeted by PP5, investigated the dephosphorylation of tau by PP5 in PC12 cells, and measured PP5 activity in AD and control human brains. We found that (a) the K_m value of PP5 toward tau is similar to that of PP2A and is within the range of intracellular tau concentration of human brain, (b) PP5 dephosphorylates tau at least at 12 phosphorylation sites with different efficiencies, (c) PP5 can dephosphorylate tau in living cells, and (d) PP5 activity, but not protein level, is decreased in AD brain. These results suggest that tau is a physiological substrate of PP5 and that the abnormal hyperphosphorylation of tau in AD brain might result in part from the decreased activity of PP5.

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