Axonopathy, Tau Abnormalities, and Dyskinesia, but no Neurofibrillary Tangles in p25-Transgenic Mice

FENG HAN,1,* RATIHA NATH,1 GREGG SOHOCINSKI,1 ROBERT N. BOOHER,1 WILLIAM J. LIPINSKI,2 MICHAEL J. CALLAHAN,1 AMY PACK,1 KEVIN K.-W. WANG,2 and LARRY C. WALKER3
1CNS Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, Michigan 48105
2Drug Safety Evaluation, Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, Michigan 48105
3Onyx Pharmaceuticals, Richmond, California 94806

ABSTRACT
Neurofibrillary tangles, one of the pathologic hallmarks of Alzheimer's disease (AD), are composed of abnormally polyubiquitinated tau protein. The hyperphosphorylation of tau alters its normal cellular function and is thought to promote the formation of neurofibrillary tangles. Growing evidence suggests that cyclic-dependent kinase 5 (cdk5) plays a role in tau phosphorylation, but the function of the enzyme in tangle formation remains uncertain. In AD, cdk5 is constitutively activated by p25, a highly unstable, 23kDa protein thought to be increased in the AD brain. To test the hypothesis that p25/cdk5 interactions promote neurofibrillary pathology, we created transgenic mouse lines that overexpress the human p25 protein specifically in neurons. Mice with high transgenic p25 expression have augmented cdk5 activity and develop severe hindlimb and mild forelimb dyskinesias beginning at approximately 3 months of age. Immunohistochemical and ultrastructural analyses showed widespread axonal degeneration with focal accumulation of tau in various regions of the brain and, to a lesser extent, the spinal cord. However, there was no evidence of neurofibrillary tangles in neuronal somata or axons, nor were paired helical filaments evident ultrastructurally. These studies confirm that p25 overexpression can lead to tau abnormalities and axonal degeneration in vivo but do not support the hypothesis that p25-related induction of cdk5 is a primary event in the genesis of neurofibrillary tangles. J. Comp. Neurol. 445:600–609, 2002.

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DOI 10.1002/cne.10136

Neurofibrillary tangles (NFTs) are atypical, filamentous assemblies of the hyperphosphorylated microtubule-binding protein tau; along with senile plaques, NFTs are two of the cardinal histologic markers of Alzheimer's disease (AD) (Mandelkow and Mandelkow, 1998; Spillantini and Goedert, 1998; Lee and Trojanowski, 1999; Tolnay and Probst, 1999). Although the evidence currently favors a primary role of β-amyloid (Aβ) in the pathogenesis of AD (Selloe, 1999), the NFTs that accompany aberrant Aβ-amyloid appearance appear to be a key player in the cognitive dysfunction that characterizes this disease (Arriagada et al., 1992; Berg et al., 1993). NFTs occur in several other degenerative brain disorders, and mutations in the gene for tau recently have been linked to hereditary tauopathies (Clark et al., 1998; Dumanchev et al., 1998; Goedert et al., 1998; Hutton et al., 1998; Poorkaj et al., 1998; Lee and Trojanowski, 1999; Tolnay and Probst, 1999; Walker and LeVine, 2001). The evidence, thus, implicates PHF-tau in the degeneration of neurons in many disorders of mid- to late life.

*Correspondence to: Feng Han, CNS Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105, Fax (734) 409-2278; feng-han@pfizer.com

Received 3 August 2001; Revised 25 October 2001; Accepted 10 January 2002

Published online the week of March 6, 2002
Six alternatively spliced forms of tau are expressed in the human central nervous system (Goodart et al., 1992; Andreasen et al., 1992). In normal human brains, tau is predominantly localized in axons, where it binds to and stabilizes microtubules (Weinberg et al., 1978; Riederer et al., 1992; Drehobl et al., 1990; Maniyan and Troncoso, 1990). In AD, tau undergoes a conformational change (Weaver et al., 2000) and becomes hyperphosphorylated. In this state, the protein is insoluble, loses its affinity for microtubule, and polymerizes in neurons to form the paired helical filaments (PHF) that constitute neurofibrillary tangles (Lee et al., 1991; Braak et al., 1995; Goodart et al., 1997). However, the importance of specific phosphorylation events in promoting NFT formation is uncertain (Matsumoto et al., 1994; Weaver et al., 2000).

Cyto-dendrin-dependent kinase (cdk5) is one of the kinases that phosphorylate tau in vitro (Villiset et al., 1992; Fuss et al., 1995). Like other cydin-dependent kinases, the activity of cdk5 is regulated by cyclins known as cyclins. A brain-specific activator of cdk5, the p85 protein, was identified as a cdk5-associated protein through coimmunoprecipitation of endogenous proteins (Lee et al., 1991). A proteolytic fragment of p85 called p55 is another activator of cdk5 (Low et al., 1994) that is much more stable than p55 (Patrick et al., 1998). In brain extracts from patients with AD, there is evidence that p55 levels are increased compared with levels in normal age-matched controls (Patrick et al., 1998). In AD, it has been suggested that p55 persistently up-regulates cdk5 activity, thereby contributing to tau hyperphosphorylation and the pathogenesis of NFTs. Particularly in the early stages of AD, p55 is localized in neurons containing NFTs (Patrick et al., 1995). To test the hypothesis that neuronal p55 overexpression will result in abnormalities of tau and the development of neurofibrillary tangles, we created transgenic mice overexpressing p55. We observed that the overexpressing mice develop profound dystrophy and central neuronal degeneration, but not neurofibrillary tangles.

**MATERIALS AND METHODS**

**Construction of the PDGF-p25 transgene**

The p25 coding region was amplified by polymerase chain reaction (PCR) from the p25 cDNA (3' primer: ATCCGCTCTGACCCGGGCTGCGAC-3' and 5' primer: ATCAGCTTCTACCACTCCCTGTCTGC-5') and subcloned into pUC18. The p25 cDNA was then inserted into the unique HindIII site of pCAGGS, which expresses the p25 cDNA under the control of the CMV promoter. The plasmid was linearized with PstI and introduced into the ES cells by electroporation. The ES cells were selected with G418, and the colonies were screened for the presence of the transgene. The transgene-positive colonies were identified by PCR. The transgene-positive colonies were then used to generate transgenic mice. The transgene-positive colonies were then used to generate transgenic mice. The transgene-positive colonies were then used to generate transgenic mice. The transgene-positive colonies were then used to generate transgenic mice. The transgene-positive colonies were then used to generate transgenic mice.

**Western blot**

Fromen, whole brain tissue from either wild-type or p25 transgenic mice was homogenized and subjected to SDS-PAGE. The protein was transferred to a polyvinylidene difluoride membrane and probed with a monoclonal antibody against tau. The blots were then incubated with a secondary antibody conjugated to horseradish peroxidase. The blots were then exposed to x-ray film. The p25 transgene was confirmed by Southern blot analysis. The p25 transgene was confirmed by Southern blot analysis. The p25 transgene was confirmed by Southern blot analysis. The p25 transgene was confirmed by Southern blot analysis. The p25 transgene was confirmed by Southern blot analysis.

**ACKNOWLEDGMENTS**

The authors thank Dr. J. B. Collin for excellent technical assistance and Dr. J. L. M. Donaldson for critically reading the manuscript.
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ology, Inc., CA) and developed by using nitro blue tetrazo-
alin and 5-bromo-4-chloro-3-indolyl phosphate. To de-
termine the protein expression levels in each line, Western
blots were analyzed densitometrically by using a color
scanner (Umax CDS40) and the NIH program, Image 1.5.
The optical density of the bands was measured and then
normalized relative to the densities of the p32 bands,
because p25 protein is relatively unchanged in transgenic
mouse brains.

Measurement of Cdk5 kinase activity

Freshly dissected mouse brains were washed in 1X PBS
at 4°C and homogenized in Buffer A (50 mM Tris buffer,
pH 7.4, 10 mM NaCl, 5 mM EDTA, 20 mM β-mercaptoethanol,
10 mM sodium fluoride, 1 mM sodium
vanadate, and a protease (aprotinin) cocktail) at a
ratio of 1:2.5 (w/v) by using a Polytron homogenizer at
a setting of 6 mm with three cycles of 1 min each. The
homogenate was centrifuged at 4°C in a SORVALL centrifuge
at 47,000 x g for 30 minutes and supernatant was col-
lected. 100 µl of protein was incubated with 4 µl of anti-p53
antibody C-19 (Santa Cruz Biotechnology, Inc.), a total
of 10 µl of 100 mM glycine buffer plus Santa Cruz Biotech-
nology Inc.) was added, and incubated for an
additional 5 hours at 4°C. The immunoprecipitate was
centrifuged and washed four times with Buffer A (1 ml
each time) followed by a wash with kinase buffer (250
mM Tris, pH 8.0, 10 mM NaCl, 10 mM MgCl2, 1 mM
DTT) and then resuspended in 150 µl of ESB. Thirty-five
microliters of immunoprecipitate in ESB was added to
each well. Subsequently, 25 µl of hot kinase buffer (119
µg/ml [histone H1 [Boehringer Mannheim Biotechnology, Inc.],
0.5 mM Tris pH 7.5, 10 mM MgCl2, 20 mM ATP, and
0.25 µg/ml [APTF25 µl] was added, and the plate was placed in
a shaker (low speed) at 30°C for 45 minutes. Fifty microlit-
eter of reaction mix was transferred to a glass microplate
filtered 96-well plate (Millipore-MAXI9600, Millip,
Corning, NY) and 100 µl of 100 mM phosphoric acid
was added. After a 15-minute incubation
at room temperature, the material was vacuum-filtered
and the wells were washed five times by using 150 µl of 75
mM phosphoric acid, allowing complete filtration after
each wash. The plate was then allowed to dry completely,
and 10 µl of 50 mM NaCl solution (mixture cocktail from Packard Bio-
technology Company, Meriden, CT) was added to the wells.
The counts were measured by using a TriLux machine, and
the values were plotted and analyzed by using GraphPad
Prism (Graphpad Software, Inc., San Diego, CA).

Immunochemistry

For immunohistochemistry, 10 transgenic mice and 4
wild-type controls were perfused transcardially under
deep sodium pentobarbital anesthesia (200 mg/kg i.p.) with
1X PBS (pH 7.2) for 3-4 minutes, followed by 2
minutes. Brains were removed, and one hemisphere was
frozen on dry ice for Western blot analysis (below). The
other hemisphere was fixed in 4% paraformaldehyde in
PBS (pH, 7.2) for 3 days and cryoprotected in 30%
 sucrose solution (pH 7.2) for at least 2 days. The brain
 tissue was then quick-frozen on dry ice and embedded in
 OCT (Tissue-Tek) matrix. Twenty 10-µm thick sections
 were prepared on a cryostat and air-dried. Sections were
 stained three times in PBS (pH, 7.2) for 5 minutes
 each, then washed with 0.5% Triton X-100 for 5
 minutes, and endogenous peroxidase was blocked by 3% 
 hydrogen peroxide in methanol. Sections were then incu-
 bated with antibody AT-8 (Polyclonal, Chicago, IL 1:50) or
 with Aβ1-42 (kindly provided by Dr. Benjamin Wolfe, Loyola
 University, Maywood, IL) overnight at 4°C. The tissue was
 washed, and the Vectastain Elite ABC
mouse kit (Vector Labs, Burlingame, CA) was used for
detection of the antibody. Before staining dehydro- and
carbons in Xylene, some sections were dehydrated
with hematoxylin (Leaver Laboratories, Pittsburgh, PA).

Neuronal degeneration staining

Five additional brains (three p25-transgenic mice and
two age-matched, nontransgenic control mice) were sec-
tioned and stained with the uniaxial-cricine-stain
for degenerating axons (as Olson et al., 1996) and with
the Campbell-Caffey silver stain for spinocerebellar and
neuropathy tangles (Campbell et al., 1987; Neuroanatomy
Annuities, Knoxville, TN).

Electrot microscopy

For ultrastructural analysis, four transgenic mice and
one nontransgenic littermate control mouse were perfused
transcardially under deep pentobarbital anesthesia
(000
mg/kg, i.p.) with 1X PBS, pH 7.2) for 2 minutes, then with 4% paraformaldehyde in
1X PBS (pH 7.2) for 5 minutes. Both cerebral hemispheres
as well as segments of the spinal cord were removed and
placed in 4% paraformaldehyde (1X PBS) for 48
hours. Samples of brain and spinal cord that were ob-
lected specifically for electron microscopy were further
fixed in a 2.5% glutaraldehyde plus 2% paraformaldehyde
fixative (in 0.1 M cacodylate buffer (pH 7.2) for 1 week.
Samples were rinsed three times in buffer, osmicated,
dehydrated, and embedded in epoxy resin. Semithin sec-
tions (0.5 µm thick) were stained with toluidine blue,
and ultrathin sections were stained with uranyl acetate
and lead citrate for digital imaging using a Philips CM100
Biocart electron microscope.

Peripheral nerve and muscle analysis

To determine whether changes in peripheral nerve
or muscle might account for hindlimb motor impairments
in p25-transgenic mice, the asthetic nerve and a sample of
medial posterior thigh muscle were taken at necropy from
two p25-transgenic mice at 10 months chronological
control. The nerves were fixed in 2.5% glutaraldehyde plus
2% paraformaldehyde in 0.1 M cacodylate buffer (pH
7.2), cut transversely into several short segments, and
embedded in epoxy resin. 1-µm thick sections were
stained with toluidine blue. The muscle samples were
fixed in 4% paraformaldehyde/1X PBS (pH 7.2), sectioned
at 20 µm thickness on a cryostat, and stained with
hematoxylin and eosin.

Light microscopy

Light photomicrographs were made with a Spot digital
camera overlay 2.1 software Nikon Instruments,
(Sterling Heights, MI) attached to an Olympus BX50 mi-
croscope (Olympus Optical Company, Japan). The final
pictures were compared from the digital images by using
Adobe Photoshop 6.0 (Adobe Systems, Inc., San Jose, CA).
**Fig. 1.** Transgenic expression of human p25 protein in platelet-derived growth factor (PDGF)-p25 mice. **A**: Schematic illustration of the human p25 transgene construct. The PDGF B chain promoter was used to encode transgenic p25 protein in mice. A green reference was added to increase the level of expression. p25 cDNA was obtained by polymerase chain reaction from the p25 cDNA with an archival mRNAs added as the first amino acid. The 300-bp poly(A) sequence was added at the 3'UTR of the transgene. B: The expression of human p25 protein in the brains of transgenic mice was examined by Western blot analysis by using an antibody specific to the C-terminal region of the p25 protein, as described in the Materials and Methods section. Thus, both p50 and p25 can be visualized in the same blot. Tailed-Brain extracts from three 3-month-old mice (lane 3) and one 3-month-old control (the KO7 line) (lane 4) were loaded on 10% SDS-PAGE and stained with Coomassie blue. The bands show the p50 bands in nontransgenic and are seen across all bands. C: The non-specific expression of p25 protein in transgenic mice. Western blot was performed by using protein extracts from different regions of a 3-month-old transgenic mouse (KO7 line). p25 protein was only detected in extracts of brain and spinal cord but not in heart, kidney, muscle, or liver. The bands detected in liver are nonspecific bands that differ in quiescent width from both p50 and p25. D: Augmented cdk5 activity in p25-transgenic mice. The kinase assay demonstrated that cortical cdk5 activity is significantly higher in p25-transgen mice (n = 3) than in wild-type mice (n = 3). *P < 0.05.

**RESULTS**

**p25 protein expression and cdk5 activation**

To examine the expression of p25 in the brains of the transgenic mice, Western blot analysis was performed by using polyclonal antibody C-19 to the C-terminus of the human p25 protein (Santa Cruz Biotechnology, Inc.); this antibody also recognizes p25. The expression of p25 in line KO7, a high transgene-expressing line (Fig. 1B), was 37% approximately five times greater than in littermate controls. The endogenous p25 protein, recognized by the same C-19 antibody used to detect p25, was expressed at the same levels in brains of control and transgenic mice (Fig. 1B). Moreover, cdk5 activity in transgenic brains was significantly increased relative to that of nontransgenic controls, as measured by a kinase assay (Fig. 1D). The brain specificity of p25 overexpression is illustrated in Figure 1C.

**Motor function**

Transgenic mice from line KO7 developed hindlimb spastic paralysis (Fig. 2) that became quite obvious by 2-3 F2

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**Fig. 2.** Hindlimb spastic paralysis in a platelet-derived growth factor-p25 transgenic mouse. A 3-month-old transgenic mouse from the KO7 line with motor dysfunction characterized by hindlimb semi-paresis. Movement of the hindlimb was relatively uncoordinated, although abnormal flexion occurred upon tail suspension. Although the mice had difficulty walking and breeding, they were able to eat and drink normally.
months of age. Although forelimb function appeared relatively unimpaired in an open field test, the forelimbs showed abnormal flexion when the mice were lifted by their tails, similar to that seen in rats after brain damage induced by percussion of the middle cerebral artery (Ikeura et al., 1990). Attempts to test the mice in behavioural tasks were thwarted by these debilitating motor deficits; even in the simple flip-screen assessment of motor function, the pd2-transgenic mice were completely unable to remain on the inverted screen even for a few seconds (transgenic littermate controls could easily master this task). Although the transgenic mice had difficulty walking (and breeding), they could eat and drink normally, and remained otherwise reasonably healthy until at least 16 months of age. A similar phenotype was evident in another transgenic founder (which lacked the transgene), suggesting that the behavioral deficits most likely are not due to an insertion effect of the transgene.

Central nervous system

Light microscopic analysis. In pd2-transgenic mice, abnormal, AT-6-immunoreactive structures (Fig. 3A,B) could be readily identified in various regions of the central nervous system (CNS), especially in the telencephalon and brainstem; the spinal cord, where transgene expression was somewhat lower than in the brain, was much less affected. The lesions were not uniformly distributed, but rather tended to cluster in certain areas; they were particularly numerous in the anterior corpus callosum and the lower brainstem (Fig. 3). The immunostained structures were mostly large, circular, or oval figures (Fig. 3, arrows) that often were located within or near white matter pathways. The silver-staining degeneration-stain confirmed a high density of swelling, silver-positive structures in the same regions (Fig. 3C). The Campbell-Caviness silver stain revealed no punctate intracellular neurofibrillary tangles, nor were neuritic plaques evident. In control mice,
neither hyperphosphorylated tau nor axonal swellings were found in any region of the CNS (Fig. 1D). At 60, another antibody that recognizes hyperphosphorylated tau, yielded a pattern of immunoreactivity closely resembling that of AT-8. Although tau immunoreactivity was focally increased in tissue sections, Western blots of whole-brain homogenates did not reveal an appreciable change in the amount of monomeric or oligomeric tau (data not shown), possibly because affected areas represented only a small fraction of the total forebrain tissue homogenate.

**Electron-microscopic analysis.** Based on the locally heavy concentration of tau-immunopositive swellings (see above), we removed blocks of tissue from the anterior corpus callosum and surrounding gray matter, the rostral pons, and the optic chiasm for electron microscopic analysis. All three regions contained numerous swellings that were identifiable as axons by the presence of a myelin sheath (which appeared thin relative to the increased axonal girth, Fig. 6B). The contents of the dilated axons varied considerably; most swellings contained comparatively sparse electron-dense structures such as mitochondria and dense bodies (Fig. 6B), whereas others took on a darker appearance, owing to the presence of abundant, densely packed inclusion material (Fig. 6C). The neuronal perikarya and dendrites appeared to be normal in the

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**Table:**

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transgenic mice. No enlarged axons were seen in non-transgenic littermate controls (Fig. 4D).

High-resolution visualization of the dysmyelinating axons revealed haphazardly oriented neurofilaments and microtubules winding among the axonemes and abnormal inclusions (Fig. 5). Solitary and clustered mitochondria were present (Fig. 5B), less often, lamellar bodies (Fig. 5A) and membrane-bound, electron-dense inclusions were also seen.

Sciatic nerve and leg muscle

To more fully define the anatomic basis of the hindlimb motor defects in p25-transgenic mice, samples of nerve and muscles from the rear legs of affected mice were collected for histologic analysis. The sciatic nerve (the main sensorimotor nerve of the caudal limbs) showed no structural evidence of axonal abnormalities in any of the segments analyzed (Fig. 6). The multipotential muscle group of the thigh also showed no evidence of significant degenerative changes in p25-transgenic mice.

DISCUSSION

We found that the neuronal overexpression of p25 protein, which constitutively activates Cdk5, results in severe motor defects and axon degeneration with the focal accumulation of tau in transgenic mice. The majority of the abnormal axons occurred in the brain, where p25 expression was most robust; there were fewer axonal swellings in the spinal cord. The sciatic nerve and proximal hindlimb muscles showed no appreciable degenerative changes, suggesting the implication that the main site of pathologic change in these transgenic mice is the central nervous system. There was no evidence of neurofilament tangles in the somatodendritic or axonal compartments in any p25-transgenic mice up to 6 months of age.

Several transgenic mouse models of tau-related pathologies have now been described, including a p25-transgenic mouse (Abilguizian et al., 2000), mice bearing various tau protein constructs (Gott et al., 1995, 2000a; Biswas et al., 1999; Ibañez et al., 1999; Pizzi et al., 1999; Daf et al., 2000; Lewis et al., 2000; Probst et al., 2000), as well as mice expressing either transgenes that promote the phosphorylation of tau (Daune et al., 1996; Breakefield et al., 1997; Tsev et al., 2000a, b). In tau-related transgenic mice with evident lesions, axonopathy is a consistent feature (Ibañez et al., 1999; Pizzi et al., 1999; Abilguizian et al., 2000; Daf et al., 2000; Lewis et al., 2000; Probst et al., 2000; Tsev et al., 2000a, b), the general features of which are similar to those in our p25-transgenics. The highest-fidelity transgenic model of human neurofilament pathology appears to be one that produces mutant (Pro121) tau protein (Lewis et al., 2000). With age, these mice develop motor dysfunction and gene dosage-related tangle-like pathologic conditions in the somatodendritic compartment of neurons. Our p25-transgenic mice did not produce neurofilament tangles, despite five-fold overexpression of p25 and widespread central axonopathy with the usual bundle of AT-8-transfected axons. This finding, in conjunction with the results of Abilguizian et al. (2000), suggest that p25 overexpression/Co2+ stimulation alone is insufficient to initiate the formation of neurofilament tangles in mice. Recently, Bitters and colleagues also showed that p25 aggregation in astrocytes was shown to be increased with exogenous AbP2 fibers (Gott et al., 2001b) or by

![Fig. 5](image-url)
the transgenic expression of the β-amyloid precursor protein (Lewis et al., 2001) in mutant tau-transgenic mice. These results establish an important link in the patho-

cpheric cascade that leads from abnormalities in Aβ to dysfunction of tau in AD. It is not yet certain which ins-


termediate species of tau is most critical for neurotoxicity, but fruit flies expressing mutant human tau furnish tantalizing

data. Tau-transgenic flies have progressive neurodegeneration in the absence of neurofibrillary tangles (Willi-

gunn et al., 2001), suggesting that a soluble, prefibrillar form of mutant tau is toxic to neurons. In future studies, it


can be informative to determine whether p25 promotes the formation or persistence of a form of soluble tau that is


critical for the axonal pathology in p25-transgenic mice.


An alternative explanation for the emergence of 


amnestic transgenic mice is that the neuronal overex-


gression per se of certain proteins is injurious to neurons. For example, older transgenic mice overexpressing human


apolipoprotein E4 in neurons develop a phenotype similar to that of p25 transgenics, including amnesticity with hyper-


phosphorylated tau as well as locomotor deficits (Tessier et al., 2000a,b). Because of their unique morphological and


certainly related to incline and prominent axons of neuronal stress. In fact, a variety of acute and subacute insults can induce


axonal hypertrophy and degenerative change (Ashbury and Brown, 1986; Tuszynski et al., 1993), including hereditary and


tumoral disorders (Jellinger and Järaskö, 1974; Cork et al., 1985), chemical intoxication (Geffen et al.,


1992; Cork et al., 1993; Jacobs and LeQuereau, 1993), and senescence (Jellinger and Järaskö, 1974; Schmidt et al.,


1980; Walker and Cork, 1990). Occasional dilated axons can even be found normally in the central nervous system of young


mice (Clark et al., 1984; Gravel et al., 1984), including humans (Clark et al., 1984). Whether the phe-


nologic phenomena and the p25 transgen-


cic and PDCB-p25 transgenics are also specifically to the hyperphosphorylation, or whether they are the manifesta-


tion of some more generalized pathologic process, remains to be determined.


The astyral accumulation of tau is clearly demonstra-


table in AD, as well as in various transgenic and nontrans-


genetic mouse models of neurodegeneration, but whether and how hyperphosphorylation influences the abnormal


amyloid pathology of tau remains ambiguous. For example, it


can be informative to note that the coexpression of glycogen synth-


ase kinase-3β, another enzyme that phosphorylates tau in vivo, actually counteracts the amnestic effects of human 


four-repeat tau overexpression in transgenic mice (Spittaels et al., 2000). In addition, the specific participa-


tion of p25-induced calpain activation in the tangle cascade remains open to question. Although initial data indicated that


p25 protein is increased in the Alzheimerian brain (Patrick et al., 1999), a recent study of a larger number of


subjects has found that p25 may not be more abundant in end-stage AD (Takuro et al., 2000). Moreover, confirmatory 


tional changes in tau correlate best with phosphorylation at Thr231 (Wiseart et al., 1998, 1996; Hof et al., 1997), a site that is not phosphorylated by calpain. Our data confirm that p25-overexpression causes amnestic pathology with the foccal accumulation of tau in the CNS of transgenic mice, but the effected neurons remain devoid of neurofibrillary tangles. p25-transgenic mice could be a useful model of spontaneous cerebrovascular amnesticity, but the weight of evidence currently mitigates against p25-induced activation of calpain as a primary event in the genesis of neurofibrillary tangles.


ACKNOWLEDGEMENTS


We thank German Vergara for microinjecting the PDCB-p25 construct, Dr. Multhaup Albusmum for helpful advice on the muscle histopathology, and Sandra Holmes for her capable assistance in tracing the p25-transgenic mice.


LITERATURE CITED


Fig. 6. Statics nerve of wild type control (A) and p25 transgenic (B) mice. Note the absence of axonal swellings in the transgenic mouse nerve. Contra:st-demonstrate plastic section, toluidine blue stain. Scale bars = 50 μm in A,B.
and translational databases to mine unappreciated human activity, an alternative of sib. Proc Natl Acad Sci USA 1979;76:4409-4413.