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Brief Communications

Synaptic Deficits Are Rescued in the p25/Cdk5 Model of Neurodegeneration by the Reduction of β-Secretase (BACE1)

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Alzheimer’s disease (AD) is the most common cause of dementia, and is characterized by memory loss and cognitive decline, as well as amyloid β (Aβ) accumulation, and progressive neurodegeneration. Cdk5 is a proline-directed serine/threonine kinase whose activation by the p25 protein has been implicated in a number of neurodegenerative disorders. The CK-p25 inducible mouse model exhibits progressive neuronal death, elevated Aβ, reduced synaptic plasticity, and impaired learning following p25 overexpression in forebrain neurons. Levels of Aβ, as well as the APP processing enzyme, β-secretase (BACE1), are also increased in CK-p25 mice. It is unknown what role increased Aβ plays in the cognitive and neurodegenerative phenotype of the CK-p25 mouse. In the current work, we restored Aβ levels in the CK-p25 mouse to those of wild-type mice via the partial genetic deletion of BACE1, allowing us to examine the Aβ-independent phenotype of this mouse model. We show that, in the CK-p25 mouse, normalization of Aβ levels led to a rescue of synaptic and cognitive deficits. Conversely, neuronal loss was not ameliorated. Our findings indicate that increases in p25/Cdk5 activity may mediate cognitive and synaptic impairment via an Aβ-dependent pathway in the CK-p25 mouse. These findings explore the impact of targeting Aβ production in a mouse model of neurodegeneration and cognitive impairment, and how this may translate into therapeutic approaches for sporadic AD.

Introduction

Alzheimer’s disease (AD) is the most common type of dementia, with an incidence that increases with age. The great majority of AD cases are sporadic and idiopathic. Amyloid plaques are a defining histological characteristic of AD (Hardy, 2006). Amyloid β (Aβ) peptides, which can exist as oligomers or aggregate into amyloid plaques, are generated upon the sequential cleavage of APP, which is initiated by the amyloid precursor cleaving enzyme (BACE1) (Vassar et al., 1999).

Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine kinase that binds to one of two activators, p35 or p39 (Ko et al., 2001). Cdk5 regulates a multiplicity of physiological events in the CNS, including neuronal migration, neurite development, synaptic plasticity, and cognition (Dhavan and Tsai, 2001; Fischer et al., 2002; Tomizawa et al., 2002; Cheung and Ip, 2007; Kim and Ryan, 2010). The proteolytic cleavage of p35 into p25 by calpain, a Ca2+-dependent protease, leads to the prolonged activation and altered subcellular localization of Cdk5 (Lee et al., 2000; O’Hare et al., 2005). The generation of p25 has been linked to neurotoxicity and several neurodegenerative disorders including AD, amyotrophic lateral sclerosis, Parkinson’s disease, Neiman Pick’s Type C disease, and ischemic brain injury (Patrick et al., 1999; Nguyen et al., 2001; Sawamura et al., 2001; Wang et al., 2003; Qu et al., 2007).

We created a transgenic mouse that overexpresses the p25 protein under the control of an inducible, calcium/calmodulin-dependent protein kinase II α (CaMKII) promoter (CK-p25 mice) (Cruz et al., 2003). These mice recapitulate many hallmark features of AD, including progressive neuronal loss, elevated Aβ, tau pathology, cognitive dysfunction, and impaired synaptic plasticity (Cruz et al., 2003; Fischer et al., 2005). p25/Cdk5 has been shown to upregulate BACE1 expression and activity through a transcriptional mechanism (Wen et al., 2008), and the CK-p25 mice accordingly exhibit increased BACE1 levels and activity, accompanied by the intraneuronal accumulation of Aβ (Cruz et al., 2006).

Mouse models of AD in which Aβ is elevated via mutations in APP or in Aβ processing express significant cognitive and synaptic deficits. However, unlike both AD patients and mice overexpressing p25, these models exhibit little or no neuronal loss. To specifically examine the role of Aβ elevation in the CK-p25 mouse model of neurodegeneration, we evaluated the impact of p25 overexpression on a background of normalized Aβ levels in the CK-p25 mouse. To achieve this, we targeted Aβ production by breeding CK-p25 mice to BACE1 knock-out mice, an approach which has led to the amelioration of pathology in several mouse models of familial AD (FAD) (Ohno et al., 2004, 2007;
Laird et al., 2005). We found that the deletion of a single copy of BACE1 in the CK-p25/BACE1+/– compound mice reduced Aβ to baseline levels, and rescued synapse density, synaptic plasticity, and memory impairments in the CK-p25 mice, but not neuronal loss. These findings indicate that increases in p25/Cdk5 activity may mediate AD-like pathology via parallel pathways in the CK-p25 mouse, one of which involves increases in Aβ generation, synaptic dysfunction and cognitive decline, and a parallel pathway that leads to neuronal death.

Materials and Methods

Mice. Single CaMKII-tTA or TetO-p25-GFP transgenic mice were crossed to BACE1 mice (Cai et al., 2001) obtained from The Jackson Laboratory, and the resulting genotypes were mated to obtain the genotypes of interest. At 2 months of age, CK-p25 mice were induced for 6 weeks to obtain forebrain-specific p25 expression (Cruz et al., 2003). Littermates and same-sex mice were used for comparison whenever possible. All transgenes were heterozygous. Upon brain dissection, one hemisphere was frozen in liquid nitrogen. Alternatively, mice were perfused with 4% PFA before dissection of the hemispheres.

Immunoblot analysis. Forebrain lysates from 6-week induced mice were prepared as described previously (Cruz et al., 2003). Proteins were subjected to SDS-PAGE and immunoblot analysis using the following antibodies (1:1000 unless noted): DC17 (Cdk5, Tsai laboratory, 1:50), p35 (Tsai laboratory), GAPDH (Santa Cruz Biotechnology), pT205 (Invitrogen), C-APP (Sigma), BACE1 (D10E5 clone; Cell Signaling Technology).

Aβ ELISA. Forebrain tissue was homogenized in an ice-cold 4X volume of PBS supplemented with 1X protease inhibitors (Roche), AEBSF (4-(2-aminoethyl)benzenesulfonyl fluoride) (Pierce), and 8.2 μm guanidine/82 mm Tris HCl, pH 8.0, to a final concentration of 5 μm guanidine. Samples were processed with the Mouse Aβ42 ELISA kit according to manufacturer’s instructions (Invitrogen).

Immunohistochemistry. Forty-micrometer-thick sections were prepared from fixed brains. Floating sections were labeled using the following antibodies (1:500): 4G8 (Covance), NeuN (Millipore), GFP (Aves Labs), and synaptophysin (Sigma). To quantify neuronal density, five comparable sections spanning the hippocampus were immunolabeled, and the total number of NeuN-positive cells in hippocampal area CA1 across all sections was counted blindly. 4G8 pictures were taken from comparable sections containing CA1 at the same rostrocaudal level. 4G8 puncta were defined as intracellular aggregates of >5 contiguous pixels of matching maximum intensity. For synaptophysin quantification, the stratum radiatum of the hippocampus was imaged using a 63X oil objective and 4X optical zoom, and the number of puncta with a diameter of ~0.4 μm was counted. Comparable sections were stained with Cresyl Violet dye, and total cell numbers were counted under a light microscope. Immunofluorescent images were acquired using a Zeiss confocal microscope. All cell counts were quantified blindly.

Animal behavior. Context-dependent fear conditioning was performed as described previously (Guan et al., 2009). Briefly, mice were trained by exposure to the context, followed by a foot shock (2 s, 0.5, 0.8 mA constant current). Freezing behavior was recorded 24 h later upon reexposure of the mice to the conditioning context.

Electrophysiological analysis. Electrophysiological analysis was performed as described previously (Guan et al., 2009). Recordings were...
pared with CK-p25/BACE1+/+ mice (Fig. 1A), and were not significantly different from control levels. To confirm the reduction in APP processing, we performed an ELISA on forebrain tissue from 6-week-induced CK-p25 mice. Importantly, Aβ(1–42) levels in CK-p25 mice hemizygous for BACE1 were comparable to those of wildtype (BACE1+/+) and BACE1+/− mice (Fig. 1B), while significantly elevated in the CK-p25/BACE1+/+ mice. Moreover, fluorescent immunolabeling of hippocampal sections with the anti-Aβ antibody 4G8 demonstrated a significant decrease in the diameter of intraneuronal 4G8-immunoreactive puncta in area CA1 neurons, although the average diameter is still higher than that of the controls (Fig. 1C,D). We also confirmed that the CK-p25/BACE1−/− mice exhibited reduced BACE1 levels compared with CK-p25/BACE1+/+ mice, which were comparable to controls (Fig. 1E,F).

Levels of Cdk5 did not differ among the genotypes, nor did p25 levels differ between the CK-p25/BACE1−/− and the CK-p25/BACE1+/+ groups (Fig. 1E,F). We found that CK-p25 mice hemizygous for BACE1 (CK-p25/BACE1−/−) exhibited normalized tau phosphorylation at several epitopes, including Thr205 (Fig. 1E,F), and Ser202 (data not shown), while their CK-p25/BACE1+/− littermates displayed the increased tau phosphorylation typical of the CK-p25 genotype. As described previously (Sankaranarayanan et al., 2008; Kim et al., 2011), BACE1+/+ and BACE1+/− mice exhibited similar processing of BACE1 substrates such as NAc, 1.1 and neuregulin 1 (data not shown). These results validate the partial deletion of BACE1 as a means to normalize amyloidogenic APP processing in the CK-p25 mouse.

**Normalization of Aβ level does not rescue neuronal loss in the CK-p25 mouse**

The expression of p25 leads to severe neuronal death and neurodegeneration in the CK-p25 mouse (Cruz et al., 2003). Accordingly, total brain weight was significantly reduced in 6-week-induced CK-p25 mice compared with controls (Fig. 2A). Lowering Aβ levels via BACE1 hemizygosity in the CK-p25 mice did not rescue the reduced brain weight in the CK-p25/BACE1+/+ mice (Fig. 2A). We observed a nearly 50% reduction in the number of NeuN-positive cells in hippocampal area CA1 in the 6-week-induced CK-p25 mice, and this neuronal loss was not rescued in the CK-p25/BACE1−/− mice (Fig. 2B,C). Additional analyses using FluoroJade staining confirmed that both CK-p25 groups showed significant neuronal death (data not shown). Furthermore, both CK-p25 genotypes presented significantly elevated levels of GFAP immunoreactivity in the cortex and

**Results**

**CK-p25 mice hemizygous for BACE1 have decreased APP processing and reduced tau phosphorylation**

We performed biochemical analyses of brain lysates from ~3-month-old CK-p25/BACE1+/+, CK-p25/BACE1+/− mice and their control littermates, following 6 weeks of p25 induction. We show that the CK-p25/BACE1+/− mice displayed lower levels of the BACE1-cleaved APP C-terminal fragment (C-APP) compared with CK-p25/BACE1+/+ mice (Fig. 1A), and were not significantly different from control levels. To confirm the reduction in APP processing, we performed an ELISA on forebrain tissue from 6-week-induced CK-p25 mice. Importantly, Aβ(1–42) levels in CK-p25 mice hemizygous for BACE1 were comparable to those of wildtype (BACE1+/+) and BACE1+/− mice (Fig. 1B), while significantly elevated in the CK-p25/BACE1+/+ mice. Moreover, fluorescent immunolabeling of hippocampal sections with the anti-Aβ antibody 4G8 demonstrated a significant decrease in the diameter of intraneuronal 4G8-immunoreactive puncta in area CA1 neurons, although the average diameter is still higher than that of the controls (Fig. 1C,D). We also confirmed that the CK-p25/BACE1−/− mice exhibited reduced BACE1 levels compared with CK-p25/BACE1+/+ mice, which were comparable to controls (Fig. 1E,F).

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hippocampus, indicative of reactive astrogliosis (data not shown). In a number of neuropathologies, including AD, that involve neuronal loss, neurons engage in aberrant cell cycle behavior and show evidence of DNA damage (Butterfield et al., 2001; Lu et al., 2004; Herrup and Yang, 2007). Likewise, the CK-p25 mouse exhibits ectopic neuronal cell-cycle protein expression and DNA double-strand breaks following 2 weeks of p25 induction (Kim et al., 2008). However, the normalization of Aβ levels in the CK-p25/BACE1+/− does not ameliorate the DNA damage or cell-cycle reentry phenotype, as detectable by γH2AX and Ki67 immunoreactivity, respectively (data not shown). Together, these results suggest that non-amyloid mechanisms may underlie the severe neurodegeneration of the CK-p25 mouse.

**BACE1 hemizygosity rescues memory impairments in the CK-p25 mice**

The CK-p25 mice exhibit significant impairments in associative learning following prolonged expression of the p25 transgene (Fischer et al., 2005). To examine how the removal of elevated Aβ levels impacts the associative learning deficits of the CK-p25 mice, we examined 6-week-induced animals using contextual fear conditioning, a hippocampus-dependent task. CK-p25/BACE1+/− mice froze significantly more than CK-p25/BACE1+/+ mice, and were indistinguishable from controls (Fig. 3A). Both exploratory behavior and response to the foot shock did not differ between the different genotypes (Fig. 3B, C). Thus, normalizing Aβ levels ameliorates cognitive impairments in the CK-p25 mice.

**The normalization of Aβ levels via BACE1 hemizygosity restores synaptic plasticity and synapse density in the CK-p25 mouse hippocampus**

We next examined long-term potentiation (LTP) in hippocampal area CA1 to determine how the normalization of Aβ levels would impact the phenotype of impaired synaptic plasticity in the CK-p25 mice. Consistent with previous observations (Fischer et al., 2005), the CK-p25/BACE1+/− mice displayed diminished CA1 LTP following a 6-week induction of p25 (red; Fig. 4A). Strikingly, LTP was fully restored to wild-type levels in the CK-p25/BACE1+/− mice (green; Fig. 4A). All groups of mice exhibited normal basal synaptic properties (Fig. 4B).

The pathology of Alzheimer’s disease includes significant synaptic loss, which correlates with memory impairments (DeKosky and Schell, 1990; Honer, 2003). The presynaptic protein synaptophysin has been widely used as a synaptic marker (Honer, 2003). We performed an analysis of synaptophysin-immunoreactive puncta (diameter ~0.4 μm) in neurons from 6-week induced CK-p25 mice and their control littermates. Consistent with previous reports in the CK-p25 mouse (Fischer et al., 2007), CK-p25/BACE1+/− mice exhibited a significantly reduced density of synaptophysin puncta in the stratum radiatum of the hippocampus (Fig. 4C, D). The normalization of Aβ levels in the CK-p25/BACE1−/− mice led to a striking recovery in the density of synaptophysin-immunoreactive puncta, to levels that were not statistically different from those of the BACE1+/+ and BACE1+/− mice. Together, the results of the current work demonstrate that the normalization of Aβ concentration in the brains of CK-p25 mice rescues the synaptic and cognitive impairments associated with p25 overexpression, but that p25-dependent neuronal loss occurs via a mechanism independent of Aβ generation.

**Discussion**

The goal of the current work is to delineate the role of elevated Aβ in the CK-p25 phenotype of AD-like neurodegeneration and cognitive impairment. In human AD patients, neuropathology is characterized by both neuronal and synaptic loss (Davies et al., 1987; Selkoe, 2002). In mouse models of AD in which amyloid processing is affected, there is a noteworthy lack of significant neurodegeneration despite heavy Aβ burdens and profound cognitive decline (for review, see Chin, 2011). However, the CK-p25 mouse also displays severe neurodegeneration, including extensive neuronal death, even though the increase in endogenous Aβ in these mice is relatively modest (Cruz et al., 2006).

Reductions in Aβ generation effected by deletion of BACE1 have been shown to ameliorate the phenotypes of mouse AD models such as the Tg2576 (Ohno et al., 2004), 5XFAD (Ohno et al., 2007), and APPswe;PS1ΔE9 lines (Laird et al., 2005). We used a similar approach to examine the contribution of elevated Aβ levels to p25-induced neurodegeneration. In our approach, BACE1 activity and Aβ generation in CK-p25 mice was normal-
immunoreactivity in stratum radiatum of the hippocampus of 6-week induced CK-p25 mice and controls.

phosphorylation, learning and memory, and synaptic plasticity. The restoration of cognitive function and synaptic plasticity that we observe in CK-p25 mice upon Aβ normalization, in the absence of protection against neuronal death, argues for a separation in the etiology of these pathologies in this mouse model, such that p25/Cdk5-induced increases in Aβ generation may be responsible for synaptic dysfunction, while other mechanisms underlie neuronal death. This concept is supported by the recent findings of a specific role for Aβ in synaptic dysfunction in the absence of neuronal loss (Cisse et al., 2011; D’Amelio et al., 2011). The apparent disconnect between functional recovery and neuronal death is striking, but not unprecedented (Pesaranto et al., 2002; Nahm et al., 2003; Fischer et al., 2007) and suggests that, in the course of neurodegeneration, the function of remaining neurons may be improved via various interventions, even though the disease itself may not be slowed or halted.

Neuronal death observed in the CK-p25 mice may be explained by the phenomena of genomic instability and ectopic cell-cycle protein expression that are observed before neuronal death, and which are mediated by the inhibition of the histone deacetylase 1 (HDAC1) protein (Kim et al., 2008). In addition, other groups have described a neurotoxic role for p25/Cdk5 in the nucleus, where its actions may trigger aberrant cell-cycle reentry (O’Hare et al., 2005; Saito et al., 2007) as well as induce the phosphorylation and degradation of the transcription factor MEF2 following neurotoxicity, leading to cell death (Gong et al., 2003; Tang et al., 2005). Cdk5, in association with p35, has also been shown to be protective in the neuronal nucleus, where it suppresses cell cycle activity in the differentiated neuron (Cicero and Herrup, 2005; Zhang et al., 2010). Together, these observations suggest a model in which Aβ production facilitate synapse loss, and learning and synaptic deficits in the CK-p25 mouse, while neuronal death occurs via mechanisms less directly linked to amyloid. As Aβ also increases p25 production in neurons (Lee et al., 2000), these two pathways are intricately linked in a feedforward mechanism of p25 overproduction that likely culminates in both the cognitive deficits and neurodegeneration observed in the CK-p25 mouse and, potentially, in human AD. Therefore, the inhibition of the p25/Cdk5 complex, while leaving the p35/Cdk5 complex intact, is a promising avenue for the therapeutic intervention of neurodegenerative disease.

References


