Cathepsins B and L Differentially Regulate Amyloid Precursor Protein Processing

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Received October 8, 2008; accepted December 5, 2008

ABSTRACT

Previous studies have shown that cathepsins control amyloid beta (Aβ) levels in chromaffin cells via a regulated secretory pathway. In the present study, this concept was extended to investigations in primary hippocampal neurons to test whether Aβ release was coregulated by cathepsins and electrical activity, proposed components of a regulated secretory pathway. Inhibition of cathepsin B (catB) activity with CA074Me or attenuation of catB expression through small interfering RNA produced decreases in Aβ release, similar to levels produced with suppression of β-site APP-cleaving enzyme 1 (BACE1) expression. To test whether the catB-dependent release of Aβ was linked to ongoing electrical activity, neurons were treated with tetrodotoxin (TTX) and CA074Me. These comparisons demonstrated no additivity between decreases in Aβ release produced by TTX and CA074Me. In contrast, pharmacological inhibition of cathepsin L (catL) selectively elevated Aβ42 levels but not Aβ40 or total Aβ. Mechanistic studies measuring C-terminal fragments of amyloid precursor protein (APP) suggested that catL elevated α-secretase activity, thereby suppressing Aβ42 levels. The mechanism of catB-mediated regulation of Aβ release remains unclear but may involve elevation of β-secretase. In summary, these studies provide evidence for a significant alternative pathway for APP processing that involves catB and activity-dependent release of Aβ in a regulated secretory pathway for primary neurons.

Accumulation of the amyloidogenic peptide Aβ42 is the hallmark pathology of Alzheimer’s disease (AD). Although it is evident that N- and C-terminal processing of APP can regulate Aβ peptides by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase in many systems, we have sought to examine other potential APP processing enzymes, particularly because these alternative pathways may be linked to synaptic activity in primary neurons. The impetus to explore alternative processing enzymes is the uncertainty of the inherent dependence of previous studies on cell-based systems that involve both the Swedish mutation of APP (APPsw) and the use of cell systems that have a predominance of a constitutive pathway for APP processing. Only 2% of all AD cases are caused by APPsw, although most models of AD involve cells overexpressing APPsw. In addition, much of the APP processing research has been performed on cell lines transfected with APP, which exhibit constitutive secretion of Aβ, as opposed to cells expressing endogenous Aβ that is primarily secreted through the regulated pathway. Therefore, it is of interest to investigate whether alternative proteases are involved in processing wild-type APP in the regulated secretory pathway as it related to spontaneous synaptic activity. Cathepsins are of particular interest because they associate with Aβ (Cataldo and Nixon, 1990), are localized to endosomes where APP is processed (Golde et al., 1992; Haass et al., 1992), and their expression is altered in aged brains (Nakanishi et al., 1994).

Cathepsins reside in the endosomal-lysosomal system and are generally known for bulk proteolysis; however, new evidence suggests they also exhibit specific proteolytic functions (Kobayashi et al., 1991; Murphy et al., 1992; Yashotharsrikul et al., 2003). Cathepsin D, an aspartyl protease, was initially implicated as a β-secretase candidate (Brown et al., 1996; Chevallier et al., 1997), although reduction in cathepsin D activity provided no evidence for an alternative pathway for APP processing that involves catB and activity-dependent release of Aβ in a regulated secretory pathway for primary neurons.

ABBREVIATIONS: Aβ, amyloid beta; AD, Alzheimer’s disease; APP, amyloid precursor protein; APPsw, Swedish mutation of APP; catB, cathepsin B; catL, cathepsin L; N2A, neuroblastoma 2A; CHO, Chinese hamster ovary; TTX, tetrodotoxin; catL inh, cathepsin L inhibitor; BTM, batimastat; siRNA, small interfering RNA; ELISA, enzyme-linked immunosorbent assay; Tricine, N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]glycine; CTF, C-terminal fragment; PKC, protein kinase C; CA074ME, (L-3-(dimethylamino)methyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione hydrochloride; DAPT, N-[(3,5-difluorophenyl)acet]y]-L-alanyl-2-phenylglycine-1,1-dimethylethyl ester.

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activity never effectively lowered Aβ levels (Saftig et al., 1996). Likewise, overexpression of cathepsin S resulted in enhanced Aβ secretion (Munger et al., 1995). Lysosomal cysteine proteases have also received attention in their ability to modulate Aβ levels. Cathepsin B (catB) exhibits β-secretase activity in chromaffin vesicles (Hook and Reisine, 2003), and inhibitors to cysteine proteases lower Aβ levels in guinea pigs by reducing β-secretase and elevating α-secretase activity (Hook et al., 2007). In contrast, general cysteine protease inhibitors did not significantly alter Aβ levels in a variety of systems (Simon et al., 1993; LeBlanc and Goodyer, 1999), and a recent article showed that catB actually protected neurons from Aβ42 toxicity by degrading Aβ42 into less toxic peptide species (Mueller-Steiner et al., 2006). For the present studies, novel mechanisms for cathepsins in modulating Aβ are explored. Our cellular model of Alzheimer’s disease uses primary hippocampal neurons, which secrete detectable levels of Aβ that can be manipulated with the pharmacological control of spontaneous synaptic activity. We show that two cysteine proteases, typically thought to act on similar substrates, exhibit dramatically different roles in modulating APP processing. Although catB elevates β-secretase activity to drive APP processing into amyloidogenic peptides, catL elevates α-secretase activity and thereby suppresses Aβ levels. It is important that the effect of catB on modulating β-secretase activity is specific to neurons expressing endogenous Aβ secreted through the regulated pathway. These data illustrate why the roles of cathepsins in APP processing may aid in broadening the perspective of therapeutic targets in Alzheimer’s disease and relating these concepts to changes in synaptic activity.

Materials and Methods

Cell Culture. Primary hippocampal neurons were isolated from E18 embryonic hippocampi (BrainBits LLC, Springfield, IL) using the Worthington papain dissociation system (Worthington Biochemicals, Freehold, NJ) according to the manufacturer’s directions. Neurons were plated on poly-l-lysine-coated multiwell plates (BD Biosciences, Freehold, NJ) according to the manufacturer’s directions. Neurobasal/B27 medium with 10% fetal bovine serum. Chinese hamster ovary (CHO) cultured for 2 to 3 weeks and fed twice per week. Mouse neuroblastoma N2A cells were plated on poly-L-lysine-coated multiwell plates (BD Biosciences, San Jose, CA) in media containing Neurobasal with B27 supplement and Glutamax (Invitrogen, Carlsbad, CA). Neurons were cultured for 2 to 3 weeks and fed twice per week. Mouse neuroblastoma 2A (N2A) cells were passaged in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum. Chinese hamster ovary (CHO) cells stably transfected with APP-751 (a gift from R. Tanzi, Massachusetts General Hospital, Boston, MA) were passaged in Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum and G-418 (Geneticin; 100 µg/ml).

Drug Treatments. CA074Me, tetrodotoxin (TTX), chloroquine, and E64D were purchased from Sigma-Aldrich (St. Louis, MO). catL inhibitor (catL inh) I, II, III, and IV and RO32-0432 were from EMD Biosciences (San Diego, CA). DAPT, batimatstat (BTM), and BACE1 inhibitor were synthesized at Johnson and Johnson Pharmaceutical Research and Development. Because treatment with CA074Me caused some toxicity in primary neurons when applied for more than 12 h, CA074Me was only added for 2 to 4 h and then rinsed thoroughly. CA074Me was left on N2A and CHO cells for the duration of the experiment. Chloroquine and BTM were used at 50 µM, RO32-0432 was used at 3 µM, and BACE1 inhibitor was used at 100 nM. All remaining compounds were added at 10 µM for the duration of the experiment.

Gene Knockdown. Primary hippocampal neurons were transfected with ON-TARGETplus SMARTpool siRNA targeting catB or BACE1 (Dharmacon RNA Technologies, Lafayette, CO) using Lipofectamine RNAmax (Invitrogen), according to the manufacturer’s instructions.

Sandwich ELISA for Aβ Detection. Primary neurons were fed with fresh media and incubated for 24 to 72 h before media collection. For N2A and CHO cells, media were replaced with serum-free UltraTreculture medium (Lonza Walkersville, Inc., Walkersville, MD). JRF/rAB2, JRF/cAB40/10, or JRF/cAB42/26 was used to capture Aβ1-x, Aβ40, or Aβ42, respectively (Pyke et al., 2003). Aβ was detected with biotinylated 4G8 (Covance Research Products, Princeton, NJ), incubated with streptavidin-horseradish peroxidase, and exposed with QuantFluo Fluorogenic Peroxidase Substrate (Pierce Chemical, Rockford, IL), used as the substrate. For measurement of Aβ1–42 and Aβ1–40, Aβ was detected with biotinylated JRF/raban. Synthetic Aβ peptides (California Peptide Research, Inc., Napa, CA) were used to calibrate fluorescence levels to Aβ concentrations. For all experimental groups, six individual wells were assayed for Aβ detection. Most data were normalized to untreated controls, and Student’s t tests were used to determine statistically significant differences between predetermined groups.

Western Blots. Proteins were lysed in radioimmunoprecipitation assay buffer containing 2% SDS, HALT protease inhibitors with EDTA (Pierce Chemical), and 1 µM pepstatin A on ice. Lysate was sonicated briefly and centrifuged at 14,600g for 10 min. Supernatant was collected and stored at ~80°C. Proteins were separated electrophoretically on precast 10 to 20% Tricine gels or 4 to 12% bis-tris gels (Invitrogen) and transferred to nitrocellulose membranes. Full-length and C-terminal fragments of APP were stained with A6717 (Sigma-Aldrich). sAPPα was detected with SIG-39139 (Covance Research Products) and normalized to full-length APP (Miliplor, Billerica, MA). Bands were illuminated with SuperSignal West Femto Maximum Sensitivity Substrate (Pierce Chemical). Band intensity was quantified using ImageJ image analysis software, and Student’s t tests were used to assess statistical significance. Sample sizes are indicated on figures.

Protease Activity Assays. Proteins were lysed in Cytobuster lysis buffer (EMD Biosciences) for 30 min on ice. catB activity was detected with the InnoZyme Cathepsin B activity fluorogenic assay kit from EMD Biosciences according to the manufacturer’s directions. For α-secretase assays, identical lysates were treated with or without inhibitors and incubated at 37°C with a fluorogenic peptide containing the α-secretase cleavage site of wild-type APP (EMD Biosciences). α-Secretase activity in the presence of inhibitor was measured by resultant fluorescence and normalized to that of untreated samples. Six replicates were performed for each experimental group.

Aβ Degradation Assay. Synthetic human Aβ42 (300 pM) was added to N2A cells, and media were collected at 1, 4, 8, or 24 h after application. Exogenous hAβ1–42 and hAβ1–42 were measured by ELISA. JRF/cAB42/26 or JRF/ABN25 was used to capture and biotinylated 6E10 or 4G8 was used to detect hAβ1–42 and hAβ1–42, respectively. For all groups, six replicates were performed.

Results

After 72 h, media were collected from hippocampal neurons (plated at 30,000 cells/well of a 96-well plate with 160 µl media/well) and assayed for Aβ1-x, Aβ40, Aβ42, and Aβ1–42. The most abundantly detected Aβ peptide was that cleaved at the 40th amino acid (419 ± 28 pM), whereas only 105 ± 3 pM Aβ42 and 319 ± 10 pM Aβ1-x were detected in the media (Fig. 1). Given the larger amount of Aβ40 than Aβ1-x, it is likely that not all detected Aβ42 was cleaved at the first amino acid. Aβ is also cleaved by β-secretase at the 11th amino acid (Wang et al., 1996; Cai et al., 2001). Only 9 ± 1 pM of the 105 ± 3 pM Aβ42 was cleaved at the first amino acid. Therefore, Aβ1-x represents total Aβ cleaved at the first amino acid, whereas Aβ40/Aβ42 represents total Aβ
cleaved at either the first or 11th amino acid and also at the 40th or 42nd amino acid. (Although the detection region of the Aβx-40/42 assay included Aβ cleaved at position 17 or lower, the assay was relatively insensitive to the nonamyloidogenic peptide, p3; data not shown).

The role of catB in APP processing was examined in multiple cell types that exhibited regulated secretory pathways. Inhibition of catB with a commercially available inhibitor, CA074Me, significantly decreased Aβx-40, Aβx-42, and Aβ1-x in primary hippocampal neurons (Fig. 2A). A similar, though slightly less effective, reduction in Aβ was observed in N2A cells treated with CA074Me (Fig. 2B). To ensure that the reduction in Aβ with CA074Me was not because of off-target effects of the inhibitor, catB expression was knocked down in primary hippocampal neurons with siRNA. Six days after transfection with siRNA, catB activity was significantly reduced by up to 50%, and this corresponded to a significant reduction in both Aβx-42 and Aβ1-x (p < 0.001 versus untreated controls; Fig. 2, C and D). Note that a similar reduction in Aβ with BACE1 siRNA was also evident, indicating that BACE1 is also involved in APP processing in primary neurons as previously reported (Kao et al., 2004; Nishitomi et al., 2006).

We next investigated whether catB-dependent APP processing was specific to Aβ secreted through either the regulated or constitutive pathway. Synaptic activity was suppressed with TTX, a voltage-dependent sodium channel blocker that inhibits action potential propagation and subsequent neurotransmitter release. After 3 days of treatment, TTX caused a significant reduction in Aβx-42 and Aβ1-x. In the absence of activity-dependent secretion of Aβ, CA074Me-dependent Aβ suppression was eliminated (Fig. 3). The reduction in Aβ with CA074Me was less effective than that reported in Fig. 2 because of the 3-day incubation time, thus allowing synthesis of new uninhibited catB. (Note that even 3 days after inhibition of catB with CA074Me, catB levels were still 37.6 ± 2.8% of untreated cells.) The necessity of catB in Aβ secreted through the regulated pathway was further verified by testing whether catB inhibition modulated APP processing in CHO cells that were stably transfected with APP751 but only exhibited Aβ secretion via the constitutive pathway. Inhibition of catB with CA074Me did not significantly alter Aβ secreted from CHO-APP751 cells (Fig. 4), indicating that catB does not modulate Aβ secreted through the constitutive pathway.

Because catL cleaves many substrates similar to those cleaved by catB, we investigated whether catL also inhibited APP processing. After 24 h of treatment with three of four catL inhibitors, we found that catL inhibition significantly lowered levels of Aβx-40 and Aβ1-x. It is surprising, though, that inhibition of catL dramatically elevated levels of Aβx-42 and Aβ1-42 (Fig. 5, A and B), suggesting that the two cysteine proteases acted very differently in modulating APP processing. The one inhibitor of catL that did not result in

![Fig. 2](https://example.com/fig2.png)

**Fig. 2.** Inhibition of catB with CA074Me significantly reduces Aβ1-x, Aβ x-40, and Aβx-42 in primary hippocampal neurons (A) and N2A cells (B), two cell types exhibiting regulated secretory pathways. Knockdown of catB in primary hippocampal neurons reduces both catB activity (C) and secreted Aβ (D). *p < 0.001 versus untreated controls.
The specific up-regulation of Aβ-secretase activity was measured in CHO APP751 cells, showing that catL-dependent Aβ42 elevation was not specific to Aβ secretion through the regulated pathway (Fig. 5, C and D). The opposing effects of catL and catB on APP processing may explain why previous investigators have found general cysteine protease inhibitors to have no effect on APP processing (Skovronsky et al., 2000), where catL was found to be active, inhibition of all cysteine proteases with E64D only reduced Aβ-secretase activity. We blocked PKC activation with Ro32-0432 in primary hippocampal neurons and measured whether catL inh IV still elevated Aβ42 secretion. Although we found that PKC inhibition slightly reduced Aβ-secretase activity (p < 0.001, compared with untreated controls), the dependence of Aβ42 on catL inh IV disappeared when PKC activation was blocked (p = 0.35; Fig. 11).

Although it was evident that catL inhibition reduced Aβ-secretase activity, thereby elevating Aβ levels, it remained unclear why the up-regulation was specific to Aβ42. A recent study showed that catB specifically degraded Aβ42 into less toxic Aβ peptides (Mueller-Steiner et al., 2006), so we hypothesized that catL also specifically cleaved Aβ42 peptides. N2A cells were treated with human Aβ42 (hAβ42; 300 pM), and hAβ1–42 and hAβ1–x degradation was measured subsequently. Neither hAβ1–42 nor hAβ1–x was detected in media not treated with synthetic hAβ42, indicating measurement was specific to the exogenous hAβ. hAβ levels subsided gradually over the course of the 24-h experiment. Inhibition of either catB or catL significantly slowed the degradation process of hAβ42 but did not affect levels of hAβtot, compared with untreated controls (Fig. 12). These data indicate that both catB and catL are involved in degrading Aβ42 into less toxic forms.
**Fig. 5.** A, catL inhibition in primary hippocampal neurons specifically elevates Aβx-42 while decreasing Aβ1-x levels with three of the four tested inhibitors. Note that Aβx-40 was only measured for catL inh IV-treated neurons and revealed a significant decrease in Aβx-40 levels. B, Aβ1–42 is also elevated in primary hippocampal neurons in the presence of catL inh IV, verifying that the effect of catL inhibition is not simply because of an increase in the α-secretase-generated p3 fragment of APP. The specific effect on Aβx-42 is duplicated in N2A (C) and CHO (D) cells, indicating that it is not specific to cells with regulated pathways. *, p < 0.001 compared with untreated.

**Fig. 6.** A, only slight though significant reductions in Aβ are evident when all cysteine proteases were inhibited in primary hippocampal neurons with E64D. B, APP processing within the endosomal-lysosomal pathways was suppressed with the weak base, chloroquine. Treatment with chloroquine reduced levels of Aβx-40 and Aβ1-x but had no effect on Aβx-42. The elevation of Aβ42 in the presence of catL inh IV was negated with chloroquine. *, p < 0.001 compared with untreated; **, p < 0.01 compared with untreated; #, p < 0.05 compared with untreated.
toxic Aβ species and may help to explain why catL specifically elevated Aβ42 secretion.

**Discussion**

The present study illustrates two novel and opposing mechanisms by which cysteine proteases modulate APP processing and a similar mechanism by which cathepsins degrade Aβ. CatB promotes Aβ formation via the regulated, activity-dependent secretory pathway, probably through its role in elevating β-secretase activity. In contrast, catL reduces the formation of Aβ42 peptides by cleaving APP within the Aβ peptide sequence. In addition, both cathepsins B and L degrade Aβ42 into less toxic Aβ peptides. These findings precisely illustrate how cathepsins B and L modulate Aβ levels and aid in understanding the discrepancies between past studies. Moreover, evidence from aged rats, where catB activity is up-regulated and catL activity is down-regulated (Nakanishi et al., 1994), shows that impaired cathepsin activity may participate in the onset of AD.

Compelling evidence exists in the literature to suggest that catB is involved in processing APP. Not only does catB colocalize with Aβ in secretory vesicles (Hook et al., 2005), but also cystatin C, an endogenous cysteine protease inhibitor with high affinity for catB, is one of the few down-regulated biomarkers evident in human CSF of AD patients (Simonsen et al., 2007). CatB was first identified as the primary β-secretase responsible for Aβ formation in chromaffin vesicles (Hook and Reisine, 2003) and was later shown to be involved in processing APP in chromaffin cells and guinea pig synaptosomes (Hook et al., 2007). Using primary hippocampal neurons, a neuronal phenotype implicated in learning and mem-
In untreated cells, we observed a decrease in Aβ secretion when cells treated with catL inhibition IV alone. However, inhibitors of catB or transfection with catB siRNA significantly reduced Aβ-secretase activity, compared with matched controls (p < 0.05), whereas inhibition of catB had no effect. Data are presented as a percentage of untreated controls. In the presence of the two inhibitors shown to blot Aβ-secretase activity, elevated APP was detected over a range of concentrations. Data are presented as a percentage difference from untreated controls. #, p < 0.05 compared with untreated.

Our results showing that catB inhibition only reduced Aβ levels in primary neurons when Aβ was secreted through the regulated pathway were in agreement with a previous study in chromaffin cells (Hook et al., 2005). This distinction illustrates an important reason why cysteine proteases were previously undiscovered as Aβ modulators and points to the importance of validating potential therapeutic targets in a variety of AD models. Because wild-type neurons secrete low levels of Aβ, many investigators use cell lines overexpressing APP to enhance constitutive release of Aβ. However, detectable levels of Aβ are also evident in untransfected cells when they are either spontaneously active, as in this study, or when synaptic activity is pharmacologically induced (Hook and Reisine, 2003). Moreover, alterations in neuronal excitability are frequently observed in the AD brain, indicating a pathologic rationale for the onset of AD. Whether synaptic activity drives APP endocytosis or Aβ secretion is unknown, although evidence in the literature points toward the former because suppression of neurotransmitter release inhibited β-secretase activity in organotypic hippocampal cultures (Kamenetz et al., 2003). Understanding this distinction will aid in determining how catB elevates APP processed through the regulated pathway.

It is unlikely that catB is the primary β-secretase in primary neurons because BACE1 siRNA and small-molecule inhibitors also significantly reduced Aβ secretion. Instead, we believe that catB either acts as a secondary β-secretase or, more likely, indirectly modulates β-secretase activity. For example, catB-dependent APP processing may be specific to the Kunitz protease inhibitor (KPI) isoform of APP, which is predominantly expressed in glia but is up-regulated in neurons in both the AD brain (Moir et al., 1998) and after enhanced excitatory activity (Lesné et al., 2005). The KPI domain of APP binds with a serine protease before internalization (Knauer et al., 1996). It is feasible that this complex
hinders the accessibility of the BACE1 cleavage site of APP and catB cleavage of the complex enhances the affinity of BACE1 for the remaining APP fragment. We attempted to test this hypothesis by using CHO cells transfected with APP751, an APP isoform incorporating the KPI domain, but found no dependence on catB; however, this was at least in part because of the absence of regulated Aβ secretion. It is interesting that neurons were transfected with the non-KPI APP isoform, APP695, in the study that failed to detect catB dependent β-secretase activity (Mueller-Steiner et al., 2006).

In contrast to the β-secretase modulation by catB, we found that catL up-regulated α-secretase activity, presenting an additional source for the contradictory data on cysteine proteases and APP processing. catL may directly cleave APP within the Aβ sequence or, alternatively, cleave the proform of another protease and indirectly up-regulate α-secretase activity. Although α-secretase was traditionally thought to cleave membrane-bound APP, we observed the effect of catL to be intracellular because the impermeable catL inhibitor had no effect on Aβ levels, intracellular sAPPα decreased with catL inhibition, and chloroquine negated the activity of the catL inhibitor. This is in line with newer data that show PKC-mediated α-secretase activity typically occurs intracellularly within the trans-Golgi network (Jolly-Tornetta and Wolf, 2000; Skovronsky et al., 2000). Of the three known α-secretase candidates that have been identified to date, ADAM9, ADAM10, and ADAM17/TACE (Asai et al., 2003), none are thought to be solely responsible for PKC-mediated α-secretase activity, suggesting that more candidates are plausible. Moreover, researchers rely on broad spectrum metalloprotease inhibitors to block α-secretase activity, and these inhibitors may indirectly alter catL activity because pro-catL cleavage into its active form has been shown to be mediated by metalloproteases (Hara et al., 1988). Finally, it cannot be ruled out that catL also modulates APP through γ-secretase. A similar specific rise in Aβ42, accompanied by a reduction in Aβ40, was observed in CHO-APP751 cells treated with E64D (Figueiredo-Pereira et al., 1999). Although we did not observe any accumulation of APP CTFs after catL inhibition, catL may also modulate, rather than inhibit, γ-secretase.

Both catB and catL were also shown to exhibit secondary functions in Aβ modulation by specifically degrading Aβ42 into less toxic Aβ peptides. Although both catB and general cysteine proteases have been identified previously in their roles of Aβ degradation (Frautschy et al., 1998; Mueller-Steiner et al., 2006), this is the first study to show that catL also specifically degrades Aβ42 into less toxic Aβ peptides. Our data suggest that cathepsins degrade Aβ peptides before secretion or after internalization by endocytosis, although catB does associate with Aβ plaques, and extracellular activity of cathepsins has been confirmed (Cataldo and Nixon, 1990). This secondary role of catB may actually exacerbate its role in elevating β-secretase activity because Aβ application elevates catB activity (Mueller-Steiner et al., 2006). Alternatively, the role of catL in Aβ degradation, in conjunction with its α-secretase activity, may explain why inhibition of catL specifically elevates Aβ42 and not Aβ40.

The opposing roles of catB and catL in APP processing present an ideal opportunity for a therapeutic target to lower Aβ levels in AD patients. CatB and catL share many similar substrates, and knockout animals have revealed that the remaining cathepsin compensates for the deficient cathepsin, thereby presenting few significant phenotypic alterations (Deussing et al., 1998; Nakagawa et al., 1998; Guicciardi et al., 2000; Roth et al., 2000). Nonetheless, opposing actions of catB and catL are not unprecedented (Röken et al., 2005). By developing a drug that lowers catB activity, elevated catL activity would be expected to follow, thereby simultaneously lowering Aβ levels through two distinct pathways.

References


