The Amyloidogenic Pathway of Amyloid Precursor Protein (APP) Is Independent of Its Cleavage by Caspases*

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Amyloid β-protein (Aβ) is the main constituent of senile plaques in Alzheimer’s disease and is derived by proteolysis from the amyloid precursor protein (APP). Generation and secretion of both Aβ40 and Aβ42 isoforms depend largely on internalization of APP and occurs mainly in the endocytic pathway. Evidence has also been presented (Gervais, F. G., Xu, D., Robertson, G. S., Vailancourt, J. P., Zhu, Y., Huang, J., LeBlanc, A., Smith, D., Rigby, M., Shearman, M. S., Clarke, E. E., Zheng, H., Van der Ploeg, L. H. T., Ruffolo, S. C., Thornberry, N. A., Xanthoudakis, S., Zamboni, R. J., Roy, S., and Nicholson, D. W. (1999) Cell, 97, 395–406) that caspase cleavage of APP at its cytosolic tail affects its processing such that it is redirected to a more amyloidogenic pathway, resulting in enhanced Aβ generation. However, caspase cleavage of APP also results in loss of its endocytosis signal (YENP), an event that would predict a decline in internalization and a concomitant decrease, not an increase, in Aβ generation. In the present study, we examined whether caspase cleavage of APP is relevant to amyloidogenesis. We found that 1) caspase cleavage of APP results in reduced internalization and, accordingly, a decline in Aβ secretion; 2) masking of the caspase site in APP did not affect Aβ levels and, 3) caspase activation in cells by serum withdrawal did not increase Aβ secretion. Thus, caspase cleavage of APP is unlikely to play a direct role in amyloidogenesis.

Alzheimer’s disease is accompanied by deposition of the amyloid peptide Aβ in senile plaques and cerebral blood vessels. Two major species of amyloid β-protein (Aβ), differing by two amino acids in length (Aβ(1–40) and Aβ(1–42)) at the C terminus, have been characterized. Aβ(1–42), the longer Aβ isoform, readily aggregates in vitro and appears to be the more amyloidogenic and hence pathogenic species (reviewed in Ref. 1). Although the precise mechanism by which Aβ is generated from its precursor, the amyloid precursor protein (APP), 1 is not well understood, internalization of APP from the cell surface with subsequent processing in the endocytic pathway is a major route for generation and secretion of both Aβ isoforms (2–4). Accordingly, deletion or site-directed mutagenesis of the endocytosis motif in APP abrogates secretion of Aβ(1–40) and Aβ(1–42) (3).

Two reports have shown that neurons undergoing apoptotic cell death secrete approximately 2- to 3-fold more Aβ than healthy neurons (5, 6). Because Aβ is neurotoxic and contributes to apoptosis in a variety of cultured cells, it has been proposed that increased Aβ secretion, due to genetic predisposition or to other factors, causes increased cell death in susceptible neurons. This initiates a cycle in which dying neurons release more Aβ, which in turn causes more cell death to account for death of neurons seen in Alzheimer’s disease (6, 7).

A number of laboratories have recently demonstrated that APP can be cleaved in the cytoplasmic domain by caspases after the aspartate residue at position 664, Val-Glu-Val-Asp664 △ Ala, (APP695 numbering, or Asp720 using APP751 numbering) (7–12). This cleavage would generate a C-terminal-truncated APP molecule that is ~3.5 kDa shorter (APPΔC31) (7, 12). The consequences of this cleavage event in the C-terminal domain, as well as those in the luminal domain, are unclear. One hypothesis suggests that following cleavage in the cytoplasmic region, a toxic fragment, coined C31, is released and contributes to neuronal death (12). Alternatively, it has been proposed that caspase cleavage of APP directly contributes to the increased Aβ secretion seen in apoptotic cells (7). Evidence for this hypothesis was obtained from B103 neuroblastoma cells where expression of APPΔC31 resulted in a ~5-fold increase of Aβ secretion. Because caspase activation and hence cleavage of APP follows an apoptotic signal, this model is consistent with the observation that more Aβ is secreted from neurons undergoing apoptosis. A corollary to this model is that increased Aβ secretion may induce further neuronal apoptosis, thereby propagating this cycle of caspase cleavage, Aβ release, and apoptosis. Although provocative, this hypothesis is inconsistent with previous observations that the APP cytoplasmic region contains a tetrapeptide motif (683YENP686) that functions as a signal for endocytosis (3). Accordingly, loss of this endocytic signal by deletion or alanine mutagenesis abrogates processing of cell surface APP in the endocytic pathway and severely impairs Aβ production and secretion. Because caspase-cleaved APP lacks the endocytic signal, the truncated APPΔC31 should in theory release less, rather than more, Aβ unless cleavage at this particular position leads to an APP molecule that behaves differently from other internalization deficient mutants.

In the present study, we have addressed this issue by characterizing both Aβ secretion and internalization rates, from a mutant that is not recognized by caspases (APP(D664A)) and from APPΔC31, in cells of both neural and non-neural origin. Our previous studies did not specifically examine APP cleaved at this position (APP695), and it is possible that caspase cleavage, as suggested by the earlier report, alters APP processing differently. In addition, we explored whether caspase activation modulates Aβ secretion. We show, in agreement with the endocytosis requirement hypothesis, that APPΔC31 is not efficiently internalized and, accordingly, Aβ secretion decreases.
Caspses recognize and cleave the sequence \(661\text{VEVD} \rightarrow A^{664}\) after the aspartic acid residue to generate an N-terminal APP molecule of 664 amino acids (APP\(_{661-664}\)) and a C-terminal fragment of 31 residues (C31). Represented are the epitopes recognized by the antibodies used in the present study: R3134, AJβ(22-41); 26D6, AJβ(1-12); and 1G7, epitope in the extraacellular region of APP. Note that the \(664\text{YENP}^{686}\) endocytosis motif is absent from the caspase-cleaved APP.

![Diagram showing caspase cleavage of APP at the cytosolic domain.](image)

**MATERIALS AND METHODS**

**Cell Lines**—Chinese Hamster Ovary (CHO) and B103 (rat neuronal-derived) cells were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum (Life Technologies, Inc.). CHO lines expressing wild type APP\(_{711}\) or truncated forms lacking the cytosolic tail (APP\(_{C31}\)) or the C-terminal 30 amino acids (APP\(_{D31}\), equivalent to C31) were cultured by transfection with 1G7 reagent (Roche Diagnostics Corp.). Clones with similar levels of transgene expression were used.

**Antibodies**—The following antibodies used have been previously described: monoclonal antibodies 5A3 and 1G7 against the mid-region of APP (2) and 26D6 against amino acids 1–12 of AJβ (12). Polyclonal antibodies included R3134 generated against residues 22-41 of AJβ (13) and 664 directed against amino acids 657 to 664 (by 695 numbering) of APP. This latter antibody is end-specific and only recognizes APP when it has been cleaved after residue 684 (see Fig. 1).1,2

**Measurement of AJβ Secretion**—CHO or B103 cells expressing comparable amounts of the indicated APP constructs were seeded in duplicate on six-well tissue culture plates at an initial confluence of 80%. Cells were incubated for 24 h, medium (900 μl) was harvested and immunoprecipitated with antibody R3134 (1:200 dilution), and samples with similar levels of transgene expression were used.

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**Measurement of AJβ Secretion**—CHO or B103 cells expressing comparable amounts of the indicated APP constructs were seeded in duplicate on six-well tissue culture plates at an initial confluence of ~80%. Cells were incubated for 24 h, medium (900 μl) was harvested and immunoprecipitated with antibody R3134 (1:200 dilution), and samples were separated on 4–12% Bis-Tris gradient gels (Novex, San Diego, CA). Bands were visualized on immunoblots using antibody 26D6 in conjunction with ECL (Fierce) either on film or by phosphorimaging (Bio-Rad, Hercules, CA) for quantitation. Cell lysates were immunoblotted in parallel to monitor APP expression. Measurements of AJβ and fragment β3 levels from \(^{35}\text{S}\)methionine metabolically labeled cells were performed as described (2). ELISA measurements of AJβ (1–40) and AJβ (1–42) in N2a cells were performed as described (2).

**Internalization Assay**—Triplicate cultures of CHO or B103 cells were grown to confluence in six-well tissue culture plates. Internalization of cell surface APP was then performed as described (3). Briefly, iodinated whole 1G7 monoclonal antibody (of a specific activity of ~3–6 \(\mu\)Ci/mg) was diluted in binding medium (BM; RPMI 1640 supplemented with 20 mM Heps, 1% bovine serum albumin), applied to triplicate confluent layers of CHO cells and incubated at 37 °C for 30 min. Cells were then chilled on ice and washed once with BM and extensively with ice-cold phosphate-buffered saline. 1G7 antibody bound to cell-surface APP was uncoupled by two 5-min washes with ice-cold phosphate-buffered saline, pH 2.5, followed by cell lysis with 0.2 M NaOH. Radioactivity from the pooled acid washes and the cell lysates was determined in a γ counter. The ratio of radioactivity of acid-resistant to acid-labile fractions represents a measure of internalized \textit{versus} cell-surface pool of APP.

**RESULTS**

**Caspase-mediated Proteolysis of APP Abrogates Internalization from the Cell Surface**—Endocytosis of APP truncated after aspartic acid Asp\(^{664}\), APP\(_{D31}\), corresponding to the product of caspase cleavage, was assessed using a well established protocol in which internalization of APP is monitored by uptake of radioiodinated 1G7 antibody (against the mid-region of APP; see diagram in Fig. 1) (2, 20). In agreement with previous reports, APP mutants lacking either the complete cytosolic tail (APP\(_{C31}\)) or the C-terminal 15-amino acids (APP\(_{D31}\)), both of which lack the YENP endocytosis motif (3), were unable to internalize efficiently in CHO cells (Fig. 2, CHO panel). The YENP motif is also absent in the APP form truncated at the caspase cleavage site (APP\(_{C31}\); see Fig. 1). Accordingly, its internalization is also severely impaired (Fig. 2). Identical experiments performed using B103 cells (Fig. 2, B103 panel) showed that neither APP\(_{D31}\) nor APP\(_{C31}\) could be efficiently endocytosed in these cells. The decrease in internalization of APP endocytosis mutants was less pronounced in B103 than in CHO cells. It should be noted, however, that constitutive APP internalization from B103 cells is less efficient (59.3% ± 4.05 of total APP) than from CHO cells (82.3% ± 2.26%), indicating that the level of internalization of APP is different between cell lines. Nevertheless, our results clearly show that deletion of the YENP motif in APP significantly impairs its internalization, both in CHO and B103 cells.

**Aβ Secretion Fully Depends on the Presence of the YENP Motif in APP**—It has been shown that secretion of both AJβ(1–40) and AJβ(1–42) in N2a cells were performed as described (2).

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In contrast with these results, a recent report showed that B103 neuroblastoma cells secreted significantly higher amounts of Aβ when expressing APPΔC31 as compared with cells expressing wild type APP (7). One obvious explanation for the apparent discrepancy is the use of different cell lines. To determine whether this was the case, we also measured Aβ secretion from B103 cells expressing either wild type or endocytosis-deficient APP695 forms. As shown (Fig. 4, lanes 1–3), the level of Aβ from medium of B103 cells expressing APPΔC31 was severely impaired, again demonstrating that cleavage of APP at the Asp664 caspase site behaved similarly to other internalization deficient mutants (2, 3, 18).

It has previously been shown (2) that cells expressing endocytosis-deficient APP secrete higher levels of the peptide generated by α and γ secretases, known as the p3 fragment. Thus, it is possible that the apparent increase in secreted Aβ levels from APPΔC31 seen by Gervais et al. (7) may have corre-
Materials and Methods.

Phosphorimaging after electrophoresis separation as described under B103 panel, forms.

Measuring directly the levels of Aβ and p3 secreted from [35S]methionine-labeled cells were visualized by autoradiography, and Aβ and p3 fragments from B103 cells were dramatically reduced (Fig. 5, middle panel). Polyclonal antibody 664 directed against amino acids 657–664 (by 695 numbering; 713–720 by 751 numbering) of APP was used to monitor caspase cleavage. This antibody constitutes an ideal tool to monitor levels of caspase-generated APP because it is end-specific and only recognizes APP when it is not a substrate for caspases. Levels of Aβ were not significantly different in cells expressing APP or APP(D664A), whereas levels from APP(D664A)-expressing cells were dramatically reduced (Fig. 7, lower panel, lanes 1, 3, 5), as expected from inefficient APP internalization (Fig. 2). Upon serum starvation, the level of Aβ in medium was unchanged as compared with basal conditions (Fig. 7, lower panel, lanes 2, 4, 6), regardless of whether APP was a substrate for caspases (i.e., wild type APP) or not, i.e., APP(D664A). Thus, the levels of Aβ mirrored those of the APP forms susceptible to internalization, i.e., steady state levels of wild type APP and APP(D664A) (Fig. 7, upper panel), and not those of caspase cleavage of APP.

**DISCUSSION**

A wide variety of cell lines, including neurons, undergo apoptosis when exposed to Aβ peptides, whereas apoptotic cells in turn have been shown in some cases to generate enhanced levels of Aβ. This has led to the hypothesis that elevated levels of Aβ seen in both sporadic and familial Alzheimer’s disease contribute to cell death, which in turn secretes more Aβ leading to a propagating cycle of cell death (6, 7). Whether enhanced Aβ secretion in response to cell insult is a common phenomenon or occurs in vivo is unknown. It was recently proposed that caspase-3 cleavage of APP at amino acid Asp<sup>664</sup> generates a truncated APP molecule (APP<sub>D664A</sub>) that is then processed in a more amyloidogenic pathway, an intriguing notion that feeds into the amyloid/cell death hypothesis (7). This idea is supported by the findings that B103 cells expressing APP(D664A) secrete significantly higher amounts of Aβ than control cells expressing wild type APP. However, these observations are in apparent contradiction with the hypothesis that the endocytic compartment is involved in generation and secretion of both Aβ-(1–40) and Aβ-(1–42) (2, 3). Because caspase-cleaved APP

**fig. 5. Increased p3 secretion from endocytosis-deficient APP forms.** B103 panel, expression of APPΔC31 derived from APP<sub>695</sub> or APP<sub>695</sub> in B103 cells results in up-regulated p3 levels concomitantly with a decrease in Aβ secretion. CHO panel, similarly, p3 levels increase, and Aβ levels decrease in CHO cells expressing endocytosis-deficient APPΔC31 or APPY738A forms but not wild type APP or caspase cleavage-deficient APP(D664A). Immunoprecipitated Aβ and p3 fragments from [35S]methionine-labeled cells were visualized by phosphorimaging after electrophoresis separation as described under “Materials and Methods”.

**sponded instead to an increase in p3 levels. The antibody used by these authors was directed against the sequence Aβ-(x-40) thus potentially recognizing p3 although further details were not provided (7). Furthermore, these authors tested APPΔC31 derived from APP<sub>751</sub> (7), whereas we tested APPΔC31 derived from APP<sub>695</sub> in the same cells (Fig. 4), thus precluding a direct comparison between both results. We addressed both issues by measuring directly the levels of Aβ and p3 secreted from cells metabolically labeled with [35S]methionine. Fig. 5 shows that both B103 and CHO cells expressing APPΔC31 secreted higher levels of p3 concomitantly with a decrease in Aβ, similarly to other endocytosis mutants including the point mutation Y738A, which disrupts the YENP motif and results in decreased internalization (2, 3, 18). Furthermore, the pattern of other endocytosis mutants including the point mutation Aβ-(1–40), independently of either the APP isoforms or the cell line.

**Removal of the Asp<sup>664</sup> Caspase Site in APP Does Not Affect Aβ Secretion**—Our results so far demonstrated that caspase cleavage at the Asp<sup>664</sup> site did not result in a more amyloidogenic processing of APP, as has been hypothesized (7). Rather, it appeared that Aβ secretion from caspase-truncated APP follows the well established model in which Aβ secretion is closely correlated with the rate of internalization of APP from the cell surface. To confirm the preceding finding, we examined the role of caspase cleavage of APP in Aβ secretion using a mutated form of APP that cannot be cleaved by caspases (APP(D664A)). We reasoned that, if cleavage at the Asp<sup>664</sup> site is involved in the generation of Aβ, removal of the caspase site should result in decreased Aβ levels. As shown in Fig. 4, this was not the case. No difference in Aβ secretion was found between cells expressing wild type APP and those expressing APP(D664A) in B103 (Fig. 4, lanes 1, 4). Moreover, ratios of Aβ42/total Aβ measured in N2a cells were not altered after expression of the APP(D664A) mutant (Fig. 6) whether derived from wild type APP or the familial Alzheimer’s disease APPV642F mutation, the latter selectively increasing the level of Aβ42.

Aβ Secretion Is Independent of Caspase Cleavage of APP—To further test a possible role of caspase activation in the generation of Aβ, we induced apoptosis in B103 cells expressing wild type APP, APP(D664A), or APPΔC31 by serum withdrawal. In B103 cells, serum withdrawal led to caspase activation and caspase cleavage of APP to generate APPΔC31 (Fig. 7, middle panel). Polyclonal antibody 664 directed against amino acids 657–664 (by 695 numbering; 713–720 by 751 numbering) of APP was used to monitor caspase cleavage. This antibody constitutes an ideal tool to monitor levels of caspase-generated APP because it is end-specific and only recognizes APP when it is not a substrate for caspases. Levels of Aβ were not significantly different in cells expressing APP or APP(D664A), whereas levels from APPΔC31-expressing cells were dramatically reduced (Fig. 7, lower panel, lanes 1, 3, 5), as expected from inefficient APP internalization (Fig. 2). Upon serum starvation, the level of Aβ in medium was unchanged as compared with basal conditions (Fig. 7, lower panel, lanes 2, 4, 6), regardless of whether APP was a substrate for caspases (i.e., wild type APP) or not, i.e., APP(D664A). Thus, the levels of Aβ mirrored those of the APP forms susceptible to internalization, i.e., steady state levels of wild type APP and APP(D664A) (Fig. 7, upper panel), and not those of caspase cleavage of APP.
In this study, we explored the role of caspase cleavage of APP on Aβ generation by analyzing internalization of cell surface APP and levels of Aβ in both caspase-cleaved APP and by the non-cleavable mutant APP(D664A). We showed that 1) caspase cleavage of APP resulted in impaired internalization of the C-terminal-truncated APP molecule, similar to other YENPTY cleavage of APP. Rather, they mirror the internalization rates of the APP forms as seen in Fig. 2.

In this study, we were careful to examine not only CHO cells, as we have analyzed in the past, but also the same B103 neuroblastoma cell line used in both studies as well as N2a cells. We used APP(D664A) and APP(D664A) and both deletion (ΔC, ΔC15, and ΔC31) and single point (Y738A) mutants to demonstrate a correlation between internalization of APP and Aβ secretion. At present we cannot explain the differences between our findings and those reported by Gervais et al. (7). One possibility, however, may reside in the method chosen to measure Aβ levels. While we directly visualized Aβ as well as the fragment and p3 production, known as the p3 fragment (2) (see diagram in Fig. 1 and Fig. 5), Gervais et al. made use of an antibody directed against the sequence Aβ-(1–42), which potentially recognize p3. Because the method used (ELISA) may not be able to differentiate between p3 and Aβ fragments, and no evidence was presented to the contrary, it is possible that what Gervais and colleagues interpreted as an increase in Aβ-(1–40) from APP(ΔC31) corresponded in fact to an increase in p3 generation, as we have shown in the present work.

In summary, our studies provided evidence that caspases are unlikely to be involved in the amyloidogenic processing of APP. In this context, it is noteworthy that caspase-6 was proposed to represent the ß-secretase activity, especially in the case of the Swedish APP mutation, where the mutant APP was shown to be an improved caspase substrate in in vitro assays (7). This is one possible explanation for the increased Aβ production associated with this mutation, a finding that places caspases as potentially important in amyloidogenesis under pathological conditions. However, cleavage by caspase-6 generates an Aβ peptide that is truncated of the N-terminal aspartate residue because caspase cleavage occurs after rather than before the aspartate at the P1 position (14). The most compelling evidence that caspases do not contribute to Aβ generation through ß-secretase activity is the recent reports that mice lacking BACE1 (ß-site APP cleaving enzyme-1) do not produce any measurable amounts of Aβ (15, 16). Thus, the concept that caspases play an important role in amyloidogenesis, though provocative, is not substantiated by current evidence, including our present work.

Finally, it is important to note that this study did not address the question of whether some apoptotic signals may exacerbate Aβ secretion under certain circumstances, as has been reported by two laboratories (5, 6). Although we did not see an increase in Aβ secretion in response to serum withdrawal and caspase activation, differences in mode of cell death induction and in the cell lines used may explain the outcomes. Clearly, it re-

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**Fig. 6.** Deletion of the caspase cleavage site in wild type or FAD(V642F) mutant APP does not modify Aβ-(1–40) or Aβ-(1–42) levels in N2a cells. Total levels of Aβ, as well as the Aβ42/Aβ40 ratio remained unaffected after introducing the mutation D664A in both APP forms. ELISA measurements were performed as described under "Materials and Methods." Results from two experiments performed in duplicate (mean ± S.D.) are shown.

**Fig. 7.** Aβ secretion in B103 cells is independent of caspase cleavage of APP. B103 cells expressing wild type APP, APP(D664A), or APP(ΔC31) were incubated in the presence or absence of serum and caspase cleavage of APP, and Aβ levels were measured as described under "Materials and Methods." Note that Aβ levels did not depend on caspase cleavage of APP. Rather, they mirror the internalization rates of the APP forms as seen in Fig. 2.
mains possible that apoptosis may eventually lead to enhanced Aβ secretion in some cell types. However, it is also clear from our present work that caspase-cleaved APP per se is not a major contributor to Aβ generation, and therefore a scenario in which caspase-cleaved APP actively contributes to Aβ secretion remains unlikely. Thus, the possibility remains that cytotoxic effects derived from caspase cleavage of APP may result from the generation of new APP-derived C-terminal peptides (10, 17, 19) or C31, as we have proposed (12).

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