Peroxidase Activity of Cyclooxygenase-2 (COX-2) Cross-links β-Amyloid (Aβ) and Generates Aβ-COX-2 Hetero-oligomers That Are Increased in Alzheimer’s Disease*

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Oxidative stress is associated with the neuropathology of Alzheimer’s disease. We have previously shown that human Aβ possesses the ability to reduce Fe(III) and Cu(II) and produce hydrogen peroxide coupled with these metals, which is correlated with toxicity against primary neuronal cells. Cyclooxygenase (COX)-2 expression is linked to the progression and severity of pathology in AD. COX is a heme-containing enzyme that produces prostaglandins, and the enzyme also possesses peroxidase activity. Here we investigated the possibility of direct interaction between human Aβ and COX-2 being mediated by the peroxidase activity. Human Aβ formed dimers when it was reacted with COX-2 and hydrogen peroxide. Moreover, the peptide formed a cross-linked complex directly with COX-2. Such cross-linking was not observed with rat Aβ, and the sole tyrosine residue specific for human Aβ might therefore be the site of cross-linking. Similar complexes of Aβ and COX-2 were detected in post-mortem brain samples in greater amounts in AD tissue than in age-matched controls. COX-2-mediated cross-linking may inhibit Aβ catabolism and possibly generate toxic intracellular forms of oligomeric Aβ.

The neocortical accumulation of β-amyloid (Aβ)1 may play a central role in Alzheimer’s disease (AD) (1, 2). Although the mechanism of neuronal damage by Aβ is uncertain, the accumulated Aβ correlates with oxidative damage to lipids, proteins, and nucleic acids in the brains of patients (3–6) and in amyloid precursor protein transgenic mice (7). The toxicity of synthetic human Aβ is exerted by the catalytic generation of H2O2 (8, 9), which may be important in designing treatment strategies for AD.

Human Aβ is a metalloprotein that binds Zn(II) and Cu(II) in amyloid plaque (9–11). The ability of Aβ to produce H2O2 is mediated by the reduction of Cu(II) and Fe(III) to Cu(I) and Fe(II), respectively (8, 12). Rat Aβ, substituted at three residues compared with human Aβ (Arg9 → Gly, Tyr10 → Phe, and His13 → Arg), is less redox active, producing less H2O2, and is correspondingly less toxic (8, 9, 12).

Human Aβ is also vulnerable to oxidative damage and cross-linking. Peroxidative activity such as horseradish peroxidase (HRP) or Cu(II)/H2O2 generates SDS-resistant oxidized Aβ oligomers linked by dityrosine (DT) bridges (13, 14). Cyclooxygenases (COX) are members of a heme enzyme family that catalyze the rate-limiting reaction to produce prostaglandins (15). COX-1 is the widely expressed constitutive form, and COX-2 is the inducible form that is up-regulated by cyto-kines and mitogens. COX-2 may play an important role in AD. Epidemiological studies indicate that nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of COX, delay the onset of AD (16–18). Ibuprofen, a nonselective COX inhibitor, attenuates plaque pathology in Tg2576 mice (19). Neuronal COX-2 expression is increased in the affected regions of AD brain (20–23), correlating to the severity of AD pathology (24). COX-2 overexpression in primary neurons potentiates Aβ neurotoxicity in vitro (25). Therefore, COX-2 may interact with the metabolism of Aβ in AD.

COX harnesses two enzymatic activities to produce prostaglandin H2 (PGH2). Authentic “cyclooxygenase” activity first converts arachidonic acid to prostaglandin G2 (PGG2), and subsequent peroxidase activity reduces PGG2 to PGH2. The peroxidase reaction of COX is analogous to that of HRP and can utilize a wide range of hydroperoxides including H2O2, rather than PGG2, as substrates (15). We suspected that the peroxidase activity of COX-2 might induce the formation of Aβ oligomers. To explore this possibility, we examined the effect of COX-2 on Aβ oligomerization and report the formation of Aβ-COX-2 complexes in vitro and in vivo.

MATERIALS AND METHODS

Reagents—Aβ peptides were synthesized, purified, and characterized by high pressure liquid chromatography (HPLC), amino acid analysis, and mass spectroscopy by the W. Keck Laboratory of Yale University (New Haven, CT). Ovine COX-2 purified from placenta and polyclonal anti-COX-2 antibody were purchased from Cayman Chemical (Ann Arbor, MI). N-Acetyl-L-methionyl and phenylglyoxal were obtained from Acros Organics (Geel, Belgium). Monoclonal anti-Aβ antibodies 4G8 (which detects Aβ residues 18–22) and 2F3 (which detects Aβ residues 5–8) (51) were obtained from Signet Laboratories (Dedham, MA). Horseradish peroxidase-conjugated anti-mouse and rabbit IgG antibod-
ies were from Amersham Biosciences. MagnaBind goat anti-mouse and rabbit IgG beads were from Pierce. The other reagents were obtained from Sigma unless otherwise noted.

**Brain Samples**—Frozen human post-mortem brain samples (superior temporal cortex, Brodmann area 22, 41/42) from moderately affected AD (Braak stage 3–4 (52), n = 5), severely affected AD (Braak stage 6, n = 4), and control cases (n = 4) were obtained from the Harvard Brain Tissue Resource Center (Belmont, MA). The profile of brain samples was homogenized by a glass homogenizer in 10 ml/g of phosphate-buffered saline with 10% dry milk, 5% bovine serum albumin for anti-Aβ membrane (Bio-Rad) at 75 mA for 90 min. The membrane was blocked by horseradish peroxidase–conjugated secondary antibody for 1 h at 4 °C. The membrane precipitates were washed three times with phosphate-buffered saline without calcium and magnesium at 37 °C.

**Preparation of Reactions**—Aβ peptide stock solutions were prepared in HPLC grade water (Fisher) on the day of the experiment. The peptide preparation was then filtered through a Spin-X cellulose acetate filter (Corning Incorporated, Corning, NY). Concentrations of Aβ were determined by BCA assay (Pierce), which we have previously validated as an assay for Aβ concentration (53). Aβ was incubated with ovine COX-2 in a final volume of 100 μl of Dulbecco’s phosphate-buffered saline without calcium and magnesium at 37 °C. Stock solutions of indomethacin (50 mM), ibuprofen (250 mM), and aspirin (250 mM) were prepared in ethanol. Where COX-2 inhibitors were used, the enzyme was preincubated with the reagent for 30 min on ice. For chemical modification of amino acids in Aβ, the peptide was incubated with the reagent for 30 min at 25 °C prior to adding COX-2 and hydrogen peroxide. The reaction was terminated by adding sample buffer for SDS-PAGE (Invitrogen) containing 5% 2-mercaptoethanol.

**Immunoprecipitation**—Solutions reacted in vitro were incubated with 2 μl of anti-COX-2 antibody overnight at 4 °C and with 30 μl of MagnaBind anti-rabbit IgG beads for 1 h, at 4 °C subsequently. For co-immunoprecipitation of Aβ or COX-2 from tissue, control and AD brain samples were homogenized by a glass homogenizer in 10 ml/g of ice-cold phosphate-buffered saline containing protease inhibitor mixture (Roche Applied Science). The supernatant was separated by centrifugation at 20,000 × g for 10 min and adjusted to a final protein concentration of 1.75 mg/ml with homogenization buffer. After pretreatment with 10 μl of MagnaBind beads to decrease the nonspecific binding of proteins, the supernatant (0.8 ml) was incubated with 3 μl of anti-Aβ (WO2–) or COX-2 antibody overnight at 4 °C and subsequently with 30 μl of MagnaBind beads for 3 h at 4 °C. For Western blot, the precipitates were washed three times with phosphate-buffered saline and boiled for 5 min at 95 °C with sample buffer containing 5% 2-mercaptoethanol.

**Immunoblotting**—The samples in sample buffer were loaded onto a NuPAGE 4–12% Bis-Tris gel and separated by electrophoresis at 200 V for 45 min. The gel was then transferred to polyvinylidene difluoride membrane (Bio-Rad) at 75 mA for 90 min. The membrane was blocked with 10% dry milk, 5% bovine serum albumin for anti-Aβ antibodies or 5% dry milk for anti-COX-2 antibody for 1 h at 25 °C. The membrane was then incubated with a primary antibody overnight at 4 °C followed by a horseradish peroxidase–conjugated secondary antibody for 1 h at 25 °C. Antibody labeling was detected by LumiGLO chemiluminescent kit (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD). The density of each band from the immunoblotting was analyzed by National Institutes of Health Image 1.62 software (National Institutes of Health, Bethesda, MD).

**RESULTS**

To study the effects of COX-2 on the oligomerization of Aβ, we incubated purified ovine COX-2 (140 nM) with human synthetic Aβ1–40 (*h40*, 2.5 μM) in the presence of H2O2 (1 μM) for 2 h at 37 °C. We observed that the synthetic Aβ1 alone remained predominantly monomeric upon SDS-PAGE but that the combination of COX-2 and H2O2 induced the conspicuous formation of an apparent Aβ dimer, as well as Aβ immunoreactive bands in the range of 50–75 kDa (Fig. 1A). Incubation of Aβ with COX-2 alone induced far lower amounts of the apparent dimer and higher molecular weight Aβ immunoreactive products, but because the incubation was performed under aerobic conditions, small concentrations of H2O2 may have been present because of the reduction and subsequent disproportionation of dissolved O2 (26). This interpretation was indeed supported by the experimental effects of the H2O2 scavenger catalase, which completely abolished all but monomeric Aβ immunoreactivity being detected upon co-incubation with Aβ, COX-2, and H2O2 (Fig. 1A). Aβ incubated with H2O2 alone remained monomeric on SDS-PAGE (Fig. 1B).

These data established that H2O2 acts in concert with COX-2 to convert monomeric Aβ into apparent dimeric and higher molecular weight Aβ immunoreactive products. MeSO and mannitol, which scavenge OH·, did not have an inhibitory effect on the generation of these modified Aβ immunoreactivities (Fig. 1A), suggesting that H2O2 in the reaction is not inducing cross-linking through Fenton or Haber-Weiss chemistry. As a positive control, we also applied human Aβ reacted with horseradish peroxidase and hydrogen peroxide, which is known to induce dimeric dityrosine cross-linking of human Aβ (DT-Aβ) (13). DT-Aβ co-migrated with the apparent Aβ dimers that we observed, and HRP, like COX-2 incubated under the same conditions, also appeared to form Aβ adducts (Fig. 1A). These data suggest that hydrogen peroxide might oxidize residues of both the COX-2- and Aβ-inducing covalent cross-links, consistent with DT interstrand bridge formation for Aβ to Aβ and Aβ to COX-2.

Alzheimer neuropathology is only seen in animal species that have the human sequence of Aβ (27) and not in rats and mice, which have three amino acid substitutions (Arg15 → Gly, Tyr18 → Phe, and His23 → Arg) (28). The tyrosine substitution in the rat/mouse Aβ (‘rat Aβ’) abolishes the possibility of DT interstrand bridge formation. To explore further whether COX-2 induces DT interstrand bridge formation, we repeated the experiment comparing the products of rat Aβ to human Aβ (Fig. 1B). Although incubation with COX-2/H2O2 (but not H2O2 alone) induced apparent dimer formation of human Aβ1–40 as well as high molecular weight immunoreactivity, no such modifications of rat Aβ 1–40 were apparent even after 15 h of incubation (Fig. 1B).

The molecular mass of COX-2 is ~75 kDa, and we determined that COX-2 itself did not cross-react with 4G8 antibody (Fig. 1B). Therefore, the Aβ immunoreactive band at ~75 kDa when synthetic human Aβ was reacted with COX-2 and hydrogen peroxide (Fig. 1, A and B, asterisk) may indeed be a complex of human Aβ and COX-2. To confirm that this ~75-kDa Aβ immunoreactivity reflects Aβ complex formation with COX-2, we immunoprecipitated the incubation products with a polyclonal anti-COX-2 antibody and immunoblotted the immunoprecipitates with anti-Aβ antibody (WO2). We again observed the 75-kDa band from the sample of human Aβ1–40 reacted with COX-2 and hydrogen peroxide (Fig. 2, arrow) but not from the samples of COX-2, human Aβ1–40 alone, or rat Aβ1–40 incubated with COX-2 and hydrogen peroxide. Therefore, human Aβ may have adducted onto the COX-2 in this reaction. In addition, an extra band at ~50 kDa was seen only in the
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**Fig. 1. Peroxidase activity of COX-2 induces the cross-linking of Aβ.** A, human Aβ 1–40 (h40, 2.5 μM) was incubated alone (2 h at 37 °C) or in the presence of COX-2 (140 nM) and H2O2 (1 μM), as indicated, and Western blotted with 4G8 anti-Aβ antibody. This reaction induced apparent dimerization of Aβ and possible Aβ adduction of COX-2. These apparent cross-links were abolished by co-incubation with catalase (CAT, 10 μg/ml), but not by dimethyl sulfoxide (DMSO, 10 mM) or mannitol (MAN, 10 mM). H2O2 alone incubated with Aβ did not induce apparent cross-linking (see panel B). As a positive control, human Aβ was reacted with HRP (10 μg/ml) to induce dityrosine cross-linking (13). B, human, but not rat, Aβ cross-linking is induced by COX-2/H2O2. Aβ (rat 1–40 (r40) or human 1–40, 2.5 μM), COX-2 (70 nM), and H2O2 (1 μM) were incubated together, or the components were incubated separately as indicated, for 15 h at 37 °C and blotted with 4G8 anti-Aβ antibody. An arrow and an asterisk indicate the apparent dimer of human Aβ and a possible complex of human Aβ with COX-2, respectively. Even after such protracted incubation, the rat homologue of Aβ did not form apparent cross-links.

Precipitate from the sample of human Aβ with COX-2 and hydrogen peroxide (Fig. 2, arrowhead), which may be a complex of human Aβ with a degraded COX-2 fragment.

We next examined the effects of several peroxidase inhibitors on the cross-linking (Fig. 3A). Desferoxamine, an iron chelator, inhibited the apparent cross-linking completely, possibly bycomplexing iron from heme in COX-2. Sodium azide and sodium cyanide, inhibitors of peroxidase, also attenuated the cross-linking. The inhibition was more complete with cyanide compared with azide at the same concentration.

NSAIDs and aspirin were examined for effects on these peroxidative reactions (Fig. 3B). Indomethacin and ibuprofen, non-specific inhibitors of COX-1 and COX-2, potently attenuated the apparent cross-linking of Aβ mediated by COX-2/H2O2. Aspirin, a more potent inhibitor of COX-1, had a lesser effect compared with the other inhibitors. Inactivation of COX-2 by heating at 95 °C for 10 min abolished Aβ cross-linking (Fig. 3B), which excludes the possibility that iron in free heme itself might cause the cross-linking of Aβ by Fenton chemistry. Therefore, the oligomerization is caused by the enzymatic peroxidase activity of COX-2.

Arg5, Tyr10, and His13 in human Aβ1–40 are substituted in rat Aβ1–40, which did not polymerize in the presence of COX-2 (Fig. 1B). Therefore, one of these three residues may be the site of dimeric cross-linking induced by COX-2/H2O2. As a preliminary analysis to identify the amino acid responsible for the cross-linking, we examined the effect of chemical modifiers for each amino acid (29) on the apparent cross-linking induced by COX-2/H2O2. Phenylglyoxal, an arginine modifier, did not have an apparent effect. N-Acetylcycteamine, which acetylates tyrosine hydroxyl groups, partially inhibited the apparent cross-linking consistent with inhibiting the formation of dityrosine bridges. Diethylpyrocarbonate, a histidine modifier, did not inhibit the cross-linking but rather promoted the oligomerization of Aβ. This result may indicate that the histidine residues play a role in minimizing radical reactivity or that the diethylpyrocarbonate is acting exceptionally in this system as a chemical cross-linker. Among the caveats with this approach is that modifications are not completely selective for amino acids. Although future studies of amino acid substituted Aβ will be needed to consolidate these conclusions, these findings do not refute our earlier interpretation (Figs. 1 and 3, A and B) that DT cross-linking could be a consequence of the peroxidative activity of COX-2.

We next explored for evidence that COX-2 might react with Aβ in vivo. There is already abundant evidence for SDS-resistant Aβ dimers and polymers being enriched in AD-affected post-mortem brain tissue (2, 30). Furthermore, there is evidence of elevated H2O2 in AD-affected brain tissue (4). Our in vitro data indicated that whenever the combination of COX-2 and H2O2 induced Aβ apparent dimeric cross-linking, a proportion of Aβ always adducted to COX-2 itself (Figs. 1–3). Therefore, if COX-2 indeed contributed to Aβ oligomeric cross-linking in vivo, the presence of such Aβ-COX-2 complexes would be anticipated in post mortem human brain tissue as a biomarker.
We investigated this possibility by co-immunoprecipitation of AD and age-matched control post-mortem human brain tissue with anti-Aβ and COX-2 antibodies, as in Fig. 1B. Two major bands were seen at approximately 70 and 50 kDa that were cross-immunoreactive with both antibodies (Fig. 4A). These bands were close to the molecular masses of the two major bands detected in anti-COX-2 immunoprecipitation of human Aβ1–40 incubated with ovine COX-2 and H2O2 detected by Aβ immunoblot (Fig. 1B). Again, the 50-kDa band might be a degraded fragment of the complex possibly formed by the attack of free radicals. As a further negative control, we also probed these blots with antibody against human copper/zinc superoxide dismutase, which is widely expressed in the brain, and no immunoreactivity was detected (data not shown).

We surveyed the relative abundance of Aβ-COX-2 complexes in post-mortem human brain samples obtained from patients with AD and age-matched controls. In moderately affected AD, Aβ-COX-2 complexes were significantly increased compared with age-matched controls (p < 0.05, paired t test; Fig. 4B) in the COX-2 blot following Aβ immunoprecipitation but not in Aβ blots following COX-2 immunoprecipitation. The increase Aβ-COX-2 complexes was more conspicuous in severely affected AD, where both COX-2 and Aβ blots revealed greater amounts of the immunoprecipitated complexes (p < 0.05, paired t test). This indicates that the Aβ-COX-2 complexes become more abundant as the disease progresses.

**DISCUSSION**

Our data indicate that the peroxidative activity of COX-2 induces the dimerization of human Aβ by a H2O2-mediated mechanism, and the enzyme itself also cross-links with human Aβ directly. These cross-links were attenuated by a scavenger of H2O2 and by peroxidase inhibitors. Our evidence, for the first time, implicates COX-2 activity in the direct oxidation of Aβ, to generate SDS-resistant oligomeric Aβ forms that resemble forms that have previously been reported to be increased in the disease and proposed to mediate pathophysiology.

Aβ is extracted from AD brains as toxic water-soluble, SDS-resistant oligomers (30, 31). Soluble Aβ levels, including the SDS-resistant oligomers, are correlated to the disease severity of AD (32). Diffusible Aβ oligomers are deleterious to hippocampal neurons in vitro (33) and in vivo (34). Recent data have proposed that Aβ oligomers are generated intracellularly and secreted subsequently to form extracellular amyloid fibrils (35). Evidence suggests that the subcellular origin of these oligomers may be microsomes (35), the same compartment that contains COX. To date, none of the reports correlating SDS-
resistant apparent oligomers of Aβ with neurotoxicity have established the basis of the SDS resistance. Aβ will form SDS-resistant oligomers to some extent in the absence of any apparent oxidative modification (Fig. 3A). However, our data establish that oxidation will lead to an apparent covalent cross-link that leads to similar SDS resistance. The possibility that oxidized Aβ SDS-resistant oligomers (e.g. produced by COX-2 activity) are more neurotoxic than the nonoxidized oligomers must be considered.

COX possesses both cyclooxygenase and peroxidase activities. The cycle of the peroxidase reaction can occur independently of cyclooxygenase activity, utilizing hydroperoxides such as hydrogen peroxide (15). During the peroxidase reaction, ferric heme of the resting enzyme is oxidized to form ferryl iron as hydrogen peroxide. The cycle of the peroxidase reaction can occur independently of COX (13). The peroxidase activity of COX-2 is a strongly redox active peptide that reduces copper and iron ions (8, 12). The same properties of the peptide may lead to redox reactions with COX-2. The redox activity of Aβ also fosters the catalytic generation of hydrogen peroxide (6, 8, 9, 12), which may supply the substrate to COX-2 for peroxidative cross-linking. Aβ 1–40 and Aβ 1–42 have high affinity for Cu²⁺ (41) and are bound to the metal ion in AD-affected brain tissue (9, 11). Therefore, Aβ accumulating in the AD-affected neocortex is very likely to be a source of H₂O₂, H₂O₂ is freely permeable across lipid boundaries, which may contribute to its potency in mediating oxidative attack to neocortical cells (4, 6). Contributions to increased H₂O₂ in AD may also come from failing mitochondrial metabolism and from microglial activation. H₂O₂ generated extracellularly (e.g. from Aβ or microglia) and intracellularly (e.g. from mitochondria) could migrate into microsomal compartments and then act as a substrate for COX-2-mediated cross-linking of Aβ. Pharmacological removal of excess copper and iron or scavenging of hydrogen peroxide may therefore be therapeutic strategies to prevent Aβ oxidation by COX-2. Such a mechanism may contribute to the efficacy of clioquinol, which blocks hydrogen peroxide production by Aβ by binding to copper and iron at its active site (42).

The tyrosine of human Aβ is thought to coordinate the metals that interact with the peptide (43, 44), and we hypothesize that it may inappropriately coordinate with the metal active site of COX-2 (Fig. 5). The DT bond that may be formed in this reaction is chemically stable and resistant to proteolytic cleavage, and so the catabolism of DT cross-linked proteins or peptides is inhibited (45). The total DT content is elevated in the regions affected by Aβ pathology in AD brains, in accordance with the regions where COX-2 expression is up-regulated (46). A polyclonal antibody raised against what may have been a DT-Aβ antigen detected highly abundant immunoreactivity in neuritic plaques (14).

The lack of tyrosine in rat (and mouse) Aβ might explain the scarcity of cerebral amyloid deposits in these animals (47). Transgenic mice that overexpress human COX-2 in neurons did not exhibit cerebral amyloid pathology (25), which would be consistent with the inability of endogenous mouse Aβ (lacking tyrosine) to cross-link. Supporting an essential role for the tyrosine residue in the human Aβ sequence causing amyloid pathology, cerebral Aβ deposition in double mutant presenilin 1/human amyloid precursor protein transgenic mice was markedly exaggerated upon crossing with the same line of human COX-2 transgenic mice (48).

Me₃SO and mannitol, scavengers of hydroxyl radicals, did not inhibit the cross-linking of Aβ (Fig. 1A). This is consistent with the oxidative reaction of the peroxidase, which is not mediated by the production of hydroxyl radicals. Both sodium azide and sodium cyanide are general inhibitors of peroxidase. However, cyanide is known to have much stronger affinity to the COX peroxidase site than azide (15). Consistent with that, cyanide showed stronger inhibitory effect on the cross-linking of Aβ (Fig. 3A).

Interestingly, nonselective NSAIDs attenuated the Aβ dimerization that was induced by COX-2 and COX-2 complex formation with human Aβ (Fig. 3B). NSAIDs inhibit cyclooxygenase activity more than the peroxidase activity of COX. However, NSAIDs such as indomethacin and flurbiprofen specifically suppress the radical formation at Tyr²⁸⁵ of COX (36), suggesting that NSAIDs inhibited COX-2/Aβ cross-linking (Fig. 3B) by decreasing tyrosyl radicals in COX-2. Alternatively, this inhibitory effect of NSAIDs may be a consequence of the direct interactions of NSAIDs with Aβ peptide that have been described (49, 50). The concentrations of indomethacin and ibuprofen used in this study are similar to those in the report by Weggen et al. (50), who demonstrated that some NSAIDs decrease the production of human Aβ1–42. The prevention of Aβ cross-linking would facilitate Aβ clearance and may be a novel mechanism for the proposed protective effect of NSAIDs on AD.

We detected the possible complexes of Aβ and COX-2 from human brains by co-immunoprecipitation with antibodies against each component (Fig. 4). These complexes are increased in AD brains, especially in severely affected cases (Fig. 4). This may be due to the increased activity of COX-2 promoting more cross-linking of COX-2 and Aβ or due to diminished clearance of the complexes in AD. The 50-kDa band of fragmented COX-2 that we observed (Fig. 4A) has also previously been detected in AD brains (21). This is consistent with our current data (Fig. 2) indicating that reaction with Aβ may lead to the fragmentation of COX-2 into such a ~50-kDa species that is adducted to Aβ, whose concentrations appear to be increased in AD brain (Fig. 4).

The significance of the COX-2-Aβ complex is not clear, although we hypothesize that abnormal Aβ reaction with COX-2 may interfere with COX-2 integrity, function, or metabolism. More importantly, we noted that COX-2 mediates the production of Aβ dimers, accompanied by the invariable generation of such COX-2-Aβ complexes (Figs. 1–4). Therefore, the detection of COX-2-Aβ complexes in human tissue is evidence that these two proteins are in biochemical proximity in vivo and that therefore the peroxidation of Aβ by COX-2 in AD may indeed...
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Contribute to the Aβ oligomeric forms that are increasingly considered to mediate the disease process. If the intracellular oligomerization of Aβ by COX-2 is an early event in the pathology of AD, its biochemical intervention may be a treatment strategy to halt or delay the disease progression at early stages.

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