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Environmental exposures and the etiopathogenesis of Alzheimer's disease: the potential role of BACE1 as a critical neurotoxic target

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Abstract

Alzheimer's disease (AD) is a major public health crisis due to devastating cognitive symptoms, a lack of curative treatments, and increasing prevalence. Most cases are sporadic (>95% of cases) after the age of 65 years, implicating an important role of environmental factors in disease pathogenesis. Environmental neurotoxicants have been implicated in neurodegenerative disorders including Parkinson's Disease and AD. Animal models of AD and *in vitro* studies have shed light on potential neuropathological mechanisms, yet the biochemical and molecular underpinnings of AD-relevant environmental neurotoxicity remain poorly understood. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is a potentially critical pathogenic target of environmentally-induced neurotoxicity. BACE1 clearly has a critical role in AD pathophysiology: it is required for amyloid beta production and expression and activity of BACE1 are increased in the AD brain. While the literature on BACE1 in response to environmental insults is limited, current studies, along with extensive AD neurobiology literature suggest that BACE1 deserves attention as an important neurotoxic target. Here, we critically review research on environmental neurotoxicants such as metals, pesticides, herbicides, fungicides, polyfluoroalkyl substances, heterocyclic aromatic amines, advanced glycation end products and acrolein that modulate BACE1 and potential mechanisms of action. While more research is needed to clearly understand whether BACE1 is a critical mediator of AD-relevant neurotoxicity, available reports provide convincing evidence that BACE1 is altered by environmental risk factors associated with AD pathology, implying that BACE1 inhibition and its use as a biomarker should be considered in AD management and research.

Keywords

BACE1; Alzheimer's disease; oxidative stress; environmental neurotoxicants

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by two hallmark pathologies: accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (1). Based on genetic predisposition and age of onset, AD is classified into two types: early-onset familial AD and late-onset sporadic AD (2). Sporadic AD accounts for >95% of cases after the age of 65 years (3–5). Although AD was discovered over a century ago, curative and disease-modifying treatments remain elusive. Multifactorial pathology and etiology involving different mechanistic pathways could be the reason for the lack of effective therapies for AD (6). Aging and genetic predisposition play significant roles in the onset of AD (3–5,7). Adjustments to modifiable risk factors, proper management of comorbidities, and maintaining a healthy lifestyle could reduce the risk of dementia (8). Therefore, it is critical to identify and limit exposure to identified risk factors. Environmental toxicants have been extensively linked to neurodegenerative disorders including AD (9). These environmental neurotoxicants have a key role in accelerating disease onset and progression. Metals (10–13), pesticides (14), and dietary toxins (15–17) have been shown to accumulate in the serum and/or the brains of AD patients. However, the pathogenic mechanisms that underlie AD-relevant neurotoxicity resulting from environmental exposures remain understudied. To date, *In vivo* and *in vitro* experimental studies have shown that chronic exposure to environmental neurotoxicants such as metals (18–32) pesticides (14,33–36), polyfluoroalkyl substances (37), particulate matter (38,39), and dietary toxins (40–45) induces AD like pathology. It is critical to identify the biochemical and molecular mechanism underlying AD-relevant neurotoxicity because this knowledge can strengthen the understanding of etiological origins and pathology of sporadic AD leading to identification and development of biomarkers and therapies.

In vivo and *in vitro* studies have shown that beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) might play a key role in environmental neurotoxicant induced AD-like pathology (14,18–49). BACE1 is required for Aβ production (50,51). BACE1 protein and activity are increased in AD patients; BACE1 activity is correlated with Aβ load and markers of oxidative stress in AD patients (52,53). Given the critical role of BACE1, inhibition, or modulation of BACE1, is considered a prime therapeutic goal for reducing Aβ production (54–56).

The role of environmental risk factors in AD has been reviewed numerous times; therefore, in this brief and focused review, we critically discuss data from experimental studies on the environmental neurotoxicants that alter BACE1 and their possible mechanisms of action.

2. BACE1 cell biology

2.1 General overview

BACE1 is a 501 amino acid type 1 transmembrane aspartic protease related to the pepsin family that has the characteristics of β secretase. The catalytic domain of BACE1 contains two signature aspartic protease motifs (Asp-Thr/Ser-Gly-Ser/Thr) that form the active site of the enzyme (50,57–62). Cysteine residues at 216/420, 278/443, and 330/380 form three disulfide bonds and tether the ectodomain of BACE1 in a native tertiary structure (63).

BACE1 contains metal binding sites; a copper binding site is present in the cytoplasmic domain (48), and calcium is able to bind to the intracellular domain (64). BACE1 is homologous to BACE2, which is another membrane-bound secretase of the pepsin family, sharing 64% similarity in amino acid sequence. BACE2 is more abundant in peripheral tissues and has low expression in the brain. BACE2 cannot generate Aβ since the preferred BACE2 cleavage site in amyloid precursor protein (APP) is within Aβ (65–68).

BACE1 is synthesized in the endoplasmic reticulum and delivered to the cell surface from the trans-Golgi network. Transcription factors such as nuclear factor κB (NF-κB) (69,70), specificity protein 1 (Sp1) (71), peroxisome proliferator-activated receptor-gamma (PPAR γ) (72), hypoxia inducible factor 1α (HIF-1α) (73,74), Yin Yang 1 (YY1) (75), and nuclear factor of activated T cells (NFAT) (76) amongst others control the transcription of BACE1 (77). Mature BACE1 is internalized from the plasma membrane or directly from the trans-Golgi network and translocated to endosomes (78–80). During its maturation and intracellular trafficking BACE1 undergoes a complex set of post-translational modifications such as glycosylation, acetylation and phosphorylation (63,79,81–85).

BACE1 cleaves membrane-bound substrates only (86). It has maximal activity at an acidic pH (87–90), with the highest activity in the acidic subcellular compartments of the secretory pathway, such as the Golgi apparatus, trans-Golgi network, and endosomes (91,92). BACE is a highly stable protein with a half-life of 12–16 h (81). BACE1 can be degraded by 1) endoproteolysis, 2) the ubiquitin proteasomal pathway (93,94), or 3) the lysosomal pathway (95–99). SUMOylation at K501 residue increases the activity and stability of BACE1 (100). Alterations in BACE1 half-life can affect the level and enzymatic activity of BACE1.

BACE1 also cleaves several other substrates that may be important for processes and functions in the central nervous system. Proteomic studies have identified about 40 novel candidates as BACE1 substrates: including: neuregulin 1 type I and III-β1α, neuregulin 3 (101–104), seizure protein 6 (105,106), sodium gated voltage channel β2 (107–109), Jagged1 and Jagged2 (110,111). Moreover, important binding partners have been identified: Golgi-localized γ-ear-containing ARF-binding proteins (112), phospholipid scramblase 1 (113), SorLAs (114), sortilins (115,116), reticulon/Nogo proteins (117,118), prostate apoptosis response-4 (117), copper chaperone for superoxide dismutase-1 (49), Presenilin (119) among others, bind with BACE1 and modulate its activity and interaction with APP.

2.2. BACE1 distribution

BACE1 is present in most tissues of the body, but the highest activity levels are found in neural tissue (120–123). In the brain, BACE1 is more enriched in the hippocampus (123,124), and hippocampal mossy fiber terminals contain greater BACE1 expression (43,123,125–127). Neurons exhibit the highest BACE1 expression while resting astrocytes in brain do not express BACE1 at detectable levels; however, cultured astrocytes do express active BACE1 protein (128). Chronic activation of astrocytes increases BACE1 (129,130). BACE1-immunoreactive astrocytes are increased in proximity to Aβ plaques in the brains of aged transgenic 2576 mice and AD patients (131,132).

2.3 BACE1 and APP interactions

Interactions between BACE1 and APP have been extensively studied. APP processing is generally divided into two pathways, non-amyloidogenic and amyloidogenic. Non-amyloidogenic α-secretase mediated cleavage of APP releases soluble APP α into the extracellular space, and the C-terminal fragment of APP (CTF83) remains embedded in the plasma membrane. Cleavage of CTF83 by γ-secretase releases a small p3 fragment into the extracellular space and the APP intracellular domain (AICD) into the cytoplasm (133–136). Amyloidogenic BACE1 mediated APP cleavage releases a smaller soluble APP β into the extracellular space, and a larger APP C-terminal fragment (CTF99) remains embedded in the plasma membrane. Cleavage of CTF99 by γ-secretase releases Aβ into the extracellular space and the AICD into the cytoplasm (50,58,137–141).

2.4. BACE1 in AD

BACE1 has a critical role in the pathophysiology of AD. BACE1 expression and activity are increased in AD (142–144). BACE1 activity is correlated with Aβ load and markers of oxidative stress in AD patients (52,53). AD patients have higher CSF BACE1 activity than controls (145). BACE1 accumulates in normal and dystrophic presynaptic terminals surrounding amyloid plaques, causing increase in Aβ production near synapses in the brains of AD patients and AD mouse models (127). Given the critical role of BACE1 in AD pathology, inhibition of BACE1 is considered a prime therapeutic strategy for reducing Aβ production.

In the AD brain, both normal (143,146) and elevated BACE1 mRNA levels have been reported (147), and evidences for the regulation of BACE1 expression at the transcriptional and translational levels has also been presented. Brain extracts from AD patients showed that levels of PPARγ, involved in transcriptional regulation of BACE1 was decreased (148). Ceramide, the lipid second messenger is elevated in the brains of Alzheimer's disease patients, has been shown to increases the half-life of BACE1 (149).

2.5. BACE1 in aging and MCI

Aging is a major risk factor for AD, where aging is associated with an increase in Aβ levels and accumulation of Aβ in the brain (150,151). BACE1 activity increases significantly in mouse, monkey, and human brains with aging. The increase of BACE1 activity and Aβ accumulation with age potentially predispose to AD (152).

BACE1 activity and protein levels are significantly increased in the brains of patients with mild cognitive impairment (MCI), who have a significant risk of developing AD (153–156). A significant increase in BACE1 activity is also found in cerebrospinal fluid (CSF) and plasma of subjects with MCI (153–155). BACE1 activity could predict progression from prodromal to probable AD stage.

2.6 BACE1 in other neurological diseases

Alteration in BACE1 is also present in other neurological diseases. Elevated levels of Aβ has been reported in human immunodeficiency virus (HIV) patients (157). HIV-associated neurotoxicity is mediated by N-methyl- d-aspartic acid or N-methyl- d-aspartate (NMDA)-

dependent elevation of BACE1 and subsequent altered processing of APP (158). BACE1 also has a role in enzymatic cleavage of seizure protein 6, a protein associated with bipolar disorder. BACE1 is significantly upregulated in the plasma of male bipolar disorder patients compared with healthy subjects (159).

3. Environmental neurotoxicants that alter BACE1

Accumulation of Aβ occurs due to overproduction of APP, enhanced amyloidogenic processing of APP by BACE1, and/or a decrease in degradation or clearance of Aβ (33,138,160–165). Here we discuss environmental neurotoxicants that alter amyloidogenic processing of APP by BACE1(Table 1).

3.1 Metals.

Chronic exposure to metals is a health hazard. Exposure to metals can be due to different sources: occupational, dietary (food or water), or in inhaled air (13,166–174). Overall, occupational exposure to metals is higher in terms of dose, but rarer, compared to other sources. Due to the aggressive pace of anthropogenic activities, humans are exposed not only to essential metals such as copper, iron, manganese, and zinc, but also to potentially toxic metals, including aluminium, arsenic, cadmium lead, and mercury (13,168–174). Several clinical studies have shown an increase in metal ions in AD, suggesting that metal ions might be a risk factor associated with the pathogenesis of AD (11–13,160,175–180).

Aluminium: Epidemiological studies have identified aluminium as a risk factor for AD. Exposure to aluminium may occur through food, drinking water, topically applied cosmetics, and hair, skin, and hygiene products, however inhalation as fine particles is the most relevant way of exposure (169). Here, it is worth noting that the link between AD and aluminium as a causative factor remains highly controversial, with a large amount of negative data (181,182). Aluminium is reported to accumulate in the brain, serum, and CSF of AD patients (11–13,183). *In vivo* and *in vitro* studies have demonstrated Aβ accumulation from aluminium exposure is BACE1 mediated. BACE1 activity is increased significantly in the hippocampus of aged New Zealand rabbits treated with aluminium-maltolate (18). Rats treated with aluminium-maltolate had significantly higher levels of BACE1 and γ-secretase enzymes, whereas α-secretase related protein decreased, resulting in increased Aβ production. (19,184,185). Aluminium-maltolate treatment also increased mRNA transcription and enzyme activity of BACE1 in rats (185). AKT/GSK-3β signalling is involved in aluminium-maltolate mediated effects (184). Wang et al. reported that exposure to aluminium-maltolate increased BACE1 expression and reduced the expression of miR29 subtypes; expression of miR29a and miR29b1 was negatively correlated with BACE1 expression (186). $AlCl_3$ exposure also induced severe neurodegeneration, marked with elevated BACE1, Aβ level, and impaired insulin signalling in rats (20). Another study showed upregulation of the gene expression of BACE1 and APP on $AlCl_3$ exposure in rats. This was accompanied by an increase in oxidative stress, neuroinflammation, and activity of acetylcholinesterase; presenilin2 and ER-β expression was downregulated (21). An increase in BACE1 and BACE2 mRNA is seen after co-exposure of SH-SY5Y cells to $AlCl_3$ and Aβ (22).

Lead: Lead was extensively used in paint, pipes, and gasoline; individuals, and particularly children, living in highly urban areas had the highest exposures to lead in the United States in 1960–1980 (187–189). Accumulating evidence suggests that childhood lead exposures may significantly increase risk for neurodegenerative disease in old age (190). Adults chronically exposed to lead also show abnormalities in brain metabolism (191–193). A positive association was found between an increase in blood lead level and AD mortality after adjustment for competing risks or design effects (194). Animal studies have provided evidence that developmental exposure to lead induces AD-like pathology through BACE1 upregulation. Monkeys exposed to lead as infants had intracellular Aβ and amyloid plaques in the frontal association cortex and expression of APP, BACE1, and Sp1 transcription factor were upregulated in old age (23). DNA methylation appears to have an essential role in these latent effects. Developmental exposure of rats to lead results in upregulation of Aβ, APP and Sp1 transcription factor. BACE1 mRNA, protein expression, and activity were also upregulated later in life (24). Ashok et al. investigated the effects of developmental exposure of rats to individual metals (arsenic, lead, and cadmium) and their combination (at concentrations detected in groundwater of India) on the AD-pathology. They have shown that metals activated the synthesis of Aβ, which was mediated by an increase in APP and APP processing enzymes such as BACE1 and presenilin. Among individual metals, lead triggered maximum induction of Aβ (25).

Copper: Chronic environmental and occupational exposure to copper causes adverse health effects. The major source of copper is dietary intake from solid food and drinking water; exposure to polluted air is another minor source of copper (171,195). Copper and other essential metals such as iron and zinc are found in Aβ senile plaques and neurofibrillary tangles in AD (175,176). Copper exposure in young 3xTransgenic-AD mice led to an increase in the accumulation of Aβ, which was found to be mediated via the upregulation of BACE1 around Aβ plaques (26). Lin et al. reported that copper increased the transcription of APP and BACE1 in PC12 cells. The increased oxidative stress following copper exposure may be relevant to the expression of BACE1 levels in neurons (27). BACE1 has a copper-binding site in its cytosolic domain (48). Upregulation of BACE1 results in the reduced activity of superoxide dismutase-1 (SOD1), as BACE1 competes with SOD1 for the interaction with CCS (copper chaperone for superoxide dismutase-1 (SOD1)), an important protein that transports copper to SOD1 for its activation (48,49).

Iron: Brain iron increases with aging, and its accumulation is enhanced in the AD brain in regions such as the parietal cortex, motor cortex, and hippocampus (177–180,196–200). Iron is found in Aβ senile plaques and neurofibrillary tangles (175). The subtoxic concentration of ferrous ions increases APP-α-carboxyl-terminal fragment (APP-α-CTF) associations with A Disintegrin and metalloproteinase domain-containing protein-10 (ADAM10) and APP-β-CTF with BACE1 in PC12 cells. Levels of ADAM10 and BACE1 mRNA and B-cell lymphoma 2 protein expression was also increased (201). In another study, iron treatment impaired APP/Ferroportin 1 complex and enhanced binding of BACE1 to APP without significant changes in the level of BACE1 in microglia (28). $FeCl_2$ is a prooxidant molecule: it can stimulate oxidative stress. In differentiated human neuroblastoma cells, $FeCl_2$

exposure increased Aβ production by up-regulation of BACE1 and gamma-secretase, and down-regulation of alpha-secretase (29).

Arsenic: Arsenic toxicity is a health concern worldwide as millions of people are exposed to arsenic via drinking water. Epidemiological studies reported that long term arsenic exposure impairs learning and cognitive abilities (170,202). Developmental exposure of rats to arsenic, lead, and cadmium at concentrations detected in groundwater of India activated the synthesis of Aβ, which was mediated by an increase in APP and APP processing enzymes, such as BACE1 (25). Developmental arsenic exposure also induces behavioral deficits accompanied by an increase in BACE1 enzymatic activity, Aβ, and RAGE (203). Gene expression of APP, BACE-1, TNF-α, IL-1β, IL-6, COX-2, and MIF-1 increased significantly in rat cortical astrocytes exposed to a sub-toxic monomethylated metabolite of inorganic arsenic (204).

Zinc: Zinc exposure could also be a risk factor for AD. Zinc is found in Aβ senile plaques and neurofibrillary tangles in AD (176). APP and presenilin1 double transgenic mice treated with a high dose of zinc in drinking water had a significantly increased amount of zinc levels in the brain. APP expression, Aβ deposition, BACE1, and γ-secretase enzymes increased, whereas α-secretase related protein decreased on Zinc exposure in these mice (205). SH-SY5Y cells overexpressing human APPsw exposed to zinc also confirmed these results (205).

Manganese: Manganese is a trace element that is essential for brain function. Exposure to toxic concentrations of manganese occurring in occupational settings during mining, ore-processing, welding, and ferroalloy production has adverse health effects (172,173). Excessive manganese is neurotoxic and has been linked to neurodegenerative disorders (206). Manganese exposure increases the transcription of APP and BACE1 in PC12 cells (27). Guilarte et al. investigated the effect of chronic manganese exposure in non-human primates. Chronic manganese exposure increases a cellular stress response that leads to increased amyloid precursor-like protein1 protein expression and diffuse Aβ plaques in non-human primates (30).

Silver nanoparticles: Silver nanoparticles (AgNPs) are used as an antimicrobial and antifungal agent in food containers, clothing, pharmaceuticals, and electronics (168). Lin et al. reported that AgNPs accumulates in astrocytes and mouse neuroblastoma neuro-2a cells due to the disruption of tight junction proteins (32). AgNP exposure increases Aβ deposition in a neuronal and triple cell co-culture model of mouse endothelial cells, astrocytes, and neuroblastoma neuro-2a cells (31,32). In another study, AgNP exposure was shown to increase the protein expression of APP, BACE1, presenilin1, and presenilin 2 (32).

3.2. Pesticides, fungicides, and herbicides.

The use of pesticides, fungicides, and herbicides in household and agricultural areas has exponentially increased and polluted the environment, resulting in bioaccumulation of toxicants (207). Exposure to pesticides, fungicides, and herbicide is a risk factor for AD

(208). Meta-analysis of data from cohort and case-control studies have shown a positive association between pesticide exposure and AD (209).

Dichlorodiphenyltrichloroethane: Serum levels of the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT), and its metabolite dichlorodiphenyldichloroethane (DDE), were found to be elevated in AD patients (14). Experimental studies provided the mechanistic link for the association of DDT exposure with AD. Exposure of SH-SY5Y cells to DDE or DDT significantly increased APP levels (14). Another study showed DDT exposure augmented Aβ levels by increasing APP and BACE1 levels, and by reducing the clearance and degradation of Aβ in human neuroglioma H4-AβPPswe cells (33).

Rotenone: Rotenone is a well-known mitochondrial respiratory inhibitor. Rotenone could produce 1-methyl-4-phenyl pyridine (MPP+) and reproduces the features of Parkinson's disease (PD) (210,211). Rotenone could also be linked to AD. Rotenone induces mitochondrial dysfunction, mitochondrion-derived ROS formation, and Aβ generation (212). Xiong et al. reported that rotenone treatment elevates Aβ and APP in the retina. Mitochondrial respiratory inhibition and oxidative stress seen on rotenone treatment also facilitate BACE1 expression and activity (34).

Paraquat: Paraquat is a widely used herbicide around the world. Paraquat exposure has been linked to PD (213). Paraquat exposure induces oxidative stress and mitochondrial damage (214,215). Mild oxidative stress induced on paraquat treatment alters BACE1 subcellular compartmentalization to favor the amyloidogenic processing of APP in primary cortical cells (36).

Cocktails of fungicides residues: Residues of fungicides cyprodinil, mepanipyrim, and pyrimethanil are detected in many foodstuffs (216). Chronic exposure of transgenic (J20, hAPP Swedish/Indiana) mice to a cocktail of fungicide residues of cyprodinil, mepanipyrim, and pyrimethanil promotes the expression of BACE1 and impairs Aβ clearance. Incubated alone or in a cocktail, these fungicides bind to amyloid plaques *ex vivo* and promote Aβ peptide fibril formation *in vitro* (35).

3.3 Synthetic compounds

Perfluorooctane sulfonate: Perfluorooctane sulfonate (PFOS) is a per- and polyfluoroalkyl substance with extensive applications. PFOS is a major public health concern due to long environmental and biological half-lives (217). Our group has shown that PFOS produces dopaminergic neuropathology in *Caenorhabditis elegans* (218) and selectively decreases brain dopamine levels in Northern leopard frogs (*Rana pipiens*) on developmental exposure (219). Developmental PFOS exposure has also been linked to AD pathogenesis. Chronic PFOS exposure in mice increases APP and Aβ1–42 levels; significant up-regulation of BACE1 mRNA was also observed on exposure to a high concentration of PFOS (37).

Bisphenol: Bisphenol A (BPA) is an environmental endocrine-disrupting chemical. Human exposure to BPA is ubiquitous as it is one of the highest-volume chemicals produced

worldwide (220). Epidemiological studies have linked BPA to metabolic disorders (221,222). Accumulating evidence suggests that early-life exposure to BPA impacts neural development in humans (223–226). BPA exposure can also be a risk factor for AD. Prenatal exposure to BPA has been shown to increase the level of NF-κB protein and its target gene BACE1. The upregulation of BACE1 was observed only in males, and there were no significant changes in Aβ levels (227). BPA induced Aβ accumulation and disruption in insulin signalling in SH-SY5Y cells. AD-associated proteins, such as APP, BACE-1, β-CTF, α-CTF, and phosphorylated tau were increased after BPA exposure, and these effects were abrogated by insulin and rosiglitazone treatment (228).

Particulate matter: Fine and ultrafine particles may be translocated to systemic circulation and the brain through the nasal olfactory pathway (229). The possibility of initial involvement of the olfactory pathway in AD has caused speculation that some inhaled agents might be a risk factor for AD (230). AD-like pathology is seen in individuals residing in cities with high levels of air pollution (231). Chronic exposure of mice to concentrated air particulate matter (PM) (particles measuring 2.5 μm or smaller in diameter and collectively termed $PM_{2.5}$) increased BACE1 protein levels, APP processing, and Aβ 1–40 levels. This was correlated with an increase in cytokine level and cyclooxygenase-1 and cyclooxygenase-2 protein levels (39). In another study, $PM_{2.5}$ exposure increased BACE1, deteriorated spatial learning and memory, and synaptic function integrity. These effects were mediated by NF-κB p65-regulated downregulation of miR-574–5p, that targets BACE1 (38).

3.4 Dietary toxins.

The role of the diet in the etiology of AD has received recent attention (232,233). High-fat diets and diets rich in saturated free fatty acids, high glucose, and oxidation products of cholesterol are potential risk factors for AD. They are known to promote amyloidogenic cleavage of APP by BACE1 (234–239). Cooking and processing of food at a high temperature can produce toxic compounds, such as advanced glycation end products (AGEs), heterocyclic aromatic amines (HAAs), acrylamide, and acrolein (240–244). The potential role of dietary toxins is being studied for AD relevance as they are encountered in higher doses and more frequently through one's life span compared to other environmental contaminants (232,245).

Advanced glycation end products: AGEs are naturally present in uncooked animal-derived foods; high-temperature cooking accelerates the formation of new AGEs within these foods. AGEs are formed through the Maillard reaction between the aldehyde group of glucose and the amino group of proteins (246,247). AGEs are also formed as a part of normal metabolism within the body, and AGEs accumulate due to certain dietary habits, aging, and in sporadic AD (15). Diets high in AGEs induce AD-like pathology in mice. Transgenic 2576 mice that received a diet high in AGEs had significantly higher levels of oxidative stress, AGEs, the receptor for advanced glycation end products (RAGE), and insoluble Aβ in the hippocampus (41,248). Guglielmotto et al. showed that AGEs such as pentosidine and glyceraldehydes-derived pyridinium (GLAP) upregulate BACE1 mRNA and protein expression through RAGE activation and the consequent activation of NF-κB (41). BACE1 is upregulated in cells overexpressing RAGE and in RAGE-injected brains of

Tg2576 mice (40). AGEs/RAGE axis upregulate BACE1 expression via reactive oxygen species (ROS) production (40,41), and activation of nuclear factor of activated T-cells 1 (NFAT1) (40) resulting in Aβ production and deposition in the brain.

Heterocyclic aromatic amines: Heterocyclic aromatic amines (HAAs) are primarily formed during high-temperature meat cooking (240,241). HAAs are formed through the Maillard reaction between amino acids and sugars, producing pyrimidine, pyridine, or pyrazine, which later reacts with creatine in a heat-dependent reaction (240,241). PhIP (2-Amino-1-methyl-6-phenylimidazo (4,5-b)pyridine) is the most abundant and extensively studied HAA isolated from the crust of cooked meat, and its levels may reach ~15 micrograms/kg uncooked meat (241,249,250). Studies from our lab have reported that PhIP generates reactive free radicals, leading to an increase in the accumulation of ROS (43,251,252). Recently, our group showed that PhIP exposure for acute, sub-acute, and sub-chronic time points produced oxidative damage and alterations in synaptic proteins. Our study demonstrated that sub-chronic PhIP exposure promotes Aβ aggregation by increasing the levels of BACE1, APP, and oxidative damage (43).

Acrolein: Acrolein is a dietary aldehyde that is present in high concentrations in alcoholic beverages, water, cheese, donuts, coffee, tobacco smoke, industrial waste, and automobile exhaust. It is also formed during deep frying of vegetable and animal fats (253). *In vivo*, acrolein is formed by the metal-catalyzed oxidation of polyunsaturated fatty acids (254). Acrolein is increased in the amygdala and hippocampus/parahippocampal gyrus in AD patients (16). Chronic acrolein exposure increased protein levels of APP, BACE1, RAGE, and decreased A-disintegrin and ADAM levels in rats (44,45). Acrolein activated MAPK signalling pathways and altered the levels of AD-associated proteins ADAM-10, BACE-1, and RAGE in HT22 murine hippocampal neuronal cells. Inhibitors of MAPK signalling pathways attenuated these effects (255). These effects were associated with oxidative stress, ROS accumulation, glutathione depletion, decreased SOD, and an elevation of MDA (256,257).

4. Exposures and mechanisms that lead to upregulation of BACE1 expression and activity:

Commonly examined detrimental processes of oxidative stress, mitochondrial respiratory inhibition, and direct physical interaction of toxicants with BACE1 are likely important in neurotoxicant induced alteration in BACE1 expression and activity. An increase in BACE1 and subsequent increase in Aβ pathology induced by most of these neurotoxicants was associated with oxidative stress (21,27,34,36,40–43). Oxidative stress has been shown to decrease the activity of α-secretase while promoting the expression and activity of BACE1 (29). Treating primary cortical neurons and HSV-APP cells with hydrogen peroxide (H_2O_2) increases BACE1 protein and its products (CTFs), in primary neurons, and BACE1 protein and Aβ in HSV-APP cell (262). Inactivating BACE1 with siRNA1 lowers the BACE1, CTF, and Aβ levels following H_2O_2 treatment. Treating APPwt and APPsw cells with antioxidants reduces superoxide anions and BACE1 activity, indicating that, at least in part, ROS-dependent BACE1 alteration is implicated in Aβ production (212,262). Oxidative

stress is also an early event in AD (263); oxidation products, such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA), increases in AD brain tissue. A significant correlation exists between BACE1 activity and markers of oxidative stress in AD, supporting the hypothesis that a direct connection exists between oxidative stress and BACE1 in sporadic AD (53,264,265).

Environmental neurotoxicants upregulate the expression and activity of BACE1, with some increasing BACE1 mRNA level (21,22,24,27,37,41,185,201,204), while others do not affect BACE1 mRNA (35,266). Transcriptional and post-transcriptional control is implicated in BACE1 modulation by oxidative stress (29,266–269). Alterations in BACE1 expression and enzyme activity induced by oxidative stress are mediated through the interplay of multiple signaling pathways (Figure 1).

Oxidative stress induced by H_2O_2 has been shown to increase BACE 1 by potentiating the BACE1 promoter activity and upregulating BACE1 transcription (270). Transcription factors such as NF-κB, NFAT1 and Sp1 have been reported to be activated after exposure to environmental neurtoxicants (23,24,40–42,227). Tamagno et al. reported that the activation of SAPK signaling is involved in oxidant-induced upregulation of BACE1 expression. Exposure of NT2 neurons to HNE upregulates expression of BACE1 and increases intracellular Aβ. HNE-dependent upregulation of BACE1 expression was found to be mediated by activation of c-junN-terminal kinase (JNK) and p38 mitogen-activated protein kinases (p38MAPK) (267). Inducers of JNKs such as hydrogen peroxide increase BACE1 protein level, and inhibition of JNKs abolished this BACE1 induction, confirming that JNK pathways mediate this response (29,267,268). Phosphatidylinositol-3-kinase (PI-3K)/Akt pathway and the extracellular signal-regulated MAP kinase (ERK) pathway are also involved in oxidative stress-mediated BACE1 upregulation. Upregulation of BACE1 protein correlated with increased levels of phosphorylated Akt and ERK1/2 in glutathione peroxidase 4+/− (Gpx4+/−) mice (266). Oxidative stress also alters BACE1 expression at the translational level, and it is mediated by the double-stranded RNA dependant protein kinase (PKR)-eukaryotic translation initiation factor-2α (eIF2α) pathway. A significant correlation was found between BACE1 levels and eIF2α activation in human AD brains. Inhibition of PKR by chemical inhibition or by siRNA significantly attenuates BACE1 protein (269).

Redistribution of BACE1 also facilitates amyloidogenic processing of APP; mild oxidative stress has been reported to promote amyloidogenic processing by redistributing the BACE1 to organelles having optimal environment for BACE1 activity (36). Tan et al. have suggested that depending on the stress intensity inflicted on neurons, oxidative stress may exert a dual effect on BACE1. Mild oxidative stress that does not induce cell death does not increase BACE1 mRNA and protein. Instead, mild oxidative stress promotes amyloidogenic processing by redistributing BACE1 to the trans-Golgi network and early endosomes, which provide an acidic environment an optimal for BACE1 activity. In contrast, in sustained or severe oxidative stress, apoptotic mechanisms would become activated, and BACE1 expression would increase, thereby promoting a more significant Aβ production (36). Hypoxia induction caused a similar biphasic increase of BACE1 (74). However, other studies have also shown the accumulation of BACE1 protein in the absence of cell death (271).

Mitochondrial dysfunction has been suggested to have an early and perhaps a causative role in AD pathogenesis (272–275). AD mice treated with a complex I inhibitor or mice with a genetic defect in complex I, or, showed enhanced Aβ levels *in vivo* (212). BACE1 expression and its activity appear to be coupled to mitochondrial function. Mitochondrial respiratory inhibition and energy inhibition elevates BACE1 levels and activity (276). Neurotoxicants such as rotenone is a known mitochondrial complex I inhibitors; mitochondrial complex inhibitors and inhibitors of succinate dehydrogenase have been shown to alter BACE1 (34,36). Applications of rotenone, other mitochondrial complex inhibitors, and inhibitors of succinate dehydrogenase increase BACE1 proteins and activity, and Aβ40 levels (34). Paraquat, a known mitochondrial neurotoxicant, induced mild oxidative stress and altered BACE1 subcellular compartmentalization to favor the amyloidogenic processing of APP (36). A strong negative correlation was found between BACE1 and cytochrome c oxidase or succinate dehydrogenase activity at the first synapse on the olfactory pathway (277). Increased BACE1 levels and activity are observed in a variety of experimental conditions likely involving mitochondrial stress and energy disruption (270,276,278). Mitochondrial respiratory inhibitors are generally considered to cause oxidative stress (210,279); it is not possible to differentiate energy inhibition from oxidative stress. Therefore, oxidative stress might be a common element in increasing BACE1. Mitochondrial proteins are also likely important in BACE1 regulation. Over expression Thioredoxin-2 (TXN2), a mitochondrial protein that has a critical role in the scavenging ROS in mitochondria (280) decreases BACE1 transcription; while silencing increases BACE1 transcription. Further, TXN2 knockdown in HEK-APP and SH-SY5Y-APP cells increased the mRNA and protein levels of BACE1 (281). BACE1 also contributes to mitochondrial dysfunction. Accumulation of β-cleaved C-terminal fragment-99 and APP through BACE1 dependent mechanism contributes to mitochondrial dysfunction, and deletion of BACE1 ($BACE1^{+/-}$) rescued mitochondrial function in 5XFAD mice (282).

Metals can directly interact with BACE1 to modulate APP processing and Aβ release. Biophysical studies have shown an interaction between BACE1, calcium (64), and copper (48,49,283). BACE1 is described as a copper-binding protein; it has a copper-binding site in its cytosolic domain (48,49,283). The cytoplasmic domain of BACE1, a 24-residue peptide corresponding to the C-terminal domain of BACE1, binds a single copper(I) atom with high affinity through cysteine residues. The cytoplasmic domain of BACE1 interacts with CCS that delivers copper to BACE1. Cytosolic CCS forms a stable association with membrane-bound BACE1; CCS protein and BACE1 have been shown to move together in axons of rat primary cortical neurons (48,49). CCS is also essential for the activation of SOD1. CCS binds copper (I) through residues in domains I and III. This enhances the binding of CCS to Zn-SOD1, leading to the formation of a non-covalent heterodimeric CCS–SOD1 complex via domain II of CCS (284). BACE1 interacts with the domain I of CCS, preventing the formation of copper-bound CCS and thereby inhibiting the activation of SOD1. Overexpression of BACE1 results in the reduced activity of SOD1, as BACE1 competes with SOD1 for interaction with CCS (48,49). This interaction provides a link between metal homeostasis and oxidative stress in AD. Calcium also binds to BACE1 and alters its activity. The intracellular domain of BACE1 contains a metal-binding motif Cys-Xaa-Xaa-Cys, one additional cysteine, and potential Calcium-binding residues. Binding studies have provided

evidence that calcium binds to BACE1 with high affinity. Low concentrations of calcium can increase the enzymatic activity of BACE1, thereby increasing Aβ production (64). This calcium-BACE1 interaction and generation of the Aβ peptide are supported by the calcium dysregulation hypothesis in aging and AD (285–289).

5. Theoretical BACE1 targets important to neurotoxicity:

Not much is known about the susceptibility of BACE1 catalytic domain and other domains to neurotoxicants. The BACE1 lumenal extension ends are attached by two disulfide bonds connecting directly to the catalytic domain. A span of approximately 11 amino acids attach the catalytic domain of the BACE1 to the lipid membrane, C-terminally of the last disulfide bonded cysteine of the lumenal extension (61). The six Cys residues in these ectodomain form three intramolecular disulfide linkages (Cys(216)-Cys(420), Cys(278)-Cys(443), and Cys(330)-Cys(380)) (62). Fischer et al. reported that the disulfide bonds between Cys(330)-Cys(380) play an important role in the catalytic domain of BACE1 and the other two disulfide bonds are less important for APP processing activity (290). Simulations studies have shown that the absence of disulfide bonds has been shown to weaken/change the interaction strength of BACE1 inhibitors with some residues in the interaction network of BACE1-inhibitors (291). This disulfide bond could be possible a neurotoxic target as disulfide bond formation in other proteins has been reported to be impaired in certain conditions such as hypoxic (292), on exposure to nicotine (293). Koelsch has hypothesized that under hypoxic conditions, two disulfide bonds that attach both ends of the lumenal domain in BACE1 might be incompletely formed, leading to release of the BACE1 catalytic domain away from the lipid bilayer membrane, allowing possibly a greater degree of freedom, increased access to the substrate, and increased activity (294). While plausible, it should be noted that this hypothesis has not yet been tested.

6. BACE1- a potential biomarker and therapeutic target for sporadic AD:

A significant increase in BACE1 level and activity is found in CSF of subjects with MCI and *ApoE ε4* genotype carriers with MCI (153,155). Plasma BACE1 activity is also increased in MCI converters and probable AD patients (154). Given the reported 1) alteration of BACE1 expression and/or activity in environmental neurotoxicant induced AD-like pathology in experimental studies and subjects with MCI and *APOE ε4* carriers with MCI are at higher risk of developing AD, 2) peripheral BACE1 could be an indicator of MCI and AD risk, and 3) ease of measuring BACE1 in plasma and CSF, and novel PET radioligand [18F]PF-06684511 for in vivo imaging of BACE1; BACE1 has promising potential for use as a clinical diagnostic biomarker for screenings during the presymptomatic stages and monitoring the disease progression in sporadic AD (153–155,295–298).

The important role of BACE1 in the amyloidogenic pathway and modulation of BACE1 by many risk factors associated with sporadic AD has led to the exploration of the potential use of BACE1 as a therapeutic target for AD. BACE1 inhibitors have shown therapeutic effects in AD animal models; however, many BACE1 inhibitors have failed in different phases of clinical trials due to safety concerns (56,299–301). BACE1 null/knockout mice exhibit hypomyelination (302), a significant increase in astrogenesis with a corresponding decrease

in neurogenesis in their hippocampi during early development (110), abnormal neuronal clustering in the dentate gyrus (303), and axonal organization defects in the hippocampus (304). Toxicity induced by BACE1 inhibitors and the physiological role of BACE1 makes it difficult to use BACE1 as a treatment for AD.

6. Conclusion and future research:

Environmental neurotoxicants such as metals, pesticides, and dietary toxins have been shown to accumulate in the AD patient; experimental studies *in vivo* and *in vitro* have strengthened knowledge about mechanisms associated with it. BACE1 is the initiating and putatively rate-limiting enzyme in Aβ generation. BACE1 expression and/or enzymatic activity are altered in aging, MCI, *ApoE ε4* genotype carriers with MCI, and after exposure to various environmental neurotoxicants, indicating that BACE1 is a crucial molecular link between these risk factors and sporadic AD pathogenesis. Although experimental studies have highlighted that oxidative stress, mitochondrial respiratory inhibition, and direct physical interactions might be a common mechanism in environmental neurotoxicant induced BACE1 alterations, the mechanism associated with many environmental neurotoxicants induced BACE1 alteration is still not clearly known. Given the key role that BACE1 has in risk factors associated-AD, future studies are needed to clearly understand these mechanisms. BACE1 undergoes physical interactions with copper and calcium; other metals and reactive environmental neurotoxicants should also be studied to determine if they directly interact with BACE1 to activate it or if they have a neurotoxic target in BACE1. Similar to findings in AD patients, *in vivo* and *in vitro* studies also report both normal and elevated BACE1 mRNA along with increased protein expression and/or activity on exposure to environmental neurotoxicants. There is inconsistency in BACE1 measurement; some studies just analyze mRNA or protein expression and/or enzymatic activity. Measuring mRNA, protein expression, activity, and the degradation pathway of BACE1 will help better understand the mechanism associated with BACE1 alteration.

Despite the challenges in BACE1 inhibitor development and failures of BACE1 inhibitor clinical trials, BACE1 inhibitor development should continue by taking into consideration the optimal timing and dose for treatment. There is substantial data indicating the important role of BACE1 in sporadic AD and proving BACE1 inhibitors as disease-modifying agents. Future studies should focus on understanding the physiological functions of other BACE1 substrates and generating inhibitors with an APP selective BACE inhibitory effect. Correlation of BACE1 with disease severity and ease of measuring of BACE1 in plasma and CSF and through *in vivo* imaging makes BACE1 an ideal candidate for use as a clinical diagnostic biomarker, together with the existing suite of amyloid and tau biomarkers, for screening the presymptomatic stages and monitoring the disease progression in sporadic AD. BACE1 could also be used as a biomarker in drug development.

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8. Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Abbreviations:

MPP+	1-methyl-4-phenyl pyridine
Aβ	Amyloid beta
ADAM10	A Disintegrin and metalloproteinase domain-containing protein-10
AD	Alzheimer's disease
APOE4	Apolipoprotein
APP	Amyloid beta precursor protein
APP-α-CTF	APP-α-carboxyl-terminal fragment
AICD	APP intracellular domain
AGE	Advanced glycation end products
BACE1	β-Site amyloid precursor protein cleaving enzyme 1
BPA	Bisphenol A
CCS	Copper chaperone for superoxide dismutase-1
CTF83	C-terminal fragment of APP
CTF99	C-terminal fragment
CSF	Cerebrospinal fluid
DDT	Dichlorodiphenyltrichloroethane
DDE	Dichlorodiphenyldichloroethane
ERK	extracellular signal-regulated MAP kinase
eIF2α	Eukaryotic translation initiation factor-2α
GLAP	Glyceraldehydes-derived pyridinium
H_2O_2	Hydrogen peroxide
HAAs	Heterocyclic aromatic amines
HIV	human immunodeficiency virus
HNE	4-hydroxynonenal
JNK	c-junN-terminal kinase

MDA	Malondialdehyde
MCI	Mild cognitive impairment
NMDA	N-Methyl- d-aspartic acid or N-Methyl- d-aspartate
NF-κB	Nuclear factor κB
PFOS	Perfluorooctane sulfonate
PI-3K	Phosphatidylinositol-3-kinase
PhIP	2-Amino-1-methyl-6-phenylimidazo(4,5-b)pyridine
PM	Particulate matter
ROS	Reactive oxygen species
RAGE	Receptor for advanced glycation end products
SOD1	superoxide dismutase-1
AgNPs	Silver nanoparticles

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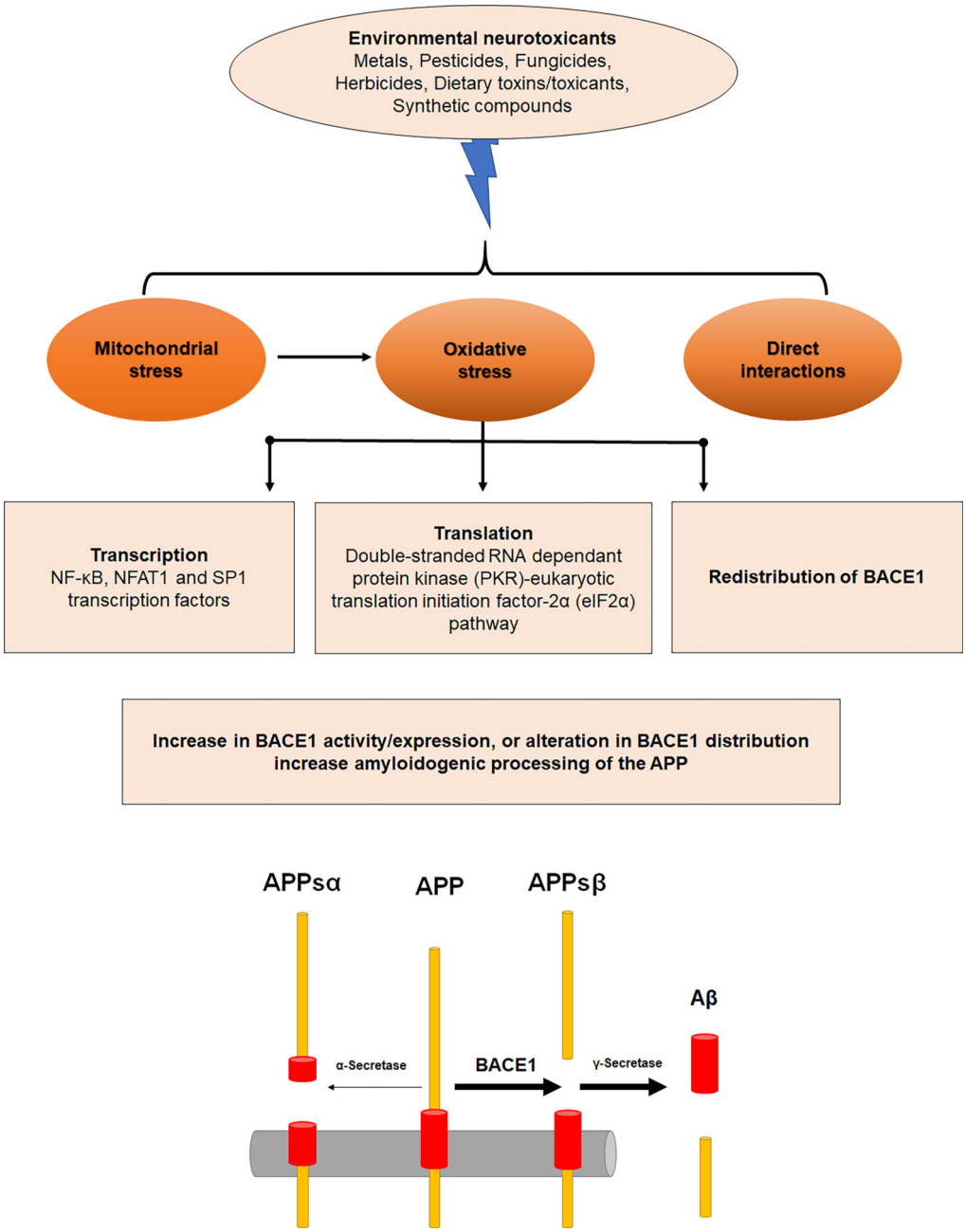

Figure 1: Neurotoxic targets that lead to upregulation of BACE1 expression and activity:

BACE1 can be an important neurotoxic target in AD-like neurotoxicity induced by environmental neurotoxicants such as metals, pesticides, fungicides, herbicides, dietary toxins/toxicants and synthetic compounds. Environmental neurotoxicants increase BACE1 expression and activity by inducing mitochondrial stress, oxidative stress or by direct interaction. Oxidative stress induced by environmental neurotoxicants can increase transcription and translation of BACE1 or induce redistribution of BACE1 to increase amyloidogenic processing of APP and increase amyloid beta production.

Table 1.

Summary of effects of environmental exposures on BACE1.[†]

Exposure	Alterations in BACE1	References
Metals		
Aluminium	Aluminium exposure increased BACE1 activity in aged New Zealand rabbits and rats, elevated BACE1 levels in rats, and increased BACE1 mRNA in rats and SH-SY5Y cells	(18–22,184–186)
Arsenic	Developmental exposure of rats to arsenic increased BACE1 enzymatic activity and BACE1 protein; gene expression of BACE-1 increased in astrocytes exposed to arsenic	(25,203,204)
Copper	Copper exposure upregulated BACE1 around Aβ plaques in mice and increased the transcription of BACE1 in PC12 cells BACE1 has a copper-binding site in its cytosolic domain; it competes with SOD1 for the interaction with CCS	(26,27,48,49)
Iron	Ferrous ion exposure increased BACE1 mRNA and protein expression in PC12 cells and neuroblastoma cells. Iron treatment enhanced binding of APP to BACE1, without significant changes in the level of BACE1 in microglia.	(28,29,201).
Lead	Developmental exposure to lead increased expression of BACE1 in monkeys while BACE1 mRNA and protein expression and BACE1 activity were also upregulated in rodents.	(23–25,258–260)
Manganese	Manganese exposure increased the transcription of BACE1 in PC12 cells	(27)
Silver nanoparticles	Silver nanoparticle exposure increased the protein expression of BACE1	(32)
Zinc	Zinc exposure increased BACE1 in mice and SH-SY5Y cells	(205)
Pesticides, fungicides, herbicides		
DDT	DDT exposure increased BACE1 levels in SH-SY5Y cells	(33)
Paraquat	Paraquat treatment altered BACE1 subcellular compartmentalization	(36)
Rotenone	Rotenone treatment facilitated BACE1 expression and activity	(34)
Residues of cyprodinil, mepanipyrim, and pyrimethanil	Cocktail of fungicide residues promoted the expression of BACE1	(35)
Synthetics		
BPA	BPA exposure has been shown to increase the level of BACE1 in SH-SY5Y cells	(227,228)
PFOS	Chronic high concentration PFOS exposure in mice increases BACE1 mRNA	(37)
Particulates	Chronic exposure of mice to particulate matter increased BACE1 protein levels	(38,39,261)
Dieatary toxins/toxicants		
Acrolein	Chronic acrolein exposure increased protein levels of BACE1 in rats and HT22 cells	(44,45,193,255–257)
Advanced glycation end products	Pentosidine and GLAP upregulates BACE1 mRNA and protein expression	(43)
Heterocyclic aromatic amines	PhIP exposure for acute, sub-acute, and sub-chronic time point increased BACE1 in mice	(43)

† Abbreviations: BPA: Bisphenol A, CCS: Copper chaperone for superoxide dismutase-1 (SOD1), DDT: Dichlorodiphenyltrichloroethane, PFOS: Perfluorooctane sulfonate, PhIP: 2-Amino-1-methyl-6-phenylimidazo (4,5-b)pyridine