The Role of Mitochondrial Aldehyde Dehydrogenase 2 (ALDH2) in Neuropathology and Neurodegeneration

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Abstract-

Aldehydes-induced toxicity has been implicated in many neurodegenerative diseases. Exposure to reactive aldehydes from (1) alcohol and food metabolism; (2) environmental pollutants, including car, factory exhausts, smog, pesticides, herbicides; (3) metabolism of neurotransmitters, amino acids and (4) lipid peroxidation of biological membrane from excessive ROS, all contribute to 'aldehydic load' that has been linked to the pathology of neurodegenerative diseases. In particular, the α, β-unsaturated aldehydes derived from lipid peroxidation, 4-hydroxynonenal (4-HNE), DOPAL (MAO product of dopamine), malondialdehyde, acrolein and acetaldehyde, all readily form chemical adductions with proteins, DNA and lipids, thus causing neurotoxicity. Mitochondrial aldehyde dehydrogenase 2 (ALDH 2) is a major aldehyde metabolizing enzyme that protects against deleterious aldehyde buildup in brain, a tissue that has a particularly high mitochondrial content. In this review, we highlight the deleterious effects of increased aldehydic load in the neuropathology of ischemic stroke, Alzheimer's disease and Parkinson's disease. We also discuss evidence for the association between ALDH2 deficiency, a common East Asian-specific mutation, and these neuropathologies. A novel class of small molecule aldehyde dehydrogenase activators (Aldas), represented by Alda-1, reduces neuronal cell death in models of ischemic stroke, Alzheimer's disease and Parkinson's disease. Together, these data suggest that reducing aldeydic load by enhancing the activity of aldehyde dehydrogenases, such as ALDH2, represents as a therapeutic strategy for neurodegenerative diseases.

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INTRODUCTION

The brain consumes and generates more ATP than any other organ [1,2]; The brain represents only 2% of the human body mass, yet it consumes ~20% of available oxygen and 25% of the body's glucose to generate ATP [3-5]. Such high energy demand is met with a high density of mitochondria in neurons and a constant generation of reactive oxygen species (ROS) as byproducts of oxidative phosphorylation [6-8]. In addition to functioning as the power house of the cell, mitochondria are critical for many important biological functions such as amino acids, and steroids synthesis, and calcium homeostasis[7-10]. Healthy mitochondria can prevent ROS-induced damage by providing sufficient anti-oxidant capacity and further metabolizing excessive ROS-induced α, β-unsaturated carbonyls. However, ROS levels can exceed that capacity, thus damaging the mitochondria and damaged

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mitochondria induce necrotic and apoptotic pathways and cell death [6,7,11]. Further, reduction in cerebral metabolism correlates with decreased activity of mitochondrial ATP generation-related enzymes, such as the pyruvate dehydrogenase complex, and alpha-ketoglutarate dehydrogenase complex (KGDHC) [12].

One of the consequences of ROS imbalance and excessive oxidative stress is the production of reactive and toxic aldehyde by lipid peroxidation from the membrane-rich mitochondria. Aldehydes are reactive and electrophilic molecules that readily form adducts with macromolecules such as DNA, proteins and enzymes. Aldehydes are also ubiquitous in the environment. Toxic aldehydes can be found in car exhaust, chemical manufacture processes, pesticides, cosmetics, smog, cigarette smoke, food and beverages [13,14] and from endogenous metabolism of neurotransmitters, amino acids and lipids[15]. Some examples of these highly reactive aldehydes include lipid peroxidation-derived α,β-unsaturated aldehydes 4-hydroxynonenal (4-HNE), malondialdehyde, acrolein, acetaldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL, MAO product of dopamine) and 3,4-dihydroxyphenylglyc oaldehyde (PDPEGAL, MAO produce of norepinephrine). One of the more studied reactive aldehyde is 4-HNE. Multiple studies have shown that when 4-HNE levels are increased excessively, a number of cellular functions are compromised, leading to cell death. Numerous proteins are modified by 4-HNE, including plasma membrane ion and nutrient transporters, receptors for growth factors and neurotransmitters, mitochondrial electron transport chain proteins, protein chaperones, proteasomal proteins, and cytoskeletal proteins and 4-HNE adduction leads to functional impairment of these proteins [16-18]. 4-HNE can also regulate protein kinases such as MAPK, ERK, and JNK indirectly, functioning as a signaling molecule or by direct with the kinase's active domains [19-21]. Notably, large portions of the damaged proteins reside in mitochondria [22]. These include critical proteins in respiratory chain and mitochondrial metabolism, such as aconitase, ATP synthase, several dehydrogenases in the Kreb cycle and aldehyde hydrogenases [23-25]. Exposure to both biogenic and xenogenic aldehydes contribute to the total aldehydic load in the neurons. This excessive aldehydic load and mitochondrial dysfunction lead to neurological diseases, including Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), dementia, ataxia, seizure, hypertension-induced encephalopathy and ischemic stroke [3,6,7,26-29].

Aldehyde dehydrogenases 2 (ALDH2) is one the of 19 ALDH isozymes in human cells that are essential for the metabolism and detoxification of a wide range of endogenous and exogenous aldehyde substrates [30]. ALDH2 is encoded by a nuclear gene, but is transported and function in the mitochondrial matrix. ALDH2 is most efficient in metabolizing short chain aliphatic aldehydes, such as acetaldehyde and propionaldehyde [31]; it is the rate-limiting enzyme in the ethanol metabolism, oxidizing acetaldehyde to acetic acid both in the liver and other tissues, including in brain [30]. ALDH2 also participates in metabolizing other biogenic aldehydes in the brain, including 4-HNE, DOPAL and DOPEGEL [32,33]. Accumulation of these endogenous aldehydes and inhibition of ALDH2 by these reactive increases vulnerability aldehyde-induced damage [34,35]. Importantly, ALDH2 is widely expressed in the frontal and temporal cortex, hippocampus, mid-brain, basal ganglia and cerebellum, in both glial cells and in neurons [36-38], highlighting its crucial function in protecting the neurons in the brain and the spinal cord.

Considering the critical role of this enzyme, it is important to highlight the fact that ALDH2 deficiency is one of the most common enzymopathy in humans, affecting an estimated 560 million or 8% of the world population [39]. ALDH2 deficiency is caused by a structural polymorphism at amino acid position 487. A substitution of lysine for glutamic acid at this position results in a transition of G (allele *1) to A (allele *2) and a dramatic reduction of the enzyme's catalytic activity. The ALDH2 alleles encoding the active wildtype monomer is designated as ALDH2*1 and the inactive monomer as ALDH2*2 [30]. In human, ALDH2*1/*2 heterozygous and ALDH2*2/*2 homozygous carriers have 17-35% and 1-3% residual ALDH2 enzyme activities, respectively [40,41]. Such a reduced enzyme activity leads to the well-known phenotype of Asian alcohol facial flushing, tachycardia, palpitation, vomiting and headache due to the elevation of blood acetaldehyde level even after a moderated intake of alcoholic beverage [42,43]. ALDH2 deficiency is East Asian-specific and is common in China, Japan, Korea, Taiwan and Singapore. The origin of the E487K mutation has been

traced back to nearly 3,000 years ago; it probably occurred in the ancient Pai-Yuei tribe that populated South China [44,45]. Epidemiological studies demonstrate that Taiwan is among the highest ALDH2 deficiency prevalence countries, with 43-45% of its residents carrying the ALDH2*2 allele [46,47].

Acetaldehyde is a Group 1 carcinogen according to WHO classification [48,49]. A great increase in risk of developing upper aerodigestive track cancers from exposure to acetaldehyde from alcohol consumption has been clearly associated with ALDH2*2 enzyme deficiency among the East Asians [39,50,51]. However, risk assessment for neurological and neurodegenerative diseases among ALDH2*2 deficient subjects due to the exposure to acetaldehyde and other reactive aldehyde has not yet well studies. This review will focus on the role of ALDH2 in ischemic stroke, Alzheimer's disease and Parkinson's disease as recent publications suggest a protective role of ALDH2 in these pathological conditions, indicating that enhancing ALDH2 activity may provide a new therapeutic strategy [30,52].

We will discuss the use of a novel small molecule Aldehyde dehydrogenase 2 activator, Alda-1, in several animal models of neurological diseases. Alda-1 (N-(1,3-Benzodioxol-5-ylmethyl)-2,6-dichlorobenzamide) was discovered in our laboratory by high throughput screening for ALDH2-specific agonists [41]. Alda-1 represents a new class of small molecule ALDH2 activators that directly enhance the catalytic activity of the enzyme and importantly also protect the enzyme against inactivation by adduct formation with its relative aldehyde substrates [41]. Furthermore, Alda-1 is effective in restoring the catalytic activity of the defective ALDH2*2 mutant enzyme by binding site at catalytic tunnel of the enzyme and correcting the structural defect of the mutant enzyme [41,53].

ISCHEMIC STROKE

The importance of ALDH2 and its activation by Alda-1 in enhancing cardiac function and protection again cardiac ischemia reperfusion injuries has been well established [34,41,54-57]. Because of the many similarities in the molecular mechanism of injuries between myocardial infarction and cerebral stroke, the role of ALDH2 in stroke was also explored.

In an epidemiological study, the ALDH2*2 allele frequency was significantly lower among stroke patients who were heavy drinkers due to the deterring effect of ALDH2*2 against alcoholism. Whereas, among the non-heavy alcohol drinking stroke patients, there was no difference in ALDH2 allele frequency as compared to the healthy control indicating that ALDH2*2 alone may not be a risk factor for stroke [58]. On the other hand, in small study, ALDH2 heterozygous genotype appeared to contribute as a risk factor of stroke in non-alcoholic hypertensive patients after a single heaving binge drinking [59]. No statistical difference was found for the association of ALDH2 genotype and the presence of lacunar infarct in a Japanese study. But, among men with lacunar infarct, ALDH2*2 genotype was associated with a smaller number of lesions [60]. Furthermore, in a more recent study, ALDH2*2 allele was clearly associated with a higher risk in Chinese women for cerebral infarction [61]. When post-stroke epilepsy susceptibility was considered, ALDH2*2 genotype significantly increased risk of post-stroke epilepsy as compared with patients with ischemic strong alone in Chinese patients [62]. In this study, plasma 4-HNE levels were higher in both stroke patients and patients with post-stroke epilepsy and this increase was even more pronounced in patients with the ALDH2*2 allele. Increased plasma 4-HNE levels were consistently observed in another group of Chinese ischemic stroke patients as compared to healthy controls [63]. Persistent elevated plasma 4-HNE were observed even up to 6 months after the initial ischemic stroke [64]. These studies suggest a potential use of plasma 4-HNE as a biomarker for ischemic stroke, perhaps more in importantly in ALDH2*2 subjects.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a late onset, progressive disease, characterized by neurodegeneration and impaired cognitive functions [65]. AD is becoming more prevalent as lifespan in the world increases [66,67]. An estimated 5.4 million Americans have Alzheimer's disease and is projected to grow to 13.8 million in the United States alone by 2050. A characteristic feature of AD is the presence of extracellular amyloid plaques composed of the amyloid β peptides (mainly $A\beta_{1-40}$ and $A\beta_{1-42}$) in the brain [66,67]. AD is also characterized by the presence of three pathological

hallmarks: synapse loss, extracellular senile plaques (SP) and intracellular neurofibrillary tangles (NFTs). Most AD cases occur sporadically, while inheritance of certain susceptibility genes enhances the risk. Familial AD, which represents a minority of AD (an estimated than 1%), is caused by mutations in genes encoding for either the amyloid β precursor protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2). Despite this knowledge, the etiogenesis of sporadic AD remains largely unclear and several competing hypotheses have been proposed. Further, none of the pharmacological strategies presently in use for AD slows or halts the neuronal loss that cause Alzheimer's symptoms.

Both structural and functional abnormalities of mitochondria in AD have recently been observed [68-75] and mitochondrial dysfunction occurs as early event in mice bearing the human Swedish and London mutations in APP. High levels of ALDH2 are found in the frontal and temporal cortex, hippocampus, mid-brain, basal ganglia and cerebellum, primarily in glial cells and neurons [76]. Further, in cerebrum and hippocampus, ALDH2 was localized to glia and to senile plaques. ALDH2 activity was found to be significantly increased in the putamen of patients suffering from AD, as compared with control subjects [76]. Multiple studies report on the accumulation of 4-HNE protein adducts as an early event in the pathogenesis of AD. Some studies show that 4-HNE induces neuronal death and synaptic dysfunction as well as inhibit neurite outgrowth. Protein-bound 4-HNE as well as free 4-HNE, TBARS, MDA, and isoprostanes (F2isoP) levels are found at higher levels in plasma, urine, and CSF in AD and amnestic mild cognitive impairment (aMCI-earliest form of AD), as compared with healthy subjects [77-81]. Brains from both AD and aMCI subjects show increased levels of protein carbonyls in AD in affected brain regions, while the cerebellum, largely devoid of Aβ pathology, remained relatively untouched [12,82-84]. In the early stages of Alzheimer's disease, 4-HNE may impair synaptic communication between neurons as suggested by studies showing that Aβ and 4-HNE impair coupling of muscarinic acetylcholine receptors to the GTP-binding protein Gq11. Also, 4-HNE hastens Aβ protofibril and curved fibril formation, but precludes the formation of long straight fibrils formed in the absence of 4-HNE [85]. 4-HNE covalently modifies $A\beta_{1-40}$ via 1,4-conjugate addition, and can crosslink Aβ peptides to each other, putatively by subsequent Schiff base formation [85]. The accumulation of 4-HNE-modified amyloid β-peptides has been shown to inhibit the proteasome, and the resulting accumulation of ubiquitinated modified proteins leads to a pro-inflammatory response amplifying neurodegeneration [86]. 4-HNE has been reported to impair Na^+/Ca^{2+} pumps and glucose and glutamate transporters, leading to ionic and energetic disturbances ultimately neuronal cell death [87,88]. Thus, disease-modifying strategies targeting 4-HNE levels, such as activators of ALDH2, might benefit AD patients.

The above data are consistent with the observation that in a meta-analysis, ALDH2*2 genotype was associated with increased AD risk among East Asia men [89]. ALDL2*2 deficiency was also shown to influence the risk for late-onset Alzheimer's disease (LOAD) in a case-control study in Japanese population (48.1% versus 37.4%,) [90]. In the same population, ALDH2*2 allele increased the risk for LOAD independently of APOE-ε4 status, and the coexistence of the APOE-ε4 allele and ALDH2*2 allele synergistically increased the frequency of LOAD. Similarly, ALDH2*1/*2 polymorphism was reported to be a risk factor for LOAD and dependent on APOE ε4 status in Chinese population (OR = 3.11, 95% CI = 2.06–4.69) [90,91]. However, in a study conducted in an older Korean population, no association was found between ALDH2*2 and AD[92]. Apart from the population studies, much of the research has been done using in vitro and knock-in/ knock out mouse models.

In vitro studies using PC12 cells transfected with ALDH2*2 mutant showed increased rapid cell death after application of as little as 10 uM 4-HNE [90,93]. When these ALDH2 deficient PC12 cells were treated antimycin A, a mitochondria electron transport complex III inhibitor that induces ROS production, accumulation of 4-HNE protein adducts increased in an antimycin A dose-dependent manner [90,93]. Transgenic mice overexpressing ALDH2*2 showed an age-dependent neurodegeneration accompanied by significant memory loss [94]. In another $ALDH2^{(-/-)}$ knockout (null) mouse model, the mice exhibited progressive, age-related cognitive deficits in novel object recognition, Y-maze tasks, non-spatial and spatial working memory together with a multitude of AD-associated pathological changes [95]. These changes

included, increased levels of 4-HNE adducts as well as age-related increases in amyloid-beta, phosphorylated-tau, and activated caspases [95]. Also, in addition to the observed AD-like pathologies in the brains of ALDH2 null mice, significant vascular alterations in cerebral microvessels (CMVs) of these mice were observed, indicating the importance of mitochondrial ALDH2 in the maintain brain energy/ detox homeostasis in both neuronal and non-neuronal cells. Since, both neural and vascular pathological changes associated with AD were observed in the ALDH2 null mice, these mice could be used as a robust sporadic AD model.

One potential intervention for the treatment of AD is to reduce the toxicity caused by the β-amyloid peptides, in particular, the $A\beta_{(1-40)}$. In human umbilical endothelial cells treated with $A\beta_{(1-40)}$, reduction in ALDH2 activity was observed along with endothelial dysfunction caused due to impaired endothelial adherens and tight junction organization and barrier function [96]. In a recent study, ALDH2 activator, Alda-1, was applied in culture to reduce the toxicity of $A\beta_{(1-40)}$ toxicity and impairment of angiogenesis [96]. In this study, Alda-1 rescued Aβ-impaired functions of the endothelium with an increase in ALDH2 activity, reduction of 4-HNE adducts, ROS formation and restoration of mitochondrial functions [96].

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease in the aging population. It is characterized by the loss of dopaminergic neurons in substantia nigra pars compacta with its prominent function in motor control. PD affects 1% of the population in people over >65 years old of age and 4-5% in the population of 85 years old of age [97]. The loss of dopaminergic neurons in substantia nigra and formation of intraneuronal protein aggregates are the hallmarks of PD [98]. Genetic defects that have been identified for familial PD include mutations in α-synuclein, PARKIN, PINK1, DJ-1 and LRRK2 [99,100]. Mitochondrial oxidative stress is an important factor in Parkinson's disease (PD) [101-103]. It has also been reported that the neurons in substantia nigra not only had fewer number mitochondria, but also smaller size of mitochondria per cell [104]. These evidences point to the importance of supporting mitochondrial function in dopaminergic neurons and the vulnerability of these neurons to aldehyde toxicity. For example, the lysine-rich α-synuclein is particularly vulnerable target to reactive aldehydes, including DOPAL (a product of dopamine metabolism), 4-HNE, MDA, acrolein and advance glycation end-products [105]. Modifications on the lysine residues on α-synuclein by aldehydes have been shown to lead to aggregation, reduced ubiquitination, cleavage and generation of neurotoxic oligomers [105].

Burke *et al*. first demonstrated the neurotoxicity of DOPAL, a reactive aldehyde and immediate dopamine metabolite by monoamine oxidase, to dopaminergic neuron by direct inject of DOPAL into rat substantia nigra [106]. At physiologically relevant concentrations, DOPAL readily caused aggregation of α-synuclein in a cell-free system, in cultured SHSY5Y cells and in substantia nigra of Sprague-Dawley rats [107]. Furthermore, in vivo treatment of the substantia nigra with DOPAL causes aggregation of α-synuclein and neuron loss [107]. DOPAL also compromised the functionality of α-synuclein even in the absence of protein oligomerization, by affecting synaptic vesicle traffic in neurons [108]. Administration of 10-50 uM 4-HNE significantly reduced dopamine receptor's binding to its agonist in PC12 cells [109]. The neurotoxin, 1-methy-4-phenylpyridinium ion (MPP+) is commonly used to model PD. In PC12 cells, treatment of MPP+ increased aldehydic load as measure by MDA and 4-HNE [109]. Since both 4-HNE and MDA cause ALDH2 inhibition, it is not surprising that a treatment of 2-100 μM 4-HNE or 2-50 μM of MDA severely impaires DOPAL oxidation and leads to significant increase in DOPAL concentration and protein modification via the inhibition of ALDH [25]. Using recombinant ALDH2 and ALDH2 extracts from rat brain mitochondrial fraction, Florang *et al*. demonstrated inhibition of DOPAL oxidation to DOPAC by incubation of low μM of 4-HNE [110]. Application of the ALDH2 inhibitor, diazin, decreased viability of PC12 cells, indicating the protective role of ALDH2 against neurotoxicity and Parkinson's disease [109]. Recently, benomyl, a commonly used fungicide that has been associated with PD incidence in epidemiological studies, was shown to be a potent and rapid ALDH inhibitor [111]. Administration of benomyl *in vivo* in mouse striatum and in vitro to PC12 cells and human cultured fibroblasts and glial cells all leads to accumulation of DOPAL [111]. Similarly, rotenone, a broad spectrum insecticide, pesticide

and known mitochondria complex I inhibitor has long been implicated in the pathogenesis of Parkinson's disease. However, rotenone has recently been shown also to be a potently inhibitor of intracellular aldehyde dehydrogenase activity as the underlying molecular cause of PD [112]. Paraquat and maneb, a herbicide and a fungicide, respectively, have been suspected to cause PD. In an animal model, treatment of paraquat and maneb biweekly for 6 weeks caused a significant increase of 4-HNE protein adducts in the striatum and cortex of mice [113]. All these results may explain the strong link between exposure of pesticides and inhibition of ALDH and DOPAL buildup as the cause of PD.

In human postmortem samples, Yoritaka *et al* [114] detected positive 4-HNE protein adduct immunostaining in an average 58% of the nigral neurons in all seven PD patients, whereas only 9% of the nigral neurons stained positively in control subjects. Accumulation of 4-HNE adducts were also detected and localized to the Lewy bodies of PD patients [115]. The increase of 4-HNE adducts were not only found in the substantia nigra of PD patients, but were also prominently present in brain tissue and cerebrospinal fluid of the AD patients and in the spinal cord of the amyotrophic lateral sclerosis (ALS) patients [16]. All these data from human samples highlight the pathophysiological role of oxidative stress and, especially, 4-HNE formation of abnormal filament deposits in neurodegenerative diseases. Interestingly, when ALDH2 activity was measured from post-mortem brain tissues derived from nine PD patients and twelve matched control individuals, higher ALDH2 activity was detected in the putamen, but not is the frontal cortex of PD patients [116]. It is not clearly whether the observed increase of mitochondrial ALDH2 activity in the putamen of patients with PD is a compensatory mechanism or a contributing etiology for the disease.

The association of ALDH2 genetic variation and PD in epidemiology has not yet been fully explored. In a population-based case-control study in California, specific ALDH2 haplotype was determined to be an increased risk factor in subjects exposed to ALDH inhibiting pesticides [117]. Since less than 2% of this population carried the East Asian ALDH2*2 allele, the association of the specific rs671 SNP (ALDH2*2) with PD could not be determined in that study. In another study, among 584 PD patients and 582 controls subjects of Han Chinese, SNP rs4767944, but not the functional ALDH2*2 SNP rs671, was found to increase the susceptibility of PD [118]. Whereas no association of ALDH2*2 enzyme deficiency has been associated with the risk of PD, a recent study in Taiwan showed that PD patients that carry the ALDH2*2 deficient allele presented a higher risk of neuropsychological and cognitive impairments [119]. For example, among 139 recruited PD patients, 46% of the patients had significant cognitive impairment in the ALDH2*2 group as compared with only 26% of the patients carrying ALDH2*1 (WT enzyme). Studies involving much larger PD patient populations are clearly warranted to understand the role of mitochondria ALDH2 in different aspects of PD pathology.

Transgenic ALDH animal models are now available for the study of PD. Using an ALDH1A1 and ALDH2 double knockout animal model, Wey *et al*., [120] described an age-dependent motor performance deficit; as expected, the behavioral deficit was accompanied by the loss of neuron in substantial nigra, a reduction in dopamine and an increase in neurotoxic aldehydes including 4-HNE and DOPAL [120]. Decreased expression of cytosolic ALDH1A1 and its protein in substantial nigra has also been reported to be associated with PD [121,122]. It is likely that deficiency in only one ALDH isozyme alone might not be sufficient to cause neuropathology of PD, but missing multiple ALDH isozymes could lead to a drop below a threshold aldehyde detoxifying capacity and overwhelmed the dopaminergic neuron with an increased aldehydic load that ultimately causes neurodegeneration and Parkinson's disease. Therefore, protecting or enhancing either ALDH1A1 or ALDH2 activity could potentially be a promising strategy in preventing or slowing downing the progression of PD. As a proof of concept of this strategy, the ALDH2-speific enzyme activator, Alda-1, was shown to be efficacious in protecting against cell death by rotenone in cultured SHSY5Y cells and primary culture of mouse substantia nigra dopaminergic neurons [32]. Furthermore, when administered intraperitoneally to either rotenone- or MPTP-injected mice, Alda-1 significantly protected mitochondria function and rescued substantia nigra neurons in these animals [32].

CONCLUSION

Aldehydes are volatile, strong electrophiles in nature. Toxic aldehydes react readily with macromolecules, interfere with normal biological processes and lead to cellular dysfunction. Brain cells are constantly exposed to many such deleterious aldehydes derived from both biogenic and xenogenic sources. Epidemiological, biochemical, and genetic studies and animal models have attributed excessive aldehydic load as one the underlying molecular mechanisms in neuropathology and neurodegenerative diseases. Since mitochondrial ALDH2 is one of the critical aldehyde detoxification enzymes in brain, its role and contribution to neuropathy needs to be further defined. This is especially important for the 540 million East Asians, who are ALDH2 deficient due the common inactivating point mutation E478K. The interaction and causal relationship between ALDH2 deficiency and low-level, long-term exposure to different types of toxic aldehydes warrants more focused systematic risk assessments and clinical observations particularly because of their implication in chronic neurodegenerative diseases such Alzheimer's diseases and Parkinson's disease.

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