



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

ALDH2 Activators

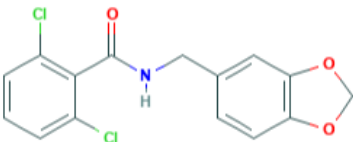
Evidence Summary

Boosting ALDH2 activity should hypothetically be beneficial for several age-related diseases, though no drugs have entered the clinic.

Neuroprotective Benefit: Evidence from postmortem Alzheimer's brain tissue and from preclinical studies suggest that an ALDH2 activator may be beneficial in Alzheimer's disease, but there is no evidence from clinical studies.

Aging and related health concerns: Genetic and preclinical studies suggest increasing ALDH2 activity might be beneficial for several age-related disease, though no clinical studies have been conducted.

Safety: Hypothetically, ALDH2 activators should be safe, though none have entered the clinic.

Availability: Not available (though ALDH2 activators in development)	Dose: Not clear, never been tested in humans	Molecular Formula: C ₁₅ H ₁₁ Cl ₂ NO ₃ Molecular weight: 324.2g/mol  Source: Pubchem
Half-life: Unknown	BBB: Possibly penetrant in animal models	
Clinical trials: None	Observational studies: None	

What is it?

Reactive oxygen species (ROS) can oxidize many molecules in cells including proteins, nucleic acids, and lipids. Lipid peroxidation leads to the formation of highly reactive species, such as malondialdehyde (MDA) and 4-hydroxy-2-noneal (4-HNE), which can further damage proteins in cells. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) is one of several proteins that a cell uses to detoxify species such as MDA and 4-HNE. It is a tetrameric enzyme that plays a role in the metabolism of toxic aldehydes. ALDH2 activity can be impaired with aging. Alda-1 is a chemical chaperone that can improve the enzymatic activity of ALDH2 ([Gu et al, 2013](#)).

The ALDH*2 allele (rs671 G>A) is common in individuals of East Asian descent (China, Korea, and Japan). It impairs ALDH2's enzymatic activity and leads to an impairment in acetaldehyde oxidation. This mutation is responsible for alcohol flushing syndrome that affects some Asian individuals ([Joshi et al, 2019](#)). Although there is some evidence that the ALDH*2 allele might be associated with Alzheimer's disease and age-related diseases, it is difficult to separate out the effects of the allele specifically versus effects that might be secondary due to reduced alcohol metabolism.



Neuroprotective benefit: Evidence from postmortem Alzheimer's brain tissue and from preclinical studies suggest that an ALDH2 activator may be beneficial in Alzheimer's disease, but there is no evidence from clinical studies.

Types of evidence:

- One meta-analysis of a genetic mutation in the ALDH2 gene
- Several studies of lipid peroxidation by-products in post-mortem Alzheimer's tissue and CSF in Alzheimer's patients
- One preclinical study in a mouse line with a dominant negative ALDH2 gene
- Several preclinical studies with Alda-1

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

In a meta-analysis of nine case-control studies with 5,315 individuals, the ALDH2 rs671 G>A allele (which reduces the function of ALDH2) was associated with an increased risk of Alzheimer's disease in a dose-dependent manner (A vs. G OR = 1.46; 95%CI = 1.01-2.11; AA vs. GG OR = 2.22; 95%CI 1.03-4.77). One complication of these studies is they were not controlled for alcohol consumption, whose metabolism is controlled by ALDH2. They did find that these results tended to be in men but not women, and men consume more alcohol in East Asian countries. There was no association between ALDH2 rs671 G>A and Parkinson's ([Chen et al, 2019](#)).

Human research to suggest benefits to patients with dementia:

Patients with MCI and AD have increased levels of lipid peroxidation by-products (such as 4-HNE and acrolein) in multiple brain regions and in the CSF compared to control subjects ([Williams et al, 2006](#); [Lovell et al, 1997](#); [Markesbery and Lovell, 1998](#)).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

[Ohsawa et al \(2008\)](#) created a transgenic mouse line expressing a dominant negative ALDH2 (DAL101). DAL101 mice accumulated higher levels of 4-HNE, exhibited muscle weakness in male (but not female mice), showed decolorization of their fur, and had a shortened lifespan. Several of the aged DAL101 mice showed signs of hippocampal neuronal loss, increased hyperphosphorylated tau, astrocytosis, and impaired cognition (data was presented as % of animals showing signs of pathology). Moreover, DAL101/apoE^{-/-} mice were more cognitively impaired than DAL101 mice. APOE can remove free 4-HNE.



ApoE^{-/-} mice, despite generally being used as a model of atherosclerosis, also develop neurodegenerative changes including synaptic loss, increased ROS formation and lipid peroxidation, and behavioral changes. In ApoE^{-/-} mice, four-month treatment with Alda-1 reduced 4-HNE protein adducts in the frontal cortex, and increased expression of genes related to neurogenesis, mitochondrial biogenesis, and apoptosis. There were no gross morphological changes in brain structure ([Stachowicz et al, 2017](#)).

In fibroblasts isolated from a familial Alzheimer's patient harboring the ALDH2*2 allele (the ALDH2 rs671 G>A allele), there were increased levels of aldehyde load, mitochondrial dysfunction, and oxidative stress. These results were replicated by overexpression of ALDH*2 in fibroblasts from Alzheimer's patients and reduced by cotreatment with Alda-1 ([Joshi et al, 2019](#)).

Stroke

Middle cerebral artery occlusion (MCAO) in rats increased levels of 4-HNE and MDA but had no effect on ALDH2 activity compared to sham surgery. Pretreatment with Alda-1 (15 or 50 mg/kg) increased ALDH2 activity and reduced 4-HNE and MDA (ALDH2 levels did not increase with MCAO or Alda-1 treatment). Furthermore, Alda-1 improved neurological score, reduced mortality, infarct size, cell death, and improved brain morphology ([Fu et al, 2013](#)). Similar results were reported in another MCAO study in rats with pretreatment of Alda-1 additionally reducing brain edema and APQ4 expression. An ALDH2 inhibitor (cyanamide) worsened these phenotypes ([Li et al, 2018](#)).

APOE4 Interactions:

None reported

Aging and related health concerns: Genetic and preclinical studies suggest increasing ALDH2 activity might be beneficial for several age-related disease, though no clinical studies have been conducted.

Types of evidence:

- One genetic study on an ALDH2 allele for lifespan
- Two meta-analyses for the effect of an ALDH2 allele on cardiovascular disease risk
- One meta-analysis for the effect of an ALDH2 allele on diabetes risk
- One meta-analysis for the effect of an ALDH2 allele on cancer risk
- One study for the effects of an ALDH2 allele and neuropathic pain
- Several preclinical studies for the use of Alda-1 in cardiovascular disease



- One preclinical study for the use of Alda-1 in neuropathy
- Several preclinical studies on ALDH2 over-expression

Lifespan

Interestingly, a study from Korea ([Park et al 2009](#)) looked at 137 elderly over 90 years old and 213 young, healthy individuals. They reported that the rs671 (A) allele of the *ALDH2* gene (the allele for reduced ALDH2 activity) was associated with longevity in only men (OR = 2.11; p=0.008). It is not clear why this is the case. It could be due to the low number of subjects in the study or that individuals who do suffer from alcohol-flushing syndrome do not drink as much (which would contradict some of the GWAS studies found for other age-related diseases).

Cardiovascular

Coronary Artery disease

In a meta-analysis from 12 case-control studies, patients with the ALDH2 rs671 G>A allele were at a greater risk of coronary artery disease (OR = 1.48; 95%CI 1.18-1.87 for AA + AG vs. GG) ([Zhang et al, 2015](#)). The allele was also associated with an increased risk of myocardial infarction in a meta-analysis of 12 case-control studies ([Han et al, 2013](#)).

Chronic Heart Failure

In rats with post-myocardial infarction (MI) heart failure, daily treatment with Alda-1 (16mg/kg) improved survival, reduced serum BNP (a marker of heart failure), improved heart morphology, reduced heart weight/body weight, improved heart function, inhibited collagen formation, and reduced 4-HNE and apoptosis ([Hua et al, 2018](#)). When started 4-weeks post-MI, 6-week treatment with Alda-1 (10mg/kg/day) improved heart function, heart morphology, and mitochondrial function, and reduced collagen, 4-HNE, and protein carbonyl levels ([Gomes et al, 2014](#)).

Cardiomyopathy

Rats with post-MI cardiomyopathy exhibited impaired heart function, increased levels of reduced glutathione (GSH), reduced mitochondrial respiration, increased H₂O₂ levels, an increase in cardiac and serum lipid peroxidases and 4-HNE, and a reduction in ALDH2 activity. These deficits were partially ameliorated by treatment with Alda-1 (10mg/kg/day) 24 hours post-MI over 4-weeks ([Gomes et al, 2015](#)).



Myocardial Ischemia/Reperfusion (I/R)

In a rat model of myocardial I/R, pretreatment with Alda-1 (10mg/kg) reduced infarct size, cell death, and 4-HNE. This was accompanied by a reduction in PINK1/Parkin-dependent mitophagy ([Ji et al, 2016](#)).

Atherosclerosis

In a mouse model of atherosclerosis (ApoE^{-/-}), Alda-1 treatment (10mg/kg/day mixed in with food) over four months reduced atherosclerotic lesion size and percentage of the aorta occupied by atherosclerotic plaques. There were no changes in macrophage content or smooth cells. Alda-1 tended to reduce 4-HNE and nitrotyrosine, but the changes were not significant. In addition, mRNA expression of genes involved with oxidative stress, apoptosis, autophagy, and mitochondrial function were unchanged. There were also no changes in plasma lipids ([Stachowicz et al, 2014](#)).

Aged mice

ALDH2 KO mice show a reduction in lifespan (image right), an increase in senescent cells in the heart, and reduced heart function. Aged mice also show the presence of senescent cells in the heart, a reduction in ALDH2 activity, an impairment in autophagic flux, an increase in 4-HNE and protein carbonyl content, and an impairment of cardiac function. These phenotypes were reversed when mice were treated with Alda-1 (3mg/kg) over four weeks, but these improvements required SIRT1 activity, as they were not present when Alda-1 was given to SIRT1 hypomorphs. Treatment of aged mice with Alda-1 also increased SIRT1 activity in heart tissue ([Wu et al, 2015](#)).

[Gu et al \(2013\)](#) reported reduced activity (but not expression) of ALDH2 in aged mouse hearts. This corresponded with an increase in 4-HNE adducts, MDA, and protein carbonyl levels, and a reduction in SIRT1 activity and expression. In cardiomyocytes exposed to 4-HNE, treatment with Alda-1 reduced levels of 4-HNE, ROS, and protein carbonyls while increasing activity of SIRT1. In cardiomyocytes exposed to hypoxia/reoxygenation injury, Alda-1 reduced the levels of 4-HNE and cell death. In an *in vivo* model of ischemia/reperfusion (I/R), Alda-1 reduced the levels of 4-HNE in both young and old animals, promoted the nuclear localization of SIRT1 in aged animals, and increased SIRT1 activity in young and aged animals. Alda-1 reduced infarct size by 32% in aged animals but had no effect in aged SIRT1^{+/-} animals, suggesting that Alda-1 and ALDH2 activity require SIRT1.

On the other hand, a couple of studies suggested that over-expression of ALDH2 increased cardiovascular dysfunction in mice and shortened lifespan. However, it is difficult to determine the characterization of the ALDH2 mutant mice, and the studies come out of one lab ([Wu and Ren, 2019](#)).



Diabetes

In a meta-analysis of eight studies, the ALDH*1 allele (the allele associated with increased ALDH2 activity) was associated with a reduced risk of diabetes than the ALDH*2 allele (associated with reduced ALDH2 activity) (OR = 0.31; 95%CI 0.11-0.89) ([Li et al, 2017](#)). In diabetes-induced mice fed sucrose, transgenic overexpression of ALDH2 improved heart function, glucose tolerance, and cardiomyocyte contractile function. ALDH2 overexpression also improved markers of mitochondrial injury such as NAD⁺ activity, ROS formation, PGC-1 α , and SIRT3 expression ([Hu et al, 2016](#)).

Neuropathy

Diabetic patients with an ALDH2 mutation associated with reduced activity experienced more instances of neuropathy ([Suzuki et al, 2004](#)). Mice with the ALDH2*2 mutation exhibited an increased sensitivity to painful stimuli. Pain sensitivity was also associated with ALDH2 activity ($R^2=0.90$). These effects were ameliorated after treatment with Alda-1 ([Zambelli et al, 2014](#)).

Cancer

A meta-analysis of 63 studies suggested that the ALDH2 rs671 polymorphism was associated with an increased risk of cancer ([Zuo et al, 2019](#)).

Safety: Hypothetically, ALDH2 activators should be safe, though none have entered the clinic.

Types of evidence:

- Several genetic studies on ALDH2 mutations
- Several preclinical studies on the use of Alda-1

Genetic mutations that reduce the activity of ALDH2 are associated with age-related diseases (e.g. [Chen et al, 2019](#); [Zhang et al, 2015](#)). In addition, Alda-1, a molecule that boosts the activity of ALDH2 ameliorates the symptoms of several age-related diseases (e.g. [Wu et al, 2015](#); [Fu et al, 2013](#)). However, the safety of a molecule that increases the activity of ALDH2 will depend on the specific drug, and Alda-1 has not been tested in humans.

Drug interactions:

Not currently known, though hypothetically they could interact with other drugs involved with detoxifying oxidation by-products.



Sources and dosing:

Alda-1 is only available for research use. No clinical tests have been conducted with Alda-1. In mouse models of atherosclerosis or cardiomyopathy, Alda-1 at doses of 10 mg/kg have been tested.

Research underway:

One ALDH2 activator is currently under development by [Forsee Pharmaceuticals](#) and will soon enter clinical studies.

Search terms:

- Alda-1
- aldh2 + alzheimer, neuropathy, cardiovascular, lifespan, diabetes, cancer

Websites visited:

- Clinicaltrials.gov
- Pubmed

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