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.

2-Hydroxybenzylamine

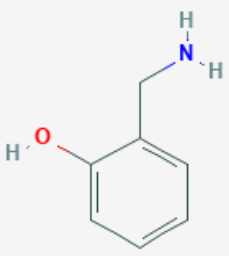
Evidence Summary

Protects against cellular damage by scavenging reactive carbonyl species. May help protect against age-related pathologies when used prophylactically, but it cannot reverse pre-existing damage.

Neuroprotective Benefit: May protect against cognitive decline stemming from neuronal damage associated with increasing brain lipid oxidation with age.

Aging and related health concerns: May protect against cardiovascular pathology by preventing protein dysfunction and inflammation associated with reactive carbonyl species. Showed evidence for lifespan extension in worms.

Safety: Well-tolerated in healthy young adults with short-term use and animals for several months. Effects of chronic use in humans need to be characterized.

Availability: Clinical trials	**Dose**: Not established Maximum tested dose: 825 mg oral capsule of 2-HOBA acetate	**Chemical formula:** C_7H_9NO **MW**: 123.15 g/mol  Source: PubChem
Half-life: 2 hours	**BBB**: Penetrant	
Clinical trials: Safety in healthy young adults (n=18).	**Observational studies**: Reactive carbonyl species (y-ketoaldehydes) increase in brain in AD and in the vasculature with hypertension.	

What is it?

2-Hydroxybenzylamine (2-HOBA, also called salicylamine and 2-aminomethylphenol) is a lipophilic analog of vitamin B6 (pyridoxine) derived from buckwheat [1]. **2-HOBA acts as a scavenger of some types of reactive carbonyl species, including y-ketoaldehydes**.

Oxidative stress can drive the peroxidation of polyunsaturated fatty acids, which can then undergo rearrangements to form reactive carbonyl species, which then exert damage by forming covalent modifications on proteins, nucleic acids, and phospholipids. They can also promote the formation of advanced glycation end products (AGEs). These modifications can cause mutations, alter function, and inhibit the efficient degradation of these damaged cellular components. Reactive carbonyl species have higher potential to elicit cell damage relative to reactive oxygen species (ROS), due to their stability, longer half-life, and ability to traverse membranes.

Different types of reactive carbonyl species modify different functional groups, therefore certain classes of scavengers may be better suited toward certain diseases than others, or a combination may be needed to achieve clinical efficacy. The two main classes of reactive carbonyl species scavengers are thiols and amines, and they tend to scavenge different types of reactive carbonyl species. y-ketoaldedhydes, which include isoketals, isolevuoglandins, and neuroketals, are the most highly reactive, and are strongly pro-inflammatory. Since they react with primary amines, they are effectively scavenged by amine-based scavengers like 2-HOBA. Malondialdehyde, which is one of the most abundant lipid peroxidation products, is also effectively scavenged by 2-HOBA. Meanwhile, other damaging species, including 4-HNE and acrolein are more effectively scavenged by thiols [1].

The scavengers act as nucleophiles and compete with endogenous nucleophilic targets, therefore they must have high potency and be highly bioavailable in tissues to effectively outcompete. 2-HOBA is able to scavenge y-ketoaldehydes 1000-fold faster than the rate of reaction with lysine residues on endogenous proteins [2]. Therefore, it can effectively prevent the formation of protein adducts, which are associated with a variety of age-related diseases.

2-HOBA is currently being developed as a dietary supplement by Metabolic Technologies Inc., and has been undergoing clinical safety testing.

Neuroprotective Benefit: May protect against cognitive decline stemming from neuronal damage associated with increasing brain lipid oxidation with age.

Types of evidence:

- 5 observational studies (Peroxidized lipids content in AD brain and CSF, Reactive carbonyl species content in AD brain)
- Several laboratory studies

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

There have not been any studies directly testing whether 2-HOBA can prevent cognitive decline, but observational studies indicate that reactive carbonyl species are elevated in the brain in Alzheimer's disease, and may contribute to cognitive decline.

The lipidome of the human brain undergoes progressive changes during aging starting around age 50 to 55 [3]. Some areas, such as the prefrontal cortex, have a high level of polyunsaturated fatty acids, including arachidonic acid and docosahexaenoic acid (DHA), which are susceptible to lipid peroxidation [4]. The oxidation of these polyunsaturated fatty acids leads to the formation of highly reactive y-ketoaldehydes. The oxidization of arachidonic acid results in isoketals, while the oxidation of DHA creates neuroketals. These pathogenic peroxidized lipids are reactive carbonyl species that induce damage by modifying proteins and nucleic acids. **During aging there is an increase in the level of lipid oxidation and associated protein damage in the human brain**, though some regions are more resistant than others.

In the context of healthy aging, the brain lipid profile is largely resistant to change, however, in the context of Alzheimer's disease (AD) there appears to be an accumulation of oxidized lipids and reactive carbonyl species [4]. Isoprostanes and neuroprostanes, are precursors to isoketals, and neuroketals, respectively, and markers of lipid peroxidation. Free F4-neuroprostanes were found to be increased in the CSF of AD patients [5], while bound F4-neuroprostanes were increased in the occipital and temporal cortices of AD patients [6]. There is also evidence for a lower reducing capacity in the AD brain, which may underlie the increase in free radical damage to DHA in the cerebrum [7]. In these studies, the levels of neuroprostanes did not correlate with plaques or tangle pathology. However, **levels of isoketal or neuroketal protein adducts (i.e. associated protein damage) did correlate with AD pathology** [8]. The isoketal adduct, levuglandin-lysine lactam was found to be 12.2-fold higher in the AD brain (n=7) relative to age-matched controls (n=5), and positively correlated with Braak stage ($r=0.92$, $P<0.0001$) [8]. Neuroketal adducts were found to be elevated in the hippocampus in a separate study (n=6 AD, n=6 age-matched controls), preferentially localized to hippocampal pyramidal neurons, and 5-fold higher than isoketal adducts [9].

y-ketoaldehydes are also highly pro-inflammatory, thus they can promote both oxidative stress damage and inflammation. The elevation in y-ketoaldehydes in AD could lead to the modification of proteins essential for neurotransmission and neuronal function, thereby promoting the mechanisms associated with cognitive decline. Therefore, compounds which can scavenge y-ketoaldehydes could potentially protect against age-related and AD-associated cognitive decline.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Reactive carbonyl scavengers, such as 2-HOBA, are likely to be most effective at early stages to slow disease progression, or as a preventative to delay disease onset by reducing oxidative stress mediated cellular damage.

Alzheimer's disease: Potential benefit (preclinical)

Highly reactive y-ketoaldehydes, such as levuglandins, have been shown to accelerate the formation of Aβ42 oligomers, and enhance their neurotoxicity in cell culture [10]. Modification of proteins by y-ketoaldehydes can also inhibit their clearance by the proteasome [11]. Therefore, it is hypothesized that y-ketoaldehyde scavengers could protect against neurodegeneration in AD.

2-HOBA treatment (1 g/L in drinking water) starting at 4 months of age was protective against deficits in spatial working memory at age 12 to 14 months, based on performance on the radial arm maze, in mice expressing human ApoE4 [9]. However, 2-HOBA had no effect on age-related motor deficits in these transgenic animals.

Seizure-associated cognitive impairment: Potential benefit (preclinical)

Highly reactive carbonyl species, y-ketoaldehydes, were found to be elevated in the hippocampus and perirhinal cortex following epileptogenic injury in the kainic acid and pilocarpine-induced temporal lobe epilepsy mouse models [12]. Treatment with 2-HOBA (200 mg/kg i.p. 30 min after seizure-inducing agent + 1 g/L in drinking water) reduced the formation of y-ketoaldehyde adducts, leading to a corresponding reduction in seizure-induced spatial and reference memory deficits. 2-HOBA protected against neuron loss, but had no effect on seizure induction.

APOE4 interactions: Unknown

Aging and related health concerns: May protect against cardiovascular pathology by preventing protein dysfunction and inflammation associated with reactive carbonyl species. Showed evidence for lifespan extension in worms.

Types of evidence:

- 2 observational studies (Isoprostane and isoketal levels in hypertensive patients)
- Several laboratory studies

Lifespan: Potential benefit (worms)

Carbonyl stress is thought to be a contributing factor to age-related pathology [13]. **Reactive carbonyls, such as isoketals, can contribute to molecular aging** by reacting with proteins, leading to chemical modifications that can inactivate or alter the activity of the protein targets. As an effective isoketal scavenger, **2-HOBA can prevent the formation of these protein adducts, thus preserving protein function**. 2-HOBA treatment was found to extend the lifespan and healthspan of *C. elegans* through the preservation of Sirtuin (SIR2.1) function, and enhancing resistance to oxidative stress damage in mitochondria [14]. Worms treated with 2-HOBA beginning at the start of adulthood had dose dependent increases in median lifespan, with worms treated at the highest dose (500 µM) experiencing a 56% increase in median lifespan (from 16 to 25 days). Treated worms also showed improvements in

healthspan based on a dose-dependent decrease in lipofuscin granule accumulation and a slowing of the decline in pharyngeal pumping rate.

Cardiovascular disease: Potential benefit (preclinical)

Reactive carbonyl species are major mediators of oxidative stress damage [15]. They form irreversible modifications to proteins, leading to protein dysfunction and the activation of the immune system. In cardiovascular tissues, isoketals and isolevuglandins have the highest reactivity, and thus are the most damaging. Levels of lipid peroxidation and associated protein adducts have been found to be increased in the blood and vascular cells of patients with a variety of cardiovascular-associated pathologies, and these pathologies can be prevented through treatment with isoketal scavengers, such as 2-HOBA. Notably, these **scavengers are best suited as preventatives to block the formation of damage inducing adducts**, as they are unable to reverse pre-existing damage.

Hypertension: Vascular oxidative stress is associated with aortic stiffening and hypertension. In a small study, hypertensive patients (n=28) were found to have higher plasma levels of F2-isoprotanes (10.7 ± 1.6 ng/ml vs. 17.7 ± 2.2 ng/ml, $P < 0.05$), which are formed by the peroxidation of arachidonic acid and serve as a precursor for reactive isoketals, relative to their normotensive counterparts (n=15) [16]. F2-isoprostane levels were also correlated with pulse wave velocity, a measure of aortic stiffness (Spearman r=0.44, $P<0.01$). In aortic biopsies from these patients, **the level of isoketal protein adducts correlated with the severity of fibrosis** based on collagen deposition (Spearman r=0.80, $P<0.01$), and with the level of inflammation based on T cell infiltration (Spearman r=0.65, $P<0.05$). These isoketal protein adducts are thought to be immunogenic by serving as neoantigens for antigen presenting cells. **The level of isoketal adducts was found to be 3-fold higher in peripheral blood cells from hypertensive patients** (n=12) relative to normotensive people (n=8) and the percentage of isoketals in antigen producing $CD14^+$ macrophages (ß=1.06, p=0.02) and $CD38^+$ dendritic cells (ß=1.14, p=0.03) was found to correlate with systolic blood pressure in these patients [17]. Similarly, in mouse models involving vascular oxidative stress and hypertension, there is an accumulation of damage inducing isoketals in the heart and vasculature [16; 17]. Notably, there is an increase of isoketals in antigen presenting cells, including dendritic cells, which in turn leads to the activation of inflammatory T cells. In these mouse models, early treatment with 2-HOBA protects against isoketal formation, hypertension, aortic stiffening, fibrosis, and vascular inflammation. However, **late administration, after the onset of pathology, was ineffective** [16].

This suggests that oxidative stress promotes the formation of reactive isoketals, which modifies proteins in a manner that activates the immune system and drives vascular pathology.

Pulmonary Arterial Hypertension (PAH): Patients with PAH that carry mutations in BMPR2, a receptor kinase mutated in >70% of familial cases of PAH, have altered cellular metabolism in their pulmonary endothelial cells, and the altered fatty acid metabolism contributes to vascular pathology. These patients have higher circulating levels of glutamine for use as a carbon source for energy production [18]. In a corresponding mouse model, it was determined that this requirement for glutamine as an energy source stems from the loss of function of the master regulator of cellular metabolism, SIRT3 [18]. The function of SIRT3 is compromised by covalent modification by reactive carbonyl species, and in the mouse model, treatment with 2-HOBA prevented the formation of these SIRT3 modifications and the development of PAH.

Atherosclerosis: Oxidative modification of lipoproteins promotes atherosclerosis related vascular pathology. Oxidation can enhance the pathogenic nature of LDL, as oxidized LDL can promote foam cell formation, and induce immune cell activation and inflammation. Meanwhile, oxidative modification of HDL can inhibit its protective functions. Individuals with familial hypercholesterolemia were found to have increased levels of the reactive carbonyl species, malondialdehyde [19]. In a mouse model of hypercholesterolemia, 2-HOBA treatment reduced atherosclerosis by 31% in proximal aortas and by 60% in en face aortas without significantly affecting blood lipid levels [19]. The protective effects stem from a reduction in macrophage cholesterol stores due to enhanced efferocytosis, and reduced inflammation. 2-HOBA treatment protected against the formation of reactive carbonyl species adducts of HDL, thereby preserving its protective functions.

Heart Failure: In a mouse model of heart failure (aortic constriction), the level of isolevuglandin protein adducts was increased in the heart and lung [20]. Treatment with 2-HOBA reduced the formation of these deleterious adducts, cardiac hypertrophy, lung fibrosis, and the infiltration of pro-inflammatory macrophages and leukocytes. In a cell culture model of atrial fibrillation, the generation of reactive γ-ketoaldehyde adducts promoted the production of preamyloid oligomer cytotoxic species, and induced a stress response. 2-HOBA treatment prevented these deleterious effects [21].

GERD: Potential benefit for reducing cancer risk (preclinical)

Individuals with gastroesophageal reflux disease (GERD) are at a higher risk for esophageal cancer, which may be related to increased levels of reactive carbonyl species and associated protein adducts. Patients with GERD were found to have a trend toward higher levels of isolevuglandins in their esophagus, while levels were largely undetectable in healthy controls [22]. Isolevuglandin protein adducts also accumulated in the esophagus of a GERD mouse model, and in esophageal cells exposed to GERD-like conditions. The tumor suppressor p53 was one of the proteins adversely affected by the

presence of reactive isolevuglandins, and its loss of solubility/function may drive cancer risk. Treating esophageal cells with 2-HOBA prevented the formation of isolevuglandins, and associated damage.

Safety: Well-tolerated in healthy young adults with short-term use and animals for several months. Effects of chronic use in humans need to be characterized.
Types of evidence:

- 1 clinical trial for safety and PK in healthy volunteers (n=18)
- Several laboratory studies

2-HOBA acetate has been shown to be **well-tolerated in a small open-label single ascending dose clinical trial in healthy volunteers** (n=18, age 27.2 ±5 years) (NCT03176940) [23]. All adverse events were mild and not expected to be drug related. Participants showed no clinically meaningful changes in vital signs, ECG measures, or clinical laboratory parameters. Orally administered 2-HOBA was rapidly absorbed with an average T_{max} of 1.6 hours, and the C_{max} increased proportionally with dose. Since this study was conducted in young adults (≤ 40 years old), it is possible that additional side effects may become apparent in an elderly population, and there is an ongoing multiple ascending dose trial (NCT03556319) in this population to address this possibility. A multiple ascending dose study (NCT03555682) was completed in 2019 in adults under age 60 at doses of 500 and 750 mg, but the results have not yet been released. 2-HOBA is readily BBB penetrant in rodents [24], and a study testing the BBB penetrance of 2-HOBA acetate in humans (NCT03554096) was completed in 2019, but the results have not yet been made public.

2-HOBA acetate was also tested for toxicity in rabbits, rats, mice, and human cells in preclinical studies. All toxicology studies, including the human study, were done using a formulation of 2-HOBA manufactured by TSI, China (Lot# 16120312). The no-observed-adverse-effect level (NOAEL) was found to be 1000 mg/kg bw/day in rodents [25; 26] and rabbits [27], which translates to a human equivalent dose of approximately 10g per day (for a 75 kg man). Mice treated orally with 10 g/L 2-HOBA showed signs of toxicity, including weight loss and hunching behavior [24]. 2-HOBA was well-tolerated in animals following subchronic administration for 90 days, and was not associated with any biologically meaningful changes in body weight, histopathology, biochemical or hematological parameters [25; 27]. Based on *in vitro* studies in human cells, it is not cytotoxic or mutagenic, does not induce CYP enzymes, and has low risk for cardiac QT wave prolongation [28].

Reactive carbonyl species scavengers are anticipated to be safer and more effective than ROS scavengers, as endogenous ROS play important cellular functions [1]. The biological roles of reactive carbonyl species are not well characterized, but similar to ROS, there is some evidence that they also impact cellular signaling, though to a lesser degree. Therefore, at high levels, the scavengers could potentially interfere with some cellular functions. Reactive carbonyl species play a role in activating the endogenous Nrf2 antioxidant pathway, however, since this activation involves thiol reactivity, it is unlikely to be significantly impacted by amine-based scavengers, such as 2-HOBA.

Although there has not been any evidence of immunosuppression in the studies conducted thus far, reactive carbonyl species are used by neutrophils and macrophages in host defense against pathogens [13]. Therefore, high levels of reactive carbonyl scavengers, such as 2-HOBA, could potentially impact immune function and the ability to fight infections.

Sources and dosing:
2-HOBA is being developed as a dietary supplement by Metabolic Technologies Inc in a 2-HOBA acetate oral capsule formulation. The maximum tested dose is an 825 mg oral gel capsule, which corresponds to 560 mg of 2-HOBA. It is still undergoing clinical testing, and is not yet marketed for consumers.

Research underway:
All of the clinical trials conducted for 2-HOBA thus far have been sponsored by Metabolic Technologies Inc, and conducted in collaboration with Vanderbilt University. There is currently one active trial for 2-HOBA, which is a multiple dosing study in older adults (age 60-79) with metabolic syndrome (NCT03556319). The trial has an expected completion date of November 2019.

Search terms:
Pubmed, Google: 2-Hydroxybenzylamine or 2-HOBA or 2-aminomethylphenol or salicylamine +

- Alzheimer's disease, neurodegeneration, reactive carbonyl species, isoketals, cardiovascular, diabetes, aging, lifespan, safety, clinical trials

Websites visited for 2-HOBA:

- Clinicaltrials.gov
- DrugAge
- PubChem
- DrugBank.ca

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