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.

α1A-Adrenergic Receptor Agonists

Evidence Summary

Studies in mice have shown that α1A-AR activation improves cognitive function, increases lifespan, and decreases cancer. No studies in humans have confirmed these findings to date.

Neuroprotective Benefit: In mice, α1A-AR activation improved/restored cognitive functions. However, one small study in aged rhesus monkeys reported that an α1A-AR agonist impaired spatial working memory. No data in humans exist to date.

Aging and related health concerns: Studies in mice have shown an increased lifespan, decreased cancer, and protection from cardiotoxicity with α1A-AR activation. No studies have tested the effects of α1A-AR agonists on age-related diseases in humans.

Safety: Dabuzalgron has been studied in clinical trials, and it did not affect blood pressure. Adverse events included scalp tingling, chills, goose bumps, and pruritus. Safety of other α1-AR agonists have not been established in humans.

What is it?

The α1-adrenergic receptors (ARs), along with other adrenergic receptors (β-AR and α2-AR), regulate the sympathetic nervous system through binding and activation by norepinephrine and epinephrine. α1-AR activation leads to increased blood pressure via vascular contraction (reviewed in Perez 2023). α1-ARs consist of 3 different subtypes: α1A, α1B, and α1D. The α1A-AR is highly expressed in brain areas important for cognitive function, including the prefrontal cortex, entorhinal cortex, and hippocampus (Papay et al., 2006). In Alzheimer's disease, there is a significant loss of locus coeruleus noradrenergic neurons; these neurons innervate the prefrontal cortex, a forebrain region that is affected in dementia. Despite the loss of noradrenergic innervation from the locus coeruleus with aging and with Alzheimer's disease, α1-AR binding sites are preserved (Szot et al., 2007). In preclinical studies, α1A-AR activation has shown some benefits in cognitive functions, but drug development has been challenging due to unwanted side effects of increased blood pressure attributed to α1-ARs.

Recently, efforts to specifically target α1A-AR have emerged, including positive allosteric modulators, for the treatment of Alzheimer's disease (Papay et al., 2023).

Below is a list of drugs that target α1A-AR:

Cirazoline: Cirazoline is a full agonist at the α1A-AR and a partial agonist at α1B-AR and α1D-AR. It has a 10- to 30-fold selectivity for α1A-ARs over other α1-AR subtypes and 100-fold selectivity over α2-AR subtypes where it displays mild antagonistic properties (Ruffolo et al., 1982; Doze et al., 2011). Cirazoline has been studied in mice and rhesus monkeys.

CCF219B (formerly known as Compound 3): CCF219B is a positive allosteric modulator for the α1A-AR with no basal activity (acts only with norepinephrine present) and with at least a 1000-fold higher affinity compared to other AR subtypes (Papay et al., 2023). This compound has been studied in mouse models of Alzheimer's disease as well as in wild-type mice.

CuraAX (also known as CST-3056): CuraAX is a novel α1A-AR agonist. As of February 2025, CuraSen Therapeutics is running a phase I trial of CuraAX in healthy volunteers. CuraAX is under development for the treatment of neurogenic orthostatic hypotension and Alzheimer's disease (CuraSen pipeline).

Dabuzalgron (also known as Ro115-1240): Dabuzalgron is an oral selective α1A-AR agonist developed by Roche that has been studied in clinical trials of urinary incontinence. During a phase 2 randomized

controlled trial, interim analysis reported no clinically meaningful effects for urinary incontinence and the trial stopped enrollment. Development of dabuzalgron was discontinued (AdisInsight).

Neuroprotective Benefit: In mice, α1A-AR activation improved/restored cognitive functions. However, one small study in aged rhesus monkeys reported that an α1A-AR agonist impaired spatial working memory. No data in humans exist to date.

Types of evidence:

- 0 clinical trials
- 2 postmortem studies of adrenergic receptor expression in the brain
- Numerous laboratory studies

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

No studies have tested α1A-AR agonists for prevention of dementia or age-related cognitive decline.

Cerebral amyloid angiopathy is a condition in which there is accumulation of Aβ within the walls of cortical and leptomeningeal arteries and is a common disorder among older people as well as people with Alzheimer's disease. Cerebral amyloid angiopathy starts with amyloid deposition, followed by loss of vasoreactivity and nonhemorrhagic injury, then hemorrhagic lesions (reviewed in Koemans and van Etten, 2025). Some studies suggest that glymphatic dysfunction plays a role in the disease process. Drainage of interstitial fluid from the brain occurs via the intramural periarterial drainage pathways along the basement membranes of cerebral capillaries and arteries. The cerebrovascular smooth muscle cells provide an important function in driving the drainage pathway. In a postmortem neuropathology study, the distribution of the α1A-AR in the brain was examined in 5 young, 5 old (non-demented), and 5 cerebral amyloid angiopathy cases (Frost et al., 2020). In the occipital lobe gray matter, α1A-AR expression was decreased in old and cerebral amyloid angiopathy compared to young cases. The α1A-AR was also present on the wall of cerebrovascular smooth muscle cells. In contrast to findings in the gray matter, there were no significant differences in the cerebrovascular α1A-AR expression across young, old, and cerebral amyloid angiopathy cases, suggesting preservation of cerebrovascular α1A-AR expression with aging and amyloid angiopathy.

Human research to suggest benefits to patients with dementia:

No studies have tested α1A-AR agonists in dementia patients.

In a study of postmortem brains, α-AR mRNA expression and binding sites were examined in the prefrontal cortex of 17 non-demented controls, 15 Alzheimer's disease, and 22 Lewy body dementia cases (Szot et al., 2007). The brains of Alzheimer's disease and Lewy body dementia showed increased postsynaptic α1-AR binding sites but lower α1A-AR mRNA expression in the prefrontal cortex (layers I/II and V/VI) compared to age-matched controls. The authors speculate that the increase in α1-AR binding sites in dementia patients despite lowered mRNA expression suggests that the surviving noradrenergic neurons innervating the prefrontal cortex show axonal sprouting. In contrast, there were no significant differences in α1A-AR mRNA expression in the hippocampus of Alzheimer's disease and Lewy body dementia patients compared to age-matched controls (Szot et al., 2006).

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

Genetically modified mouse models: Mice engineered to express a constitutively active mutant (CAM) form of α1A-AR (CAM-α1A-AR mice) exhibit better cognitive function compared with wild-type mice, while mice with the α1A-AR gene knocked out displayed poor cognitive function (Doze et al., 2011). In CAM-α1A-AR mice, performances on the Barnes maze, Morris water maze, and multi-T maze were superior to wild-type mice. These mice took less time to solve the Barnes maze and made fewer errors during the learning trials compared to wild-type mice. During the memory trials, CAM-α1A-AR mice better remembered the escape box's location (lower mean solve time) and made fewer errors compared to the wild-type mice. For both learning and memory trials of the Barnes maze, CAM-α1A-AR mice traveled a shorter distance compared to wild-type mice. In the Morris water maze, CAM-α1A-AR mice solved the maze in less time during the learning phase and took less time to find the platform during the memory phase compared to wild-type mice. In the multi-T maze, CAM-α1A-AR mice took less time to solve the maze during learning trials and made fewer errors than the wild-type mice. Aged CAM-α1A-AR mice also have enhanced synaptic plasticity, as measured by enhanced basal synaptic transmission and increased long-term potentiation compared to wild-type mice. CAM-α1A-AR mice exhibited antidepressant-like behavior, measured by less time spent immobile on the tail suspension test. CAM-α1A-AR mice also exhibited less anxiety-like behavior, measured by a greater amount of time spent in open areas compared to wild-type mice.

In contrast, α1A-AR knock-out mice showed impaired learning and memory compared with wild-type mice measured by the Barnes maze (Doze et al., 2011). In the learning trials, α1A-AR knock-out mice took longer to solve the maze and made more errors than control mice. During the memory trials, α1A-AR knock-out mice displayed a poorer recollection of the escape box's location (longer mean solve time) and made more errors compared with wild-type mice. For both learning and memory trials, α1A-AR knock-out mice traveled a longer distance than wild-type mice.

Cirazoline: Wild-type mice treated with an α1A-AR-selective agonist, cirazoline (10 mg/L of bottled water), spent less time to solve the Barnes maze while making fewer errors compared to control mice, in both learning and memory trials (Doze et al., 2011). Similarly, wild-type mice treated with cirazoline spent less time solving the multi-T maze and made fewer errors than control mice.

In contrast to positive findings in mice, a study in aged rhesus monkeys paint a mixed picture. In a study of 4 aged rhesus monkeys, low doses of cirazoline (0.00001-0.001 mg/kg, orally in chocolate rice cereal, 1 hour before cognitive testing) impaired spatial working memory, measured by the delayed response task (Arnsten and Jentsch, 1997). The impairment was not a result of nonspecific changes in behavior as cirazoline had no significant effects on control trials where the delay was 0 seconds, and there were no significant effects on behavioral ratings of agitation, sedation, aggression, or appetite. Impairment was reversed with a pretreatment with an α1-AR antagonist, prazosin. When aged rhesus monkeys were given higher cirazoline doses (0.001-0.01 mg/kg), performance on the delayed response was either unchanged or improved; the improvement was not reversed by prazosin, but it was reversed by α2-AR antagonist, idazoxan, suggesting that the improvement was a result of α2-AR-related mechanisms. Improvement in delayed response performance with cirazoline was only replicable in one monkey, who showed enhanced performance following both the 0.001 mg/kg and 0.01 mg/kg doses.

CCF219B (formerly known as Compound 3): In mice, a single dose of CCF219B administered orally penetrated the blood-brain barrier with a brain to plasma ratio of 0.27 and a longer half-life in the brain than plasma (Papay et al., 2023).

In a mouse model of Alzheimer's disease (3xTg-AD mice), CCF219B treatment (2.6 mg/kg/day) started at 2 months of age and continued until 12 months of age resulted in improved synaptic plasticity, as measured by long-term potentiation (Papay et al., 2023). In 3xTg-AD mice, CCF219B treatment (2.6 mg/kg/day) also significantly improved spatial learning and memory, measured by the number of correct hole pokes in the Barnes maze, compared to vehicle-treated mice. CCF219B treatment also

significantly improved memory retrieval in the fear conditioning test in 3xTg-AD mice compared to vehicle treatment.

In a different mouse model of Alzheimer's disease (hAPP-Tg mice), CCF219B treatment (40 mg/kg) for 2 weeks, started at 9 months of age when long-term potentiation deficits are already present, did not restore long-term potentiation (Papay et al., 2023). However, a longer duration (3 months) of CCF219B treatment at 3 or 9 mg/kg/day restored long-term potentiation deficits to levels comparable to non-transgenic mice, while lower doses (0.2 or 2 mg/kg) showed no effects on long-term potentiation. In hAPP-Tg mice, CCF219B treatment at 6 and 9 mg/kg significantly reduced plasma Aβ40 and Aβ42 levels. There was a numerical lowering of the neurodegeneration marker, NfL, with CCF219B treatment (9 mg/kg) in hAPP-Tg mice, but the difference compared to vehicle was not statistically significant ($p<0.12$).

CCF219B potentiates phospho-ERK and increases the expression of α1A-AR, which may contribute to its cognitive effects (Papay et al., 2025).

APOE4 interactions:

No studies have evaluated whether α1A-AR agonists work differentially in APOE4 carriers versus non-carriers.

Aging and related health concerns: Studies in mice have shown an increased lifespan, decreased cancer, and protection from cardiotoxicity with α1A-AR activation. No studies have tested the effects of α1A-AR agonists on age-related diseases in humans.

Types of evidence:

- Several laboratory studies

Lifespan: INCREASED IN MICE WITH CONSTITUTIVELY ACTIVE α1A-AR

No studies have tested whether an α1A-AR agonist affects lifespan in humans.

Mice engineered to express a constitutively active mutant (CAM) form of α1A-AR (CAM-α1A-AR mice) have significantly increased lifespan compared to wild-type mice (Doze et al., 2011). The median lifespan in CAM-α1AAR mice was 819 days, 72 days (~10%) longer than wild-type mice that had a median

lifespan of 747 days. Both sexes of CAM-α1AAR mice had a longer median lifespan. In addition, the 90th percentile age (982 days) for CAM-α1AAR mice was also increased by 73 days (~8%) compared with wild-type mice (909 days), suggesting the possibility that α1A-AR stimulation may also increase maximal lifespan. The authors speculate that the mechanism underlying longevity in these mice may be related to their cardioprotective and anti-cancer effects of α1A-AR stimulation.

Cancer: DECREASED INCIDENCE IN MICE WITH CONSTITUTIVELY ACTIVE α1A-AR

CAM-α1A-AR mice (which express a constitutively active mutant form of α1A-AR) have a significantly lower incidence of cancer compared to wild-type mice (Collette et al., 2014). At death, 45.7% of wild-type mice had cancer, compared to 13.2% of CAM-α1A-AR mice. The types of cancers included 25.7% epithelial, 18.6% hematological, and 1.4% mesenchymal cancers in wild-type mice, and 5.7% epithelial, 7.5% hematological, and 0% mesenchymal cancers in CAM-α1A-AR mice.

Cardiovascular diseases: BENEFIT IN CHEMOTHERAPY-INDUCED CARDIOTOXICITY

Some chemotherapeutic agents have cardiotoxicity, such as doxorubicin. In a mouse model of heart failure induced by doxorubicin, dabuzalgron treatment (20 or 200 µg/kg/day, oral gavage, twice daily) for up to 7 days protected against cardiotoxicity and numerically improved survival compared to vehicle treatment (Beak et al., 2017). In doxorubicin-treated mice, dabuzalgron treatment preserved contractile function and reduced fibrosis. In doxorubicin-treated mice, survival was 86% in the dabuzalgron group and 78% in the vehicle group (statistically not significant). In mice lacking the α1A-AR, survival after doxorubicin treatment was 38% and survival was unaffected by dabuzalgron treatment, suggesting that the beneficial effects of dabuzalgron require the presence of α1A-AR.

In heart tissue from mice given doxorubicin, dabuzalgron administration restored RNA transcripts related to energy production and mitochondrial function, including mitochondrial complex I (42 genes) and ATP synthase subunits (17 genes)(Beak et al., 2017).

Safety: Dabuzalgron has been studied in clinical trials, and it did not affect blood pressure. Adverse events included scalp tingling, chills, goose bumps, and pruritus. Safety of other α1-AR agonists have not been established in humans.

Types of evidence:

- Several clinical trials in stress urinary incontinence
- Numerous laboratory studies

Non-selective α1-AR activation have been associated with increased blood pressure, vascular tone, or promotion of cardiac hypertrophy. However, selective α1A-AR agonists have generally not caused these adverse events so far.

Dabuzalgron: In phase I and II trials in women with urinary incontinence, dabuzalgron treatment did not significantly affect blood pressure, suggesting that dabuzalgron had no negative effects on vascular tone (Beak et al., 2017).

In a randomized controlled crossover study of 37 women with stress urinary incontinence, dabuzalgron (1.5 mg twice daily, orally) for 2-4 weeks resulted in adverse events including scalp tingling (58% vs 11% with placebo), headache (31% vs 25%), chills (28% vs 0%), goose bumps (11% vs 3%), and pruritus (11% vs 3%)(Musselman et al., 2004). These adverse events were mild to moderate in severity and transient. There was a slightly lower mean sitting heart rate with dabuzalgron, but there were no differences in mean systolic or diastolic blood pressure between dabuzalgron and placebo.

In wild-type mice, dabuzalgron treatment (1 to 100 µg/kg/day, oral gavage twice daily) for 5 days did not affect body weight, heart weight, heart rate, or blood pressure compared to vehicle-treated mice (Beak et al., 2017).

CCF219B (formerly known as Compound 3): As of 2025, CCF219B is in pre-investigational new drug (IND)-enabling studies and the 14-day repeated dosing studies in both rats and dogs have been completed without any major adverse reactions, including changes in blood pressure (Papay et al., 2025).

In a mouse model of Alzheimer's disease (3xTg-AD mice), CCF219B treatment (2.6 mg/kg/day) after 1 and 6 months did not significantly alter mean systolic blood pressure (Papay et al., 2023). In separate studies performed by ReMYND, CCF219B treatment at a much higher dose (40 mg/kg/day, orally) for 2

weeks in 9-month-old hAPP-Tg mice also did not significantly change blood pressure compared to vehicle-treated mice. There were also no effects on general health or body weight.

Cirazoline: In wild-type mice treated with an α1A-AR-selective agonist cirazoline (10 mg/L of bottled water), no adverse events were observed (Doze et al., 2011).

Genetically modified mouse models: In a study of mice engineered to express a constitutively active mutant (CAM) form of α1A-AR (CAM-α1A-AR mice), no adverse effects were noted; however, one case of endocarditis/myocarditis was seen (Doze et al., 2011). Body weight in CAM-α1A-AR mice and wild-type mice was compared into old age (10-14, 16-20, and 22-24 months old) and was unaffected by long-term α1A-AR activation.

Drug interactions: Drug interactions with α1A-AR agonists have not been documented.

Sources and dosing:

CuraAX, also known as CST-3056, is under development by CuraSen Therapeutics for the treatment of neurogenic orthostatic hypotension and Alzheimer's disease (CuraSen pipeline). Dosage is not established and the ongoing phase I study is testing various doses.

CCF219B is undergoing pre-investigational new drug (IND)-enabling studies, as of 2025 (Papay et al., 2025).

Research underway:

In February 2025, CuraSen Therapeutics treated the first subject in the phase I trial of CuraAX (also known as CST-3056) to treat neurogenic orthostatic hypotension, a condition characterized by a sudden and significant drop in blood pressure upon standing (BioSpace.com). This trial is aimed to assess CuraAX's dosage levels and tolerability, pharmacokinetics, and safety in 56 healthy volunteers. The study will also investigate food effects in a cohort of 6 subjects.

Search terms:

Pubmed, Google: α1A-adrenergic receptor agonists, CST-3056, CCF219B, dabuzalgron

- + Alzheimer, + dementia

Websites visited for CST-3056, CCF219B, dabuzalgron:

- Clinicaltrials.gov (0)
- NIH RePORTER (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)