

*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.*

## Fasudil

### Evidence Summary

Fasudil is efficacious for certain vascular conditions; however, it is unclear whether it will be beneficial in Alzheimer's disease.

**Neuroprotective Benefit:** Some preclinical studies suggest a potential benefit with fasudil, but there is no clinical data to support its use.

**Aging and related health concerns:** Fasudil is efficacious for certain vascular indications.

**Safety:** Short-term use is safe with few adverse effects; however, it is unclear how safe the drug is for chronic use.

**What is it?**

Fasudil (also known as HA-1077 or AT877) is an inhibitor of Rho-kinase (ROCK). There are two isoforms of ROCK (ROCK1 – expressed in liver, testes and kidney; ROCK 2 – expressed in brain and skeletal muscle), both of which are inhibited by fasudil. ROCK mediates its downstream effects through myosin light chain (MLC) and is reportedly involved in actin cytoskeleton organization, cell migration, smooth muscle contraction, chemotaxis, cell adhesion, ROS formation, tau phosphorylation, autophagy, and apoptosis. Clinical trials for fasudil started in the early 1990's, before the discovery of ROCK (1996), and was initially reported as an intracellular  $\text{Ca}^{2+}$  channel blocker. At higher doses, fasudil may inhibit other kinases including PKA, PKG and PKC, possibly limiting some of its applications.

Asahi Kasei Pharma Corporation received approval for fasudil in Japan in 1995 for the treatment of cerebral vasospasm. The company entered into a licensing agreement with CoTherix to develop fasudil in the United States and Europe for the treatment of cardiovascular diseases, such as pulmonary arterial hypertension (PAH), in 2006 (the composition of matter patent ended in 2016).

**Neuroprotective Benefit:** Some preclinical studies suggest a potential benefit with fasudil, but there is no clinical data to support its use.

*Types of evidence:*

- 1 case-study of 2 dementia patients with wandering symptoms
- Human Alzheimer's disease post-mortem data for increased ROCK expression
- 3 preclinical studies in mouse models of Alzheimer's disease or aging
- *In vitro* studies for anti-inflammatory effects

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

None

*Human research to suggest benefits to patients with dementia:*

In one case study of two dementia patients with wandering symptoms, periodic treatment with fasudil at 30-60mg/day improved wandering symptoms and increased MMSE scores by about 3 points. The study was published in 1996, of relatively poor quality, and is confounded by other drugs ([Kamei et al, 1996](#)).

Human autopsy data suggests that ROCK1 protein is elevated in patients with asymptomatic Alzheimer's, MCI, and Alzheimer's disease ([Henderson et al, 2016](#)). In addition, human autopsy data suggests that ROCK1 and ROCK2 protein levels are elevated in patients with two tau neurodegenerative diseases (progressive supranuclear palsy and corticobasal degeneration) ([Gentry et al, 2016](#)).

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

In an animal model of Alzheimer's disease, high-dose fasudil (10mg/kg) improved cognition, decreased hippocampal neuron death, and decreased inflammatory markers in the hippocampus (IL-1 $\beta$ , TNF $\alpha$ , NFkB) ([Song et al, 2013](#)). In an animal model of cognitive dysfunction (cerebral streptozotocin injection), fasudil treatment over 4 weeks reversed cognitive decline and increased the number of synapses in the hippocampus ([Hou et al, 2012](#)). In an aged rat model, 4 daily injections of fasudil were associated with dose-dependent improvements in cognition ([Huentelman et al, 2009](#)).

One potential mechanism for fasudil's improvements in Alzheimer's animal models may be due to its anti-inflammatory effects. In microglia cell cultures exposed to advanced glycation end products (which activate the ROCK pathway), fasudil decreased ROS production, NLRP3 expression, NFkB nuclear localization, iNOS expression, COX expression and promoted an anti-inflammatory microglial phenotype ([Chen et al, 2017](#)). Another potential mechanism by which fasudil might be beneficial in Alzheimer's disease is its ability to induce autophagy. In a transcriptional network analysis looking for drugs that might be repurposed, [Iorio et al \(2010\)](#) reported that fasudil induces a transcriptional response similar to other autophagy inducing drugs and was confirmed to induce autophagy in human fibroblasts.

*APOE4 interactions:*

None reported

**Aging and related health concerns:** Fasudil is efficacious for certain vascular indications.

*Types of evidence:*

- Multiple RCTs in multiple vascular indications (most related to vascular spasms)
- Preclinical animal studies in stroke and atherosclerosis and lifespan

*Longevity*

In a screen of protein kinases that might increase lifespan in *Drosophila*, fasudil was reported to increase lifespan by 14.5% ([Spindler et al, 2012](#)).

### Subarachnoid Hemorrhage

Fasudil was approved in Japan for surgical treatment of subarachnoid hemorrhage. In a double-blinded RCT in 267 patients undergoing surgery for subarachnoid hemorrhage, treatment with fasudil (30mg/day IV within 24 hours of surgery for 14 days) reduced angiographically demonstrable vasospasm by 38%, symptomatic vasospasm by 30%, and the number of patients with poor clinical outcome associated with vasospasm by 54% compared to placebo. There were no serious adverse events associated with fasudil ([Shibuya et al, 1992](#)).

Two randomized open trials compared fasudil (30mg 3xday IV for 14 days) to nimodipine (a calcium channel blocker) after subarachnoid hemorrhage surgery and reported similar efficacy or better clinical outcomes with fasudil treatment. Adverse events between drugs were similar ([Zhao et al, 2006](#); [Zhao et al, 2011](#)).

### Angina

Eighty-four patients with stable angina received either oral fasudil (titrated up to 80mg b.i.d.) or placebo for 8 weeks. Exercise duration was non-significantly improved compared to placebo, and angina score significantly improved (a score of the severity of angina). There were no differences in time to or frequency of angina. Fasudil did not affect heart rate or blood pressure ([Vicari et al, 2005](#)).

### Stroke

In a clinical study, 160 patients with acute ischemic stroke received either placebo or fasudil (60mg 2xday for 14 days). Fasudil improved neurological function and clinical outcome compared to placebo ([Shibuya et al, 2005](#)).

### Atherosclerosis

In a cross-over trial with healthy individuals or patients with coronary artery disease (n = 29), oral fasudil (40mg 3xday) for 30 days improved flow-mediated dilation (a measure of endothelial function) and decreased Rho-kinase activity in lymphocytes in coronary artery disease (CAD) patients but had no effect on healthy patients. There was no effect on endothelium-independent vasodilation in any group (suggesting that fasudil affects endothelial cells). Rho-kinase activity in lymphocytes was lower in healthy subjects than in CAD patients suggesting that fasudil did not decrease activity below a healthy baseline. Additionally, the percent change in Rho kinase activity was correlated with the percent improvement in flow-mediated dilation suggesting that it might be useful to measure Rho-kinase activity to see if the drug would be beneficial ([Nohria et al, 2006](#)). Fasudil was also reported to reduce lesion size in a mouse model of atherosclerosis ([Wu et al, 2009](#)).

**Safety:** Short-term use is safe with few adverse effects; however, it is unclear how safe the drug is for chronic use.

[Suzuki et al \(2007\)](#) conducted a post-marketing survey of 1,462 patients receiving fasudil after undergoing surgery for subarachnoid hemorrhage. Adverse events were similar between the post-marketing survey analysis and the phase 3 trial from [Shibuya et al \(1992\)](#), with the most common AEs including hemorrhage (1.7% of patients), blood and lymphatic system disorders (0.8%), and hepatic disorders (0.5%). Overall, fewer adverse events were reported in the post-marketing survey than in the placebo group from the phase 3 trial (3.8% vs. 5.7%), so it is difficult to tell whether any adverse events were drug-related rather than surgery-related. Since fasudil causes vasodilation, higher doses may lower blood pressure, especially in dehydrated patients ([Shibuya et al, 1992](#)). In an RCT in 84 patients with stable angina, fasudil and placebo had similar numbers of side effects ([Vicari et al, 2005](#)). Importantly, fasudil is only given temporarily after subarachnoid hemorrhage and no clinical trials have investigated use of the drug longer than eight weeks, so long-term effects are unclear. It is not clear if there are other drug-drug interactions.

#### Sources and dosing:

Fasudil is only available with prescription in Japan from Asahi Kasei Pharma Corporation. Doses used in clinical trial for the oral formulation range from 20-80mg three times per day and for the intravenous formulation 30mg three times per day.

#### Research underway:

Fasudil is currently undergoing a trial for ALS according to [clinicaltrials.gov](https://clinicaltrials.gov), however the status is unknown ([NCT01935518](#)). It is reported to be taking place in China and was supposed to be completed in March 2015.

#### Search terms:

Pubmed:

- fasudil + Alzheimer, cognition, dementia, longevity, aging

Websites visited for Fasudil:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Treato.com](https://treato.com)
- [DrugAge \(0\)](#)
- [Geroprotectors \(0\)](#)

- Drugs.com
- WebMD.com

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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).*