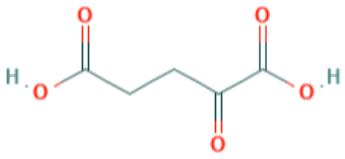
Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists 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.

Alpha-ketoglutarate

Evidence Summary

If the reported mechanisms are true (inhibition of mTOR and ATP-synthase), there may be a rationale for boosting alpha-ketoglutarate levels in the cell, but alpha-ketoglutarate itself does not get into cells well.

Availability: Sold by Rejuvant	**Dose**: 1000mg calcium alpha-ketoglutarate; 900mcg Vitamin A; 190mg Calcium	**Chemical formula:** $C_5H_6O_5$ **MW:** 146.1g/mol  **Source:** Pubchem
Half life: Not reported	**BBB**: Unknown	
Clinical trials: None in Alzheimer's or age-related diseases	**Observational studies**: 0	

What is it?

Alpha-ketoglutarate (AKG) is a metabolite involved in energy production and amino acid synthesis. It is part of the Krebs cycle and a precursor for several amino acids (e.g. glutamate, glutamine, leucine, and proline). In the Krebs cycle, alpha-ketoglutarate dehydrogenase (AKGDH), the rate-limiting step in the Krebs cycle, decarboxylates AKG to succinyl-CoA. Studies in *C. elegans* suggest that AKG may also inhibit mTOR and/or ATP-synthase. In Alzheimer's patients, there is a downregulation of AKGDH in post-mortem tissue, suggesting a possible rationale for boosting AKG levels. However, AKG is charged and not very cell permeable (thus concentrations used in lifespan studies are high) (Bayliak et al, 2017).

Intravenous AKG is sometimes used during heart surgery, for preventing muscle breakdown during surgery or trauma (WebMD), and in dialysis patients to prevent ammonia buildup (rxlist.com).

Lifespan studies

Chin et al (2014) reported that AKG (8mM) extended lifespan in *C. elegans* by ~50% and delayed age-related phenotypes (such as body movement) and reduced oxygen consumption. Inhibition of AKG dehydrogenase, which metabolizes AKG, also extended lifespan. They reported that AKG binds to and inhibits ATP-synthase and confirmed that in ATP-synthase knock-down experiments, AKG no longer extends lifespan (whereas in *daf-2* mutants, AKG further extends lifespan). Lifespan extension also required the TOR pathway, and treatment with AKG induced autophagy. Life extension with AKG was dose-dependent, with the concentration for maximal lifespan at 8mM. The reason for the high levels of AKG needed are possibly because AKG is a charged molecule that does not readily cross the cell membrane (Baylink et al, 2017). Although the previous study suggested that ATP-synthase and mTOR were required for lifespan extension in *C. elegans*, another study suggested that an AKG mimetic, 2,4-PDA, also increased lifespan and was dependent on HIF-1, as both HIF-1 knockout and a constitutively active HIF-1 abrogated these effects (Mishur et al, 2016).

In adult flies, supplementation with AKG increased median lifespan by 8.54% in a similar dose-response pattern seen in *C. elegans*. It also decreased fecundity, increased climbing ability, and increased tolerance to heat stress, but had no effect on tolerance to oxidative stress or change in triacylglyceride levels. AKG increased the expression of genes downstream of AMPK, reduced ATP levels, reduced the expression of genes downstream of mTOR, and increased the expression of autophagy genes (Su et al, 2019). Another study suggested that supplementation with AKG in flies increased protein, glucose, and triacylglyceride levels. Supplementation with AKG conferred protection from heat shock, but not oxidative stress or starvation (Baylink et al, 2017). Another fly study suggested mixed results with AKG

supplementation with no benefits in male flies (and a decrease in lifespan at the highest concentration) and an increase in lifespan in female flies (Lylyk et al, 2018).

Ca-AKG was reported to increase total antioxidant status of aged mice and improve arterial elasticity. This was reported to be due to its function as an antioxidant (Niemiec et al, 2011). In another mouse study, dietary AKG was reported to promote skeletal muscle hypertrophy through an increase in protein synthesis (via activating mTOR) (Cai et al, 2016).

Safety and drug interactions: There is currently no safety data on human use of AKG supplementation or potential drug interactions.

Sources and dosing: Sold by Rejuvant at 1000mg/day.

Research underway: None listed on clinicaltrials.gov.

Search terms:

alpha-ketoglutarate + lifespan, aging,
alzheimer
calcium alpha-ketoglutarate [best match]

Websites:

- Clinicaltrials.gov
- Pubmed