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.

Trehalose

Evidence Summary

Some preclinical evidence suggests benefits in multiple indications, but there is very little data from human studies.

Neuroprotective Benefit: Trehalose provides benefits in some studies of neurodegenerative disease, but the evidence is scant.

Aging and related health concerns: Trehalose might be beneficial for some indications, but there is still very little evidence.

Safety: A few small, unpublished studies of IV trehalose reported no adverse events up to one year, and there is not a strong rationale for it to be dangerous.

What is it?
Trehalose is a glucose disaccharide synthesized by bacteria, fungi, plants, and invertebrates. It is responsible for the ability of many organisms to withstand long periods of desiccation. In humans, it is broken down into glucose in the gut by the enzyme trehalase. In cell culture, worms, and mice, it stabilizes proteins and modifies energy metabolism by inhibiting sugar transporters. The therapeutic interest in trehalose, however, is due to its ability to increase autophagy in an mTOR independent manner.

Neuroprotective Benefit: Trehalose provides benefits in some studies of neurodegenerative disease, but the evidence is scant.

Types of evidence:

- 2 preclinical studies in Alzheimer's mouse models
- Preclinical studies in animal models of Huntington's, Parkinson's, ALS, prion disease, and Batten disease
- *In vitro* protein aggregation and inflammation studies

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:
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
A study in an Alzheimer's amyloid animal model reported that trehalose improved cognition and reduced amyloid beta deposition in the hippocampus (Du et al, 2013). In an Alzheimer's tau animal model, trehalose increased markers of autophagy, decreased tau levels, and decreased neuronal death in the brain (Schaeffer et al, 2012).

Oral and intraperitoneal (IP) trehalose also increased lifespan and/or delayed disease progression in mouse models of Huntington's, ALS, and prion disease – primarily by a reduction in the aggregation of misfolded proteins. Trehalose also decreased inflammation and increased markers of autophagy, possibly by increasing nuclear localization of an autophagy transcription factor, TFEB (Emanuele, 2014;

Castillo et al, 2013; Palmieri et al, 2016; Tanaka et al, 2004). In an *in vitro* study, trehalose prevented the production of inflammatory cytokines (IL-1β, IL-6, and TNFα) and nitric oxide in microglia exposed to LPS or alpha-synuclein. In addition, when microglia were pre-treated with trehalose, neuron death was mitigated in neuron/microglia cultures exposed to LPS or alpha-synuclein (Bussi et al, 2017). Some *in vitro* studies suggest that trehalose can directly prevent the aggregation of misfolded proteins (Emanuele, 2014).

APOE4 interactions:
None reported

Aging and related health concerns: Trehalose might be beneficial for some indications, but there is still very little evidence.

Types of evidence:

- 2 human studies for cardiovascular function, metabolism, and Oculopharyngeal Muscular Dystrophy (OPMD)
- Preclinical mouse studies for aging, atherosclerosis, non-alcoholic fatty liver disease, and OPMD
- 1 C. elegans study for longevity
- Multiple cell culture studies

Longevity
In one lifespan study in *C. elegans,* early treatment of trehalose increased mean lifespan by 30% while late treatment (toward the end of life) increased mean existing lifespan by 60%. Trehalose also increased reproductive span in *C. elegans* and reduced lipofuscin aggregates (Honda et al, 2010).

Pagliassotti et al (2017) treated young and aged mice with trehalose (2% in drinking water) for four weeks. There was no change in plasma glucose, plasma triglycerides, or liver triglycerides with treatment. Trehalose reduced the increase in liver transaminases seen in old mice. In addition, trehalose reduced liver markers of ER stress, increased liver markers of autophagy, and decreased plasma inflammation in old mice. There were no changes in any measures in young mice.

In vitro experiments in human fibroblasts, endothelial cells, and ESC-derived neurons infected with cytomegalovirus suggested that trehalose induced autophagy, reduced the expression of virus proteins, and reduced levels of cell-free virus (Belzile et al, 2016).

Cardiovascular

Kaplon et al (2016) reported that in middle age/elderly patients, 12 weeks of oral trehalose (100g/day) (but not maltose) slightly improved endothelial function compared to baseline. However, there were no changes in inflammatory cytokines or pulse wave velocity.

Sergin et al (2017) reported a decrease in autophagy markers in advanced atherosclerotic plaques in animal and human tissue. Additionally, they reported that mice with atherosclerosis overexpressing TFEB in macrophages had increased autophagy in lesion sites, decreased lesion size, decreased apoptosis in lesion sites, and decreased plasma levels of IL-1β. These phenotypes, with the exception of decreased IL-1β, were mediated by the autophagic pathway – suggesting another mechanism for TFEB to decrease IL-1β. Intraperitoneal (IP) trehalose in an atherosclerosis mouse model increased autophagy in aortic roots and decreased lesion size. Interestingly, IP trehalose, but not oral administration, increased serum trehalose levels, and oral trehalose had no effect on lesion size.

Non-Alcoholic Fatty Liver Disease (NAFLD)

Mizote et al (2016) reported that in patients with a BMI > 23, 10g/day of oral trehalose over 12 weeks improved performance on the oral glucose tolerance test but did not change HbA1c or HOMA-IR.

In an animal model of NAFLD (high fructose diet), trehalose (10 days, 3% in drinking water) decreased plasma and liver levels of triglycerides, cholesterol, and free fatty acids. In addition, it increased markers of autophagy and decreased fat in the liver. A single oral administration increased serum levels of trehalose at 30 minutes but not 1 hour. However, markers of autophagy in the liver remained elevated for 4 hours (DeBosch et al, 2016).

In vitro experiments suggest that GLUT8, AMPK1, and ULK1 partially mediated trehalose-induced autophagy. Trehalose also partially inhibits mTORC1, but this does not seem to be responsible for its ability to induce autophagy. The exact mechanism of trehalose-mediated autophagy is still being investigated (Mayer et al, 2016; DeBosch et al, 2016).

Oculopharyngeal Muscular Dystrophy/Spinal cerebellar ataxia

Bioblast Pharma reported that intravenous trehalose (13.5g or 27g/week) showed stabilization of spinal cerebellar ataxia, and another study suggested improvements in multiple secondary efficacy endpoints versus baseline in patients with OPMD(press release, press release). Anecdotal evidence suggest stabilization of patients with SCA ingesting 40-90g/day (website).

Bioavailability

Trehalase, an enzyme that breaks trehalose into two glucose molecules, is expressed in the intestines, kidneys, and liver (Muller et al, 2013). However, individuals may have different genetic variations that determine human trehalase activity (Muller et al, 2013). Therefore, it is difficult to predict the effects of oral trehalose in individuals (Oku and Nakamura, 2000). Animal studies using the same concentrations of oral trehalose reported either an increase in plasma trehalose after 30 minutes or no change (DeBosch et al, 2016; Sergin et al, 2017). It is unclear why there are variable results, and more human pharmacokinetic studies are needed to determine whether oral trehalose will be beneficial.

Because of the expression of trehalase in the intestines, intravenous trehalose has been proposed as an alternative means for treatment. Bioblast Pharma is currently using this approach. The company reported that in eleven patients 30g weekly infusions for 9-16 weeks was safe. Levels of plasma trehalose reached expected concentrations (1000-2000 mg/mL after 1 hour up to 5 hours) (Argov, 2015).

Safety: A few small, unpublished studies of IV trehalose reported no adverse events up to one year, and there is not a strong rationale for it to be dangerous.

Types of evidence:

- Two small studies of intravenous trehalose

Ingestion of trehalose is generally safe as part of the diet (trehalose is a GRAS listed substance) and doses up to 50g have generally been safe. Depending on how well an individual can digest trehalose, increased doses may lead to gastrointestinal side effects.

The safety in intravenous trehalose is less well known. 24 30g/week treatments in small numbers of patients were reported as safe (Argov, 2015; Press release), with small changes in plasma glucose and short term glucosuria (glucose in the urine), but there are no long-term studies. Bioblast pharma also reported that intravenous trehalose (13.5g or 27g/week) up to one year resulted in no serious adverse events. There is no strong reason to believe trehalose will be dangerous, but there is little data. Preclinical studies do not report adverse effects.

Drug Interactions:
There are no known drug interactions for oral trehalose. Drug interactions for IV trehalose have not been investigated.

Sources and dosing:
Trehalose is available online or at supplement stores. Prepared intravenous trehalose may not be available. Oral doses vary widely from 40-90g/day (anecdotal evidence) to 10-100g/day (clinical studies). Safety IV studies used weekly 30g infusions while clinical studies have used weekly 13.5-27g infusions.

Research underway:
Oral trehalose is currently being investigated as an add-on therapy for bi-polar disorder (NCT02800161).

BioBlast Pharma is reportedly doing a Phase 2b study for OPMD (here).

Junaxo is reportedly developing oral trehalose as a medical food for Parkinson's (here).

Search terms:
Pubmed:

- **trehalose + alzheimer, cognition, bioavailability, lifespan, longevity, atherosclerosis, diabetes, cardiovascular, aging, neuropathy**

Google:

- Trehalose, Trehalose intraventricular