CAN Trehalose HELP ALLEVIATE HUNTINGTON OR ALZHEIMER DISEASE?

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[Received August 5, 2007; Accepted: October 8, 2007]

ABSTRACT: Trehalose, a disaccharide of glucose + glucose with an α,α-1,1 bond, when made available to proteins in states of severe dehydration, has been shown to have physico-chemical properties that make it possible to replace water molecules being lost from the protein, thereby keeping the protein 3-dimensional structures in place. Such events are of crucial importance to stabilize proteins during thermal dehydration and freeze-drying on the effect of trehalose on brain function associated protein structures. One in vivo, in a mouse model of Huntington disease and one in vitro, to study the aggregation process of beta-amyloid proteins known to be involved in the etiology of Alzheimer’s disease. In the papers of both studies, that observed positive outcomes, it was suggested that oral trehalose might be beneficial to patients suffering from these diseases. Careful evaluation of the digestion, absorption and metabolism of trehalose, however, indicates that more research is required before any recommendation is justified.

KEYWORDS: Alzheimer disease, Huntington disease, Trehalose

INTRODUCTION

Trehalose is a disaccharide composed of 2 glucose units connected by an α,α-1,1 linkage, compared to maltose that has a similar disaccharide composition but differs in the saccharide bond (α-1,4). The specific bond of trehalose impacts on its digestion and post-absorptive metabolism, resulting in a moderately reduced glycemia and a significantly reduced insulinemia compared to maltose. Trehalose is known to have extraordinary properties in terms of its ability to help preserve protein structures in stressful conditions avoiding their denaturation and aggregation. The latter has recently triggered scientific attention for disease conditions that involve protein folding and aggregation, such as Huntington and Alzheimer Disease. Trehalose was originally identified by Wiggers as an unknown sugar in a fungal crop blight, called “ergot”, which plagued farmers, affecting rye, cereals and corn. Later Berthelot (Wiggers 1963) found trehalose in the Larinus beetle, which was used in Persia and Ottoman Empire for medicinal purposes and was called Trehala, the precursor word of Trehalose. In the early 70’s Crowe (1984) observed anhydrobionts to synthesize up to 25% of their body weight as trehalose during periods of progressing dehydration. This formation of trehalose was thought to be required to endure long periods of up to 99% water loss and start “living again” once some water is available.

Today trehalose is being produced industrially using food grade enzymes from Arthrobacter ramosus, Pseudomonas amylofera, Bacillus stearothermophilus (Maruta K. 1994) In October 2000 trehalose was posted as “Generally Recognized As Safe (GRAS)” for human consumption through a notification at the FDA website (FDA, USA, Oct 5, 2000) and in Sept 2001, the EU Commission approved trehalose as a novel food for the European market allowing its use as food ingredient in all foodstuffs. The current low cost of producing trehalose has made this sugar of particular interest for many protein stabilization applications ranging from medicine to food. In 2000 Crowe & Crowe published a wonderful review paper in Nature Biotechnology under the title “Preservation of mammalian cells: learning nature’s tricks” in which the history of this exiting molecule in nature is described. Several theories have been put forward on how trehalose is able to function in keeping 3-dimensional protein structures intact when the water molecules are being lost from it during dehydration. 1) Formation of a water layer around the protein often referred to as glass transition, entrapping water molecules inside, 2) Full replacement of water molecules in the spatial protein structure, keeping the full 3-dimensional structure intact, and 3) Mechanical entrapment, by which trehalose forms a higher viscosity layer around the protein and water molecules are trapped on the protein surface to keeps its structures in place. Independently of which theory is most acceptable, trehalose has been observed to be able to stabilize proteins during thermal dehydration and freeze-drying and its application for in vitro preservation of cells has been studied extensively for cell, tissue and food preservation. In 2001 Tablin et al. reviewed that during extensive dehydration membrane
fusion, membrane leaking and structure loss of organelles proteins takes place. This induces leakage of cell contents from internally to the environment, disturbed cell membrane organization and impaired cell function and viability. It was shown that these events that can be prevented by making trehalose available to the cells so that during the subsequent rehydration phase transition of the cells trehalose prevents damage to cell membranes. It was also shown that trehalose helps prevent protein aggregation during chilling which had significant implications for long term storage of cells and tissues. For example, when trehalose was introduced in the system during freeze-drying, fully functional platelets were recovered after subsequent rehydration, something that was impossible without it (Crowe et al 2003). Low concentrations (0.2 M) of trehalose were shown to permit long-term post-thaw survival of human keratinocytes and fibroblasts (Eroglu et al 2000). Additionally it was shown that trehalose protects corneal epithelial cells from death by drying (Matsuo 2001) and that cryo-preservation of fetal skin is improved by extra-cellular trehalose (Erdag et al 2002). It needs to be noted here that in all these experiments trehalose was used as intact molecule. Lately, because of its properties to stabilize proteins, trehalose has been used in trials of food preservation, showing that its addition to protein rich foods like tempeh, miso, surimi, fish and vegetables improves significantly the maintenance of their structural protein characteristics during freezing and subsequently thawing, or during drying and subsequent rehydration (Patist and Zoerb 2005).

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Recently two publications have shed a beneficial light on the protein structure preserving properties of trehalose and its theoretical potential to help reduce the derangement of structures that are known to cause functional disorders of the brain, as observed in Alzheimer Disease and Huntington Disease.

In 2004 Tanaka et al published data showing that trehalose alleviates poly-glutamine mediated pathology in liver and brain in a mouse model of Huntington disease. These authors found that due to this effect the life span and motor function of the mice was significantly improved. Based on the beneficial effects observed, the authors concluded that lack of toxicity and high solubility coupled with efficacy upon oral administration make trehalose promising as a therapeutic agent. Their publication lead to a comment by Archibald (2004) in the Lancet entitled “A spoonful of trehalose makes the protein aggregations go down”, a title which is suggests that oral trehalose may be helpful to Huntington Disease patients.

Recently, Liu et al (2005) published data showing that trehalose differentially inhibits aggregation and neurotoxicity of beta-amyloid proteins. Their data provided evidence that aggregation of beta-amyloid into soluble oligomeric forms is a pathological step in Alzheimer’s disease and can be inhibited by trehalose. Based on their findings the authors concluded that the use of trehalose “as part of a potential therapeutic cocktail” for Alzheimer patients deserves further study.

The observations of Tanaka (2004) and Liu (2005) are highly interesting but leave us with a number of questions that cannot be ignored. In the study of Tanaka (2004), trehalose was given orally to R6/2 transgenic and wild type mice in drinking water, which the mice spontaneous drank. However, no measurement of the intact sugar in circulation was performed. Their control, glucose, did not show any effect. This raises the question whether it possible that trehalose can be absorbed intact from the small intestine and whether it can subsequently pass the blood brain barrier. In the study of Liu (2005) trehalose was added, as intact molecules, to the in vitro system. The effects observed in this particular study, as well as all other effects observed on red and white blood cell preservation and tissue preservation (see some citations above) are related to the intact disaccharide. This presents a potential hurdle, as in humans, trehalose consumed at typical dietary rates is known to be digested in the small intestine by membrane bound trehalase, which splits the disaccharide into free glucose, which is available for subsequent absorption.

Clearly, trehalose warrants further study as a potential preventative or therapeutic agent for Huntington’s, Alzheimer’s and other diseases with an etiology that includes protein aggregates as a principal lesion. However, although in vitro models have been useful to demonstrate a possible mode of action for trehalose’s efficacy in vivo, given what we know of trehalose’s typical post-ingestion digestive and metabolic fate, clinical data need to be developed demonstrating both location and rate of intact trehalose absorption against an oral dose response curve. Additionally, an understanding of the minimum circulating trehalose concentration, and required location for efficacy (brain or periphery), that would elicit significant ameliorative effects against pathological protein aggregations needs to be elucidated. Site of action is made even more critical, as evidence demonstrating the ability of trehalose to cross the blood-brain barrier does not currently exist. Until this work has been completed, the hypothesis that oral trehalose can be useful as part of a treatment program for Huntington or Alzheimer patients remains equivocal.

REFERENCES


FDA, USA, Oct 5 2000: trehalose is GRAS. (http://vm.cfsan.fda.gov/~rdb/opa g045.html)


