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Trehalose – Current Applications in Ophthalmology And Future Perspectives

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ABSTRACT

Trehalose, a disaccharide of glucose, is a stress response factor synthetized by many organismims when cells are exposed to stressful conditions, including dehydration, heat, oxidation, hypoxia or even anoxia. Trehalose is not synthesized by mammalian cells; however, it has been recently demonstrated to have a number of unique properties that point to its utility in humans. Trehalose enables wound healing by protecting cells, especially cell membranes, from oxidative injury and dessication. In the injured cornea trehalose suppresses inflammation, scar formation and corneal neovascularization. In dry eye disease trehalose decreases cell apoptosis a reduces inflammatory and proteolytic activity at the ocular surface. Trehalose may prevent neurodegenerative disorders by stabilizing proteins and promoting autophagy. In animal models of neurodegenerative disorders trehalose decreases levels of toxic protein aggregates, increases autophagy and improves clinical symptoms and survival. The low toxicity of this bioactive sugar allows its administration in humans for extended periods and enables its use in various disease states.

KEYWORDS : STRESS RESPONSIVE FACTOR, DRY EYE, NEURODEGENERATION

INTRODUCTION

Trehalose is a nonreducing disaccharide of glucose that is produced and stored in many lower and higher forms of organisms, including bacteria, yeast, fungi, insects, intervertebrates and plants.[1] It does not occur in mammalian cells, although humans have the enzyme trehalase in intestinal villae cells and in kidney brush border cells, probably to handle ingested trehalose.[2] Trehalose is synthetized in lower organisms as a stress responsive factor when cells are exposed to environmental stress conditions such as heat, cold, dessication and oxidation. When these organisms are exposed to stress, they adapt by synthesizing huge amounts of trehalose, which helps them to retain the cellular integrity. This is thought to occur by prevention of denaturation of proteins by trehalose, which would otherwise degrade under stress.[3] Recently, our understanding of the role of trehalose has expanded, and it has been implicated in various situations in mammals.

Trehalose – a stress-responsive factor

Trehalose has been used to protect cells of the anterior eye surface against dessication, particularly in dry eye disease.[4-9] Trehalose suppressed pro-inflammatory cytokine induction and matrix metalloproteinase expression in corneal and conjunctival epithelial cells. The effect of trehalose was potentiated by addition of hyaluronate, an anionic glycosaminoglycan polysaccharide with lubricative and water-retaining properties.[10,11] Trehalose protected cell membranes against oxidative damage and reduced cell apoptosis and inflammation in in vivo as well as in vitro studies.[12-16] Cejkova et al.[12-14] described that trehalose strongly reduced serine protease, matrix metalloproteinase and xanthine oxidase expressions in the corneal epithelium damaged by oxidative stress, suppressed cell apoptosis and decreased the development of an antioxidant/pro-oxidant imbalance which significantly accelerated corneal healing and reduced corneal neovascularization.These antiinflammatory and antioxidant effects of trehalose are very important because oxidative stress accompanies a number of severe corneal injuries (including corneal alkali burns) and is involved in human corneal diseases, such as keratokonus, bullous keratopathy and Fuchs' endothelial dystrophy.[17,18] Takeuchi et al.[19,20] suggested that trehalose has the potential for the use as a new agent to control fibrosis – and is thus promising for the use in glaucoma surgery. These authors found in in vitro experiments that growth activities of cultured fibroblasts and keratinocytes were inhibited by trehalose in a dose-dependent manner. Fibroblasts were strongly inhibited by trehalose concentrations 5% of trehalose, whereas keratinocytes were less inhibited compared to fibroblasts. Expressions of vimentin and α-smooth muscle actin were reduced by trehalose. With in vivo experiments, postoperative application of trehalose resulted in less firm adhesion between conjunctiva and sclera compared to controls. Immunohistochemical studies showed reduced staining of isolectin B4, vimentin and α-smooth muscle actin in conjunctival wounds treated by topical trehalose. Also, after trabeculectomy, intraocular pressure remained in a low range during instillation of topical trehalose solution. Kateuchi et al.[19,20] concluded that trehalose has inhibitory effects on proliferation of fibroblasts and vascular tissues, partially due to inhibition of transformation of fibroblasts into myofibroblasts in wound tissues.

Trehalose - a cryoprotectant and an effective agent in neurodegenerative diseases

Trehalose was considered as a cryoprotectant.[21,22] These authors report that the introduction of low concentrations of intracellular trehalose can greatly improve the survival of mammalian cells during cryopreservation. Using a genetically engineered mutant of *Staphylococcus aureus* α-hemolysin to create pores in the cellular membrane, the authors were able to load trehalose into cells. Low concentrations (0.2 M) of trehalose permitted long-term post-thaw survival of more than 80% of 3T3 fibroblasts and 70% of human keratinocytes. These results indicate that simplified and widely applicable freezing protocols may be possible using trehalose as intracellular cryoprotective additive.

Trehalose protected both hypoxic and anoxic injury[1,14] and inhibited the proinflammatory phenotype in a transgenic mouse model of oculopharyngeal muscular dystrophy: it reduced aggerage formation and delayed the pathology of this disease.[23] Trehalose significantly protected prion-infected cells from induced oxidative damage in cellular models of Alzheimer's and and Huntington's disease.[23] Trehalose delayes the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons.[25] According to Emanuele[26] trehalose may act in neurodegenerative diseases as a potent stabilizer of proteins and is able to preserve protein structural integrity. Wada et al.[27] elucidate the role of trehalose in neurodegenerative diseases as follows: Autophagy is a catabolic process that involves degradation of unnecessary or dysfunctional cellular components through the action of lysosomes. The accumulation of abnormal proteins in neural cells is a common feature in neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease and prion diseases, and which causes the progression of such diseases. The accumulated proteins can be decreased by autophagy, which leads to an increased survival of neural cells and improvement in the disease condition. The authors[27] further explain that although other autophagy inducers, such as rapamycin and ver-

apamil exist, trehalose is a food constituent and thus attracts special attention as a safe candidate for the treatment of neurodegenerative diseases. However, orally taken trehalose is digested by the hydrolyzing enzyme trehalase expressed in the intestine and kidney, making its bioavailability lower. Therefore Wada et al.[27] developed enzyme-stable analogs of trehalose, such as lentztrehalose, that may be more beneficial for human health.

Conclusions

Trehalose is naturally occurring non-toxic bioactive sugar with unique properties which proves it for a large therapeutic use in various human disease states.

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