# Amyotrophic Lateral Sclerosis (ALS): Stimulating Proteasome Activity in Motor Neurons to accelerate degradation of misfolded proteins

By

**Choctaw Doc***

One of the players in ALS as well as many other neurodegenerative diseases is misfolded intracellular proteins (Click to access a review paper that delves into this). Click this link to read a National Institute on Aging (NIH) on TDP-43 and ALS. Ordinarily proteasomes inside cells ably regulate the concentration of particular proteins and degrade misfolded proteins. In ALS and other diseases this process breaks down. With the thought in mind that *maybe*, just maybe kicking the activity of proteasomes into high gear might speed up the degradation of misfolded proteins like TDP-43 (in ALS) I pondered ways to pull this off. Interestingly, a line of research involving how glycerol stimulates proteasomal activity crossed my desk at the very moment I launched out on this quest (2006). Armed with this, I proceeded to combine glycerol with a variety of non-pharmaceutical neuroprotective compounds and farm this out to friends involved in bench research. Long story short one particular combo seemed to outperform other permutations in petri dish cultures. Will it do anything for, say, people with ALS? No one knows. But as only natural compounds are involved (and glycerol molecules transverse the blood-brain barrier) there is nothing to preclude ALS & other neurodegenerative disease patients trying it with their primary care physician's consent and response monitoring/testing. Here is the formula tweaked for use in yogurt or smoothies or such:

Each day: Mix 0.75 mL per kg. body weight* vegetable glycerin + 4 tablespoons Now Sports Liquid Ribose (Each tbsp. contains 3.0 grams D-ribose & 500 mg. L-Carnitine) & 3-6 tbsp. coconut oil together. Blend this into 6 ozs. or so plain or flavored yogurt and eat throughout the day until completely consumed. This blend can alternately combined in whole or part with smoothie ingredients & fruit and consumed throughout the day. The main thing is that the glycerol/ribose/coconut oil mix is mixed up and completely consumed during the course of each day.

Nota bene: I have **no** commercial or other financial ties to any of the products mentioned herein.

* Let's say a person weighs 64 kgs (141 lbs) = 64 x 0.75 = 48 mL

Glycerol interactions, side effects & such: http://bit.ly/zDN11x

What is interesting is that the use of glycerol has since racked up a modicum of evidence indicating that it may serve an anti-aging function. It would be a hoot to see if it complements or synergizes with the activity of the telomerase activator, TA-65®.

Biogerontology. 2008 Aug;9(4):269-82. Epub 2008 Mar 15.

**Glycerol stimulates innate chaperoning, proteasomal and stress-resistance functions: implications for geronto-manipulation.**

Deocaris CC, Takano S, Priyandoko D, Kaul Z, Yaguchi T, Kraft DC, Yamasaki K, Kaul SC, Wadhwa R.

**Source**

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**Abstract**

Aging is associated with accumulation of toxic intracellular and extracellular protein aggregates. Cells manage "aged" proteins by mobilizing their molecular chaperones or heat shock proteins that are also considered as determinants of lifespan in diverse species. In this study, we tested whether an exogenous addition of the non-toxic chemical chaperone 'glycerol' could elicit stress and geronto-protective activities. We found that glycerol enhanced chaperoning of heat-denatured proteins. In addition to stimulating proteasome activity, glycerol led to an increased expression of the stress chaperone 'mortalin' and decreased p53 function in human cells. Glycerol-fed worms exhibited thermo-tolerance and lower level of age-associated auto-fluorescence. Through the combined stimulation of the proteasome and chaperoning activities of mortalin, in particular, glycerol treatment resulted in increased survival and fitness against oxidative- and heat-stress. These results may have significant implications in the use of glycerol as a candidate geronto-modulator in development of practical interventions for "healthy aging".

PMID: 18344010

*Web address:*
**http://www.sciencedaily.com/releases/2011/09/110920075516.htm**

# Human Body Rids Itself of Damage When It Really Matters

ScienceDaily (Sep. 21, 2011) — Although the body is constantly replacing cells and cell constituents, damage and imperfections accumulate over time. Cleanup efforts are saved for when it really matters. Researchers from the University of Gothenburg, Sweden, are able to show how the body rids itself of damage when it is time to reproduce and create new life.
"I have a daughter. She is made of my cells yet has much less cellular damage than my cells. Why didn't she inherit my cells including the damaged proteins? That's the process I'm interested in," says Malin Hernebring from the Department of Cell- and Molecular Biology at the University of Gothenburg.

A few days after conception, the cells in the embryo all look the same -- they are unspecified stem cells that can develop into any bodily cell type. As the process of cell specification (differentiation) begins, they go from being able to keep dividing infinitely to being able to do so only a limited number of times. This is when they start cleansing themselves.
"Quite unexpectedly we found that the level of protein damage was relatively high in the embryo's unspecified cells, but then it decreased dramatically. A few days after the onset of cell differentiation, the protein damage level had gone down by 80-90 percent. We think this is a result of the damaged material being broken down."

In the past, researchers have believed that the body keeps cells involved in reproduction isolated and protected from damage. Now it has been shown that these types of cells go through a rejuvenation process that rids them of the inherited damage.

Some types of protein damage in the body increase with age. Although all the necessary information is stored in the DNA, something keeps the body from using it to keep repairing the body.

"These types of protein damages are what make us appear old, like wrinkles around the eyes. While wrinkles are relatively harmless, serious problems may arise elsewhere in the body. I'm thinking of age-related diseases like Parkinson's, Alzheimer's, type 2 diabetes and cancer."

Hernebring can show that the damaged proteins in the cells are probably broken down by molecular machines called proteasomes. The proteasome activity increases considerably during the initial steps of embryonic stem cell differentiation in mice. Deciphering this rejuvenation process helps us better understand what aging really is, which in turn may help us slow it down and also prevent the occurrence and ill effects of age-related diseases.

**Story Source:**
The above story is reprinted (with editorial adaptations by Science*Daily* staff) from materials provided by **University of Gothenburg**, via AlphaGalileo.

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Ann N Y Acad Sci. 2006 May;1067:488-92.

**Geroprotection by glycerol: insights to its mechanisms and clinical potentials.**

Deocaris CC, Shrestha BG, Kraft DC, Yamasaki K, Kaul SC, Rattan SI, Wadhwa R.

**Source**

National Institute of Advanced Industrial Science & Technology (AIST), Tsukuba, Japan.

**Abstract**

Chaperones, particularly the heat-shock proteins, are considered as key players in the maintenance of protein homeostasis and are associated with longevity and cellular immortalization. In this study, we investigated the geroprotective activity of the chemical

chaperone glycerol. Glycerol showed significant chaperoning activity in refolding heat-denatured luciferase in vivo and in protecting cells from heat stress-induced cytotoxicity. This was accompanied by decrease in p53, an upregulation of a stress chaperone mortalin/mtHsp70, and an increase in proteasome activity in the presence of oxidative stress.

PMID: 16804031

Neurochem Res. 2009 Mar;34(3):453-62. Epub 2008 Aug 8.

**Long-term exposure to low lithium concentrations stimulates proliferation, modifies stress protein expression pattern and enhances resistance to oxidative stress in SH-SY5Y cells.**

Allagui MS, Nciri R, Rouhaud MF, Murat JC, El Feki A, Croute F, Vincent C.

**Source**

Laboratoire de Biologie Cellulaire et Pollution, Faculté de Médecine Purpan, Université Paul Sabatier Toulouse III, 37 Allées Jules Guesde, 31073 Toulouse, France.

**Abstract**

SH-SY5Y cells, derived from a human neuroblastoma, were submitted to short- or long-term exposures to lithium carbonate concentrations ranging from 0.5 to 8 mM. Short-term exposures (4 days) to concentrations higher than 6 mM were found to reduce cell growth rate while exposure to 8 mM resulted in significant cell mortality. These ranges of concentrations induced an overexpression of (1) the HSP27 stress protein, (2) a 108 kDa protein (P108) recognized by an anti-phospho-HSP27(Ser78) antibody, and probably corresponding to a phosphorylated HSP27 tetramer, (3) a 105 kDa protein (P105), possible glycosylated or phosphorylated form of the GRP94 stress protein and (4) a phosphorylated (inactivated) form of glycogen synthase kinase (GSK3alpha/beta) SH-SY5Y cells, when cultured in the presence of 0.5 mM lithium for 25 weeks, displayed interesting features as compared to controls: (1) higher cell growth rate, (2) increased resistance toward the inhibitory effects of high lithium concentrations on cell proliferation, (3) lower basal level of lipid peroxidation (TBARS) and improved tolerance to oxidative stress induced by high lithium concentrations, (5) reduced expression of monomeric HSP27 versus an increase of corresponding tetrameric protein (P108) and (6) overexpression of a 105 kDa protein (P105). In conclusion, our study suggests that chronic treatment (over several months) by therapeutic relevant lithium concentrations could favour neurogenesis, decrease the vulnerability of neuronal cells to oxidative stress and induce posttranslational changes of molecular chaperones.

PMID: 18688712

http://onlinelibrary.wiley.com/doi/10.1046/j.1471-4159.2003.01762.x/pdf - Neuronal uptake and metabolism of glycerol and the neuronal expression of mitochondrial glycerol-3-phosphate dehydrogenase

Glycerol may have two roles in energy production. First, it may fuel ATP formation by entering glycolysis and oxidative metabolism. Second, glycerol-3-phosphate may serve in the glycerol-3-phosphate shuttle, which translocates reducing equivalents into mitochondria. In this shuttle cytosolic glycerol-3-phosphate dehydrogenase reduces dihydroxyacetone phosphate at the expense of NADH and H+ to glycerol-3-phosphate which, as a substrate for mitochondrial glycerol-3-phosphate dehydrogenase, leads to intramitochondrial formation of FADH2.

An interesting aspect of cerebral handling of glycerol is the transmembrane movement of glycerol through aquaporins. So far, mRNA for six aquaporins has been detected in brain or cultured brain cells: AQP1 (Pfeuffer et al. 1998), AQP3, AQP5 and AQP8 (Yamamoto et al. 2001), AQP4 (Nagelhus et al. 1998) and AQP9 (Ko et al. 1999). Of these, AQP3, AQP8 and AQP9 are permeable to glycerol (for review see Verkman and Mitra 2000). Until now, brain aquaporins have only been found in glia (for review see Badaut et al. 2002). mRNA for AQP3 and AQP8 has been detected in neurones (Yamamoto et al. 2001), but whether it is translated into protein is not known.

Bull Exp Biol Med. 2002 Jan;133(1):1-5.

**Mechanisms underlying geroprotective effects of peptides.**

Khavinson VKh, Malinin VV.

**Source**

St. Petersburg Institute of Bioregulation and Gerontology, Northwestern Division of the Russian Academy of Medical Sciences.

**Abstract**

We review the role of peptides in aging and the mechanisms underlying the geroprotective effect of peptide preparations. Geroprotective properties of peptides are associated with their influence on systems maintaining homeostasis in the body and regulation of mechanisms underlying aging. Peptides normalize synthesis of tissue-specific proteins and regulate expression of genes responsible for proliferation and differentiation of cells. Thus, peptides maintain normal physiological functions and decelerate aging.

PMID: 12170291

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*I am no expert on biology, stem cell biology or such. My focus is on writing and theory.