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Studying molecular mechanisms of glucose damage in the model system *C. elegans* with respect to lifespan and neuronal damage.

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Objective: Studying molecular mechanisms of glucose damage in the model system *C. elegans* with respect to lifespan and neuronal damage.

Research Design and Methods: C. elegans was maintained to achieve glucose concentrations resembling the hyperglycemic conditions in diabetic patients. The effects of high glucose on lifespan, glyoxalase-1 activity, advanced glycation end products (AGEs) and reactive oxygen species (ROS) formation and on mitochondrial function were studied.

Results: High glucose conditions reduced mean lifespan from 18.5 ± 0.4 to 16.5 ± 0.6 days and maximum lifespan from 25.9 ± 0.4 to 23.2 ± 0.4 days, independent of glucose effects on cuticle or bacterial metabolization of glucose. The formation of methylglyoxal-modified mitochondrial proteins and ROS was significantly increased by high glucose conditions and reduced by mitochondrial uncoupling and complex II inhibition. Overexpression of the methylglyoxal-detoxifying enzyme glyoxalase-1 attenuated the life shortening effect of glucose by reducing AGE accumulation (by 65%) and ROS formation (by 50%) and restored mean (16.5 ± 0.6 to 20.6 ± 0.4 days) and maximum lifespan (23.2 ± 0.4 to 27.7 ± 2.3 days). In contrast, inhibition of glyoxalase-1 by RNAi further reduced mean (16.5 ± 0.6 to 13.9 ± 0.7 days) and maximum lifespan (23.2 ± 0.4 to 20.3 ± 1.1 days). The lifespan reduction by

glyoxalase-1-inhibition was independent from the insulin signalling pathway, since high glucose conditions also affected daf-2 knock-down animals in a similar manner.

Conclusions: C. elegans is a suitable model organism to study glucose toxicity, in which high glucose conditions limit lifespan by increasing ROS formation and AGE modification of mitochondrial proteins in a Daf-2 independent manner. Most importantly, glucose toxicity can be prevented by improving glyoxalase-1 dependent methylglyoxal detoxification or restoring mitochondrial function.