Peptides (small proteins) sharing an active nerve cell protecting site

Activity-dependent neuroprotective protein (ADNP), essential for brain formation, is frequently mutated in children on the autism spectrum. This protein, together with Activity-dependent neurotrophic factor (ADNF) are two proteins that were discovered in the laboratory of Prof. Illana Gozes at Tel Aviv University in collaboration with the laboratory of Dr. Douglas E. Brenneman at the NIH. NAPVSIPQ (NAP) and all D-amino acid SALLRSIPA (D-SAL) are neuroprotective peptides derived from activity-dependent neuroprotective protein (ADNP) and activity-dependent neurotrophic factor (ADNF), respectively. Both proteins were shown to protect against cognitive impairment, using different animal models and to increase survival of nerve cells, following exposure to toxins. NAP was extensively tested and found to increase the stability of microtubules - tubes within nerve cells that maintain cellular shape and serve as “train tracks” for movement of biological material through the brain.

Here, a further evaluation and correlation was performed at the behavioral level, in a rat model of diabetes. Diabetes is primarily a metabolic disorder that presents secondary neurological manifestations. Diabetes induces peripheral nervous system damage which is translated into impaired sensory perception and is termed diabetic neuropathy. Diabetes-related central nervous system damage causes cognitive decline. Therefore, the aim of the present study was twofold: (1) to evaluate the effect of neuroprotective peptide treatment in an animal model of diabetes and (2) to assess the impact of the common SIP motif consisting of 3 amino acids, the building blocks of peptides and proteins - Serine, Isoleucine and Proline, in NAP and D-SAL.

The behavioral study aimed to evaluate the effect of NAP and D-SAL on peripheral neuropathy and cognitive decline. Peripheral neuropathy was tested by measuring the response to a thermal stimulus, and cognitive ability was measured by a social memory test and a spatial memory test using long- and short-retention-dependent tasks and a reference memory task.

Results indicated an immediate sensory neuropathy in the diabetic model, which was prevented by both peptides and a later neuropathic phase, prevented only by NAP treatment. In addition, cognitive tests revealed impaired performance in both social and spatial memory tests in the diabetes model. Each of the peptides improved different aspects of cognitive behavior, with NAP being more potent than D-SAL. Mechanistically, both NAP and SAL contain a SIP domain that has been shown to interact with microtubule end-binding proteins. The finding of a potential direct interaction of D-SAL with NAP, may implicate an interaction of D-SAL with the endogenous ADNP to provide microtubule and neuroprotective fortification.

In conclusion, our current results implicate D-SAL activity with potentially reduced potency compared to NAP, thus placing the SIP motif as a central focus for microtubule-based protection.

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