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Synthesis of humanin and its derivatives to treat traumatic brain injury in mice

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Humanin is a 24-amino acid peptide known for its anti-apoptotic activity, especially against neuronal cell death caused by Alzheimer insults. Herein, we show a novel function of humanin and its derivatives, namely protection against necrosis, demonstrated both *in vitro* and *in vivo*. The synthesis of humanin is difficult due to the involvement of the hydrophobic amino acids that impose aggregation on the resin. Solid-phase peptide synthesis of humanin and its three derivatives, AGA-HNG, HNG and HN17 gave low yields. In order to avoid aggregation and overcome difficult sequences couplings, we developed efficient synthetic procedures that are based on fragment condensation in solution. Furthermore, native chemical ligation was applied to overcome resin aggregation for synthesis of peptides that contain cysteine. We found that humanin and its derivatives conferred protection in PC-12 and NSC34 cell lines in which necrosis was induced in glucose-free medium by either chemohypoxia or upon staurosporine/oligomycin-A treatment. Moreover, *in vivo* protective effect was shown in traumatic brain injury model in mice, where necrosis is the main mode of the neuronal cell death. We show that humanin derivatives antagonize the decrease in ATP levels associated with necrosis and also directly enhance the activity of isolated ATP synthase complex, indicating that humanin derivatives target the mitochondria, regulating ATP levels. The present findings could provide new therapeutic protocols for treatment of brain ischemic states, such as stroke, and traumatic brain injury, conditions for which no efficient drug-based treatment is currently available.

Biography

David Meridor has completed his MSc and PhD studies in Chemistry from Bar-Ilan University in Israel, during which he published 4 papers. In the current position as a Postdoctorate Researcher at Ben-Gurion University, he is involved in a project that entails synthesis of humanin derivatives, cell culture as well as *in vivo* studies in a model of traumatic brain injury. This work was recently published in *Mol. Med. 2015 (doi: 10.2119/molmed.2015.00073*).

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