NEUROPEPTIDE TREATMENT IN EPILEPSY:

AN INTRANASAL APPROACH

Michael C. Veronesi

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Michael Kubek, Ph.D.
(Chairperson)

Jay Simon, Ph.D.

Doctoral Committee

Vincent Gattone, Ph.D.

Date of
Oral Examination: 12/12/2007

Robert Worth M.D., Ph.D.

Asok Sen, Ph.D.

ABSTRACT

Michael C. Veronesi

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A major barrier to entry of neuropeptides into the brain is low bioavailability and presence of the blood-brain barrier. Intranasal delivery of neuropeptides provides a potentially promising alternative to other routes of administration since a direct pathway exists between the olfactory neuroepithelium and the brain. We have determined the location of fluorescent molecules released from sustained-release biodegradable polylactide nanoparticles within the brain parenchyma following intranasal delivery and the time course for uptake during fluorescence microscopic visualization in several subregions. Fluorescence microscopy of dye-loaded and dye-attached NPs provided additional data on the uptake and transport of NPs in neuronal processes *in vitro*.

TRH is known to have anticonvulsant effects in several animal seizure models and is efficacious in treating patients with certain intractable epilepsies. The kindling paradigm, as a model of temporal lobe epilepsy, was used to show that intranasal administration of a TRH analog, 3-Methyl-Histidine TRH (3Me-H TRH) significantly inhibits seizure characteristics in fully kindled animals at 30 and 60 min prior to seizure induction. More importantly, polylactide nanoparticles containing TRH (TRH-NPs) applied during kindling acquisition modulates seizure duration, severity and number of stimulations to reach stage 5 and the fully kindled state.

Since Glutamate (Glu) toxicity has been implicated in neurodegenerative (epilepsy) disorders, we utilized primary enriched cultures of rat fetal (E 17) hippocampal neurons

to determine whether an analog of TRH, 3-Methyl-Histidine TRH (3Me-H TRH) or TRH-NPs given concurrently with Glu would protect such neurons against cell damage and cell death. 3Me-H TRH or TRH-NPs, when co-treated with 500 μM Glu protected fetal neurons against cell death in a concentration-dependent manner.

In conclusion, we have developed a novel method to detect and characterize the time-course, distribution and concentration of fluorescent compounds released from NPs throughout the CNS over time in the brain following intranasal delivery. We have also shown that intranasal delivery of 3Me-H TRH can attenuate multiple seizure characteristics over short durations and that TRH-NPs may be a viable means to suppress the development of epileptogenesis/kindling acquisition over much longer periods of time. Finally, we have demonstrated that the mechanism of TRH's neuroprotective (anti-epileptic) effects, in part, involves modulation of glutamate toxicity.

Michael Kubek, Ph.D.
(Chairperson)

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