THYROTROPIN-RELEASING HORMONE (TRH) EXPRESSION ENHANCED AFTER SEIZURES IN RAT HIPPOCAMPUS AND ITS INHIBITION EFFECT ON GLUTAMATE RELEASE *IN VITRO*

YING NIE

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Doctoral Committee

Michael J. Kubek, Ph.D.
(Chairperson)

Darryle D. Schoepp, Ph.D.

Bang Hwang, Ph.D.

Wei-Hua Lee, MD., Ph.D.

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Recent pharmacological studies indicate that TRH and TRH analogs have anticonvulsant functions, but its neurochemistry has not been defined. We hypothesize that the anticonvulsant function of TRH is due, in part, to an interaction with glutamate. The present studies were undertaken to examine whether increased postictal TRH release is accompanied by increases in glutamate/aspartate release; whether the anticonvulsant function of TRH involved inhibition of glutamate/aspartate release; whether TRH mRNA and TRH-receptor mRNA were differentially modified in hippocampus by generalized seizures.

A unique superfusion method and LDH assay was established to assess potassium and glutamate mediated neuronal cell injury in rat hippocampal slices *in vitro*. Morphological assessment was accomplished by cresyl violet and H-E staining. Radioimmunoassay was used to examine TRH release, while HPLC was used to examine glutamate and aspartate release. TRH gene and TRH-receptor gene expression were studied by ribonuclease protection assay following 1-3 ECS.

Our results indicate that morphological integrity is maintained in slices for at least six hours and that the LDH assay is a reliable method for assessing brain slice viability. Potassium-stimulated TRH release was low in slices from sham-ECS rats, but significantly increased 48 hours after three alternate-day ECS, whereas, glutamate and aspartate release was the same pre- and post-ECS. Interestingly, aspartate but not glutamate release was significantly

increased following a kindled seizure. TRH at concentrations of 0.1 to 10 μM markedly inhibited potassium-stimulated glutamate and aspartate release from superfused slices. TRH mRNA was markedly elevated and TRH-receptor mRNA was reduced >17% in the hippocampus 6 hours after a single ECS while subsequent seizures failed to reduce receptor mRNA.

This work strengthens our hypothesis that TRH acts as an endogenous modulator of seizure activity. Elevated postictal TRH may be coreleased and then pre- and/or postsynapticlly modulate glutamate and aspartate release by a novel mechanism. The clinical potential of this research lies in the design of TRH analogues that can be used as a new family of drugs in the treatment of epilepsy.

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