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Presentation Abstract

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Title: In vivo real time measurement of synaptically-evoked glutamate release from hippocampal-medial prefrontal cortical (hipp-mPFC) pathway: Effects of glutamate modulating compounds

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Abstract: Glutamatergic transmission in the HIPP-PFC pathway is crucial for cognitive processes and is sensitive to stress. Dysregulation of the HIPP-mPFC synapses plays a critical role in psychiatric disorders, including schizophrenia and depression. We have utilized the high temporal resolution (1 sample/sec), needle-type enzyme immobilized biosensors (Pinnacle Technology) to detect the dynamic changes of medial PFC glutamate upon HIPP stimulation. In urethane-anesthetized rats, electrical stimulation (15 seconds at 0.3, 1, and 3 mA at 50 Hz) of the fimbria of the HIPP resulted in a delayed (~10s), stimulation intensity-dependent increase in glutamate signals which lasted for ~ 1 minute. This increase in evoked glutamate was followed by an undershoot below the baseline which also lasted ~1 minute, suggesting a physiological refractory period, perhaps due to neurotransmitter depletion. The evoked glutamate rise was attenuated ~50% by local infusion of tetrodotoxin (1mM, 2 μ l) into the PFC, suggesting the evoked synaptic glutamate is via action potential-dependent release. The HIPP-mPFC evoked glutamate signal in the mPFC was also modulated pharmacologically by the mGlu2/3 agonist LY379268

(attenuated by 3mg/kg, i.v., or s.c.), and the mGlu 2/3 antagonist LY341595 (augmented by 3mg/kg, s.c.), suggesting that the HIPP-mPFC pathway is subjected to modulation via presynaptic mGluR2/3 receptors. Given the rapid-reuptake of glutamate, the biosensors offer a very useful tool to understand extracellular glutamate dynamics and the effects of novel glutamate modulating therapeutics.

Disclosures:

P.A. Ardayfio, Eli Lilly and Co., A. Employment (full or part-time); **K.W. Perry**, Eli Lilly and Co., A. Employment (full or part-time); **K.A. Svensson**, Eli Lilly and Co., A. Employment (full or part-time); **T.E. Fitch**, Eli Lilly and Co., A. Employment (full or part-time); **C.R. Yang**, Eli Lilly and Co., A. Employment (full or part-time); **G.J. Marek**, Eli Lilly and Co., A. Employment (full or part-time).

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