BIOCHEMISTRY SEMINAR SERIES

“In vivo Brain KOR Signaling Elucidated by Phosphoproteomics”

Jeffrey J. Liu

Bridge Institute, University of Southern California;
Department of Proteomic and Signal Transduction,
Max Planck Institute of Biochemistry

A systems view of G protein-coupled receptor (GPCR) signaling in its native environment is the key in development of GPCR therapeutics with fewer side effects. Using the kappa-opioid receptor (KOR) as a model, we employed high-throughput phosphoproteomics to investigate signaling induced by structurally diverse agonists in five mouse brain regions. We employed the classic unbiased KOR agonist U50,488H as the reference and comparatively studied downstream phosphorylation changes induced by 6’GNTI and newly reported compounds in one study, and Nalfurafine in another. From these two different phosphoproteomic studies, we observed strong regional specificity of KOR signaling, due to differences in protein-protein interaction networks, neuronal contacts and the different tissues in neuronal circuitries. Agonists with distinct signaling profiles elicited differential dynamic phosphorylation of synaptic proteins, linking GPCR signaling to the modulation of brain functions. The large-scale de-phosphorylation of synaptic proteins in striatum after 5 min agonist stimulation was partially blocked by Protein Phosphotase 2A (PP2A) inhibitors, underscoring the involvement of PP2A in KOR mediated synaptic functions. Pathway analysis in both phosphoproteomic studies revealed enrichment of mTOR signaling by agonists associated with aversion. Consequently, mTOR inhibition during KOR activation abolished aversion, while preserving beneficial antinociceptive, anti-scratch and anticonvulsant effects. Our results establish high-throughput phosphoproteomics as a general strategy to investigate GPCR in vivo signaling, enabling prediction and modulation of behavioral outcomes.

Friday, May 29, 2020

via Zoom

link will be provided on Friday before the seminar

3:30 pm

More information: marla@chem.ucla.edu

UCLA College | Physical Sciences Chemistry & Biochemistry