Novel contributions of protein dopaminylation to maladaptive neuronal and behavioral plasticity induced by drugs of abuse

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Drug addiction has long been thought of as a disorder of dopamine (DA) signaling. However, therapeutic interventions targeting receptor mediated DA-signaling have not yet resulted in efficacious treatments. Our laboratory recently identified a non-canonical, neurotransmission-independent signaling moiety for DA in brain, termed dopaminylation, whereby DA itself acts as a donor source for the establishment of post-translational modifications (PTM) on substrate proteins (e.g., histone H3) via transamidation by the Transglutaminase 2 enzyme. In our previous studies, we demonstrated that these histone PTMs play critical roles in the regulation of permissive transcription and, when perturbed within monoaminergic neurons (e.g., DAergic neurons of the ventral tegmental area/VTA), contribute to pathological states including drug relapse vulnerability.

Methods: Using a unique combination of chromatin biochemistry, chemical biology, proteomic, epigenomic, gene therapy and behavioral approaches, we are characterizing the functions of these novel histone monoaminylation states, and well as synaptic protein monoaminylations, in the contexts of normal neural function and in rodent models of substance use disorder.

Results: In recent efforts by our lab to identify the full repertoire of monoaminylated substrates in brain (now additionally focusing on synaptic and other non-nuclear proteins in nucleus accumbens/NAc and prefrontal cortex/PFC), we developed a novel chemical tagging approach that, when coupled to liquid chromatography-mass spectrometry (LC-MS/MS), allowed for the discovery of thousands of novel catecholaminylated proteins in brain, both in the context of normal neural function and in response to aberrant dopamine signaling following chronic drug (e.g., heroin) self-administration (SA). For example, among them, γCaMKII: 1) was found to be dopaminylated at only a single amino acid residue within its autoinhibitory helix [glutamine 285], a site that exists only two amino acids away from a critical threonine residue (287), which is phosphorylated to direct Calmodulin sequestration and shuttling to the nucleus; 2) is upregulated in its dopaminylation following abstinence from heroin SA; and 3) represents a critical substrate involved in mediating long range signals from the synapse to nucleus in NAc, ultimately promoting CREB activation and neuronal plasticity, which contribute importantly to addiction relevant phenotypes.

Discussion: Given γCaMKII's roles in learning/memory, late-LTP and excitation-transcriptional coupling, we have found that this novel dopaminylation event on γCaMKII represents a critical convergent mechanism linking altered dopaminergic signaling in response to drugs of abuse to CREB mediated transcriptional abnormalities and relapse vulnerability.

References: Farrelly et al., *Nature,* 2019; Lepack et al., *Science,* 2020; Zhao et al., *PNAS,* 2021; Fulton et al., *Neuropsychopharmacology,* 2022; Lukasak et al., *PNAS,* 2022

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