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New chemical tools to elucidate the interactomics and the epigenetics of opioid drugs

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The opioids morphine and heroin, unlike natural opioid peptides, are highly addictive substances that induce changes in neuronal gene expression that contribute to addiction. The biomechanism underlying this neuroadaptive activity causing opioid use disorder (OUD), outside of associated biomarkers, has yet to be rigorously described in animals and humans. Here, we propose that the opioids directly interact with, bind to, and perturb protein targets within the cellular proteome that contribute to OUD. To identify these intracellular interactions of the opioids, we have developed two probes with specific chemical functionalization to enable the unbiased detection and visualization of these protein interactions, termed photo-morphine and dialkynylacetyl morphine (DAAM). Photo-morphine was identified following systematic structure–activity relationship studies for use as a binding site probe that retains the activity of the parent compound. In parallel, we developed DAAM for profiling acetylation sites that arise specifically from opioid treatment in the cell. We employed these two probes within a chemical proteomics platform to characterize protein binding partners of the opioids throughout the cell. This platform involves: (1) treatment of cells or an animal model with the opioid probe, (2) chemical enrichment of the protein binding partners or acetylation sites, and (3) unbiased identification of the protein target and binding site. We present recent proteomics data from our in vitro cellular studies and in vivo studies employing both acute and chronic regimens and analyzed the striatum and other relevant organs. These data provide a map of novel interactions of the opioids inside of the cell, which may drive mechanisms of the opioids leading to OUD. The opioid probes additionally expand the chemical toolbox to study opioid addiction by introduction of a straightforward mechanism to visualize and measure the opioid interactome.