Submitter Name: Marta Pratelli
Submitted email: mpratelli@ucsd.edu
PI Name: Nicholas C. Spitzer
PI email: nspitzer@ucsd.edu

Drugs of abuse drive activity producing changes in gene expression that switch neurotransmitters and behaviors

Marta Pratelli[1,2], Nicholas C. Spitzer[1,2]

[1]Neurobio. Department, University of California San Diego; [2]Kavli Inst. for Brain & Mind, University of California San Diego

Exposure to drugs of abuse influences brain activity and causes maladaptive neuronal plasticity. These changes have been associated with behavioral alterations that can lead to addiction. Our previous work has shown that sustained changes in activity can induce a subset of neurons to stop expressing the transmitter they were expressing and start expressing a different one: a form of plasticity called “neurotransmitter switching”. Although shown to cause to behavioral changes, neurotransmitter switching has received little attention in relationship to the behavioral consequences of the use of drugs of abuse. We hypothesized that repeated exposure to drugs produces changes in neuronal activity inducing neurotransmitter switching, which in turn contributes to the appearance of drug-induced behavioral deficits.

Multiple injections of either phencyclidine (PCP) or methamphetamine cause a subset of prelimbic cortex glutamatergic neurons to gain a GABAergic phenotype (i.e. GABA, its synthetic enzyme GAD67, and its vesicular transporter VGAT), while decreasing their expression level of the vesicular glutamate transporter VGLUT1. Remarkably, AAV-mediated GAD1sh-RNA-interference, preventing these glutamatergic neurons from gaining GABA upon PCP exposure, is sufficient to rescue PCP-induced cognitive deficits and locomotor sensitization. These results demonstrate that this glutamate-to-GABA transmitter switch is causally linked to PCP-induced behavioral alterations. Furthermore, chemogenetic activation of parvalbumin-positive prelimbic cortex interneurons during PCP treatment is sufficient to prevent both the switch and the associated behavioral alterations. This observation suggests that manipulation of neuronal activity can potentially be used to interfere with neurotransmitter switching and thus counteract some of the detrimental behavioral effects of PCP.