Sex differences in and sex hormone effects on the glutamatergic mechanisms that regulate dopamine levels of the prefrontal cortex in adult rats

Mary Kritzer1*, Mallory Locklear1, Erika Betancourt2, Jonathan Wachtel2, Dana Lengel1 and William F. Collins1

1Department of Neurobiology and Behavior, Stony Brook University School of Medicine, Stony Brook, NY, United States of America;
2Stony Brook University School of Medicine, Stony Brook, NY, United States of America

Our lab examines sex differences and hormone effects on prefrontal cortex (PFC) and its top-down modulation of midbrain dopamine (DA) systems in rats. The PFC is responsible for executive operations including working memory and behavioral flexibility. Impairments in these functions number among the most disabling symptoms of Parkinson’s disease, schizophrenia and other disorders. Given that normal operations of the PFC depend on intracortical DA levels being maintained within precise limits, it is not surprising that imbalances in midbrain DA systems contribute to the pathophysologies underlying the PFC and non-PFC deficits seen in disorders where executive functions are at risk. However, treatment of these cognitive deficits is difficult and complex. For example, in schizophrenia, the DA antagonists that quell hallucinations and other positive symptoms tend to worsen cognitive deficits. Unfortunately, this is not an uncommon scenario. Our work could lead to new ways to resolve this problem by defining the sex-specific mechanisms that influence the functional regulation of mesoprefrontal DA systems. Sex differences in and sex hormone effects on DA-dependent PFC function in healthy human and animal subjects and on PFC dysfunction in patient populations and preclinical models of hyper- and hypo-dopaminergic disease have been well described. However, there are significant gaps in knowledge about the basic neurobiology of DA-dependent PFC function particularly in females, and about the mechanisms of hormone action especially in the male PFC. In addressing these areas, we discovered functionally relevant, androgen-driven sex differences among the intracortical glutamate and GABAergic systems that regulate PFC projections to the ventral tegmental area—where mesoprefrontal and mesolimbic DA cells of origin reside. This presentation will describe behavioral, biochemical and electrophysiological data that support NMDA receptor-mediated glutamate signaling within the PFC as a major axis of hormone action that is relevant for DA modulation of both PFC function and PFC dysfunction in rat models of schizophrenia and Parkinson’s disease. Recent efforts to identify brain-specific androgen actions in hopes of identifying DA-correcting therapies that benefit brain and behavior and avoid cardiovascular and other health risks associated with hormone treatment will also be presented.

*Submitting author e-mail: mary.kritzer@stonybrook.edu