Cheryl Frye  
Department of Psychology

Sponsor:  National Institute of Mental Health (NIMH)  
Dates:  August 15, 2010 – April 30, 2014  
Amount:  $1,287,752

**Progestogens’ Non-Classical Effects and Mechanisms for Social and Mood Processes**

Progesterone (P) mediates exploration, anxiety, social responding of female rodents in part through actions of its product, 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP). In the ventral tegmental area (VTA), 3α,5α-THP has actions to facilitate affective and social behaviors through GABA/ Benzodiazepine (GBRs) and/or NMDA type glutamate (NMDARs), rather than via intracellular progestin receptors. 3α,5α-THP levels in the midbrain VTA both facilitate, and are enhanced by, affective and social behavior. The pregnane X receptor (PXR) mediates the production of, and/or metabolism to, various neurobiological factors. PXR is localized to the midbrain VTA of rats. Our hypothesis is that PXR-dependent biosynthesis of 3α,5α-THP in the VTA underlies facilitation of, and/or response to, affective and social behavior. Using classic methods of behavioral endocrinology, pharmacology, in conjunction with tools of molecular biology, in a rat model of affective/social behaviors, the following aims will be to investigate. 1) The causal actions of PXR in the midbrain VTA for 3α,5α-THP to facilitate affective/social behaviors. 2) The effects of affective/social behaviors on PXR-dependent midbrain 3α,5α-THP levels. If PXR and 3α,5α-THP are altered in response to affective/social behaviors, and blocking PXR attenuates behavior induced 3α,5α-THP, then effects of 3α,5α-THP in the midbrain to mediate, and be dynamically altered by, social stimuli are PXR-dependent. 3) 3α,5α-THP can be formed in the VTA from metabolism of P produced peripherally by ovaries or adrenals or centrally via biosynthesis in brain. The role of PXR for 3α,5α-THP in the VTA to be produced from central biosynthesis and/or metabolism from peripheral P to facilitate, or be increased by, affective/social behaviors will be investigated. 4) 3α,5α-THP may have PXR-dependent actions involving GBRs and/or NMDARs. Whether behavioral effects of 3α,5α-THP, or 3α,5α-THP formation in response to affective/social behaviors, are in part due to XR-dependent effects at GBRs and/or NMDARs, will be examined. Investigating novel behavioral functions of 3α,5α-THP will extend our knowledge of the neurobiology of progestogens, relevant for affective/social behaviors, and their connections to systems that regulate emotions. 3α,5α-THP is implicated in stress regulation, pathophysiology and/or treatment of neuropsychiatric disorders. Thus, further understanding of 3α,5α-THP’s role and mechanisms to enhance reproduction/social bonds, minimize aggression, influence affective aspects of social behaviors, and to mediate responses to stress, are essential.