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

**Progesterogens' 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 ($3\alpha,5\alpha$ -THP). In the ventral tegmental area (VTA), $3\alpha,5\alpha$ -THP has actions to facilitate affective and social behaviors through GABA_A/Benzodiazepine (GBRs) and/or NMDA type glutamate (NMDARs), rather than via intracellular progesterin receptors. $3\alpha,5\alpha$ -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 $3\alpha,5\alpha$ -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 $3\alpha,5\alpha$ -THP to facilitate affective/social behaviors. 2) The effects of affective/social behaviors on PXR-dependent midbrain $3\alpha,5\alpha$ -THP levels. If PXR and $3\alpha,5\alpha$ -THP are altered in response to affective/social behaviors, and blocking PXR attenuates behavior induced $3\alpha,5\alpha$ -THP, then effects of $3\alpha,5\alpha$ -THP in the midbrain to mediate, and be dynamically altered by, social stimuli are PXR-dependent. 3) $3\alpha,5\alpha$ -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 $3\alpha,5\alpha$ -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) $3\alpha,5\alpha$ -THP may have PXR-dependent actions involving GBRs and/or NMDARs. Whether behavioral effects of $3\alpha,5\alpha$ -THP, or $3\alpha,5\alpha$ -THP formation in response to affective/social behaviors, are in part due to XRdependent effects at GBRs and/or NMDARs, will be examined. Investigating novel behavioral functions of $3\alpha,5\alpha$ -THP will extend our knowledge of the neurobiology of progesterogens, relevant for affective/social behaviors, and their connections to systems that regulate emotions. $3\alpha,5\alpha$ -THP is implicated in stress regulation, pathophysiology and/or treatment of neuropsychiatric disorders. Thus, further understanding of $3\alpha,5\alpha$ -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.