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Progestins' Non-genomic Actions for Socio-sexual Behavior

Progesterone (P) mediates exploration, anxiety, social and sexual (socio-sexual) behaviors of female rodents in part through actions of its product, 3 α -hydroxy-5 α -pregnan-20-one (3 α ,5 α -THP). In the ventral tegmental area (VTA), 3 α ,5 α -THP has actions to facilitate socio-sexual behavior through GABA_A/Benzodiazepine (GBRs) and/or NMDA type glutamate (NMDARs), rather than via intracellular progesterin receptors. 3 α ,5 α -THP levels in the midbrain VTA both facilitate, and are enhanced by, socio-sexual behavior. The Pregnane Xenobiotic Receptor (PXR) may underlie 3 α ,5 α -THP's actions in the VTA. PXR is a nuclear receptor that regulates gene transcription for cytochrome P450 enzymes, necessary for biosynthesis of 3 α ,5 α -THP. Our pilot microarray, reverse transcriptase polymerase chain reaction and Western blot data show the PXR gene, RNA, and protein are expressed in the midbrain of rats. Our hypothesis is that PXR-dependent biosynthesis of 3 α ,5 α -THP in the VTA underlies facilitation of, and/or response to, socio-sexual behaviors. Using classic behavioral endocrinology, pharmacology, and radioimmunoassay methods, in conjunction with tools of molecular biology, in a rat model of socio-sexual behaviors, aims will be to investigate the causal actions of PXR in the midbrain VTA for 3 α ,5 α -THP to facilitate socio-sexual behaviors. In Aim 1a, the effects of estrous cycle variations in behaviors and PXR expression will be determined. In Aim 1b, whether differential effects of estrogen (which co-varies with progestogens across the estrous cycle) on 3 α ,5 α -THP-facilitated behavior related to PXR will be determined. In Aim 1c, whether effects of estrogen-priming and 3 α ,5 α -THP-replacement to the VTA are attenuated with PXR antisense ODNs, and can be reinstated with 3 α ,5 α -THP-replacement will be determined. Together, these studies will demonstrate whether PXR is a novel target of progestogens in the midbrain VTA for their functional effects. Investigating novel behavioral functions of 3 α ,5 α -THP will extend our knowledge of the neurobiology of progestogens, relevant for socio-sexual behaviors, and their connections to systems that regulate emotions. 3 α ,5 α -THP is implicated in stress regulation, pathophysiology and/or treatment of neuropsychiatric disorders. Thus, further understanding of 3 α ,5 α -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.