

Pleiotropic Effects of 3 α -DIOL on the Sexual Differentiation of Hormone-Sensitive Behaviors

INTRODUCTION

Sexual differentiation of the brain and behavior is imparted by gonadal steroids. The distinct differences between the sexes in brain morphology and neurochemistry are believed to be responsible for a number of sex-specific behavioral differences. For example, it has been proven that females are more active and less fearful than males. Classically, it was thought that steroid hormones act through nuclear hormone receptor-dependent pathways. This implicates the activation of genomic material, and therefore, the induction of physiological processes in a long-term time scale. However, gonadal steroids can produce neuroactive metabolites, also called neurosteroids, which can also mediate sex-specific behaviors. Acute effects of neurosteroids on behavior include modulation of sexual behaviors, anxiety-related behaviors, aggression, memory processes, and social behaviors. Neurosteroids are synthesized from cholesterol by both peripheral organs and in the CNS by glial cells. Evidence suggest that neurosteroids act via allosteric modulation of membrane delimited neurotransmitter receptors such as the of γ -aminobutyric acid Type A (GABA $_A$) receptor. This non-genomic process takes into effect in milliseconds to seconds. Among the many membrane delimited neurotransmitter receptors, it has been proven that gonadal steroids have significant effects on GABA $_A$ receptor expression and function. Therefore, our interest in the GABA $_A$ receptor is due to its potential to be involved in the sexual differentiation of the brain, its involvement in disease processes, and its potential for therapeutic agents that can act on these receptors in a sex-specific and hormone-dependent manner.

The neurosteroid (3 α -DIOL) is an endogenous androgenic neuroactive steroid that acts as a positive modulator of GABA $_A$ -R. Preliminary data in our laboratory showed that 3 α -DIOL treatment from postnatal (PN) day 1 to PN 14 altered several sexually dimorphic behavior during adulthood. However, it is unclear whether the effects of 3 α DIOL on sexually dimorphic behaviors is mediated through nuclear hormone receptor pathways, or perhaps via allosteric modulation of membrane-delimited neurotransmitter receptors like GABA $_A$ R. My project is specifically designed to address if: (1) 3 α -DIOL has an impact on the sexual differentiation of anxiety, locomotor and/or exploratory behavior. If 3 α DIOL exposure during neonatal development has significant behavioral effects, we want: (2) to determine if these effects are mediated through the androgen receptor, the GABA $_A$ R, or a combination of these mechanisms. To test this principle, flutamide (FLU) will be used to block androgen receptors, whereas picotroxin (PTX) will be used to block the GABA $_A$ R in conjunction with 3 α DIOL exposure.

CONCLUSION

- Possibly both mechanisms are responsible for the effects observed
- Effects are sex-specific since the behavior of females was not affected by DIOL
- Non-genomic pathways during a critical developmental period can produce long-term effects in males