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Perspective

Sex Matters: Gonadal Steroids and the Brain

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Sex matters to every cell of the body and thus gonadal steroids have the capability of affecting numerous behaviors and neurotransmitters. Several reports in this issue highlight the importance of gonadal steroids: estradiol and progesterone modulate the serotonin transporter in rodents changes in D2 receptors across the menstrual cycle in female cynomolgus monkeys testosterone influences amygdala reactivity in women and temporary suppression of gonadal steroids influences sexual in both men and women. This body of work challenges all of neuropsychopharmacology to consider the importance of sex and gonadal steroids in future studies.
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Sex matters to every cell of the body (Wizemann and Pardue, 2001). Despite this conclusion by the IOM, the area of sex and gonadal hormones is frequently ignored in the field of neuropsychopharmacology and other basic biomedical fields. This is to a large extent because of the difficulty of parsing the roles of chromosomal sex, gonadal sex, and gonadal steroid hormones (Becker *et al*, 2005). Nevertheless, these are factors that are increasingly important to address, as evidenced by the articles in this issue of *Neuropsychopharmacology*. In this issue of *Neuropsychopharmacology* the importance of sex/gender differences in the brain as well as the effects of steroid hormones on brain function are examined from the perspective of psychiatric disorders, the neurological basis of sexual behavior and neurotransmitter receptor/transporter function.

Depression is more common in women, and women appear to respond better to SSRIs than men (Kornstein *et al*, 2000; Young *et al*, 2008). In addition, SSRIs are an excellent treatment for premenstrual dysphoria disorder. Thus, the report by Benmansour *et al* (2008) demonstrating a sex specific effect of estradiol and progesterone on function of the serotonin transporter is quite important. However, the effect is the opposite of what would be predicted from the clinical literature, further underscoring the complexity of understanding the interactions between ovarian hormones and serotonin systems. Perhaps these findings help us to better understand the vulnerability to mood disorders at times when estradiol and progesterone are high, such as the luteal phase of the menstrual cycle. Of note is the fact that these changes in response to estradiol and progesterone were not observed in hippocampi of male rats, underscoring the importance of sexual differentiation of the brain on the effects of gonadal steroids.

Studying nonhuman primates with PET imaging of D2 receptors, Czoty *et al* (2008) found that [18F]FCP binding sites showed a greater availability in the caudate and putamen during the luteal phase, suggesting more unoccupied receptors during this menstrual cycle phase. Although the changes might be due to increased numbers of receptors, the use of a ligand displaceable by endogenous DA suggests the alternative possibility that higher receptor availability reflects decreased DA release during this phase. Of note, the follicular phase scans were conducted on day 9 of the follicular phase when estradiol levels should still be low, whereas the luteal scans (days 21–26) may have occurred during high estradiol phases in some animals. Studies have found that high physiological doses of estradiol enhance the release of DA (Becker *et al*, 2001) and decrease D2 DA receptor binding (Becker, 1999) in female rodents. In women, the subjective effects of drugs of abuse are enhanced during the follicular phase relative to the luteal phase and progesterone is found to attenuate the subjective response to drugs like cocaine and nicotine (Becker and Hu, 2008). Taken together, we see again the complexity of understanding the effects of menstrual cycle phase on DA neurotransmission, but the importance of these studies for the clinical condition.

Finally, two papers focus on behavioral effects of gonadal steroids: one on amygdala reactivity and another on sexual functioning. The study by van Wingen *et al* (2008) is based on animal studies that testosterone regulates activity in the amygdala of male and female rodents. They report that there is an age-related decline in serum testosterone as well as in amygdala reactivity in women. Using a placebo-controlled design they administered testosterone to older women and reexamined the effect on amygdala reactivity and found that testosterone reliably increased the amygdala response to faces. It also increased neural activity in response to faces in several brain regions including inferior frontal and middle temporal gyri, suggesting widespread

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modulation of neural activity. The timeframe of these actions was short (30 min) but, as with all experiments utilizing testosterone, we do not know for sure that these actions are through the androgen receptor *vs* conversion of testosterone by aromatase intracellularly in the amygdala to estradiol. It is possible, therefore, that these effects are mediated by estradiol acting at estrogen receptors. Nonetheless, it provides interesting new leads to think about the role of sex steroids in gender differences in anxiety and depression and changing rates across the reproductive life course of women.

The report by Schmidt *et al* (2008) examines data from their studies examining gonadal suppression and subsequent hormone replacement on aspects of sexual functioning in men and women. The effects of gonadal suppression were sex specific. In men, sexual function was reduced by gonadal suppression and restored by testosterone. In women, the gonadal suppression did change the quality of orgasm, but this effect was not reversed by replacement with either estradiol or progesterone alone. Unfortunately, as acknowledged by the authors, gonadal suppression also lowered testosterone in women and there was no testosterone replacement, nor any combination of sex steroids, which would approach the normal hormonal milieu of women. Still, this is an interesting report pointing to sex differences in the effects of sex steroid suppression in men *vs* women on normal sexual function.

All these authors are to be congratulated on these studies examining sex differences and the important role of gonadal steroid hormones.

DISCLOSURE/CONFLICT OF INTEREST

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