

Commentary

Perinatal, non-aromatized androgen exposure produces male superiority in discriminating between odors of social importance
A commentary on “Enhanced urinary odor discrimination in female aromatase knockout (ArKO) mice” by Wesson et al.

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Received 14 December 2005; revised 18 December 2005; accepted 20 December 2005

Available online 3 February 2006

This new manuscript examining the role of testosterone-derived estrogen on olfactory discrimination in mice has three particularly interesting points. First, early hormone exposure apparently alters the brain such that the ability to discriminate between socially important odors as well as some non-social odors is sexually dimorphic. Second, the role of perinatal androgens (that are not aromatized to estrogen) on sexual differentiation of the brain may be more important than previously thought. Third, tests of the ability of an animal to detect an odor, using habituation tests for example, do not necessarily reflect the ability of an animal to discriminate among odors.

The authors used a deceptively straightforward approach for determining the role of aromatized androgens on whether mice can learn to discriminate odors. They compared wild-type (WT) adult males and females, gonadectomized (GDX), and treated with a very low dose of estrogen (E) with aromatase knockout (ArKO) males and females similarly treated. Thus, both sexes were exposed to their own endogenously produced steroid hormones during development, but ArKO animals are unable to aromatize testosterone to estrogen. Earlier studies demonstrated that female mice typically detect low concentrations of volatile urinary odors more readily than males (Baum and Keverne, 2002; Pierman et al., in press) and that ArKO males demonstrated a female-like ability to detect odors. Those data suggested that perinatal estrogen increases the threshold for detection of socially important odors, and, since only males are producing steroids, the estrogen would derive from aromatization of testosterone in the brain. However, the ability to detect

an odor is not the same as the ability to discriminate among odors once they have been detected. When Pierman et al. (in press) found that ArKO female mice produced more variable responses to urinary odors than WT females in a habituation task, it was unclear whether they were unable to detect the odors or lacked motivation to engage in the investigatory behavior. The current paper tested the hypothesis that ArKO females would show a deficit in a food-motivated olfactory discrimination task because they showed weaker performances in the habituation/dishabituation odor detection task. The results support exactly the opposite conclusion.

In the discrimination task, WT females demonstrated the poorest performance across 2 urinary odor comparisons (intact, WT male vs. E + P-primed, WT female, and intact vs. castrated male) and a non-animal odor comparison. In a fourth test, only the ArKO females were quickly able to discriminate between urine from GDX, WT females treated only with E, and GDX and WT females treated with E + P. The authors conclude that ArKO females have the best discrimination abilities overall. ArKO males and WT males do not differ significantly on any test, while WT females performed less well than ArKO females on every test. These data support the conclusion that WT male superiority in discriminating between most odors compared with WT females is a function, at least in part, of androgen exposure since ArKO male and WT males do not differ from each other and perform better than WT females. For those of us well-versed in the lore of estrogen as the primary masculinizing agent of the rat brain, this is a surprising result. However, Sato et al. (2004) have already demonstrated that WT female mice treated with DHT across the perinatal period

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demonstrate marked increases in male-typical sex behaviors which do not occur in the absence of androgen receptors. Thus, at least in the mouse, androgens may play a more significant role in differentiation than previously recognized.

ArKO females' superior performance on the most difficult discrimination task is most likely not because their brains are masculinized since the ovaries are not producing steroids during the perinatal period and adrenal androgens are quite limited. In addition, their other sexually dimorphic behaviors are feminine. The authors point out that ArKO mice have increased estrogen receptor- α , and the low dose of estrogen given to all animals may have had disproportionate activational effects on the female ArKO mice. The male ArKO may not have been as sensitive to the activational effects of estrogen because of their perinatal exposure to their own testosterone. This interaction between perinatal and adult hormones on olfactory discrimination provides an important opportunity to further explore how perinatal hormones determine responses to adult hormone exposure at a cellular/molecular level of analysis. In addition, the difference between the female groups suggests that perinatal estrogen, however little may be present, plays some role in differentiation.

Lastly, it is important to attend to the distinction made between sex differences in detection of odors and discrimination between odors. Earlier work has repeatedly found that female rodents (and female mammals in general) are better at detecting threshold levels of odorants. Based on such findings, one would predict that females would be better able to discriminate between odors—but the data in this paper demonstrate that that assumption is not true, at least in mice. WT females learned discriminations more slowly than WT males. ArKO females, which demonstrated the weakest performance in detecting urine-based odors (habituation/dishabituation task; Pierman et al., *in press*), performed as well or better than any group on the learned discrimination

task. This suggests three things: (1) if an odor is detectable to an individual, discrimination ability is a separate behavior entirely; (2) animals need to be motivated to investigate the odors (ArKO females seem to spend less time investigating odors); and/or (3) it is possible that the decreased performance on the detection task reflects an increased ability to detect differences in odors. The last 2 suggestions may be alternative explanations for the same behavior. Perhaps ArKO females spend less time investigating the bodies and odors of other mice (Pierman et al., *in press*) because they rapidly discriminate the “meaning” of the odor and require less time investigating to do so. If the odor sources being used in the habituation tasks are at all varying between trials, the superior ArKO females may discern that and therefore respond with behavior in the detection task that suggests a lack of habituation and therefore a lack of ability to detect the odors. However, in the discrimination task, motivated by the need to eat, they continue to engage in the task and outperform the WT females on every test and males on the most difficult urine odor task, perhaps demonstrating that superior discrimination ability can cause problems in a detection test.

References

- Baum, M.J., Keverne, E.B., 2002. Sex difference in attraction thresholds for volatile odors from male and estrous female mouse urine. *Horm. Behav.* 41, 213–219.
- Pierman, S., Douhard, Q., Balthazart, J., Baum, M.J., Bakker, J., *in press*. Attraction thresholds and sex discrimination of urinary odorants in male and female aromatase knockout (ArKO) mice. *Horm. Behav.* doi:10.1016/j.yhbeh.2005.05.007.
- Sato, T., Matsumoto, T., Kawano, H., Watanabe, T., Uematsu, Y., Sekine, K., Fukuda, T., Aihara, K., Krust, A., Yamada, T., Nakamichi, Y., Yamamoto, Y., Nakamura, T., Yoshimura, K., Yoshizawa, T., Metzger, D., Chambon, P., Kato, S., 2004. Brain masculinization requires androgen receptor function. *Proc. Natl. Acad. Sci. U. S. A.* 101, 1673–1678.