Reviewer’s report

Title: The role of androgens in human sex development

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Reviewer: Sheri Berenbaum

Reviewer’s report:

This paper provides a short review of an area that has seen significant advances in the recent past, with important questions still remaining. The topic has relevance for understanding basic developmental processes and for clinical issues, including broad issues of sex differences in health and disease and specific issues regarding treatment of children with disorders of sex development and perhaps individuals with gender dysphoria. There are a number of ways in which the manuscript might be modified to increase its impact.

(1) The target audience and level of discussion are not clear. On the one hand, the audience seems to be a general audience, given the scope of the journal, and the coverage at a basic level, as seen in the simplicity of Figure 1. On the other hand, the paper as written seems targeted to readers already interested in sex development, and the denseness of the discussion of androgen response. To make the paper more attractive to a general audience, I suggest that the author (a) begin by discussing why sex matters, e.g., listing diseases with sex differences in incidence, manifestations, or treatment response; describing sex differences in basic physiological processes, (b) list possible explanations for the sex differences, and (c) move into this detailed discussion of the role of androgens, with a clearer exposition of the main points written for readers without detailed background.

(2) The author should make clear that the focus is on androgens during early development, and refer to other work reviewing effects of androgens during later life, particularly controversies about androgen depletion and replacement in middle-aged and older men.

(3) It is important to acknowledge other genetic and physiological factors that have been suggested to contribute to sexual differentiation, particularly effects of genes on the sex chromosomes (e.g., work of Arnold), active feminizing processes (e.g., role of ovarian hormones), and pubertal hormones. The author mentions puberty, but does not consider the relatively recent work suggesting that puberty may represent another sensitive period for permanent effects of sex hormone exposure on the brain and behavior. Most of the empirical work is in rodents (spurred by the work of Sisk), but there has been considerable interest in extending it to human beings (see, e.g., review by Berenbaum & Beltz in Frontiers in Neuroendocrinology, and work of Casey, Dahl, Forbes, Paus, Steinberg).
(4) The section on gender development could more accurately capture both the complexity of androgen effects on gender-related behaviors and the fact that this is a very active area of research with direct relevance for medical practice. For example, females with CAH are more masculinized on some characteristics (especially activity interests) than others (e.g., aggression); individuals with 5alpha-reductase deficiency are notable among those with DSD in showing relatively high probability of male gender identity, as reviewed in papers by Cohen-Kettenis. It is, indeed, possible to study biological effects on gender identity in people (making the statement on page 5 inaccurate); this is done ethically with natural experiments, as noted in several places in the paper in discussions of gender identity in individuals with DSDs. The references regarding androgen effects on gender-related behavior are very selective and it is not clear why the particular ones were chosen. Jurgensen et al. is not the only – and probably not the best – study on gender identity and sex-typed play in children with DSD. There are a number of recent, more comprehensive reviews than the one by Ngun et al.

(5) The author should be cautious in concluding that androgen effects on the brain cannot be reversed. The brain is plastic, and there is good evidence that experience changes the brain; furthermore, gender-related characteristics subserved by the brain are modifiable by the environment. Sex differences in brain structure and function are small and inconsistent, and neuroimaging studies in individuals with CAH have not provided strong evidence for prenatal androgen effects on the brain. Of course, this field is in its infancy, so effects may be found, but, given what we already know about brain and psychological development, it seems unlikely that all androgen effects on brain structure parallel their permanent effects on genital structure.

(6) A minor point: Most females with CAH do not have completely masculinized genitalia (top of page 5). It might be interesting to consider this in relation to other comments, e.g., about variations related to the form of androgen, to androgen sensitivity, or to other processes of sexual differentiation.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.