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INVITED REVIEW

Assessing gonadal hormone contributions to affective psychopathologies across humans and animal models

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Summary Despite increasing acknowledgement of hormonal contributions to mood and anxiety disorders, the underlying mechanisms by which gonadal hormones influence psychopathology-related behaviours remain unknown. This review focuses on recent research that examines the influence of gonadal steroid hormones, including androgens, oestrogens, and progesterone, on mood and anxiety-related behaviours in human health and disease. To this aim, the literature was surveyed for studies that assess conditions with suspected underlying hormonal imbalances in otherwise healthy participants (e.g., premenstrual dysphoric disorder, postmenopausal depression) as well as conditions linked to congenital endocrine abnormalities (e.g., Turner Syndrome, Klinefelter Syndrome, polycystic ovary syndrome, congenital adrenal hyperplasia, familial male precocious puberty, androgen insensitivity syndrome). Furthermore, to better inform clinical work and to create a translational bridge, a second goal was to set human psychopathologies and animal models of these conditions side-by-side. In the second part of the review, based on consistencies revealed in the existing literature across conditions, a new model for the impact of gonadal hormones on anxious and depressed behavioural states is proposed. Finally, we conclude by proposing directions for future research, including the development of specific tasks suitable for cross-species comparisons to increase our knowledge of the role of gonadal hormones in mood and anxiety.

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> ''The creatures outside looked from pig to man, and from man to pig, and from pig to man again; but already it was impossible to say which was which.''
>
> George Orwell, *Animal Farm*

1. Introduction

The clinical picture of hormonal dysfunction of the gonads (hyper- or hypogonadism) is frequently accompanied by some presentation of psychopathology, most notably in forms of anxiety and/or depression. Awareness of comorbid psychopathology is important for the clinical care and management of affected individuals, but it may also provide valuable information on the fundamental contributions of gonadal hormones, specifically androgens, oestrogens, and progesterone, to affective cognition. Conversely, some manifestations of mood disorders, such as premenstrual dysphoric disorder or postmenopausal depression have been intimately linked to underlying imbalances of the hormonal milieu. While research on basic cognitive-affective processes in human endocrine conditions is slowly increasing (Mueller, 2013), parallel research employing animal models indicates important relationships between gonadal dysfunction and the presentation of anxiety-like and depressive-like behaviours in non-human species (ter Horst et al., 2012). Surprisingly, few attempts to reconcile how human and animal literatures can inform one another have been made despite the possibility that findings obtained in one species may provide insights into the basic mechanisms that are better addressed in the other species. Such cross-species comparisons and validation of animal models are essential when aiming to develop effective therapeutic and/or pharmacological interventions for various disorders.

This review focuses on recent developments of affective processing in humans suffering from perturbations of gonadal hormones and corresponding models in non-human species, particularly rodents. As will be shown, these conditions may serve as an essential intermediary between behavioural neuroscience in animal models and basic neuroscience in human populations. To limit its scope, this review primarily focuses on changes in gonadal hormones and the HPG (hypothalamic-pituitary-gonadal) axis, however, some conditions presented here also affect HPA (hypothalamic-pituitary-adrenal) axis functioning. Given the breadth of this topic and the number of disorders and species being involved, and to emphasize similarities rather than differences, we decided to selectively focus on perturbations in sex hormones. To maintain this focus, the review will not address underlying biology or aetiology or examine possible interactions between hormones and other molecular systems including neurotransmitters or immunochemistry. Instead, it will address the relevance of sex hormones for behavioural aspects of anxiety and depression. In this sense, the reviewed literature has to be regarded as being limited and only constituting one aspect of a broader, complicated scenario.

First, conditions of hypogonadism in women and men will be reviewed followed by discussion of conditions of hypergonadism in both sexes. Given the current scarcity of research in this area, inclusion of published reports in the review was guided by available studies. To obtain these available studies, we searched PubMed from 1970 onwards with the search terms for the disorder or the rodent equivalent, i.e., Klinefelter, XXY, TFM and testicular feminization model, CAH and congenital adrenal hyperplasia, PMDD and premenstrual dysphoric disorder, postmenopausal syndrome, ovariectomy, Turners Syndrome, hypogonadal, castration PLUS anxiety OR depression AND/OR psychopathology AND human OR rodent. In addition, reference lists of identified articles were also searched for relevant literature. Thus, while some conditions are not included in this article, a secondary purpose of this review is to highlight the need for further studies of the consequences of hormonal imbalances. Following these sections, we highlight consistencies in the reviewed literature and discuss