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Hormone-specific psychiatric disorders: do they exist?

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A stated goal of the DSM-V process is to try to use the biological pathophysiology of mental disorders to inform psychiatric diagnoses, including dimensional features which may cut across diagnostic categories (Charney et al. 2002; Regier et al. 2009). At this point in time, however, biological markers have not been identified which are robust enough to be incorporated in diagnostic criteria. Progress in developing biologically-based diagnoses will depend on more detailed examination of clinical phenomenology associated with particular genetic, physiological, and neural processing characteristics. It is reasonable to expect that such an effort could result in identification of syndromes that map more closely to biological abnormalities than current diagnostic categories. As part of this effort, hormone-related syndromes deserve close attention as potential diagnostic entities or potential supraordinate dimensions that would cross diagnostic boundaries.

Because mood and behavior are emergent properties, it is difficult to focus on a level of physiology that would be most informative for diagnostic classification. It is now recognized that individual genetic polymorphisms are unlikely to contribute more than a very small degree of risk for psychiatric disorders. Moreover, the pathway from genes to behavior is now known to incorporate multiple opportunities for modulation of risk, including epigenetic modification of gene expression and plasticity of neurons, synapses and neural networks. Hormones can impact each of these biological processes. Hormonal abnormalities may arise at the synthesis, metabolism or receptor level, but still form organized, identifiable psychiatric syndromes.

There are several challenges to identifying hormone-related syndromes. First, in naturalistic reproductive hormone fluxes, such as puberty, the menstrual cycle, pregnancy, lactation and menopause, multiple hormonal changes occur simultaneously. There is an unfortunate tendency to attribute psychiatric symptoms to fluctuations in estrogen, rather than considering a more complete set of hormonal changes. In some cases, such as postpartum OCD, the full syndrome may not be evident following exposure to pregnancy levels of estrogen or progesterone alone. Another major challenge in sorting out hormonal influences on psychiatric disorders is the complex metabolism of circulating steroid hormones. Circulating hormone levels can differ from levels in specific brain areas or within specific cells because local tissue and cellular enzymes can metabolize steroid hormones to other compounds with distinct activities, such as neurosteroids. Approaches to sort out the hormone metabolite most proximal to symptom generation are to study the effects of enzyme inhibitors, receptor antagonists and hormonal agents which are resistant to metabolism. Finally, examination of psychiatric effects of peptide hormones such as oxytocin and inflammatory cytokines is complicated by lack of agonists and antagonists

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which can access the brain, and separate pools of hormone at specific brain sites and in the periphery.

PMDD: a candidate hormone-specific psychiatric disorder

PMDD, under consideration as a new diagnosis for DSM-V, is the prototypical example of an hormonally based mood disorder. The symptoms are induced by luteal hormones and are relieved in the follicular phase of the cycle and when hormonal cycling is interrupted. Symptom severity is continuous, with only a small minority of women experiencing significant impairment. At this point, it is unclear whether women with PMDD experience luteal hormones more intensely because of abnormalities in luteal hormone metabolism or receptors, or because of vulnerabilities in downstream systems affected by luteal hormones such as serotonin and vasopressin or prefrontal inhibitory circuits (Protopopescu et al. 2008). Although circulating androgen hormones are not elevated during the luteal phase, several lines of evidence suggest that androgen hormones play a primary role in PMDD. First, irritability is the most prominent symptom of PMDD. Second, an oral contraceptive, Yaz, known to be an effective treatment for PMDD, contains drospirenone, which antagonizes androgen receptors. Third, SSRIs can suppress androgen hormone levels (Tanrikut et al. 2009) and modulate steroid metabolic enzymes (Pinna et al. 2009), raising the possibility that SSRI efficacy in PMDD is mediated by reduction of androgen activity. This model of PMDD, if confirmed, could potentially lead to an “Androgenic Irritability Syndrome” which could have consistent phenomenology and treatment response in both men and women.

Other less clear examples of hormonally based mood disorders could be mood disorders which develop during pregnancy or postpartum, affective disorders which develop during perimenopause or puberty, and syndromes associated with hyper or hypothyroidism or hypogonadism. For men, it is more difficult to conceptualize a reproductive hormone based mood disorder, because hormones are stable during adulthood and andropause is a much slower, gradual process. However, the more dramatic hormonal changes of adrenarche, puberty and androgenic steroid abuse may be linked to specific symptoms.

Research needed to investigate the importance of hormones in psychiatric diagnosis

To fully appreciate the nature of hormonally-induced disorders, it is necessary to more carefully characterize the symptomatology associated with hormonal abnormalities, considering more detail than categorical DSM-IV diagnoses. It remains to be determined the degree to which symptomatic responses to hormonal changes are heterogeneous among different individuals. If symptomatic responses are very heterogeneous, this would imply that hormonal changes are a non-specific stressor and would weigh against consideration of hormonal factors in a diagnostic system. Further support for a non-specific effect of hormones would be observation of similar symptoms profiles within individuals for episodes associated with hormonal changes and episodes which occur independent of hormonal changes. There is accumulating evidence suggesting that hormonal exposures during gestation can impact psychiatric status in adulthood, so future research should consider these potential hormonal syndromes as well.

Conclusion

Excessive or reduced hormonal activity during development or in adulthood may be associated with particular clusters of psychiatric symptoms. However, more work is needed to clearly characterize the nature of such syndromes. If discrete syndromes can be identified,

hormonal mechanisms should be considered in future DSM diagnostic systems. If hormonally induced psychiatric syndromes do exist, expression may depend on other elements of individual vulnerability, in addition to the hormonal challenge.

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