Adrenarche

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Adrenarche is a process of postnatal sexual maturation occurring only in higher primates, during which the secretion of adrenal androgens is increased. This is the consequence of an expansion of the adrenal zona reticularis (ZR), concurrent with a series of changes in the adrenal expression of steroidogenic enzymes needed for the biosynthesis of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). The mechanisms underlying this phenomenon remain poorly understood.

The present volume represents a comprehensive review of adrenarche from the viewpoints of many disciplines including biochemistry, cell biology, physiology and medicine. The enzymes and pathways of steroidogenesis, which are central to an understanding of adrenarche, are reviewed by Walter Miller. Whereas the quantitative regulation of steroidogenesis occurs at the first biosynthetic step—the conversion of cholesterol to pregnenolone—qualitative regulation, which determines the type of steroid produced in a cell, is principally at the level of 17 α -hydroxylase/17,20-lyase (CYP17, P450c17). When both activities of CYP17 are present in the ZR, the androgen precursor DHEA is produced. The discrimination between 17 α -hydroxylase and 17,20 lyase activities is regulated by two post-translational events, the serine

phosphorylation of CYP17 and the allosteric action of cytochrome b5 (CYB5), both of which act to optimize the interaction of CYP17 with its obligatory electron donor, P450 oxidoreductase.

William Rainey and colleagues extend these observations at the level of gene expression, describing how, as adrenarche proceeds, the expanding ZR expresses greater levels of CYB5 and steroid sulfotransferase (SULT2A1) than the adjacent fasciculata. In contrast, the growing ZR is deficient in 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2). The resulting profile of steroidogenic enzymes lends itself to the production of adrenal androgens and appears to track the progression of adrenarche.

Richard Auchus provides additional biochemical insights by discussing the potential existence of alternate biosynthetic routes and variable order of reactions encountered by steroid hormone precursors in the adrenal gland, the variables influencing flux through these secondary pathways, and the significance of these diversions in health and disease.

Neil Hanley and colleagues turn their attention from adrenarche to prenatal development. Significant components of human sexual differentiation unfold during the first 3 months of gestation when they are sensitive to disruption by abnormal hormonal influences. Excessive exposure of female development to androgens (as occurs in conditions such as congenital adrenal hyperplasia) causes virilization. However, the authors' work suggests that female development normally takes place in the presence of low yet significant levels of androgen, implying a biological role for androgens in female development.

In considering mechanisms affecting adrenarche, Alicia Belgorosky and colleagues suggest a relationship between circulating insulin-like growth factor-1 (IGF-I) levels, insulin sensitivity, and adrenal androgens. Paracrine IGF-1

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actions could regulate adrenal progenitor cell proliferation and migration. A role for estrogens in the ontogenesis of the ZR is suggested by the presence of aromatase (CYP19) in the subcapsular zona glomerulosa and in the adrenal medulla. Estradiol-induced increases in DHEA/cortisol ratio are indeed seen in cultures of adrenocortical cells from post-adrenarche adrenals. Thus, multiple factors may influence postnatal ZR growth.

Turning to pathological conditions related to adrenarche, Lourdes Ibanez and colleagues review premature pubarche, defined as the appearance of pubic hair before age 8 years in girls and 9 years in boys. Whereas this is often considered a benign entity, premature pubarche in girls may be a forerunner of the metabolic syndrome, particularly the development of clinical androgen excess. This seems to occur more frequently when premature pubarche is preceded by reduced fetal growth and followed by excessive postnatal catch-up in height and particularly in

weight; hyperinsulinemia appears to be a key factor in this sequence of events. In girls with this history, puberty tends to start earlier and to have a more rapid course. Therapy for this condition using either glucocorticoids or insulin sensitizing agents is still a controversial topic.

Finally, Phyllis Speiser reviews nonclassic adrenal hyperplasia, which is most commonly attributable to partial 21-hydroxylase deficiency caused by relatively mild mutations in CYP21. This causes an imbalance in cortisol synthesis with consequent adrenal androgen excess. This is a potential cause of premature adrenarche and pubarche in children, virilization in young women, and variable symptoms in young men.

Taken together, these articles provide the background for further research in this area to better understand the potential links between states of androgen excess, insulin resistance and metabolic dysregulation from infancy to adulthood.