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Current and novel approaches to children and young people with congenital adrenal hyperplasia and adrenal insufficiency

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Congenital adrenal hyperplasia (CAH) represents a group of autosomal recessive conditions leading to glucocorticoid deficiency. CAH is the most common cause of adrenal insufficiency (AI) in the paediatric population. The majority of the other forms of primary and secondary adrenal insufficiency are rare conditions. It is critical to establish the underlying aetiology of each specific condition as a wide range of additional health problems specific to the underlying disorder can be found. Following the introduction of life-saving glucocorticoid replacement sixty years ago, steroid hormone replacement regimes have been refined leading to significant reductions in glucocorticoid doses over the last two decades. These adjustments are made with the aim both of improving the current management of children and young persons and of reducing future health problems in adult life. However despite optimisation of existing glucocorticoid replacement regimens fail to mimic the physiologic circadian rhythm of glucocorticoid secretion, current efforts therefore focus on optimising replacement strategies. In addition, in recent years novel experimental therapies have been developed which target adrenal sex steroid synthesis in patients

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with CAH aiming to reduce co-morbidities associated with sex steroid excess. These developments will hopefully improve the health status and long-term outcomes in patients with congenital adrenal hyperplasia and adrenal insufficiency.

Adrenal steroidogenesis

The cells forming the adrenal cortex originate from the intermediate mesoderm and differentiate under the influence of various transcription factors during pregnancy and postnatal life. During foetal life and up to 12 months of age, two distinct zones are evident, an inner prominent foetal zone and an outer definitive zone that differentiates into the adult adrenal gland. After birth, the foetal zone regresses and the definitive zone, which contains an inner zona fasciculata and an outer zona glomerulosa, proliferates. The innermost zone, the zona reticularis, becomes evident after 2 years of life. These form three major functionally distinct parts of the adrenal cortex: the outer zona glomerulosa synthesizes mineralocorticoids, the middle zona fasciculata produces glucocorticoids, and the inner zona reticularis synthesises the androgen precursors dehydroepiandrosterone (DHEA) and androstenedione.

Glucocorticoid synthesis is negatively controlled by a feedback loop via the hypothalamus-pituitary-adrenal axis. A variety of central stimuli lead to the circadian and stress related secretion of corticotropin-releasing hormone stimulating the cleavage of polypeptide proopiomelanocortin (POMC) by prohormone convertase. This results in adrenocorticotropic hormone (ACTH) release from corticotroph cells of the anterior pituitary. ACTH is the key regulator of cortisol synthesis and has additional short-term effects on mineralocorticoid and adrenal androgen synthesis [1].

ACTH binds to its adrenal receptor (melanocortin receptor 2, MC2R) and stimulates the rapid import of cholesterol into the mitochondrion by steroidogenic acute regulatory protein (StAR). In parallel, the transcription of steroidogenic genes (*CYP11A1, HSD3B2, CYP17A1, CYP21A2, CYP11B1*) and co-factors relevant to glucocorticoid synthesis increases. Corticotropin-releasing hormone and subsequently ACTH are released in a pulsatile fashion. Following the pattern of ACTH secretion, adrenal cortisol secretion exhibits a distinct circadian rhythm, with peak concentrations in the morning and low concentrations in the late evening hours [2].

Mineralocorticoid synthesis is mainly controlled by the renin-angiotensin-system and a potassium feedback loop. Renin secretion from the renal juxtaglomerular cells are stimulated by a variety of factors with renal arterial perfusion (closely correlating with renal arterial pressure) being the most important regulator. Non-endocrine conditions affecting renal blood flow have significant pathophysiologic consequences on the renin-angiotensin-system. The rate limiting step of the renin-angiotensin-system is the secretion of renin. Angiotensinogen is converted by renin to angiotensin I, which itself is converted by angiotensin converting enzyme to Angiotensin II, a potent stimulator of aldosterone synthesis and secretion [2].

The distinct regulation of glucocorticoid and mineralocorticoid biosynthesis has important clinical consequences for the differential diagnosis and management of adrenal insufficiency (AI). Secondary AI manifests with isolated glucocorticoid deficiency, whereas most classic forms of primary adrenal insufficiency (PAI) have signs and symptoms of combined glucocorticoid and mineralocorticoid deficiency. Classic familial glucocorticoid deficiency characterised by unresponsiveness of the adrenal to ACTH leading to isolated glucocorticoid deficiency represents an exception.

Clinical presentation

The epidemiology of AI in children and adolescents is different to the situation during adulthood. The majority of cases in paediatrics are either due to genetic causes, most commonly due to congenital adrenal hyperplasia (CAH), a group of recessively inherited disorders of adrenal steroid biosynthesis