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Aberrant G-Protein coupled hormone receptor in adrenal diseases

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The regulation of cortisol or aldosterone production when ACTH of pituitary origin or the renin-angiotensin systems are suppressed in primary adrenal Cushing's syndrome or in primary aldosteronism is exerted by diverse genetic and molecular mechanisms. In addition to recently identified mutations in various genes implicated in the cyclic AMP or ion channel pathways, steroidogenesis is not really autonomous as it is frequently regulated by the aberrant adrenocortical expression of diverse hormone receptors, particularly G-protein coupled hormone receptors (GPCR) which can substitute for the normal function of ACTH or angiotensin-II. In addition, paracrine or autocrine production of ligands for the aberrant GPCR such as ACTH or serotonin is found in some adrenal tumors or hyperplasias and participates in a complex regulatory loop causing steroid excess. Targeted therapies to block the aberrant ligands or their receptors could become useful in the future, particularly for patients with bilateral source of steroid excess.

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Introduction

Cushing's syndrome

Cushing's syndrome (CS) results from chronic exposure to excess cortisol concentrations activating glucocorticoid receptors in most tissues and causing diversified morbidities [1]. Corticotropin (ACTH)-independent causes (15–25%) of endogenous overt hypercortisolism are mainly due to primary unilateral cortisol secreting adenomas and carcinomas [1]. Rare etiologies (<2%) include primary bilateral macronodular adrenal hyperplasia (BMAH) and primary pigmented (micro)nodular adrenal disease (PPNAD) [1]. Unilateral or bilateral adrenal incidentalomas (4% of adults) can secrete in 10–15% of cases mild dysregulated amounts of cortisol which may still increase cardiovascular morbidity [2].

Normal regulation of cortisol secretion is exerted mainly by ACTH activation of its melanocortin type 2 receptor (MC2R), a GPCR expressed on zona fasciculata cells where it interacts with MC2R-associated proteins (MRAP) for its action [3]. Activation of MC2R dissociates Gs-alpha from G-protein complex to activate adenylate cyclase (AC) and cyclic AMP (cAMP) formation. Binding of two cAMP molecules to specific regulatory domains of protein kinase A (PKA) releases the catalytic subunit (PRKACA) from its inactivating sub-units. Activated PRKACA phosphorylates intracellular targets, including the transcription factor cAMP-responsive element-binding protein (CREB); the latter activates the transcription of genes including cholesterol transporters and steroidogenic enzymes, which acutely stimulate cortisol synthesis and chronically cellular proliferation [3]. Specific phosphodiesterases (PDEs) degradate cAMP to allow reassembly of PKA to its inactive state.

In primary adrenal CS, excess cortisol secretion suppresses CRH and ACTH [1]. Recently, diverse genetic and molecular mechanisms leading to ACTH-independent production of cAMP and cortisol were elucidated [1,4,5]. In 35–65% of unilateral adenomas with CS, cortisol oversecretion results from *PRKACA* somatic mutations which prevent its binding to the R inhibitory proteins; those mutations are rare in adenomas secreting less cortisol [4,5]. Germline genomic rearrangements in chromosome 19p13.2p13.12 locus resulting in *PRKACA* amplification occurs rarely in micronodular or macronodular hyperplasias [4].

Inactivating mutations of protein kinase A regulatory subunit 1A (*PRKAR1A*) are responsible for CS in isolated or familial PPNAD and Carney complex or in some adrenal tumors. Inactivating germline mutations in phosphodiesterase 11A isoform 4 gene (*PDE11A*) or 8B (*PDE8B*) have been identified in rare kindreds with non-pigmented micronodular hyperplasia with no *PRKAR1A* mutation [4,5].

Activating mutations of the *Gs-α* subunit of heterotrimeric G protein also termed *gsp* mutations (*GNAS*) can occur in some fetal adrenal cells during early embryogenesis in patients with the McCune-Albright syndrome (MAS) causing nodular adrenal hyperplasia and CS. Isolated somatic *GNAS* mutations can also occur in 5–17% of cortisol-secreting adenomas and in rare cases of BMAH [4,5].

Activating somatic mutations of the beta-catenin gene (*CTNNB1*) occur in ~25% of both adrenocortical adenomas and carcinomas of non-secreting and cortisol-secreting tumors and are associated with less differentiated tumors and poorer survival of ACC patients [4].

In BMAH, germline mutations of Armadillo Repeat-Containing Protein 5 (*ARMC5*) were found in approximately 25% of cases of apparently sporadic and familial BMAH; additional distinct biallelic *ARMC5* somatic mutations can be found in each the adrenal macronodules [4–6].

In contrast with mechanisms which would mainly lead to constitutive activation of the cAMP system, abnormal regulation of steroidogenesis can also result from the aberrant adrenal expression of several hormone receptors, particularly GPCR and their ligands, which will be reviewed here. Aberrant hormone receptors can also exert their activity by regulating the paracrine secretion of ACTH or other ligands for those receptors in BMAH or unilateral tumors [5,7–9].

Primary aldosteronism

In primary aldosteronism (PA), aldosterone production is abnormally increased, inappropriately high for sodium status, relatively autonomous from its major secretagogues (angiotensin II, plasma potassium concentration), and incompletely suppressible by sodium loading [10]. This results in

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