ACTH-Independent Hypercorticism in Adrenal Tumors and Adrenocortical Hyperplasia

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ABSTRACT: Cortisol production is normally under the regulation of adrenocorticotropic hormone (ACTH). Hypercortisolism or Cushing's syndrome, characterized by excessive cortisol levels, may be caused by ACTH-independent mechanisms. The present work aims to review the current knowledge on ACTH-independent mechanisms through aberrant expression of hormone receptors in adrenal tumors and adrenocortical hyperplasia. In particular, the effects of epinephrine, norepinephrine, serotonin, arginine vasopressin, and gastric inhibitory polypeptide are discussed.

KEYWORDS: hypercorticism, adrenal tumors, adrenocortical hyperplasia, Cushing's syndrome, ACTH-independent

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Introduction

Cortisol is a glucocorticoid hormone produced by the adrenal cortex. Cytochrome P450 enzymes and hydroxysteroid dehydrogenases are present in adrenocortical steroidogenic cells to catalyze sequential reactions to produce cortisol from cholesterol.[1] The production of cortisol is under the control of the central nervous system via the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 1). The hypothalamus produces corticotrophin-releasing hormone (CRH), a 41-amino acid peptide hormone, and stores it in the median eminence before releasing it into the hypothalamus portal vein.[2] CRH binds to receptors on cells within the anterior pituitary, stimulating the release of adrenocorticotropic hormone (ACTH), a 39-amino acid peptide hormone.[3] ACTH is the main regulator behind cortisol secretion and adrenocortical growth, by binding to the melanocortin receptor-2 (MC2) on the steroidogenic cell membrane in the zona fasciculata of the adrenal cortex.[4] The regulation of cortisol production is highly dynamic and influenced by age, gender, stress, body composition, and diseases.[5] Depression, mania, dementia, posttraumatic stress disorder, chronic fatigue syndrome, alcoholism, visceral adiposity, diabetes mellitus, polycystic ovarian disease, acute illness, systemic disease, and multiorgan failure impact cortisol secretion.[6] The HPA axis demonstrates a classic circadian rhythm under unstressed conditions,[7] consisting of high cortisol levels in the morning followed by low levels in the evening. Furthermore, the circadian rhythm exhibits an ultradian pattern with rapid pulsatile secretions of glucocorticoids from the adrenal gland.[7] Once cortisol is released, it binds to glucocorticoid receptors on target cells, altering gene transcription[8–10] and regulating multiple physiological functions, including cellular metabolism of glucose, proteins, and lipids[11,12] for energy homeostasis,[13,14] salt and water balance,[15] blood pressure,[16,17] and functions of the immune system.[18,19]

Abnormal activity of the adrenal cortex leads to hypercortisolism or 60% of Cushing's syndrome cases, characterized by excessive cortisol levels. Cushing's syndrome is a rare disease with an incidence of 1.2–1.7 per million people a year. This includes 0.6 adrenal adenoma and 0.2 adrenal carcinoma cases per million people per year.[20] The majority of patients with Cushing's syndrome exhibit elevated ACTH secretion due to ectopic ACTH-secreting tumors. However, some cases of Cushing's syndrome result from cortisol-secreting adrenal tumors, most of which are benign adrenocortical adenomas, adrenal cancer, or precancerous nodular adrenal hyperplasia[21] and some cases in an ACTH-independent manner. ACTH-independent stimulation of cortisol production was discovered in 1971,[22] with more reports in recent years. This review attempts to summarize in vivo case reports and the studies with cell cultures in vitro on hypercortisolism. The reports and studies focus on ACTH-independent hormone stimulation involving epinephrine, norepinephrine, serotonin, arginine vasopressin (AVP), and gastric inhibitory polypeptide (GIP), due to illegitimate or aberrant expression of hormone receptors in adrenal tumors and adrenocortical hyperplasia (Fig. 1).

ACTH-dependent Hypercortisolism

ACTH is a peptide hormone produced and secreted by the anterior pituitary under the influence of CRH from the hypothalamus (Fig. 1). In some cases, normal human adrenal

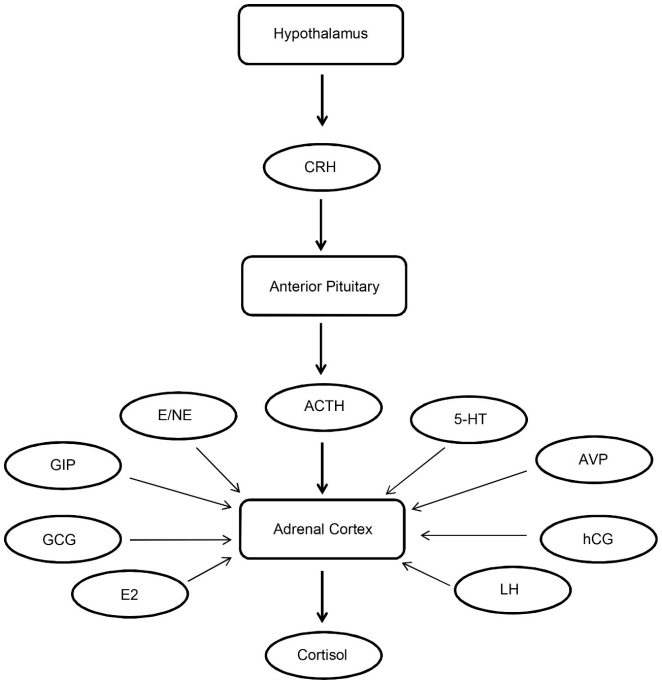

Figure 1. A classic HPA axis and ACTH-independent stimulation of cortisol production. Thick arrows indicate sequential steps between the structures (in rounded rectangles) and the hormones (in ovals) in the HPA axis that stimulate cortisol production under normal physiological conditions. Thin arrows indicate the ACTH-independent aberrant pathways of cortisol production under the effects of other hormones from adrenal tumors and adrenocortical hyperplasia. See the list of abbreviations for the full names of the hormones.

medulla and other tissues under benign or malignant tumor conditions may become ectopic origins for both ACTH and CRH,[23] causing 10%–15% of Cushing's syndrome cases.[24] In ACTH-producing thymic neuroendocrine tumors, overexpression of p21-activated kinase-3 as well as enhanced cell migration and invasion were detected.[25] Elevated production of ACTH is also observed in cases of pheochromocytoma, the adrenal medullary tumor.[26–31]

Epinephrine and Norepinephrine

Epinephrine and norepinephrine are tyrosine-derived catecholamines. Both are produced in the adrenal medulla and bind to adrenergic receptors (alpha and beta) in brain, heart, kidney, stomach, and smooth muscle of multiple organs. Adenylyl cyclase is normally coupled exclusively to ACTH in normal adrenocortical tissue, but some early studies found that it responded to epinephrine and norepinephrine in adrenocortical cancer tissue.[22,32] Alpha-2A adrenergic receptors were identified in cell cultures from ACTH-independent macronodular adrenal hyperplasia (AIMAH).[33] Beta-2 adrenergic receptors were identified in human adrenocortical cortisol-producing adenomas[34,35] or hyperplasia.[36–38] Cell cultures from AIMAH showed hyperresponsiveness to isoproterenol, a nonselective beta-adrenergic receptor agonist, and salbutamol, a beta-2 adrenergic receptor agonist.[37] Propranolol, a beta-adrenergic antagonist usually used to treat hypertension and heart dysrhythmias, greatly decreased the patient's urinary cortisol excretion.[37,38] Meanwhile, treatment with isoproterenol, a beta-adrenergic agonist usually used to treat bradycardia and heart block, stimulated cortisol production.[39] Incubation of cultured cells expressing the beta-adrenergic receptors with the peptide hormone AVP and epinephrine together induced a stronger cortisol response than the individual agents alone.[40] Catecholamines also promoted cortisol production through beta-adrenergic receptors in provocation tests with AIMAH cell cultures.[36]

5-HT

5-Hydroxytryptamine (5-HT), or serotonin, is a monoamine neurotransmitter derived from tryptophan. It is synthesized in the gastrointestinal (GI) tract and the central nervous system to regulate intestinal movements, mood, appetite, and memory through a group of receptors (5-HT_1 to 5-HT_7) in nervous, cardiovascular, and digestive systems.[41] All 5-HT receptors except 5-HT_3 are G-protein coupled receptors (GPCRs), and most of them are coupled with adenylyl cyclase. Both 5-HT and cisapride, a 5-HT_4 receptor agonist, stimulated cortisol production in vivo,[42] in cultured cells from adrenal hyperplasia[37,43,44] and adrenocortical carcinoma.[45] Patients with Cushing's syndrome treated with 5-HT_4 receptor agonists cisapride,[43,46–50] metoclopramide,[46,48] and zacopride demonstrated increased cortisol levels.[51] The presence of 5-HT4 receptor was also detected by reverse transcription polymerase chain reaction (RT-PCR) in other studies.[52,53] The cultured AIMAH cells exhibit T-type Ca^{2+} currents enhanced by 5-HT(10^{-5}M) at –50 and –30 mV.[44] These data are consistent with the results in animal experiments, suggesting that the activation of adenylyl cyclase via 5-HT_4 receptors and the subsequent rise of intracellular Ca^{2+} through T-type calcium channels stimulated the secretion of corticosteroid in adrenocortical cells.[54,55] Treatment with H-89, a protein kinase A (PKA) inhibitor, greatly reduced the spontaneous production of cortisol in the cell cultures and blocked the action of 5-HT cells in most patients.[44] Clusters of steroidogenic cells demonstrated 5-HT and AVP-like (detailed in the next section) immunoreactivity, suggesting that these two factors may use paracrine or autocrine mechanisms to stimulate cortisol secretion.[43] In some cases, the corticotropic effect of 5-HT was mediated by ectopic 5-HT_7 receptors.[44,45] 5-HT_7 receptor-like immunoreactivity was identified in the central zones of the hyperplastic nodules, spongiocytic cells, small compact cells, arterial walls of hyperplasia,[44] and carcinoma cells.[45]

Arginine Vasopressin

AVP, or argipressin, is a peptide hormone that increases the water permeability in the kidney for reabsorption and peripheral vascular resistance, which increases blood pressure.[56] AVP is mainly produced by magnocellular neurosecretory neurons in

the paraventricular nucleus and supraoptic nucleus of the hypothalamus and is released from the posterior pituitary gland.[57] There are four types of AVP receptors, namely, V1a, V1b, V2, and OT, located at different tissues in the body, including the uterus, the pituitary, the kidney, and the cardiovascular system.[58] AVP is also produced in normal human adrenocortical tissue as cells containing AVP were observed in both the adrenal cortex and medulla.[59] Some steroidogenic cells exhibited AVP immunoreactivity, suggesting that AVP may act as an autocrine or paracrine chemical messenger in the adrenal cortex to stimulate cortisol secretion.[43,60] Administration of AVP to some patients with Cushing's syndrome increases the plasma cortisol concentration without changing the corticotropin concentration.[36–40,46] The same effect was observed with lysine-8-vasopressin,[61] but not with desmopressin (DDAVP, a synthetic V2 receptor agonist alternative for vasopressin).[36–40] Cortisol secretion stimulated by AVP was suppressed by oral administration of SR 49059[38] or OPC-21268,[62] both V1-vasopressin–receptor antagonists, only with patients in a horizontal, supine position.[38] In vitro tests showed that AVP triggered cortisol secretion in a dose-dependent manner using V1-A receptors in both normal adrenocortical cells[59,63] and AIMAH tissues.[40,60,64,65] The stimulating effect of AVP was enhanced by combinations with ACTH or epinephrine.[40] Overexpression of V1-AVP receptor mRNA in AIMAH tissue was determined by RT-PCR in cultured AIMAH adrenal cells.[40,64,65] Some cases also had overexpression of V2[40,44] and positive V3 expression in AIMAH.[40]

Gastric Inhibitory Polypeptide

GIP, also called glucose-dependent insulinotropic peptide, is a 42-amino acid peptide produced by the mucosa of the duodenum and the jejunum in the GI tract. It binds to the corresponding GPCRs.[66] GIP level is elevated after the ingestion of fat-rich and glucose-rich meals.[67] Patients with food-dependent Cushing's syndrome experienced symptoms of low fasting plasma cortisol levels but increased cortisol levels induced by a meal, glucose administered orally,[43,47,50,68,69] or responded to GIP stimulation in a dose-dependent fashion.[43,62] The meals can be standard,[47] lipid rich, or protein rich[70] for patients with nodular adrenal hyperplasia[50,68,70] or unilateral adrenocortical adenoma.[47,69] The GIP receptor was found to be overexpressed in the adenoma tissue.[47,68,69] Since the GIP receptors are apparently coupled to the cAMP-dependent protein kinase A (AC/PKA) signaling pathway, the PKA inhibitor H-89 suppressed spontaneous cortisol production in cultured AIMAH cells.[44] Activation of GIP receptors reduced the amplitude of both transient and sustained K^+ currents but enhanced T-type Ca^{2+} current,[44] in which both currents contributed to the depolarization of the cell and entry of Ca^{2+} as part of the steroidogenic response. In a recent in vitro study,[71] transient transfection of GIP receptor into cultured human adrenocortical carcinoma cells followed by GIP treatment upregulated enzymes and proteins related to cortisol production (CYP17A1, CYP21A2, HSD3β2, CYP11A1, the cholesterol transport protein StAR, and the ACTH receptor, as well as the ACTH precursor proopiomelanocortin). The expression of steroidogenic enzymes such as CYP17A1 and CYP21A2 were also induced in the adjacent GIP receptor (–) cells, suggesting that GIP-dependent steroidogenesis is activated by endogenously secreted ACTH in an autocrine or paracrine mechanism, following GIP administration.

Other Hormones

A study showed that a glucagon (GCG) response was observed in 58% of the patients with subclinical Cushing's syndrome.[72] Aberrant expression of GCG receptors in adrenal glands were detected in a patient with Cushing's syndrome and AIMAH. The results showed abnormally high levels of serum cortisol after stimulation with GCG.[73] The growth hormone inhibitor octreotide, GCG, and insulin suppressed cortisol production in some patients with Cushing's syndrome and 92% of the patients with subclinical Cushing's syndrome in this study.[68,72] Human chorionic gonadotropin stimulated cortisol production in vivo[48] and in AIMAH cell cultures,[42,47] demonstrating that an effect coupled to AC/PKA pathway.[44] Luteinizing hormone (LH) stimulated cortisol production in vivo[48] and LH receptors were identified in cultured cells,[40,47,48] which can be indirectly induced by gonadotropin-releasing hormone in vivo.[43,47] In addition, sex hormones such as estradiol (E2) have been shown to increase cortisol through ACTH in female animals.[72,74]

Conclusion

The majority of hypercortisolism is caused by elevated ACTH secretion. However, in recent years, studies show that hypercortisolism is caused by ACTH-independent hormone stimulation, due to adrenal tumors and adrenocortical hyperplasia. Recent studies have also shown ACTH-independent hormone stimulation involving epinephrine, norepinephrine, serotonin, AVP, and GIP is due to aberrant expression of hormone receptors and activation of the receptors in an autocrine or paracrine pattern. Antagonists to the receptors or inhibitors of downstream intracellular target receptors were used in patient treatment and showed promising results. The current knowledge and ongoing research will facilitate the development of more effective diagnostic methods and pharmaceutical interventions.

Abbreviations

5-HT, 5-hydroxytryptamine or serotonin; AC/PKA, adenylyl cyclase/protein kinase A; ACTH, adrenocorticotropic hormone; AIMAH, ACTH-independent macronodular adrenal hyperplasia; AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; DDAVP, trade names of desmopressin, a synthetic replacement for vasopressin; E2, estradiol; E/NE, epinephrine/norepinephrine; GCG,

glucagon; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GIPR, gastric inhibitory polypeptide receptor; GnRH, gonadotropin-releasing hormone; GPCR, G-protein coupled receptor; GR, glucocorticoid receptors; hCG, human chorionic gonadotropin; HPA, hypothalamic–pituitary–adrenal; LH, luteinizing hormone; LVP, lysine-8-vasopressin; MC2, melanocortin receptor-2; mRNA, messenger ribonucleic acid; OPC-21268, a nonpeptide AVP V1a-receptor selective antagonists; PKA, protein kinase A; PVN, paraventricular nucleus; RT-PCR, reverse transcription polymerase chain reaction; SON, supraoptic nucleus; SR 49059, a nonpeptide AVP V1a-receptor selective antagonists; StAR, steroidogenic acute regulatory protein.

Author Contributions

Wrote the first draft of the manuscript: HL. Contributed to the writing of the manuscript: HL, KH. Agree with manuscript results and conclusions: HL, KH. Jointly developed the structure and arguments for the paper: HL, KH. Made critical revisions and approved final version: HL, KH. Both author reviewed and approved of the final manuscript.

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