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

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 corticotropin-releasing hormone (CRH), a 41-amino acid peptide hormone, and stores it in the median eminence before releasing it into the hypothalamic 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 transcription8–10 and regulating multiple physiological functions, including cellular metabolism of glucose, proteins, and lipids11,12 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 hyperplasia21 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
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. In ACTH-producing thymic neuroendocrine tumors, overexpression of p21-activated kinase-3 as well as enhanced cell migration and invasion were detected. Elevated production of ACTH is also observed in cases of pheochromocytoma, the adrenal medullary tumor.

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-HT1 to 5-HT7) in nervous, cardiovascular, and digestive systems. All 5-HT receptors except 5-HT1 are G-protein coupled receptors (GPCRs), and most of them are coupled with adenylyl cyclase. Both 5-HT and cisapride, a 5-HT4 receptor agonist, stimulated cortisol production in vivo in cultured cells from adrenal hyperplasia and adenocortical carcinoma. Patients with Cushing’s syndrome treated with 5-HT4 receptor agonists cisapride, metoclopramide, and zacopride demonstrated increased cortisol levels. The presence of 5-HT4 receptor was also detected by reverse transcription polymerase chain reaction (RT-PCR) in other studies. The cultured AIMAH cells exhibit T-type Ca2+ currents enhanced by 5-HT(10−5M) at −50 and −30 mV. These data are consistent with the results in animal experiments, suggesting that the activation of adenylyl cyclase via 5-HT4 receptors and the subsequent rise of intracellular Ca2+ through T-type calcium channels stimulated the secretion of corticosteroid in adrenocortical cells. 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. 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. In some cases, the corticotrophic effect of 5-HT was mediated by ectopic 5-HT7 receptors. 5-HT7 receptor-like immunoreactivity was identified in the central zones of the hyperplastic nodules, spongiocytic cells, small compact cells, arterial walls of hyperplasia, and carcinoma cells.

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. 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. 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. AVP is also produced in normal human adrenocortical tissue as cells containing AVP were observed in both the adrenal cortex and medulla. 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. Administration of AVP to some patients with Cushing’s syndrome increases the plasma cortisol concentration without changing the corticotropin concentration. The same effect was observed with lysine-vasopressin, but not with desmopressin (DDAVP, a synthetic V2 receptor agonist alternative for vasopressin). Cortisol secretion stimulated by AVP was suppressed by oral administration of SR 49059 or OPC-21268, both V1-vasopressin–receptor antagonists, only with patients in a horizontal, supine position. In vitro tests showed that AVP triggered cortisol secretion in a dose-dependent manner using V1-A receptors in both normal adrenocortical cells and AIMAH tissues. The stimulating effect of AVP was enhanced by combinations with ACTH or epinephrine. Overexpression of V1-AVP receptor mRNA in AIMAH tissue was determined by RT-PCR in cultured AIMAH adrenal cells. Some cases also had overexpression of V2 and positive V3 expression in AIMAH.

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, and GIP level is elevated after the ingestion of fat-rich and glucose-rich meals. 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, or OPC-21268 both V1-vasopressin–receptor antagonists, only with patients in a horizontal, supine position. In vitro tests showed that AVP triggered cortisol secretion in a dose-dependent manner using V1-A receptors in both normal adrenocortical cells and AIMAH tissues. The stimulating effect of AVP was enhanced by combinations with ACTH or epinephrine. Overexpression of V1-AVP receptor mRNA in AIMAH tissue was determined by RT-PCR in cultured AIMAH adrenal cells. Some cases also had overexpression of V2 and positive V3 expression in AIMAH.

Other Hormones

A study showed that a glucagon (GCG) response was observed in 58% of the patients with subclinical Cushing’s syndrome. 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. 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. Human choricon gonadotropin stimulated cortisol production in vivo and in AIMAH cell cultures, demonstrating that an effect coupled to AC/PKA pathway. Luteinizing hormone (LH) stimulated cortisol production in vivo and LH receptors were identified in cultured cells, which can be indirectly induced by gonadotropin-releasing hormone in vivo. In addition, sex hormones such as estradiol (E2) have been shown to increase cortisol through ACTH in female animals.

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,
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