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Review

Molecular genetic aspects and pathophysiology of endocrine hypertension

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INTRODUCTION

Blood pressure (BP) is the outcome of the interaction of intravascular volume, cardiac output and peripheral resistance. Hypertension is defined as BP exceeding 139/89 mmHg, whereas "pre-hypertension" refers to systolic BP of 120 to 139 mmHg or a diastolic BP of 80 to 89 mmHg. Traditionally, hypertension has been subdivided into two forms: essential or primary and secondary. Essential hypertension is a term applying to cases in which no cause can be identified (idiopathic) and accounts for approximately 85% of hypertensive patients.

Secondary hypertension, on the other hand, denotes BP elevation that results from an underlying identifiable cause. About 15% of hypertensive patients are identified as having secondary hypertension. Recently, the notion that secondary hypertension is rare has been challenged by the suggestion that primary aldosteronism, originally thought to be present in about 1% of individuals with hypertension, is present in up to 15% of hypertensives with a mean age of 54.1±11.2 years.[1,2] Endocrine hypertension is characterized by hormonal derangements that result in secondary hypertension. Its most common causes are excessive production of mineralocorticoids, catecholamines and glucocorticoids. Others include growth hormone excess, parathyroid hormone (PTH) excess and excess or deficiency of thyroid hormones production.

This review will focus on the pathophysiologic mechanisms by which hormone excess results in hypertension and will provide new molecular genetic data on disorders leading to endocrine hypertension.

Key words: Acromegaly, Aldosteronism, Cushing's syndrome, Hyperparathyroidism, Hyperthyroidism, Hypothyroidism, Pheochromocytoma, Secondary hypertension.

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MINERALOCORTICOID EXCESS - PRIMARY HYPERALDOSTERONISM

Primary hyperaldosteronism (PA) is characterized by aldosterone overproduction and concomitant suppression of the angiotensin-renin system, independent of angiotensin II (Ang II). Its main features include hypertension and altered potassium homeostasis. Numerous studies have recently reported a marked increase in its prevalence due to the wider use of the plasma aldosterone to plasma renin activity ratio (ARR) as a screening and diagnostic test. PA is currently considered to be the most common form of secondary hypertension affecting 5-15% of all hypertensives.[2-6] ARR leads to the recognition

of milder clinical forms of PA, mainly caused either by idiopathic bilateral adrenal hyperplasia (approximately two thirds of all cases),[7] or microadenomas, with normokalemia and clinically indistinguishable from essential hypertension. PA prevalence approaches 20% in patients with resistant hypertension.[8]

The most common subtypes of PA are idiopathic bilateral hyperplasia (IBH) (~65% of cases) and aldosterone-producing adenoma (APA) (~30%). Unilateral adrenocortical adenoma is also known as Conn's syndrome. Minor causes include unilateral hyperplasia or primary adrenal hyperplasia (PAH) (~3%), aldosterone producing adrenocortical carcinoma (<1%) and familial varieties (<1%). Two forms of familial hyperaldosteronism (FH) have been described: FH type I (FH-I) and FH type II (FH-II). FH-I, or glucocorticoid-remediable aldosteronism (GRA), is autosomal dominant in inheritance and is associated with variable degrees of adrenocorticotropin hormone (ACTH)-dependent hyperaldosteronism, renin suppression and high levels of hybrid steroids,[9] while hypokalemia is uncommon.[10] FH type II is more common than FH-I and refers to the familial occurrence of APA, IBH or both.[11] The underlying genetic basis for FH-I is well defined so that diagnosis can be reached by the use of genetic testing. For FH-II, the search for responsible gene mutations has not reached definite conclusions.

FH-I

Aldosterone, the principal human mineralocorticoid, is produced in the zona glomerulosa by aldosterone synthase (AS) after sequential 11β-hydroxylation, 18-hydroxylation and 18-oxidation of deoxycorticosterone (DOC).[12] AS is encoded by the *CYP11B2* gene that is located on chromosome 8q24.3, in tandem with the highly homologous *CYP11B1* gene, which encodes 11-β-hydroxylase.[13] The latter enzyme acts in the zona fasciculata to convert 11-deoxycortisol to cortisol, but is devoid of 18-hydroxylation and 18-oxidation activities. *CYP11B1* is widely expressed at high levels throughout the adrenal cortex, with ACTH as its main positive regulator. Conversely, *CYP11B2* is selectively expressed in the zona glomerulosa and is primarily regulated by serum potassium and Ang II levels. Both *CYP11B2* mRNA and AS activity have also been detected in various tissues, including the heart, the vessels, the brain and lymphocytes.

The genetic defect leading to FH-I was described in 1992.[9] It is the result of unequal recombination between *CYP11B1* and *CYP11B2*. This generates a chimeric (hybrid) *CYP11B* gene containing *CYP11B1* sequences at its 5' end and *CYP11B2* sequences at its 3' end.[9,14] Therefore, the hybrid gene encodes an enzyme that synthesizes excessive amounts of aldosterone throughout the adrenal cortex but, unlike *CYP11B2*, is ACTH- rather than AngII-dependent under the control of the 5' *CYP11B1* regulatory elements, and therefore glucocorticoid suppressible. Moreover, the 18-hydroxylation and 18-oxidation of cortisol generates the hybrid steroids 18OH- and 18oxo-cortisol, which can be detected at high levels in affected patients.

FH-II

FH-II is clinically and biochemically indistinguishable from the more common Conn's syndrome.[15,16] Its diagnosis requires PA to be confirmed biochemically in more than two family members.[11,15,17] FH-II is not associated with the hybrid gene mutation. Mutations in the coding region of *CYP11B2*, in the gene encoding the Ang II type I receptor (*AT1*) and *p53,* were not found in FH-II.[11,18,19] Linkage analyses have excluded the involvement of several genes including *CYP11B2*, the *AT1* gene and the *MEN1* locus, but a recent genome-wide search identified a locus on chromosome 7p22.[20,21] The best candidate among genes located in this region is *PRKAR1B*, being a functional partner of *PRKAR1A*, which encodes the regulatory subunit type 1A of protein kinase A. However, *PRKAR1B* was recently excluded as a candidate gene for FH-II.[22]

APA-IBH

Sporadic PA might originate from one or more gene variants. The presence of the chimeric gene has been ruled out in APAs, no point mutations of

the *CYP11B1* gene in the two regions examined were found and no mutations have yet been identified in genes coding for *p53, RAS, Gsa*, *renin, AT1*, *CYP21* and the *MEN1* locus.[22-25] Conversely, gene expression assays have shown that APAs over-express several genes including renin, *CYP21* and *CYP11B2*.[26] In studies of IBH patients, germline variants of *CYP11B2* and the chimeric *CYP11B1/B2* gene were not detected.[27]

Mechanisms of hypertension in PA

Aldosterone production is regulated by ACTH, Ang II and plasma potassium. Ang II stimulates aldosterone secretion in response to sodium depletion and reduced extracellular fluid volume, while increased plasma potassium also acts as a powerful stimulus. In PA excessive aldosterone production results in concomitant suppression of the renin and Ang II. Aldosterone affects BP regulation mainly by plasma volume expansion and increase in cardiac output. Aldosterone binding to the mineralocorticoid receptor (MR) creates a complex that leads to the induction of gene products called aldosterone induced proteins (AIPs).[29] AIPs bind to DNA regulatory elements and may have effects on the apical membrane, the cellular energy production and/or the basolateral Na^+/K^+-ATPase pump, resulting in increased sodium reabsorption and potassium and hydrogen ion excretion.[29] Major sites of these actions are luminal cells of the cortical collecting renal tubules and the distal convoluted tubules.[30] Apically located epithelial sodium channel (ENaC) is the major determinant of renal sodium reabsorption.[30] Aldosterone activates serum glucocorticoid regulated kinase (sgk), an AIP which increases ENaC activity by raising the number of channels at the cell surface.[31,32]

Other mechanisms, apart from volume expansion, are also likely to exist. For example, activation of the MR in vascular smooth muscle cells (VSMC) results in alteration in pressor responsiveness to adrenergic stimulation. Moreover, excessive levels of aldosterone binding to the MR in cardiac and vascular tissue are thought to regulate collagen formation, promotion of cardiac and vascular hypertrophy, remodeling and fibrosis independently of BP elevation.[33] Indeed, patients with PA exhibit more severe left ventricular hypertrophy (LVH) than patients with essential hypertension.[34] Such actions in peripheral blood vessels might result in vascular remodeling, which could sustain an elevated BP. The remodeling effects of aldosterone result from activation of NADPH oxidase, stimulation of xanthine oxidase and mitochondrial reactive oxygen species (ROS) generation.[35] Inflammation may also activate the renin-angiotensin-aldosterone system (RAAS) and contribute to vascular remodeling, but it is unclear whether aldosterone is associated with the inflammatory response found in hypertension.[36]

Finally, an interesting hypothesis linking 11β-hydroxylase activity and hypertension with PA was recently put forward based on association studies regarding the *CYP11B2* gene.[37] Two common polymorphisms within the *CYP11B2* gene have been described that are in linkage disequilibrium, one being a single nucleotide polymorphism in the 5′ promoter region at -344(C-T) that alters a putative regulation site for the transcription factor SF-1, and the other involving intron 2 of *CYP11B2,* which is partly replaced by the corresponding intron of *CYP11B1*.[38] Recent studies have shown that the C-344T polymorphism is associated with higher plasma and urinary aldosterone levels as well as elevated ARR among patients with hypertension.[37,39,40] Interestingly, the T allele and intron 2 conversion of *CYP11B2* are also associated with raised basal and ACTH-stimulated levels of the 11-deoxysteroids, DOC and deoxycortisol, which are converted to corticosterone and cortisol, respectively, by 11β-hyrdroxylase within the zona fasciculata.[37] This evidence suggests that the T allele of *CYP11B2* is associated with impaired activity of the enzyme 11β-hyrdroxylase which is encoded by the adjacent gene *CYP11B1.* Based on this evidence, Freel and Connell have hypothesized that -344 T polymorphism of *CYP11B2* may be in close linkage disequilibrium with a key quantitative trait locus in *CYP11B1*, adversely affecting its expression or function.[37] Thus, individuals with less efficient cortisol synthesis, as a consequence of reduced 11β-hyrdroxylase activity, will maintain, through negative feedback regulation, a slightly enhanced ACTH drive to the adrenals, that in the long term is likely to cause hyperplasia of both zona fasciculata and zona glomerulosa of the adre-

nal cortex, resulting in increased biosynthetic capacity for both cortisol and aldosterone.

MONOGENIC FORMS OF LOW RENIN HYPERTENSION

Hypertensive forms of congenital adrenal hyperplasia (CAH)

11β-hydroxylase deficiency

This is a rare autosomal recessive disorder caused by mutations in the *CYP11B1* gene.[41] *CYP11B1* mutations result in reduced activity of 11β-hydroxylase, leading to low plasma cortisol, chronic elevation of ACTH and accumulation of the steroid precursors 11-deoxycortisol and deoxycorticosterone. Excessive DOC production exerts a net mineralocorticoid effect, leading to sodium retention, volume expansion and finally hypertension in approximately two thirds of untreated patients.[41] Hypokalemia is variable, renin production is suppressed as a result of sodium retention and volume expansion, and aldosterone formation is low because of low plasma renin activity and low serum potassium concentrations.

17a-hydroxylase deficiency

This is a rare form of CAH caused by mutations of the *CYP17* gene which is located on chromosome 10q24.[42] *CYP17* enzyme acts both as steroid 17α-hydroxylase and as 17,20-lyase. Enzyme deficiency leads to diminished production of cortisol and sex steroids. Secondary elevation of ACTH causes an increased production of DOC and corticosterone with subsequent hypertension and hypokalemia. Aldosterone production is reduced as a result of suppressed renin.

Apparent mineralocorticoid excess (AME)

AME is a rare autosomal recessive disorder caused by deficiency of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) resulting from inactivating mutations of the *11β-HSD2* gene.[43,44] The 11β-HSD2 enzyme is co-expressed with the MR in renal tubular cells and converts cortisol to inactive cortisone, protecting the MR from saturation by cortisol and other glucocorticoids.[45] Both aldosterone and cortisol bind to the MR so that the 11β-hydroxysteroid dehydrogenase system acts as a gatekeeper to prevent excessive activation of MR by high levels of cortisol.[46] Defects in 11β-HSD2 will lead to more cortisol being available to bind to the MR. Affected individuals have hypertension and hypokalemia, low renin and aldosterone levels and normal plasma cortisol levels, but the ratio of urinary free cortisol/free cortisone and/or of their metabolites (tetrahydrocortisol+allotetrahydrocortisol/tetrahydrocortisone) are elevated.[47]

Constitutive activation of the mineralocorticoid receptor (Geller's syndrome)

The inheritance pattern of this syndrome is autosomal-dominant. "Gain of function" mutations of the *MR* gene located on chromosome 4q31 lead to the onset of hypertension that is markedly exacerbated in pregnancy.[48]

The ligand-binding domains of steroid hormone receptors are characterized by a conserved structure with 12 alpha-helices around a hydrophobic core. On agonist binding, a repositioned helix 12 forms a pocket with helix 3 (H3) and helix 5 (H5), where transcriptional coactivators bind.[49] A mutation in the *MR* gene results in the gain of a van der Waals interaction between helix 5 and helix 3 that substitutes for interaction of the steroid 21-hydroxyl group with helix 3 in the wild-type receptor.[49] Consequently, H3-H5 interaction permits progesterone-mediated activation of the MR, functioning as a switch that regulates its activity.[49,50] This mutation results in constitutive MR activity and alters receptor specificity, with classic MR antagonists like progesterone becoming potent agonists.

Liddle's syndrome

This is an autosomal dominantly inherited syndrome the main features of which include severe hypertension, hypokalemia, low plasma aldosterone levels and plasma renin activity. "Gain of function" mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located on chromosome 16p12, lead to constitutive activation of renal sodium reabsorption and subsequent volume expansion. Ten mutations causing Liddle's syndrome have been identified on the *SCNN1B* gene and one on the *SCNN1G* gene.[51-54]

Gordon's syndrome (pseudohypoaldosteronism type 2)

Gordon's syndrome is an autosomal dominantly inherited disorder with defective genes, mapping to chromosomes 1, 12 and 17.[55] Recently, mutations have been identified in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively.[55] Abnormalities such as mutations in the amiloride-sensitive sodium channel of the distal renal tubule are also accountable. Hypertension in these patients may develop as a consequence of increased renal Na reabsorption. Hyperkalemia follows reduced renal K^+ excretion despite normal glomerular filtration and aldosterone secretion.[56] The reduced renal excretion of K^+ and consequent hyperkalemia causes this condition to resemble an aldosterone-deficient state (pseudohypoaldosteronism).

GLUCOCORTICOID EXCESS - CUSHING'S SYNDROME

Cushing's syndrome is usually due to excessive ACTH production from the pituitary gland, ectopic ACTH secretion by a non pituitary tumor, or excessive secretion of cortisol from an adrenocortical tumor. Hypertension is a major complication of hypercortisolemia but the underlying pathology is not fully defined. Several mechanisms of BP elevation have been proposed, including increased responsiveness to vasoconstrictors, decreased vasodilator production, increased hepatic production of angiotensinogen, increased cardiac output by glucocorticoids, reduced production of prostaglandins via inhibition of phospholipase A, increased insulin resistance and over-saturation of 11β-HSD activity.[57]

L-arginine is the substrate precursor of nitric oxide (NO), an endothelium-derived vasodilator implicated in animal models of cortisol-induced hypertension. NO is an inhibitor of platelet aggregation and adhesion, proliferation of VSMC and leukocyte adhesion to the endothelium.[58,59] Glucocorticoids have a variety of effects on the NO system, including inhibition of NO synthase (NOS) isoforms and inhibition of transmembrane arginine transport.[60] Glucocorticoid excess raises BP in association with abnormalities in the NO pathway in both animals and humans.[61-63] L-arginine prevents and reverses the development of ACTH-induced hypertension in rats,[64] but in humans cortisol induced hypertension has not so far been associated with abnormalities in the L-arginine metabolism.[57,62,64] Human studies revealed that cortisol impairs acetylcholine induced vasodilation, as detected by using bilateral forearm plethysmography, and decreases NO metabolites.[61] On the other hand, short-term cortisol infusions in volunteers did not alter biochemical or physiological markers of NO activity.[65]

In the past, it had been generally accepted that steroid hormones produce hypertension by acting through renal type I MRs to produce sodium and water retention. Recent studies are consistent with substantial dissociation between sodium retention and BP-raising effects of cortisol.[66] Increase in cardiac output is not essential for the glucocorticoid-induced rise in BP, while the precise role of increases in peripheral resistance as a primary mechanism has not as yet been defined. Nevertheless, increased pressor responsiveness, particularly to catecholamines and Ang II, is a prominent feature.[66] In vitro studies have shown that the number of AT1 receptors of VSMC is increased by glucocorticoids, whereas activity of depressor systems (i.e. the kallikrein-kinin system, vasodilator prostaglandins and NO) is reduced.[66]

In addition, deficiency of 11β-HSD may allow increased exposure of MR to glucocorticoids in extrarenal sites, particularly VSMC and heart. Moreover, endogenous renal 11β-HSD-inhibitory factor was significantly increased in patients with low-renin essential hypertension.[67]

The role of activation of classic type II glucocorticoid receptors (GRs) in cortisol-induced hypertension is unclear. There is evidence for the presence of GRs on endothelial cells and VSMC.[68,69] Variations in the GR gene might contribute to essential hypertension; however, no evidence for an association of the GR gene locus in essential hypertension has been found, whilst the glucocorticoid antagonist RU-486 did not modify cortisol-induced elevations in BP.[70,71] Nevertheless, Mulatero et al. found impaired binding of cortisol to the GR in hypertensives and decreased sensitivity to cortisol, while Walker et al. reported increased glucocorti-

coid sensitivity in subjects at risk for hypertension and cardiovascular disease and in hypertensives.[72,73] Effects of glucocorticoids on vascular resistance have been explained in part by an increased response of the vasculature to catecholamines and Ang II.[66] Conversely, other studies suggest that sympathetic activity is unaltered or reduced by cortisol and cortisol induced hypertension in humans is not a result of overactivity of the autonomic nervous system. According to this notion, ganglion blockade in human volunteers did not significantly alter BP in the pretreatment phase or on the last day of cortisol treatment.[74]

Erythropoietin (EPO) is another candidate in the pathogenesis of glucocorticoid hypertension. EPO exerts direct vasoconstrictor effects in vitro and its concentrations correlate with BP in patients with essential hypertension.[75] EPO-induced hypertension appears to be in part due to NO resistance.[76] Cortisol increased both BP and serum EPO concentrations and there was a positive correlation between the change in systolic BP and the change in EPO concentration. It is possible that the rise in EPO concentration occurs as a consequence of some physiological effect of cortisol such as increased renal vascular resistance.

Glucocorticoid resistance

This autosomal recessive or dominantly inherited disorder is caused by inactivating mutations of the *GR* gene.[77] Cortisol and ACTH are elevated without clinical features of Cushing's syndrome. Chronic ACTH rise can lead to stimulation of adrenal compounds with mineralocorticoid activity, and of cortisol which lead to stimulation of the MR, resulting in hypertension.

CATECHOLAMINE EXCESS - PHEOCHROMOCYTOMA

Pheochromocytoma is a rare neuroendocrine tumor composed of chromaffin-staining tissue that primarily secretes catecholamines but also neuropeptide Y (NPY).[78] The clinical manifestations can vary depending on the type of catecholamines being produced and the amount and frequency of their release into the circulation. About 90% of pheochromocytomas are benign and 90% arise from the adrenal medulla, but they can also develop in extra-adrenal sympathetic/parasympathetic ganglia and in such cases they are referred to as paragangliomas.[79]

Classic symptoms include hypertension, headache, diaphoresis, perspiration, palpitations, tremor and tachycardia. The hypertension is caused by excessive plasma levels of catecholamines and may be sustained (20%), sustained with paroxysms (50%) or only paroxysmal (25%).

Most pheochromocytomas are sporadic but ~10% are familial.[80] Recent data suggest that germline mutations may be detected in up to 24% of unselected cases.[81] Inherited predisposition to pheochromocytoma occurs in patients with multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau disease (VHL), those with germline mutations in the *SDHB/C/D* genes and less commonly in patients with neurofibromatosis type 1.[82]

Hereditary pheochromocytoma

Von Hippel-Lindau disease

VHL disease is a dominantly inherited familial cancer syndrome with variable expression resulting from germline mutations in the *VHL* tumor suppressor gene.[83-85] VHL protein has been implicated in the regulation of hypoxia-inducible gene expression, mRNA stability, cell cycle control and control of extracellular fibronectin matrix assembly.[86-88] *VHL* inactivation results in upregulation of a wide range of hypoxia-inducible genes that promote angiogenesis and regulate glucose metabolism, apoptosis and matrix metabolism.[89-91] The three major features of VHL disease are retinal and central nervous system hemangioblastomas and clear cell renal cell carcinoma and the lifetime risk for each of these tumors has been estimated as >70%.[92] However, tumor specific risks are influenced by allelic heterogeneity and four phenotypic subclasses of VHL disease have been distinguished. In type 1 VHL, pheochromocytoma is absent and the most frequent manifestations are retinal and cerebellar hemangioblastomas and renal cell carcinoma (RCC). Type 2 VHL kindreds include individuals with pheochromocytoma with type 2B being characterized by the

development of pheochromocytoma, retinal and cerebellar hemangioblastomas and RCC, whereas in VHL type 2A, patients are at risk of pheochromocytoma, retinal and central nervous system hemangioblastomas but RCC is rare. Finally, type 2C VHL is characterized by the detection of germline *VHL* gene mutations in kindreds with a pheochromocytoma-only phenotype.[92] The overall frequency of pheochromocytoma in VHL disease is 10–20%, but it is very frequent in VHL type 2A and 2B kindreds, being the only feature in type 2C families and absent in type 1. All 2A and 2C types and the majority of 2B type kindreds have missense mutations, whereas type 1 families share a greater proportion of germline mutations.[93-96] Maher et al. estimated that, whereas the pheochromocytoma risk in patients with VHL gene deletions or truncating mutations is up to 5% at 50 years, this is increased 10-fold in patients with missense mutations.[96]

Succinate dehydrogenase mutations (SDH)

Mitochondrial complex II is crucial for both the Krebs tricarboxylic acid cycle and the aerobic electron transport in mitochondria, and is composed of four subunits: SDH A, SDHB, SDHC and SDHD. The mechanism by which SDH subunit mutations predispose to pheochromocytomas is as yet unknown, but dysregulation of hypoxia-responsive genes and impairment of mitochondria-mediated apoptosis have been suggested.

Germline *SDHD* and *SDHB* mutations may cause pheochromocytoma susceptibility and are an important cause of familial and isolated pheochromocytoma.[97,98] Germline mutations in *SDHD* were found in *VHL* and *RET* mutation-negative familial pheochromocytoma.[98,99] Moreover, in a study of non-familial, non-syndromic pheochromocytomas, up to 18% were found to harbor germline *SDHD* mutations.[97] Additionally, *SDHD, SDHB* and *SDHC* germline mutations were implicated in the genesis of hereditary paragangliomas and may be found in ~20% of unselected patients.[100-102] In another study, *SDHD* and *SDHB* germline mutations accounted for 70% of familial head and neck paragangliomas and ~8% of apparently sporadic head and neck paragangliomas.[103]

MEN 2

MEN 2 is an autosomal dominantly inherited syndrome which is comprised of three clinical subtypes, MEN 2A, MEN 2B and familial medullary thyroid carcinoma MEN 2A. The most common clinical subtype is characterized by the classic triad of medullary thyroid carcinoma (MTC), pheochromocytoma and hyperparathyroidism. MEN 2B is less common and is characterized by MTC and pheochromocytoma. Approximately 50% of MEN 2 patients develop pheochromocytoma and ~95% of MEN 2 cases are caused by germline *RET* proto-oncogene mutations.[104,105] Analyses on a referral series of MEN 2 suggested that germline mutations at *RET* codon 634 were associated with the development of pheochromocytoma.[84,106]

Glial cell line-derived neurotrophic factor (GDNF) is a recently identified natural ligand for RET and a good candidate for pheochromocytoma susceptibility.[107,108] GDNF receptor-alpha seems to bind GDNF and subsequently is recognized by RET. This results in tyrosine phosphorylation of RET, leading to cell signaling. So far *GDNF* germline mutations do not appear to have a major role in the pathogenesis of familial or sporadic pheochromocytomas, whereas allelic variation at the *GDNF* locus may influence pheochromocytoma susceptibility.[99]

Sporadic pheochromocytoma

Somatic *VHL* mutations are infrequent (<5%) in sporadic pheochromocytomas.[109,110] Similarly, somatic *RET* mutations are found in ~10% of sporadic pheochromocytomas suggesting that *VHL* and *RET* are minor players in its pathogenesis. In addition, somatic *SDHB* and *SDHD* mutations do not play a major role in the pathogenesis of sporadic pheochromocytomas, nor do *GDNF* germline mutations.[99] The involvement of additional genes in pheochromocytoma susceptibility is very likely, particularly in patients with extra-adrenal pheochromocytoma. In a study of 271 non-syndromic, non-familial pheochromocytomas, 24% were found to have a germline mutation in one of the *VHL, RET, SDHB* or *SDHD* genes.[81,102,111-113]

These data suggest that all patients with pheochromocytoma or paraganglioma should be subject-

ed to genetic testing for these four genes. Mutation analysis should begin with *VHL*, although the presence of extra-adrenal disease might prompt commencement with *SDHD*.

Mechanisms of hypertension in pheochromocytoma

Hypertension in pheochromocytoma is a result of noradrenaline and NPY excessive secretion. Catecholamines stimulate the adrenergic system receptors resulting in their activation with subsequent increase in the vascular tone and accentuation of the VSMC response to pressor events. Elevation of BP has generally been attributed to effects of catecholamines despite the fact that many patients are under adrenergic blockade.

NPY is a neurohormone colocalized with catecholamines in the adrenal medulla and the NPY1 receptor is the major vascular receptor which mediates non-adrenergic vasoconstriction and vascular growth promoting activity.[114] Although the action of catecholamines in pheochromocytoma related hypertension is of primary importance, studies have suggested that plasma levels of NPY are elevated in about 50–80% of patients with pheochromocytoma, this being within the range which is vasoconstrictive in humans.[115] Some studies suggest that NPY is exclusively secreted together with adrenaline from the adrenaline-producing cells, while others report that it can be released together with both noradrenaline and adrenaline during the activation of the adrenal medulla.[116,117] NPY may also be related to growth of pheochromocytoma due to the induction of vascular growth.[118]

GROWTH HORMONE (GH) EXCESS - ACROMEGALY

Acromegaly is caused by GH hypersecretion mostly due to a benign pituitary adenoma. GH operates in periphery through IGF-1 which is produced in different tissues. Both GH and IGF-1 modulate the expression of various growth factors and their receptors in several tissues. The prevalence of hypertension in acromegalic patients is reported to be approximately 35% (18-60% in different clinical studies).[119-121]

Mechanisms of hypertension in acromegaly

Surgical or medical therapy reduces GH levels and results in a concomitant BP fall, indicating an important association between GH and hypertension.[122,123] On the other hand, there are studies reporting no difference in plasma GH levels between normotensive and hypertensive acromegalics and no correlation between BP and GH or IGF-1 levels.[124,125] These findings indicate that the exact pathogenetic mechanisms of hypertension in acromegaly are still unclear, although several mechanisms have been proposed (Figure 1).

In acromegaly, increased sodium retention associated with extracellular volume expansion may be due to the sodium retaining effect of GH.[126] Experimental and clinical studies suggest an inhibitory action of GH on atrial natriuretic peptide (ANP) release which could contribute to reduced natriuresis.[127] GH, IGF-1 and IGF-1R expression in the kidney and direct activation of distal tubular sodium channels by IGF-1 could account for this effect.[128] GH administration increases glomerular filtration rate and renal plasma flow, an effect mediated probably via IGF-1.[128] IGF-1 is also reported to lower NH_2 terminal proANP and urinary sodium excretion.[129]

Acromegaly is often associated with insulin resistance, diabetes mellitus (DM) and hyperinsulinemia. GH excess stimulates lipolysis and glucose production and reduces glucose utilization. A rise in plasma insulin levels may induce hypertension by stimulating renal sodium absorption and sympathetic nervous activity.[130] In addition, insulin stimulates vascular RAAS and growth of VSMC, while insulin resistance is associated with impaired NO production and vasodilation. Hyperinsulinemic patients with acromegaly have higher BP and hypertensive patients show higher insulin resistance after oral glucose tolerance load (OGTT) than normotensives.[125]

GH and IGF-1 may be involved in hypertension as a result of their growth-promoting action and effects on vascular tone. IGF-1 is an important mitogen expressed in endothelium and VSMC and stimulates angiotensinogen production in cultured VSMC.[131] GH, either directly or via IGF-1, could

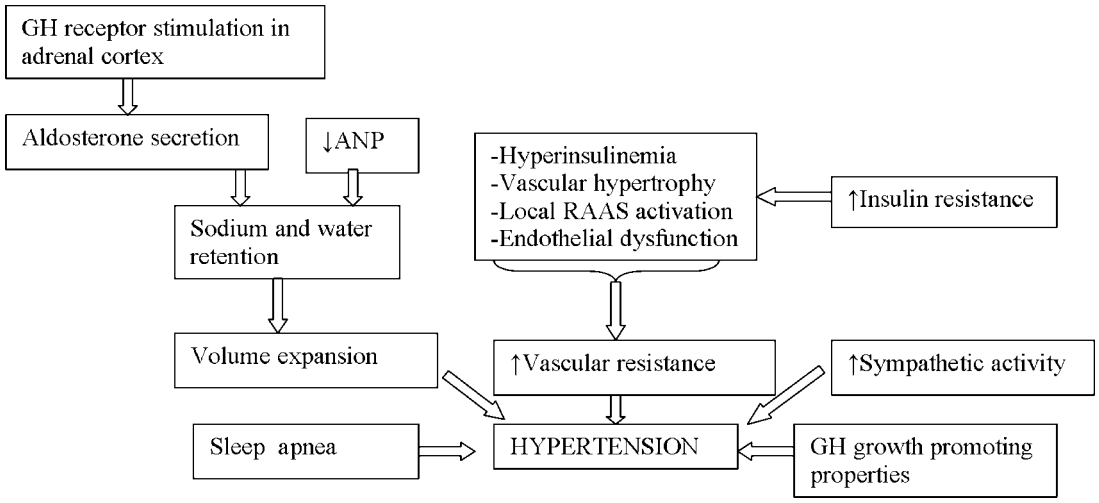

Figure 1. Mechanisms of GH induced hypertension in acromegaly. ANP, atrial natriuretic peptide; RAAS, renin angiotensin aldosterone system.

increase myocardial hypertrophy and contractility in animal models.[132,133]

The presence of GH receptors in human adrenal cortex raises the possibility of a direct GH effect on aldosterone secretion.[134] Indeed, patients with acromegaly on sodium restriction have reduced aldosterone responsiveness and increased BP response to Ang II compared to controls. Nevertheless, other studies state that aldosterone levels are within normal limits.[135,136]

Finally, sleep apnea is associated with hypertension in the general population.[137] It occurs in 60-75% of patients with acromegaly and may decrease the physiologic nocturnal fall in the BP.[138] It is also associated with increased urinary metabolites of catecholamines, suggesting an increased sympathoadrenergic activity in hypertensives.[139]

PRIMARY HYPERPARATHYROIDISM (PHPT)

PHPT is caused by excessive secretion of parathyroid hormone (PTH), usually due to a single solitary parathyroid adenoma (~80%) or less commonly diffuse hyperplasia. PTH oversecretion causes hypercalcemia associated with an increased incidence of hypertension. The cause as well as the question of reversibility after parathyroid removal are controversial. Significantly higher aortic BP is found in patients with mild PHTP compared to a control group.[140] However, others find no differences in central BP.[141] PHPT is also associated with disturbances in the RAAS, whereas contradictory results exist as to whether structural and functional alterations in the vasculature are associated with PHPT.[142-145]

Mechanisms of hypertension in PHPT

Potential mechanisms producing hypertension in PHPT include increased blood calcium levels, elevated intracellular calcium, increased PTH, raised plasma renin activity, hypomagnesemia and glucose abnormalities.

An increased prevalence of cardiac structural abnormalities, such as left ventricular hypertrophy (LVH), has been observed in PHPT.[146,147] It has been suggested that LVH in PTHP may be augmented by increased arterial pressure though others do not support this.[141,147] PTH can act as a vasodilator stimulating VSMC and reducing the influx of calcium.[148,149] Despite these properties, PTH infusion in man has produced contradictory results with regard to BP response.

Endothelium could be a target organ for PTH since PTH receptors were found on rat vascular endothelial cells.[150] Human studies also report that increasing endothelial dysfunction is correlated with high PTH levels independently of calcium.[151] Hypercalcemia induced by calcium infusion in healthy sub-

jects has also been reported to impair endothelial vasodilatory function and increase systolic BP.[152]

Abnormal glucose metabolism, insulin resistance, high prevalence of DM and impaired glucose tolerance (IGT) have been reported in PHPT patients.[153] Insulin resistance is associated with endothelial dysfunction which may contribute to the development of hypertension.[154]

Hypomagnesemia can potentiate the contractile activity of a variety of neurohumoral substances and induce vasospasm. Mean serum magnesium was found lower in hypertensive patients with surgically proven PHPT compared to normotensive patients, thus linking hypomagnesemia and hypertension.[155]

Parathyroid hypertensive factor (PHF) is a substance of parathyroid origin elevated in 30-40% of hypertensive patients. It may contribute to hypertension by potentiating the intracellular calcium-raising effects of vasoconstrictors. 1,25-$(OH)_2D_3$ seems to stimulate PHF release, thereby playing a role in BP regulation.[156]

THYROID HORMONE EXCESS

Graves' disease has an estimated incidence of approximately 0.05% in the United States of America, according to the National Women's Health Information Central (NWHIC). Hyperthyroidism is accompanied by systolic hypertension in up to one third of patients. This results in part from the inability of the vascular system to accommodate the increase in stroke volume. Diastolic hypertension is uncommon in hyperthyroidism because of the fall in systemic vascular resistance (SVR).[157] Treatment of the hyperthyroidism leads to a complete reversal of these changes in most patients.[157]

In animal models thyroid hormones have a positive inotropic effect by favoring fast myosin heavy chain-alpha synthesis, prolonging the inactivation of the Na^+ channels in cardiomyocytes, enhancing the intracellular uptake of Na^+ and the secondary activation of the myocardial sarcolemmal Na^+-Ca^{2+} exchange and increasing calcium-adenosine triphosphatase and cAMP levels, together with an increase in the number and sensitivity of β-adrenergic receptors.[158] Thyroid hormones therefore enhance calcium entry into cardiomyocytes,[159] thus improving myocardial contractility.

Thyroid hormones exert a direct effect on the heart and vasculature, increasing the heart rate, blood volume, left ventricular stroke volume, ejection fraction and cardiac output. Thyroid hormones can increase sympathetic system activity and angiotensinogen levels and decrease vasopressin levels.[160]

T_3 has a vasodilatory effect on arterioles.[161] Vasodilation results in a decrease in SVR followed by an increase in heart rate, a selective increase in blood flow to certain organs such as skeletal muscles and heart and a drop in diastolic BP. Vasodilation and the lack of rise in renal blood flow cause a decrease in renal perfusion pressure. The increase in renin release secondary to the hormone-dependent decrease in SVR may stimulate the angiotensin-aldosterone axis, thus increasing sodium reabsorption and blood volume.[160] This contributes to an increase of preload, while the drop in SVR and the improved myocardial contractility result in a smaller afterload. The net effect translates into a significant increase in ventricular stroke volume which, when combined with the rise in heart rate, causes an increase in cardiac output (Figure 2).

THYROID HORMONE DEFICIENCY

Hashimoto's thyroiditis has an incidence estimate of about 0.5% in the United States according to NWHIC. Chronic hypothyroidism is frequently accompanied by cardiac dysfunction, increased vascular resistance and a greater prevalence of hypertension.[160-162] Thyroid hormones can act as vasodilators on skeletal muscle in animal models[161] and share the ability of regulating SVR by changes in VSMC contractility. Patients with hypertension and hypothyroidism have increased aortic stiffness which is decreased in most patients along with BP after treatment.[162] Additionally, the induction of hypothyroidism by radioiodine therapy significantly increased diastolic BP, whereas restoration of euthyroidism reduced both systolic and diastolic BP.[163]

Thyroid hormone deficiency may be associated with a reduction of the glomerular filtration rate and renal blood flow.[160] Cardiac output is reduced and

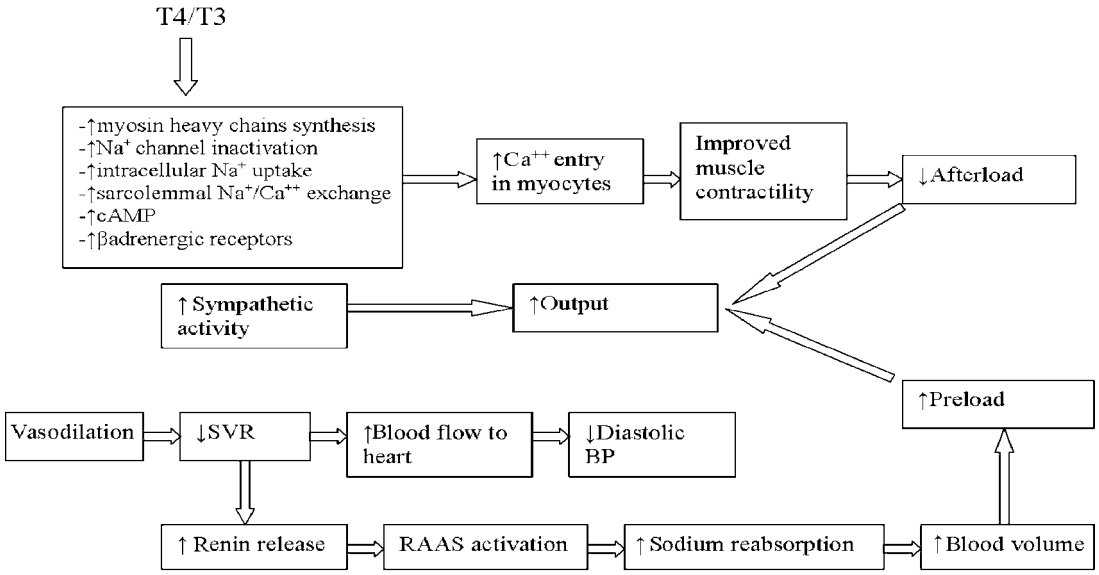

Figure 2. Thyroid hormones action on the heart and the vasculature. *Abbreviations:* RAAS, renin angiotensin aldosterone system; SVR, systemic vascular resistance; BP, blood pressure.

total peripheral resistance is elevated, probably as a result of increased sympathetic nervous tone and alpha-adrenergic response. There is also a tendency to increased diastolic BP as a result of increased SVR.[164] Hypothyroid patients, even those with subclinical hypothyroidism, have impaired endothelial function, normal/depressed systolic function, left ventricular diastolic dysfunction at rest and systolic and diastolic dysfunction on exertion.[164] All these abnormalities regress with L-T4 replacement therapy.[164] Hypothyroidism has also been associated with an increase in plasma norepinephrine and epinephrine, indicating a stimulatory effect on the sympathetic/adrenal systems, which contributes to hypertension and counteracts the decrease in myocardial inotropism and cardiac output.[160] During hypothyroidism relatively higher levels of cortisol as well as aldosterone were observed. Recent studies have reported an increase in ACTH secretion in response to adrenal cortex dysfunction induced by acute hypothyroidism in experimental animals.[165] Nevertheless, one cannot exclude the possibility that the increase in catecholamines, aldosterone and cortisol reflect, at least partially, a secondary response to reduced clearance or to decreased intravascular volume in hypothyroidism.

CONCLUSIONS

Secondary hypertension is a correctable form of hypertension. Endocrine hypertension has recently emerged as a very common cause of secondary hypertension, particularly after the recognition that PA is not as rare as formerly considered, encountered as it is in 5-15% of hypertensives. Detailed medical history, thorough physical examination, appropriate laboratory tests and evaluation of risk factors can lead physicians to an early identification of endocrine hypertension, especially since affected individuals are often young. Understanding the pathophysiology of disorders causing endocrine hypertension will help us implement specific antihypertensive treatments and/or surgical interventions that could lead to the cure of hypertension.

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