Mechanism of Hypertension in Cushing’s Syndrome: Possible Role of 11β-hydroxysteroid Dehydrogenase Type 2 in Kidneys and Vascular Cells

Key words: apparent mineralocorticoid excess, vascular 11β-HSD, cortisol

Hypertension is a cardinal symptom of Cushing’s syndrome. Although several mechanisms have been postulated, the hypertensinogenic effect of cortisol is not fully understood. In some cases of Cushing’s syndrome and exclusively in ectopic ACTH syndrome, hypertension is associated with hypokalemic metabolic alkalosis, suppressed renin and aldosterone suggesting apparent mineralocorticoid excess state (1). Other than aldosterone, deoxycorticosterone, corticosterone, and 18-hydroxydeoxycorticosterone possess weak mineralocorticoid action in humans, with a potency of less than 1/50 of aldosterone.

In ACTH-independent bilateral macronodular adrenocortical hyperplasia (AIMAH), a subset of adrenocortical Cushing’s syndrome, these corticosteroids may also be hypersecreted (2). Such a rare case of autonomous cortisol production without classical Cushinoid features has been reported in this issue of the journal (3).

See also p 304.

The authors considered that the pathogenesis of hypertension with metabolic alkalosis is likely due to hypersecretion of the weak mineralocorticoids. Except for such rare cases, corticosteroid secretion is usually within the normal range in most cases of Cushing’s syndrome. An alternative mechanism to explain apparent mineralocorticoid excess state associated with cortisol overproduction is related to 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD type 2 or renal isofrom of 11β-HSD converts cortisol to inactive cortisone in mineralocorticoid target tissue such as the renal distal tubules. Substrate saturation or ACTH per se inhibits this enzyme activity resulting in an abundance of cortisol. Since cortisol binds to mineralocorticoid receptor with an equal affinity for aldosterone, cortisol overproduction in the presence of suppressed 11β-HSD type 2 activity causes hypertension mimicking mineralocorticoid excess. Thus the enzyme 11β-HSD type 2 confers aldosterone specificity on mineralocorticoid receptor.

In addition to its effect on kidneys, cortisol may also exert vascular effects in most cases of Cushing’s syndrome. A series of our recent experiments ex vivo indicate that human vascular smooth muscle cells express genes encoding 11β-HSD type 2 and corresponding enzyme activity (4). Since cortisol can upregulate angiotensin type 1 receptor and α1 adrenergic receptor, it is plausible that both angiotensin II and catecholamines are hypertensinogenic unless cortisol is inactivated by 11β-HSD in the vasculature. In ACTH-independent Cushing’s syndrome such as AIMAH, ACTH is suppressed throughout, favoring the enzyme saturation by cortisol overproduction.

In preclinical Cushing’s syndrome, cortisol is produced autonomously and not suppressed by dexamethasone. Diurnal variation of cortisol is also diminished. However, the serum level of cortisol or urinary free cortisol is not as prominent in comparison with overt Cushing’s syndrome. Hypertension is present in preclinical Cushing’s syndrome but may not be as severe. It would be interesting to speculate whether 11β-HSD enzyme activity is saturated by overnight secretion of cortisol while in normal subjects the level will generally remains substantially low.

Among factors which inhibit 11β-HSD enzyme activity, glycyrrizic acid is well documented. In an animal experiment, endothelin receptor antagonist normalizes hypertension induced by glycyrrizic acid; suggesting vascular endothelin 1 is upregulated in this setting (5). This finding is in keeping with our previous study that glucocorticoid enhances endothelin 1 expression (6). Thus, the mechanism of cortisol induced hypertension may also involve the vascular endothelin system.

In the treatment of hypertension in Cushing’s syndrome angiotensin II receptor antagonist or α1 adrenergic receptor blockers may be recommended. In cases where mineralocorticoid excess is obvious, spironolactone may be effective. Our previous experiment shows that spironolactone alone is not effective for inhibiting cortisol-induced unregulation of angiotensin II type 1 receptor. However, when vascular 11β-HSD type 2 expression is transiently knocked out by antisense oligonucleotide, spironolactone significantly reduces angiotensin II binding. These findings implicate that hypertension in Cushing’s syndrome regardless of its ACTH dependency with or without apparent mineralocorticoid excess state may be rationally controlled by adding spironolactone. Eplerenone, a novel selective aldosterone antagonist with little adverse effects (7) will likely be beneficial for the treatment of hypertension in Cushing’s syndrome in the near future.
References


