Aldosterone regulation in primary aldosteronism

The syndrome of primary aldosteronism is characterized by definition by an autonomous hypersecretion of aldosterone (aldo), i.e. independent from the known regulatory factors. In fact, plasma renin activity is suppressed. ACTH levels are normal and serum K potassium levels are low. However, there are two major subtypes of primary hyperaldosteronism (PHA) with different characteristics; in patients with aldosterone-producing adenoma (APA) aldosterone secretion is unresponsive to angiotensin II stimulation, but is still modulated by ACTH; this is reflected in the circadian rhythm of plasma aldosterone levels which parallel cortisol levels, while aldosterone does not respond to upright posture. Furthermore, a transient decrease of aldosterone levels can be obtained by a short-term dexamethasone administration. In the other subtype of PHA, idiopathic hyperaldosteronism (IHA), a certain degree of sensitivity to the renin-angiotensin system persists, as demonstrated by the absence of diurnal rhythmicity, the clear-cut increase of plasma aldosterone after postural stimulation and exogenous angiotensin II administration and occasionally even a decrease of aldosterone after captoril administration (1).

This rather schematic distinction between the two main forms of primary aldosteronism is today challenged by the description of a certain number of cases of so-called renin-responsive aldosterone-producing adenoma which show an in vivo response to posture and angiotensin II. According to Gordon et al. these tumours present with characteristic histological findings (2). Furthermore, another unusual subgroup of patients with adrenal hyperplasia behave as far as the functional tests are concerned as patients harbouring an aldosterone-producing tumour. They have been termed by Biglieri et al., as having primary adrenal hyperplasia, and are insensitive to angiotensin II (3). Finally, the molecular genetics of a hereditary form of hyperaldosteronism, called glucocorticoid-remediable hyperaldosteronism, has been recently clarified (4). The disease, which is due to a chimeric gene comprised of the regulatory region of 11 beta hydroxylase (ACTH dependent) and the coding region of aldosterone synthase, results in a chronic ACTH-stimulated aldosterone hypersecretion and in an unresponsiveness to angiotensin II.

As demonstrated in the paper by Yagi et al. in this issue, these functional characteristics are far from being strict (5), since long-term treatment with spironolactone may profoundly affect the mechanisms of aldosterone regulation in the different forms of primary aldosteronism. Our group has previously shown in patients with aldosterone-producing adenoma that a short-term treatment with spironolactone reduces serum aldosterone levels without restoring normal renin levels. This is probably due to the direct inhibiting effect on steroidogenic enzymes. A more prolonged treatment is characterized by an increase in serum renin levels and a return of aldosterone to pretreatment levels (6). Even after a much more prolonged period of observation, Kater and Biglieri have shown that as spironolactone-induced natriuresis progresses and extracellular volume expansion decreases, plasma renin activity rises but aldosterone levels remain within the baseline values, and do not increase after upright posture (7). However, when challenged with a more potent stimulus, such as the furosemide test used by Yagi, the zona glomerulosa of the normal adrenal and/or the adenoma again become sensitive to angiotensin II stimulation. When the ACTH drive is excluded by dexamethasone, this sensitivity becomes even greater. Contrary to this, the sensitivity to ACTH was greater in untreated patients than in those under chronic spironolactone treatment. Thus under conditions of continuous renin stimulation, the functional characteristics of APA resemble those of idiopathic hyperaldosteronism. In the latter case, however, the control of aldosterone secretion by angiotensin II becomes even more apparent under spironolactone; with increasing renin activity and concomitant increase (paradoxical increase) in aldosterone levels. On the basis of this different behaviour, baseline aldosterone levels under chronic spironolactone treatment were suggested by Kater and Biglieri as an additional criterion for the differential diagnosis between the two main subtypes of primary aldosteronism. It is likely that in APA aldosterone levels reflect the balance between the direct inhibitory effect of spironolactone on the tumour and the action of angiotensin II on the adjacent and controlateral adrenal. However, it cannot be ruled out that even the adenoma can become responsive to angiotensin II. In fact, in vitro, these cells may respond to angiotensin II, although with a lower sensitivity in aldosteronoma (8). Angiotensin II binding sites and angiotensin type I receptors mRNA have been found in similar or even greater amounts to normal adrenal tissue by our group and by Saruta et al. (9, 10). Thus, the in vivo and in vitro reduced response of these tumoral cells to angiotensin II could be due to a post-receptor mechanism rather than to an abnormality of the receptor itself. Molecular biology studies are in progress in several laboratories with the aim of possibly elucidating the intracellular mechanisms (mutations of G protein, allelic losses, changes in gene expression of steroidogenic enzymes, etc.) which might be involved in the pathogenesis of different types of adrenal tumours.
A major advance in understanding the cause of one of the above-mentioned forms of primary aldosteronism has been the very recent demonstration of the chimeric gene resulting from the unequal crossing-over of the two separate gene encoding respectively for 11 beta hydroxylase and aldosterone synthase; as already discussed in this editorial, this offers a clear explanation as to why patients with this genetic abnormality present with an ACTH-dependent and glucocorticoid remediable hyperaldosteronism. More than 200 new patients with this syndrome have been identified (unpublished data). Screening candidate families is now done very simply by Northern blot analysis. If one considers that many of these patients are normokalemic, it is likely that this disorder is more frequent than previously thought. Raising the question whether one should screen for such patients. Since molecular analysis or the specific but seldom available measurement of 18-hydroxycortisol is not convenient, an exaggerated aldosterone response to ACTH testing could be of diagnostic aid when applied routinely in familiar cases of young "essential" hypertensives. In keeping with the topic of the paper of Yagi, it has to be noted that even in this form of ACTH-dependent hyperaldosteronism, chronic administered dexamethasone restores sensitivity to the previously inactive angiotensin II (11). In fact, the normal aldosterone synthase gene is regularly expressed in zona glomerulosa, as well as the normal 11 beta hydroxylase in zona fasciculata.

If the pathogenesis of this relatively rare subset of primary aldosteronism now seems fully clarified, not the same can be said for the other forms; in particular, it remains to be discovered which is the primus movens of idiopathic hyperaldosteronism. Here, as we all know, a hypersensitivity to angiotensin II does exist. But how can it be that circulating levels of angiotensin II are almost undetectable? Can a form of tertiary hyperaldosteronism be postulated? Or can we suggest a role for the adrenal renin-angiotensin system? Is there a role for another so far unidentified aldosterone-stimulating substance which could sensitize the zona glomerulosa to angiotensin II? Further studies are needed in order to clarify this enigma but are difficult to perform since these patients are not candidates for adrenal surgery.

References

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