Dopaminergic Regulation of Aldosterone Secretion: Its Pathophysiologic Significance in Subsets of Primary Aldosteronism

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Although aldosterone (Aldo.) secretion is regulated by various humoral factors, evidence has accumulated to support an involvement of dopaminergic system in its regulation. The pathophysiological significance of the dopaminergic system in primary aldosteronism (PA) however remains unknown. In the present study, we examined the effects of metoclopramide (MCP) on Aldo. secretion in normal subjects (n = 11) and patients with essential hypertension (EH, n = 8), aldosterone-producing adenoma (APA, n = 10), and idiopathic hyperaldosteronism (IHA, n = 6). Plasma Aldo., prolactin (PRL), renin, cortisol, serum sodium, and serum potassium levels were determined before and 30 min after i.v. bolus injection of 10 mg MCP at 9 a.m. Plasma Aldo. showed a significant increase after MCP in normal subjects, EH, and APA, but not in IHA. The incremental response of plasma Aldo. was largest in APA and smallest in IHA. The percentage increase in plasma Aldo. from the basal level was significantly attenuated in IHA, while no significant difference was seen among other groups. Although plasma PRL showed a significant increase in response to MCP, no difference of the change was seen among the groups. There was no significant change in plasma cortisol, renin, serum sodium, and serum potassium levels in response to MCP. In addition, the response of Aldo. to MCP was normalized in APA after unilateral adrenalectomy, while that of PRL did not change. These results indicate that the adrenal dopaminergic activity is enhanced in APA and attenuated in IHA and suggest an involvement of the dopaminergic system in the pathogenesis of IHA. The MCP challenge test could be an useful diagnostic tool for the differential diagnosis of subsets of PA.

Key Words: aldosterone, dopamine, metoclopramide, primary aldosteronism, idiopathic hyperaldosteronism

Aldosterone secretion is under the control of various systemic factors: renin/angiotensin system, ACTH, and potassium concentration as stimulatory factors and natriuretic factors such as ANP and BNP as inhibitory factors. In addition, various local factors including tissue renin/angiotensin system (1), endothelin (2), and CNP (3) have been suggested to play some roles through an autocrine/paracrine mode of action, although details of the physiological significance remain unknown.

In contrast to these humoral mechanisms, evidence has accumulated to support an involvement of neural mechanism with dopamine as a neurotransmitter in the regulation of aldosterone secretion (for review, see ref. 4-8). Metoclopramide (MCP), a selective dopamine receptor antagonist, increases plasma aldosterone (9), while dopamine inhibits the MCP-induced aldosterone secretion (10). The dopaminergic activity has been shown to be deeply involved in the changes of the adrenal sensitivity to angiotensin II (Ang II) under different sodium intake: increased sensitivity on low salt intake and decreased sensitivity on high salt intake (11, 12). It was also shown that release of the dopaminergic inhibition is an important component of the increase in aldosterone that occurs with upright posture (13). In contrast to these physiological aspects of the dopaminergic inhibitory regulation of aldosterone secretion, its pathophysiological significance has not been elucidated.

Primary aldosteronism (PA) is a clinical entity comprised of two major subsets: aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA), respectively. Although recent advances in imaging techniques including computerized tomography and magnetic resonance imaging have made the diagnosis much easier than before, these methods do not provide functional information. Accordingly, we sometimes experience patients in which diagnosis of the subsets is difficult. Therefore, diagnostic procedure relevant to endocrine features, especially to aldosterone secretion, could be of clinical significance.

Kuchel et al. (14) have demonstrated an en-
hanced dopaminergic inhibition of aldosterone in patients with PA. While the finding was subsequently confirmed (15, 16), more recent studies (17) do not support the hypothesis. The aim of the present study was to investigate whether the extent of endogenous dopaminergic inhibition of aldosterone secretion is different between patients with two subsets of PA: APA and IHA, respectively.

**Subjects and Methods**

Eleven normotensive healthy subjects (10 men, 1 woman, aged 24–69 years), 8 patients with essential hypertension (EH) (5 men, 3 women, aged 26–75 years), 10 patients with APA (3 men, 7 women, aged 33–55 years), and 6 patients with IHA (3 men, 3 women, aged 31–56 years) were studied. Unilateral adrenal adenoma was surgically confirmed in all the patients with APA. The diagnosis of IHA was made based on the lack of findings indicating the laterality of the hypersecretion of aldosterone by adrenal computerized tomography, adrenal scintigraphy, and/or adrenal venous sampling.

Although all subjects were studied without prior salt restriction, any medication which may affect plasma aldosterone and prolactin (PRL) was withdrawn at least for 2 weeks before the study. Ten mg MCP was administered intravenously at 9 a.m. after an overnight fast and 30 min of recumbency. Plasma aldosterone, PRL, cortisol, and renin activity were determined by radioimmunoassay before and 30 min after the administration. Serum sodium and potassium levels were also determined. The protocol for blood sampling was selected according to the previous results (16) and our present results in normal subjects showing that both plasma PRL and aldosterone reach their peak levels after 30 min of MCP injection. Informed consent was obtained from each patient before the study. The study was approved by the ethical committee of the Institute of Clinical Endocrinology, Tokyo Women’s Medical College.

Values were expressed as the means ± SE. Differences between groups were analyzed by the Student’s t test.

**Results**

Figure 1 shows the results in normal subjects. Both plasma PRL and aldosterone showed significant increases with peak levels at 30 min following intravenous bolus administration of MCP.
Fig. 2. Changes in plasma PRL (a) and aldosterone (Aldo.) (b) level before and after i.v. bolus administration of 10 mg MCP in normal subjects (n = 11), patients with EH (n = 8), patients with APA (n = 10), and patients with IHA (n = 6). Values are the mean ± SE. *p < 0.05, **p < 0.01 vs. before; *p < 0.01 vs. normal and EH; tp < 0.01 vs. IHA.

Fig. 3. Incremental responses of plasma PRL (a) and aldosterone (Aldo.) (b) between basal and 30 min after administration of MCP in normal subjects (n = 11), patients with EH (n = 8), patients with APA (n = 10), and patients with IHA (n = 6). Values are the mean ± SE. *p < 0.05 vs. other groups; †p < 0.01 vs. other groups.

Fig. 4. Percentage increases in plasma PRL (a) and aldosterone (Aldo.) (b) 30 min after administration of MCP in normal subjects (n = 11), patients with EH (n = 8), patients with APA (n = 10), and patients with IHA (n = 6). Values are the mean ± SE. *p < 0.01 vs. other groups.

Fig. 5. Changes in plasma cortisol (a) and renin activity (PRA) (b) before and after administration of MCP in normal subjects (n = 11), patients with EH (n = 8), patients with APA (n = 10), and patients with IHA (n = 6). Values are the mean ± SE.
incremental change in PRL was however much greater than that in aldosterone. On the contrary, there was no significant change in plasma cortisol and PRA.

Figure 2 shows the changes in plasma PRL and aldosterone before and 30 min after MCP administration in normal subjects, and patients with EH, APA, and IHA. Although basal plasma PRL level did not differ significantly among the 4 groups (Fig. 2a), basal plasma aldosterone level was significantly higher in patients with APA and patients with IHA than in normal subjects and patients with EH (Fig. 2b). Although plasma PRL showed a significant increase after MCP administration, there was no significant difference of the values among the 4 groups (Fig. 2a). Plasma aldosterone level showed a significant increase in normal subjects, patients with EH, and patients with APA, but not in patients with IHA (Fig. 2b).

The incremental response of plasma PRL between basal and peak levels in response to MCP did not show a significant difference among the 4 groups (Fig. 3a). By contrast, the incremental response of plasma aldosterone level was significantly greater in patients with APA and smaller in patients with IHA than in normal subjects and patients with EH (Fig. 3b).

The percentage increase in plasma PRL level was 1,146 ± 150% in normal subjects, 1,214 ± 437% in patients with EH, 568.2 ± 127.9% in patients with APA, and 721.5 ± 175.4% in patients with IHA, respectively. There was no significant difference among the four groups (Fig. 4a). The percentage increase in plasma aldosterone level was 58.8 ± 17.5% in normal subjects, 66.0 ± 25.3% in patients with EH, 57.1 ± 11.4% in patients with APA, and 5.9 ± 6.0% in patients with IHA, respectively. The values in patients with IHA were significantly smaller than that in other 3 groups (Fig. 4b).

By contrast to plasma PRL and aldosterone, there was no significant change in plasma cortisol (Fig. 5a), plasma renin activity (Fig. 5b), serum sodium, and serum potassium levels (data not shown) before and after MCP administration.

Effects of MCP administration were reexamined in 4 patients with APA during the period of one week to 3 months after unilateral adrenalectomy. While changes in plasma PRL by MCP were similar to that of the before even after the adrenal surgery (Fig. 6), changes in plasma aldosterone showed significantly attenuated responses after the adrenal surgery (Fig. 7).

Discussion

The present study clearly demonstrated that admin-
administration of MCP produces significant increase in plasma aldosterone level in patients with APA. In agreement with the previous studies (14-16), the incremental change was significantly higher in patients with APA than in normal subjects and patients with EH, suggesting an increased endogenous dopaminergic activity inhibiting aldosterone secretion in APA. The increased dopaminergic activity may play a compensatory role in counteracting the hyperaldosteronism. In support of this concept, the enhanced aldosterone response to MCP was normalized after adrenal surgery.

By contrast, plasma aldosterone level did not show any significant response to MCP administration in patients with IHA, indicating a decreased endogenous dopaminergic activity. Since it is expected that the extent of the dopaminergic inhibition is related to the basal plasma aldosterone level, the attenuated response to MCP in patients with IHA may be attributed to the lower plasma aldosterone level than in patients with APA. However, this may not be the case since both normal subjects and patients with EH showed a significant increase in plasma aldosterone after MCP despite of their lower basal plasma aldosterone level than in patients with IHA.

The increased basal plasma aldosterone level with the attenuated response to MCP suggests that a decrease in the dopaminergic inhibition may be involved in the pathogenesis of hyperaldosteronism in IHA. The bilateral adrenal lesion of the disease is also compatible with the neuronal mechanism. In addition, interesting is the report by Mazzocchi et al. (18) that dopaminergic system may be involved in an inhibitory way in the growth of the rat adrenal zona glomerulosa. The attenuated dopaminergic activity may be related to the adrenal hyperplasia in IHA.

The attenuated response of aldosterone to MCP in patients with IHA is contrast to the previous reports demonstrating a significant increase of aldosterone in IHA (16, 17, 19). However, the details of the actual data in each subset of PA were not described in the two manuscripts (16, 17). In addition, the magnitude of the aldosterone response shown in the study by Gniadek et al. (15) appears to be smaller in patients with IHA than in patients with APA.

The predictive value of the postural stimulation test in the differential diagnosis of PA has been described by Biglieri (20). Most of the patients with IHA show a significant increase in plasma aldosterone in response to upright posture, while most of the patients with APA do not. Although the details of the mechanism responsible for the aldosterone...
response to upright posture are not known, involvement of the release of dopaminergic inhibition was demonstrated to be an important component (13) in addition to the stimulation of the renin/angiotensin system. The attenuated aldosterone response to upright posture in patients with APA may be attributed to the failure to release the activated dopaminergic inhibition as suggested from the present study. On the contrary, the increased aldosterone response to upright posture in patients with IHA may be related to the increased sensitivity to Ang II (21) in addition to the attenuated dopaminergic inhibition. Further studies in larger number of patients with IHA are needed however to prove the hypothesis and to establish the clinical significance of the present findings.

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References