Inhibition of the renin–angiotensin–aldosterone system by L-dopa with and without inhibition of extracerebral dopa decarboxylase in man

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Summary

1. The present study was undertaken to investigate the possibility that central nervous system mono-aminergic pathways may play a role in the control of the renin–angiotensin–aldosterone system in man.

2. Eight normal subjects received in a randomized order placebo, L-dopa (500 mg, orally) and L-dopa (100 mg, orally) plus carbidopa (35 mg, orally) after pretreatment with carbidopa (50 mg every 6 h for four doses).

3. L-Dopa administration elicited a significant fall in plasma renin activity (PRA) ($P < 0.01$ at 120, 150 and 180 min) and in plasma aldosterone levels ($P < 0.05$ at 90, 120, 150 and 180 min); L-dopa plus carbidopa induced a decrease in PRA ($P < 0.05$ at 120 and 150 min, $P < 0.01$ at 180 min) and in plasma aldosterone concentration ($P < 0.05$ at 30 and 60 min, $P < 0.01$ at 90 and 120 min), in comparison with placebo administration; between-drugs analysis revealed no difference in the decreases in PRA and plasma aldosterone levels induced by the two regimens.

4. Since L-dopa, as well as L-dopa plus carbidopa, has been shown to augment catecholamine levels in the brain of various animal species, the present data suggest that in man PRA and plasma aldosterone concentration might be inhibited by increased central nervous system catecholamine levels.

Introduction

It is well known that the central nervous system plays a major role in the control of renin and aldosterone secretion. The release of renin is augmented by medullary [1], pontine [2], mesencephalic [3] and hypothalamic defence area [4] stimulation, while activation of the so-called sympatho-inhibitory area in the anterior hypothalamus decreases renin secretion [5]. These changes are believed to be mediated by the renal sympathetic nerves, since they are abolished by renal denervation. The present study was undertaken to evaluate whether a change in central nervous system catecholamines may affect plasma renin activity (PRA) and plasma aldosterone levels in man.

Patients and methods

Eight healthy subjects (five females aged 24–28 years, three males aged 25–27 years) with normal blood pressure and no evidence of renal, gastrointestinal or endocrine disorders, volunteered for the study. Informed consent was obtained from all individuals. The subjects were put on a constant daily diet containing 130 mmol of sodium, 60 mmol of potassium, 1 g of protein/kg and 2500 cal (10.46 kJ), for 5 days before the...
studies. On day 5, a 24 h urine sample was collected and analysed for sodium and potassium.

Subjects fasted overnight and were in the supine position in a quiet room throughout the study and for 90 min preceding it. Arterial blood pressure was then measured and blood samples were drawn through an indwelling catheter inserted into an antecubital vein, at -30 and 0 min, as basal values. To maintain the patency of the cannula, 150 ml of glucose solution (0.28 mol/l, 5 g/100 ml) was infused during the studies. All subjects were given in a randomized order, at 2 day interval, placebo, L-dopa (500 mg, orally) and L-dopa (100 mg, orally) plus carbidopa (35 mg, orally), after pretreatment with carbidopa (50 mg, orally every 6 h for four doses). Blood pressure was determined and blood samples were collected at the time intervals indicated in Fig. 1. All blood samples for PRA and plasma aldosterone determinations were collected in chilled glass tubes, with ethylenediaminetetraacetate (EDTA) as anticoagulant, centrifuged immediately and plasmas were separated and frozen until the assays, which were performed within 2 weeks after collections. PRA was determined by radioimmunoassay of angiotensin I generated, as described by Haber, Koerner, Page, Kliman & Purnode [6]; plasma aldosterone was measured by the radioimmunoassay method of Vetter, Vetter & Siegenthaler [7]. In our laboratory the interassay variation is 9% for PRA and 8% for plasma aldosterone, while the intra-assay variation is 6% for both PRA and plasma aldosterone. Each plasma was assayed in triplicate. Serum and urinary sodium and potassium were measured by flame photometry (Corning model 450). Plasma cortisol was determined as described by Mattingly [8]. Blood pressure was measured with a mercury sphygmomanometer, the point of muffling of sounds being taken as diastolic pressure.

The statistical assessment of data was performed by trend analysis and analysis of variance followed by Tukey's t-test for multiple comparisons. \( P \) values of \(< 0.05\) were considered significant. Data are means \( \pm \) SEM.

Results

The results of the present study are outlined in Fig. 1.

The subjects were in sodium and potassium balance, as indicated by the 24 h urinary sodium and potassium excretion, which closely matched intakes. Trend analysis revealed no significant changes in arterial blood pressure as well as in PRA and plasma aldosterone levels, after placebo.

L-Dopa administration elicited a significant fall in PRA \(( P < 0.01\) at 120, 150 and 180 min\) and in plasma aldosterone concentration \(( P < 0.05\) from 90 to 180 min\) versus placebo study, without significant changes in blood pressure, plasma cortisol or serum electrolytes; the nadir values of PRA and plasma aldosterone were \(41.9 \pm 4.1\) and \(53.9 \pm 7.1\)% of the basal levels respectively.

L-Dopa plus carbidopa induced a decrease in PRA \(( P < 0.02\) at 120 and 150 min, \( P < 0.01\) at 180 min\) and in plasma aldosterone levels \(( P < 0.02\) at 30 and 60 min, \( P < 0.01\) at 90 and 120 min\), in comparison with placebo administration; the nadir values of PRA and plasma aldosterone were \(44.3 \pm 7.3\) and \(52.4 \pm 9.4\)% of basal; no changes were observed in blood pressure. The between-drugs analysis revealed that decreases in PRA and plasma aldosterone after L-dopa alone and after L-dopa plus carbidopa were not significantly different.

Discussion

In the present study L-dopa administration with and without inhibition of extracerebral dopa decarboxylase reduced PRA in healthy individuals, in general agreement with the findings by Barbeau, Gillo-Joffroy, Boucher, Nowaczynski & Genest [9] who showed a decreased PRA in Parkinsonian patients chronically treated with high doses of L-dopa.

Systemic administration of L-dopa is followed by its conversion into catecholamines not only within the central nervous system, but also in peripheral nerve terminals. This raises the possibility that some effects of systemically administered L-dopa may be due to a peripheral activity. When the conversion of L-dopa into dopamine outside the central nervous system is prevented, it is possible to discriminate between centrally and peripherally mediated L-dopa effects. Carbidopa is an agent which in a limited dose range does not cross the blood–brain barrier [10] and therefore inhibits extracerebral but not cerebral dopa decarboxylase activity [11].

The present data indicate that the observed decrease in PRA depends on a centrally mediated L-dopa effect. It has been previously observed in animal models that L-dopa, as well as L-dopa plus carbidopa administration, augments catecholamine levels in the brain [12, 13]. However, the neurotransmitter system activated in the central nervous system remains to be elucidated, since augmented brain L-dopa levels
increase dopamine and noradrenaline concentration and probably affect serotonin release [14]. Blair, Reid & Ganong [15] have shown that L-dopa plus carbidopa administration decreases the renal sympathetic outflow and inhibits PRA in dogs, an effect prevented by renal denervation. Although the mechanism in man mediating the reduction of PRA after L-dopa as well as L-dopa plus carbidopa is not clarified, it is likely that these treatments increase central nervous system catecholamine levels with a resulting decrease in sympathetic activity in the renal nerves and inhibition in PRA.

The present findings also show that L-dopa, both alone and in combination with carbidopa, induces a fall in plasma aldosterone levels. The mechanism(s) mediating this effect are not clear. The difference in the time course of the changes in PRA and plasma aldosterone suggests that decreased renin secretion does not have a major role in reducing plasma aldosterone levels under the experimental conditions, although the low PRA might contribute to the effect on plasma aldosterone at later sampling times. The other major factors regulating aldosterone secretion do not seem to be involved in L-dopa-induced aldosterone inhibition, since plasma cortisol and serum sodium and potassium concentrations were not modified by L-dopa. It has been proposed that the dopaminergic system may exert an inhibitory control on aldosterone secretion [16, 17]; the present findings seem to be in keeping with this view and are in partial disagreement with data reported by Carey, Thorner & Ortt [18], and by Noth, McCallum, Contino & Havelick [19] who, on the basis of results obtained respectively with bromocriptine and dopamine administration, suggested that in man in conditions of normal sodium balance aldosterone is under maximal tonic dopaminergic inhibition. A previous investigation by Ogihara, Matsumura, Onishi, Miyai, Uozumi & Kumahara [20], showing lack of a significant effect of metoclopramide on plasma aldosterone in man, is not in keeping with these findings. The discrepancy between this [20] and the above studies [16–19] may depend on the different drug doses used and, in any case, does not provide a firm evidence against a dopaminergic modulation of aldosterone. Few other studies of dopaminergic effects on al-

Fig. 1. Effect of (a) oral placebo, (b) L-dopa (500 mg, orally) or (c) L-dopa (100 mg, orally) plus carbidopa (35 mg, orally) after pretreatment with carbidopa (50 mg every 6 h for four doses) on plasma renin activity (PRA), plasma aldosterone (PA) concentration and systolic (syst.) and diastolic (diast.) blood pressure in eight normal subjects. Significance of differences vs placebo study: *P < 0.05; **P < 0.01. Data are means ± SEM.
dosterone secretion have been performed, none, however, involving normal subjects under conditions of metabolic balance. It is unlikely that other humoral factors which are modified by L-dopa administration, such as prolactin and growth hormone [21], are involved in the inhibition of aldosterone release observed in the present study, inasmuch as they do not seem to be implicated in the control of aldosterone secretion in man [22-25]. In conclusion, the present data suggest that the observed inhibition of plasma aldosterone levels after L-dopa, with and without carbidopa, may depend on a central dopaminergic stimulation.

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References