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Effect of Aging and Sodium Deprivation on Plasma Concentration of Aldosterone and on Plasma Renin Activity in the Rat

Key Words
Aldosterone
Plasma renin activity
Sodium deprivation
Age-related changes, rat

Abstract
Age-related changes in plasma aldosterone and corticosterone concentrations as well as in plasma renin activity in response to 10 days of sodium deprivation were studied in old as compared to adult male Long-Evans rats. Chronic sodium deprivation greatly increased plasma concentrations of aldosterone both in old and in adult animals. However, this effect was significantly higher (+85.2%) in old (+3,574 pmol/l) as compared to adult (+1,820 pmol/l) rats. Concomitantly, adrenal weights were statistically increased in sodium-deprived old rats (+25%) whereas they were unchanged in adult animals; plasma corticosterone concentration was unchanged by sodium restriction in the two age groups. Because a putative modest decline with age of the metabolic clearance rate of aldosterone could not account totally for such an important increase in plasma concentration, it is assumed that it is, in its most part, due to an increased production. Furthermore, although plasma renin activity of senescent rats, fed either a normal or a sodium-deprived diet, was lower as compared to adult rats, the absolute and percent increases of this activity in response to sodium deprivation were, respectively, similar and higher in old as compared to adult rats and so could partially contribute to the higher aldosterone response.

Introduction

We have recently reported a reduced biosynthetic capacity of adrenal glomerular cells of old rats in response to challenge with exogenous corticotropin-releasing hormone (CRH) [1], adrenocorticotropic hormone (ACTH) [2] and especially with angiotensin II [3].

Although angiotensin II is not the sole mediator [4, 5], it is commonly proposed that an increased activity of the renin-angiotensin system is the major stimulator involved in the

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aldosterone production in response to sodium deprivation.

Therefore, the effect of aging on plasma aldosterone secretion in sodium-deprived rats needed to be investigated. The only available data is the recent report of Jover et al. [6] who showed that after day 9 of sodium restriction, urinary aldosterone excretion of 30-month-old Wistar rats was slightly but not significantly lower as compared to that of 10- and 20-month-old animals.

In the present study, we have measured concomitantly in the same animals, plasma aldosterone and corticosterone concentrations, plasma angiotensin I levels and plasma renin activity (PRA) in response to 10 days of sodium deprivation in adult as compared to old male Long-Evans rats.

Materials and Methods

Animals

Adult (7 months old and weighing 433 ± 11 g) and aged (26–28 months old and weighing 430 ± 10 g) male Long-Evans rats were housed for at least 8 days before the experiment in individual cages and maintained under standard laboratory conditions (temperature: 23 ± 1 °C; photoperiod: 12 h darkness, 12 h light; lights on at 07.00 h) and fed a standard pellet diet (UAR, Epinay-sur-Orge, France) with free access to tap water.

Experimental Protocols

Two days prior to the beginning of the experiment, all the rats were trained to consume the normal sodium diet. Thereafter, they were divided into four groups and then kept for 10 days on a normal or sodium-deprived diet; i.e. 7 adult and 16 old rats used as controls were given a normal sodium diet (UAR, ref. 210: 4,000 mg Na/kg) and 9 adult and 17 old rats received the same diet deprived of sodium (UAR, ref. 212: 20–50 mg Na/kg). Animals had free access to bidistilled water. On the 11th day, rats were killed by decapitation between 09.00 and 10.00 h; 2 ml of the trunk blood was collected on EDTA (1 mg/ml) for PRA evaluation; the rest was collected on calcium heparinate to measure plasma concentrations of aldosterone, corticosterone and electrolytes. After centrifugation, 200 peptidase inhibitory units aprotinin (Iniprol; Choay, Paris, France) were added to plasma for PRA determination. Plasma samples were stored at −30 °C until assays.

Adrenals and kidneys were removed rapidly, dissected free of fat and weighed. The bladder was compressed for urine collection.

Assays

Urine and plasma electrolytes were determined using an Eppendorf flame photometer.

Plasma concentration of aldosterone was measured after dichloromethane extraction and chromatographic purification (Bush B5 solvent system; Whatman paper No. 2) by a radioimmunoassay method, using the antialdosterone dihemisuccinate-BSA antiserum kindly supplied by the NIDDK (Bethesda, Md., USA) previously described [7]. Corticosterone was measured by a competitive protein binding radioassay, using a 0.2% diluted adrenalectomized female rat plasma.

PRA was measured using the angiotensin I radioimmunoassay kit (ref. SB-REN-2) of Cis-Biointernational (Gif-sur-Yvette, France). The angiotensin I antiserum cross-reacted 100%, < 0.1% and << 0.02%, respectively, with angiotensin I, angiotensin II and hepta- and hexa-angiotensin-related peptides; the detection limit was 0.2 ± 0.04 ng/ml; the within- and between-assay coefficients of variations were, respectively, < 9.9 and 11.5%.

Statistical Analysis

Results are expressed as means ± SEM. Student's t test was used to determine the levels of significance.

Results

Weights and Metabolic Studies (table 1)

At the beginning of the experiment and at the end of the 10-day diet period the mean body weights of adult and old rats were not significantly different.

The mean left kidney weight and kidney to body weight ratio were greater (+23.2%, $p < 0.05$ and +52.0%, $p < 0.02$, respectively) in old than in adult rats. They were slightly, but not statistically, increased by sodium deprivation and so the age-group differences were +33.1% ($p < 0.001$) and +40.0% ($p < 0.01$).

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Table 1. Effects of 10 days' sodium deprivation on plasma concentrations of corticosterone, aldosterone and angiotensin I and in PRA in old compared to adult male Long-Evans rats

Parameters	Adult animals		Old animals	
	normal sodium diet (n = 7)	sodium-deprived diet (n = 9)	normal sodium diet (n = 16)	sodium-deprived diet (n = 17)
Body weight, g	449 ± 8	448 ± 11	431 ± 16	425 ± 13
Left kidney weight				
g	1.29 ± 0.06	1.33 ± 0.01	1.59 ± 0.07*	1.77 ± 0.07***,+++
g/100 g body weight	0.25 ± 0.05	0.30 ± 0.01	0.38 ± 0.02*	0.42 ± 0.02**,++
Adrenals weight				
mg	40.5 ± 1.2	38.9 ± 1.7	41.5 ± 1.6	52.3 ± 2.1***
mg/100 body weight	9.3 ± 0.5	9.2 ± 0.5	9.9 ± 0.7	12.5 ± 0.7**
Plasma sodium, mmol/l	133.7 ± 3.7	132.8 ± 3.7	139.2 ± 1.9	135.1 ± 1.2
Urinary sodium, mmol/l	115.5 ± 26.6	5.0 ± 1.4+++	121.6 ± 17.3	8.1 ± 1.8+++
Urinary potassium, mmol/l	122.3 ± 21.9	101.7 ± 20.2	75.2 ± 6.4	34.0 ± 2.3*,+++
Plasma corticosterone, nmol/l	55.1 ± 11.6	66.4 ± 17.3	147.2 ± 26.0**	112.6 ± 34.6
Plasma aldosterone, pmol/l	227.5 ± 41.6	2,047.7 ± 280.2+++	219.2 ± 22.2	3,793.0 ± 435.6*,+++
Plasma angiotensin I, ng/ml	4.1 ± 0.6	3.5 ± 0.6	2.1 ± 0.3**	3.4 ± 0.5+
Plasma renin activity, mg angiotensin I/ml/h	6.8 ± 0.6	11.1 ± 1.6+	1.6 ± 0.3***	6.3 ± 0.8**,+++

Number of rats are shown in parentheses. Values are means ± SEM. Statistically significant differences (Student's t test): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared with adult rats; + $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$ compared with normal values.

Adrenal weights, expressed as mg or mg/100 g body weight, of adult and old rats fed a normal sodium diet were not significantly different. Following sodium deprivation they were increased by 26.0% ($p < 0.001$ and $p < 0.02$, respectively) in old rats whereas they did not change in adult animals. So, in sodium-deprived rats, they were greater (+34.5%, $p < 0.001$, and +35.6%, $p < 0.01$) in old than in adult animals.

At the end of the diet period, plasma concentrations of sodium were similar in the two age groups fed the normal or the deprived sodium diet. Sodium deprivation greatly decreased and to similar degrees the urinary concentration of sodium both in adult and in old rats; also it seemed to lower (–62.0%, $p < 0.10$) the urinary concentration of potassium only in old animals.

Plasma Concentrations of Aldosterone and Corticosterone (table 1)

The plasma concentration of aldosterone was essentially the same in adult and in old rats fed a normal sodium diet.

In response to 10 days of dietary sodium deprivation, aldosterone levels greatly increased in the two age groups. Nevertheless, the sodium depletion effect was greater in aged (+3,573.8 pmol/l) than in adult (+1,820.2 pmol/l) rats. At the end of the diet period the old/adult difference in plasma aldosterone concentration was +85.2% ($p < 0.02$).

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Concomitantly, sodium restriction was without any significant effect on plasma concentration of corticosterone both in adult and in old rats.

Plasma Concentration of Angiotensin I and PRA (table 1)

The plasma concentration of angiotensin I was significantly lower (–49.3%, $p < 0.01$) in old as compared to adult rats fed a normal sodium diet. Following sodium deprivation, it was unchanged in adult rats whereas it was increased (+63.8%, $p < 0.05$) in old animals; so, there was no old/adult difference.

PRA of old rats was markedly depressed (–75.8%, $p < 0.01$) as compared to adult animals fed a normal sodium diet. In response to 10 days of dietary sodium deprivation it was equally increased in adult (+4.3 ng angiotensin I/ml/h) and in old (+4.7 ng/angiotensin I/ml/h) rats; nevertheless, PRA of old rats remained significantly lower (–43.3%, $p < 0.01$) than that of adult sodium-deprived rats.

Discussion

The present results clearly show that 10 days of chronic sodium deprivation induced a significantly higher increment in plasma aldosterone concentrations in old as compared to adult male Long-Evans rats.

These unexpected original data are worth discussing. Firstly, it may be assumed that the higher plasma concentration of aldosterone we observed in old rats, results likely, for its most part, from an increased production. The effect of aging on the metabolic clearance rate (MCR) of aldosterone has to date, never been investigated either in a normal sodium diet or in sodium-restricted rats. Besides, in normal recumbent men, Hegstad et al. [8] reported that the MCR of aldosterone was the same in subjects over 50 years of age (960 ± 71.0 liters/24 h/m^2) and in the younger persons under 29 years of age (856 ± 56.4 liters/24 h/m^2). In contrast, Flood et al. [9] have previously concluded that 'the MCR of aldosterone in elderly subjects (67–88 years old; mean body surface area: 1.73 m^2) was probably significantly lower (about –20%) than values previously obtained in a young group (18–35 years old; mean body surface area: 1.97 m^2)'. However, it is noteworthy that when the MCR values of Flood et al. [9] are expressed relatively to body surface area, the old/young differences are reduced (about –10%) and insignificant. Therefore, it is very likely that a putative modest decrease in the MCR of aldosterone with age could not account totally for the higher increase (+85%) in plasma concentration of our old rats; all the more because, in view of our previous report [3] on aldosterone production in response to angiotensin II administration, a reduced plasma concentration of aldosterone should have been expected in old as compared to adult rats.

Moreover, an increased aldosterone production is consistent with our observation that the adrenal weights of old rats were significantly increased (+26%) whereas those of the adult rats were unchanged after the 10 days' sodium deprivation period. Despite that no morphological study was carried out, it is likely that increased adrenal weight is actually due to an increase in the width of the zona glomerulosa, for the plasma concentration of corticosterone released from the zona fasciculata was unchanged by sodium deprivation in the two age groups. Besides, interesting was the only other study in the rat by Jover et al. [6] who fed female Wistar (WAG/Rij) rats with low-sodium chow for a 12-day period and showed that whereas the early (days 1–6) increase in urinary aldosterone excretion observed in 10- and 20-month-old rats was consistently blunted, in 30-month-old animals,

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after day 9, urinary aldosterone excretion increased in the oldest rats and then was slightly but not significantly lower as compared to 10- and 20-month-old rats. So, it appears that the increased aldosterone response of old rats to sodium deprivation should be a characteristic of a prolonged restriction.

Nevertheless, the renin-angiotensin system being commonly considered to be the major mediator involved in the stimulation of aldosterone secretion in response to sodium restriction, the above conclusion is seemingly contradictory with our own previous report [3] showing a diminished aldosterone production by the adrenal cortex of the old rats in response to exogenous angiotensin II.

Whatever the case may be, an old/adult difference dealing with the effect of sodium deprivation on the activity of the renin-angiotensin system can be hypothetized. The PRA of our old sodium-restricted rats was 43.3% lower as compared to adult rats. However, the PRA of normal sodium-fed old rats being four-fold lower than that of adult animals, the absolute and percent increases in response to sodium deprivation were, respectively, similar and higher in old than in adult animals. It was increased fourfold in the old rat versus only twofold in the adult. Besides, Jover et al. [6] reported that on day 10 of sodium restriction PRA was equally increased in the three age groups but remained lower in the oldest rats as compared with the other two groups. Conditionally, these changes in PRA paralleled similar changes in plasma concentrations of angiotensin II, our data would be consistent with a part of the greater increase in aldosterone secretion of the old rat. It should also be investigated whether the well-known stimulating effect of sodium depletion on angiotensin II binding characteristics [10] were enhanced in old compared with adult rats.

Moreover, in view of reports that have suggested that angiotensin II is not the sole mediator of aldosterone response to sodium restriction [4, 5], we are led to formulate the following overall hypothesis that a chronic sodium depletion over a certain duration might have, in the old rats, either suppressed other putative causes of the reduced aldosterone production or induced other systemic or cellular mechanism(s) which may have offset it. Sodium restriction, in old as compared to adult rats, might have differently either increased or initiated the action of the numerous stimulating factors of aldosterone secretion or induced a suppression of the effect of inhibitory factors [for refs. see 11, 12]. The effect of sodium deprivation on these various factors is to date largely unknown and moreover a putative old/adult difference remains to be investigated. It is to be noted that a higher stimulation of the hypothalamo-pituitary adrenal axis, and particularly of the ACTH secretion, is unlikely to be involved because we found that plasma corticosterone was unaffected by sodium deprivation and was the same in the two age groups.

In conclusion, the most striking result of the present study is that chronic 10 days' sodium deprivation induced a greater increase in plasma aldosterone concentration in old as compared to adult male Long-Evans rats; the reduced aldosterone production we have previously found in old rats in response to exogenous angiotensin II seemed to be blunted after chronic sodium deprivation.

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