Involvement of Renal Dopaminergic System in Experimental Neurogenic Arterial Hypertension

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The effect of chronic salt loading (10 g of NaCl for a period of 7 days) on urinary dopamine release has been investigated in 3 groups of beagle dogs: normotensive dogs (group 1: n = 7), and 2 groups of dogs made hypertensive by chronic sinoaortic denervation (group 2: (n = 6) during the first 4 months after sinoaortic denervation i.e. a model of arterial hypertension with high levels of plasma catecholamines and group 3: (n = 6) one year after denervation i.e. a model of arterial hypertension with normal sympathetic tone). In normal dogs (group 1), salt loading induced an increase in urinary dopamine excretion during the two first days after salt loading. The rise in urinary dopamine was blunted in group 2. It was not observed in group 3. Salt loading failed to change arterial pressure and heart rate in the three groups of animals. These data show an alteration of the renal dopaminergic system in hypertensive sinoaortic denervated dogs suggesting that a dopaminergic impairment can appear during the development of arterial neurogenic hypertension. (Hypertens Res 1995; 18 Suppl. I: 5187-5190)

Key Words: dopamine, hypertension, sinoaortic denervation, kidney

Although its physiological relevance is still unclear, it is now admitted that endogenous renal dopamine (ERD) plays a role in the regulation of sodium excretion (1) through activation of specific receptors (2). Moreover, as alteration of sodium handling is one of the factors involved in pathophysiology of arterial hypertension (AHT), a great interest focuses on the potential role of ERD in this pathology. Indeed, several studies showed impairment of renal dopamine mobilization during salt loading in hypertensive models (3). Most of the time, these studies concerned models of genetic AHT. The aim of our work was to investigate whether ERD could be altered during the development of acquired AHT elicited by sinoaortic denervation in dogs.

Material and Methods

Nineteen beagle dogs weighting from 13 to 16 kg were studied: seven normal normotensive dogs (group 1) were compared to 12 animals made hypertensive by sinoaortic denervation (SAD) as previously described (4). Briefly, carotid and aortic nerves were cut under chloralose anesthesia (80 mg/kg i.v.) during 2 successive procedures, 1 at time 0, and the second 7 weeks later. During surgery, care was taken to keep both vagal and sympathetic fibers in the vagus intact. The effectiveness of baroreceptor denervation was checked by the failure of norepinephrine (2 mg/kg) to induce bradycardia and nitroglycerine (1, 3, 10 and 30 mg/kg) to induce tachycardia. During the 4 first months, AHT elicited by SAD is associated with a high level in plasma catecholamines. One year after SAD, plasma catecholamine levels return to basal values (4). Furthermore, functional (5) and histological (6) renal alterations are similar to those observed in human AHT.

Two groups of hypertensive dogs were used: group 2 (n = 6) was studied less than 4 months after SAD, i.e. when sympathetic tone is high. Group 3 (n = 6) was investigated one year after SAD, i.e. the period in which plasma catecholamine levels had returned to basal values whereas blood pressure remained elevated (4). Before collecting urines, animals were acclimatized for 3 days in individual cages. Salt (10 g of NaCl) was given each day during 7 days. The food was identical for the 3 groups. Water was given at libidum.

Urinary Parameters

The 24 h urines were collected in bottles containing 20 ml of HCl 5 M and maintained in the dark and at 4°C. Urinary catecholamines were measured by HPLC with electrochemical detection. Urinary sodium and potassium were measured by a flame photometer. The urinary parameters were studied 2 days before initiation of salt loading and during all the protocol period.

Cardiovascular and Blood Parameters

Dogs were trained to stand still for 3 h on a Pavlov table, and were accustomed to blood sampling procedures. Systolic and diastolic blood pressures were

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recorded by mean of a catheter introduced in the abdominal aorta via the femoral artery and connected to a Gould P231D transducer on 1 channel of a Honeywell recorder. Heart rate was obtained using a heart period (pulse interval) meter triggered by the electrocardiogram. Arterial blood pressure and heart rate were evaluated before (Day-1) and at the end of salt loading (Day 7). At the same time, plasma catecholamines as well as creatinine and urea were assayed.

**Statistic Tests**
The comparisons between groups and in a same group of urinary parameters during all the salt loading period were made by ANOVA with repeated measures. Blood and cardiovascular parameters were compared between groups by ANOVA and in a same group by a Wilcoxon test. Results are mean values ± SEM.

**Results**

**Urinary Dopamine (Fig. 1)**
In the normotensive group (Group 1), salt loading was associated with a rise in urinary dopamine (+103% of basal values the first day) which lasts 2 days. In group 2, the urinary dopamine increment was less marked (+73% of basal value) than in group 1. It was only observed on day 1. In group 3, no rise in urinary dopamine level occurred. Urinary norepinephrine was comparable between groups and in each group, before and after salt loading (data not shown).

**Natriuresis (Fig. 2)**
Natriuresis increases from the first to the last day of salt loading. There was no difference between the three groups.

**Cardiovascular Parameters (Fig. 3)**
As previously reported, blood pressure was higher after SAD than in normal dogs (4). Salt loading did not change blood pressure and heart rate in the three groups of animals.

**Blood Parameters**
Salt loading failed to modify plasma catecholamines in the different groups. Creatinine and urea plasma levels were similar in the three groups (data not shown).

**Discussion**
The present study investigates the involvement of ERD during the development of a non genetic model of arterial hypertension elicited by SAD in dogs. This model is particularly interesting since the development of arterial hypertension is associated with changes in sympathetic tone as well as functional (5) and morphological (6) renal alterations close to those observed in humans. In fact, a biphasic variation of the sympathetic tone characterizes this form of neurogenic arterial hypertension: first, an increase in catecholamine plasma levels during the 4 first months after surgery and secondly, a nor-
normal sympathetic tone. Such an increase in plasma catecholamine concentration is observed in nearly 40% of the patients with essential hypertension (7).

Since renal dopamine appears to be largely under the control of sodium ion, we performed oral salt loading in these two groups of hypertensive dogs in order to quantify renal dopamine mobilization. Concerning basal conditions, two points must be discussed: urinary excretion in dogs is lower (about 7 times) than in humans (8). These data might be explained by the lower ability of dog renal tissues to decarboxylate L-Dopa, due to a decreased activity of the enzyme in the dog kidney (9). Moreover, we failed to find any statistical difference in urinary dopamine basal values between hypertensive and normotensive animals whatever the time after surgery. These results are not surprising since conflicting results have been reported concerning dopamine values in essential AHT: similar (10, 11) as well as increased (12, 13) or decreased levels (14, 15) have been observed. Our data are in agreement with the fact that the involvement of ERD in resting eunatremic conditions seems to be unlikely (16, 17) asking the question of the reality of a dopaminergic defect in AHT has been already described (20-23), but mainly in genetic models of AHT. Our results suggest that in this experimental model of acquired AHT, dopamine impairment can appear during the evolution of AHT.

Despite defects in urinary dopamine mobilization, natriuresis rise in hypertensive as well as in normotensive animals in a comparable way. This increment persists during all the protocol period. These results differ from most of the previous works that found a positive correlation between natriuresis and urinary dopamine excretion in AHT (8, 10, 20). By contrast, these data agree with the observation of De Feo et al. (24) who showed that a potential dopaminergic defect did not compromise sodium excretion in 2 strains of Dahl rats (Salt Sensitive and Salt Resistant) on high sodium chloride diet. The decrease in aldosterone already described in this model of neurogenic arterial hypertension probably accounts for the observed persistent natriuresis (6). Finally, in our experimental model, salt loading failed to induce any increase in arterial blood pressure.

In conclusion, using an experimental model of acquired neurogenic AHT elicited by SAD in dogs, we have demonstrated that ERD impairment can appear during the initiation and the development of AHT. However, natriuretic response to high salt diet is not altered and permits salt elimination without repercussion on arterial blood pressure suggesting that ERD plays a minor role in sodium balance in dogs.

References