# CHANGES IN SYSTEMIC HEMODYNAMICS DURING THE DEVELOPMENT OF DOCA–SALT HYPERTENSION. EFFECT OF NEONATAL SYMPATHECTOMY

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DOCA–salt hypertension in rats is known to be volume-dependent: As a result of an increase in $Na^+$ reabsorption there is an increase in the effective blood volume and in the volume of extracellular fluid [14], and this may lead to an increase in cardiac output. However, results obtained on this question are highly contradictory. According to some workers, the cardiac output in DOCA–salt hypertension remains normal [15], whereas according to others it is increased [12].

According to Guyton [11], the initial increase in minute volume is the basic stage in the development of volume-dependent forms of arterial hypertension, for it induces autoregulatory constriction of resistive vessels, an increase in the total peripheral resistance, and stabilization of the arterial pressure (BP) at a high level. Increased functional activity of the sympathetic nervous system (SNS), an important determinant of cardiac output and vascular tone [2], in Guyton's opinion, is not an essential condition for elevation of BP. However, there is evidence in the literature of a change in SNS activity in this form of artertial hypertension: an increase in discharge frequency in cerivical sympathetic fibers [6], an increase in the noradrenaline turnover at the level of neuroeffector synapses in the brain [10], and delay or complete prevention of the elevation of BP after destruction of SNS [7]. Meanwhile, there are no data in the literature on changes in the hemodynamics in rats with DOCA–salt loading combined with sympathectomy.

In the investigation described below the systemic hemodynamics and the effect of neonatal chemical sympathectomy on it was studied in the course of development of DOCA–salt hypertension in rats.

## EXPERIMENTAL METHODS

The cardiac output was determined in waking rats by the thermodilution method using a Cardiomax apparatus (Columbus, USA). Cold (19°C) sterile physiological saline in a volume of 0.2 ml was injected rapidly by automatic pneumatic transmission into the right atrium through a catheter implanted 24 h previously. The thermodilution curve in the aorta was recorded by means of an implanted thermocoupled. It was analyzed by the Cardiomax computer, and values of the cardiac output were put out on its display panel. The BP and the heart rate were measured through a catheter inserted previously into the caudal artery. This catheter was fixed to the animal's back, and the venous catheter and temperature transducer were fixed to its head. To prevent the rat from damaging the catheters and transducer, the animals were kept in individual cages after the operation. On the basis of values of BP, cardiac output, and body weight, the cardiac index (CI) and relative peripheral resistance (RPR) were calculated.

DOCA–salt hypertension was induced by unilateral nephrectomy, subcutaneous implantation of DOC pellets (40 mg per rat) every 2 weeks, and replacement of water for drinking by 1.5% NaCl solution. Hemodynamic parameters were studied in 4 groups of animals: 1) DOCA–salt loading with intact SNS, 2) the same, but after sympathectomy, 3) control unilaterally nephrectomized rats, receiving water or 1.5% NaCl to drink, 4) sympathectomized rats with unilateral nephrectomy, receiving water to drink.

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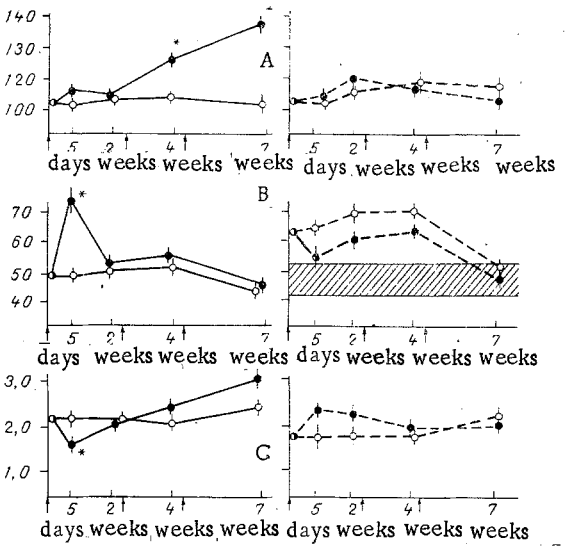


Fig. 1. Changes in systemic hemodynamics in rats with intact SNS (on left) and sympathectomized rats (on right) in response to DOCA–salt loading. A) Mean BP (in mm Hg), B) CI (in ml/min/100 g), C) RPR (in conventional units). Empty circles denote normotensive rats, filled circles – DOCA–salt loading, continuous line – rats with intact SNS, broken line – sympathectomized rats. Arrows indicate time of DOCA implantation. Shaded zone represents limits of normal values of CI for rat with intact SNS. *P < 0.05 compared with control.

Neonatal chemical desympathization of the rats was carried out by subcutaneous injection of guanethidine, in accordance with the scheme devised previously [5].

## EXPERIMENTAL RESULTS

In rats with an intact SNS, DOCA–salt loading led to the development of an arterial hypertension. Starting from the 4th week after implantation of DOCA, their BP rose significantly compared with that in the unilaterally nephrectomized rats not receiving DOCA. However, it must be pointed out that BP also rose a little in the group of control rats receiving 1.5% NaCl solution instead of water, but only during the first 7-10 days after the beginning of salt loading, and later their BP returned to normal. In sympathectomized rats, arterial hypertension did not develop during DOCA–salt loading (Fig. 1), in agreement with results obtained previously [1, 7].

The value of CI in control animals with an intact SNS, which received water to drink, varied from 48.3 ± 2.7 ml/min/100 g on the 5th day after the operation to 45.7 ± 2.3 ml/min/100 g in the 7th week of observation. These figures agree with values of CI given in the literature for normal waking rats, obtained by the thermodilution method [9].

On the 5th day of administration of DOCA + NaCl to rats with an intact SNS bradycardia was observed, RPR of the vessels decreased, and CI rose very considerably (by 48%). This took place evidently as a result of an increase in the effective blood volume and an increase in the venous return [11]. RPR decreased because of reflex depression of SNS activity through pressure and volume receptors and a "stress-relaxation" response of the arterioles [11]. The changes described above were observed only in the initial stage of development of DOCA–salt hypertension: CI was back to normal only two weeks after the first implantation of DOCA. This could be due to an increase in the mean capacity of the blood stream (an increase in blood deposition in the venous part of the system), observed in the second week of development of DOCA–salt hypertension [15].

RPR began to increase 1-2 weeks after the beginning of DOCA–salt loading and in rats with stable hypertension it exceeded the control level by 31% (Fig. 1). The initial increase in CI is possibly one of the factors triggering an increase in RPR through an autoregulatory mechanism [11]. Meanwhile, an increase in CI was found in the present experiments in control unilaterally nephrectomized rats also, during the first few days after replacement of drinking water by 1.5% NaCl solution. Despite this, no prolonged elevation of BP took place in them, as already mentioned. Similar results were obtained in a study of changes in CI in response to salt loading in Dahl rats sensitive and resistant to $Na^+$ [8, 9]. Elevation of BP in the latter in response to increased NaCl consumption did not take place, but CI was increased in these animals to the same degree as in rats sensitive to $Na^+$. BP did not rise in the resistant rats because of a compensatory fall of RPR. Consequently, for RPR and BP to rise in rats with DOCA–salt hypertension, and for Dahl rats sensitive to $Na^+$, autoregulatory vasoconstriction in response to a blood flow which exceeds the metabolic demands, and subsequent development of adaptive-structural changes in them are insufficient by themselves [1, 11]. For a permanent rise of BP in such cases, either administration of DOCA or activation (genetic) of the mineralocorticoid function of the adrenal cortex [8], noted in Dahl rats, and affecting sodium reabsorption by the kidneys, is probably essential in these cases. The results of the present investigation also revealed the great importance of noradrenergic mechanisms of elevation of RPR and BP in pathogenesis of DOCA–salt hypertension. This is demonstrated by results showing that neonatal sympathectomy prevents the development of DOCA–salt hypertension (Fig. 1).

CI was higher in sympathectomized rats than in animals with an intact SNS (Fig. 1), in agreement with data obtained previously by the use of other methods of recording systemic hemodynamics [3, 5]. Elevation of CI was probably connected with an increase in blood volume [13] and also with a compensatory increase in the plasma adrenalin concentration [5], which could increase myocardial contractility. RPR was lower in sympathectomized rats than in rats with an intact SNS.

DOCA–salt loading in sympathectomized rats did not cause any additional increase in CI but, on the contrary, a tendency for it to fall was actually noted. Possibly not only the "volume" factor participates in the rise in CI in the early stages of DOCA–salt hypertension, but also noradrenergic mechanisms, activation of which may lead to an increase in the venous return of blood to the heart, on account of an increase in venous tone. The results of the present investigation also suggest that activity of SNS is definitely increased in rats with DOCA–salt hypertension, and as a result this, elimination of SNS blocks the rise of BP, despite the possibly activation of those same "compensatory" mechanisms which, as has already been mentioned, are activated after sympathectomy in normotensive rats.

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