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Original articles

P. ABRAMCZYK, R. ZIĘCINA, A. LISIECKA, K. PAPIERSKI, J. PRZYBYLSKI

THE ADRENAL RENAL VASCULAR CONNECTION PLAYS AN ESSENTIAL ROLE IN THE PATHOGENESIS OF RENOVASCULAR HYPERTENSION IN THE RAT

Department of Experimental and Clinical Physiology, Medical University of Warsaw, Poland

The adrenal renal portal circulation (ARPC) contributes to decrease in renal blood flow occurring after renal artery clipping. The aim of present study was to determine the role of the ARPC in the development of the renovascular hypertension in 1-kidney 1-clip model in the rat. Experiments were performed on male Wistar rats. In the control group (A) the right nephrectomy and adrenalectomy were done. In the experimental groups renovascular hypertension was produced by clipping the left renal artery (silver clip ID 0.40 mm). In the first of the experimental groups (B) the right nephrectomy and adrenalectomy were done. In the second experimental group (C), for elimination of the ARPC, the right kidney and the left adrenal gland were removed. In the half number of rats from each group plasma renin activity was measured 48 hours after surgery. An increase in SBP was significantly higher in the group B (ARPC intact) than in the group C (ARPC eliminated) (172 $\pm$4 vs 144 $\pm$2 mmHg, $p<0.01$). PRA was significantly higher in the group C than in the group B (39.0 $\pm$1.4 vs 31.2 $\pm$ 2.0 mmol/l/min, $p<0.05$). In the control group (A) PRA was significantly lower as compared to the both experimental group (2.0 $\pm$ 1.6 mmol/l/min, $p<0.05$).

Key words: *renovascular hypertension, plasma renin activity, adrenal-renal portal circulation, blood pressure, rat.*

INTRODUCTION

In 1934, Goldblatt and associates produced chronic renal hypertension by constricting the renal arteries in dogs (1). Subsequently, numerous studies have attempted to elucidate the mechanisms involved in the pathogenesis and the maintenance of this model of hypertension. Special emphasis is accorded to the renin-angiotensin system (2, 3, 4). The rapid rise in plasma renin activity (PRA) in response to the renal artery constriction is the hallmark of the acute phase of Goldblatt hypertension (5). In addition to salt and water retention it plays a fundamental part in the development of high blood pressure in 1-kidney, 1-clip model (1K1C). It is well known that a main stimulus to an increase in renin secretion is a decrease in blood pressure in the afferent glomerular arteriole. Another potent stimulus is an increased activity of adrenergic fibres in the kidney.

Gordon et al. measured plasma catecholamines concentration in patients with renovascular and essential hypertension. In adrenal venous plasma, noradrenaline and adrenaline levels were higher in the renovascular group than in the essential hypertension group (6). Since the adrenal medulla is an organ specifically responding to sympathetic stimulation, adrenal venous catecholamines offer a good index of the sympathetic activity. Thus these data confirms an activation of the sympathoadrenal system in the renovascular hypertension (RVH). Adrenal medullectomy lowered the arterial pressure in RVH (7). However, in Goldblatt hypertension there is an attenuation of efferent sympathetic activity in the clipped kidney (8), despite the enhanced activity of peripheral sympathetic nerves (9).

Besides efferent sympathetic nerves, kidney's function remains under the control of catecholamines reaching it through the adrenal renal portal circulation (ARPC). The ARPC was described for the first time in 1914 by Cow in the cat (10). Later, other authors confirmed existence of this vascular connection in the rat (11), dog (12) and humans (13). These vessels are larger than capillaries, abundantly innervated by the nonmelinated fibres and have the valves determining the unilateral, adrenal-renal blood flow. Blood samples, collected from vessels of the ARPC, demonstrated markedly elevated catecholamine concentration (14).

The ARPC provides a direct route for adrenal catecholamines reaching the kidney without affecting systemic circulation. This is also consistent with Więcek *et al.* results who described elevated noradrenaline level in renal venous blood in the ischaemic kidney in patients with the renovascular hypertension (15).

In 1998 Zięcina *et al.* provided evidence that catecholamines reaching the kidney through ARPC, contribute to decrease in RBF and increase in RVR during acute renal artery stenosis in the rat (16).

The aim of the present study was to investigate the role of ARPC in the development and maintenance of hypertension and in changes of PRA in the acute phase of 1K1C Goldblatt hypertension in the rat.

MATERIALS AND METHODS

Experiments were performed using male Wistar rats weighing 300—350g, obtained from Medical University animal house (Warsaw, Poland). Four rats were kept per standard laboratory cage, at controlled 12-hour dark and light phases, with food and water available *ad libitum*.

Animals were anesthetized with chloral hydrate (Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany) at the dose of 0.36 g /kg of b.w., i.p. Animals were divided into three groups. In the first group (A) (n = 20) the right nephrectomy and adrenalectomy were performed, and the left renal artery was sham clipped by touching with forceps. This group served as a control one. In the second group (B) (n = 20) to induce 1K1C hypertension a silver clip (ID 0.40 mm) was placed around the left renal artery and the right nephrectomy and adrenalectomy (ARPC intact) were performed (17). In the third group (C) (n = 20) hypertension was produced as in the group (B) and for elimination of the ARPC, the right nephrectomy and the left adrenalectomy were performed.

Systolic blood pressure (SBP) of all animals was measured using tail-cuff method (MK Design, Warsaw, Poland) every third day up to 4 weeks after the operation.

Ten animals from each group were sacrificed by decapitation 48 hours after surgery. Trunk blood samples were collected. Plasma renin activity (PRA) was evaluated by fluorometric assay using substrates containing 7-amino-4-methylcoumarin (AMC) (18).

Statistical methods

Results are presented as mean ± SEM (Standard Error of the Means). Statistical analyses were performed by the Student's t-test or Anova analysis of variance. A value of $p < 0.05$ was accepted to be significant.

RESULTS

Clipping the renal artery produced a rise in SBP either in the group B (from 123±2 mmHg to 147±3 mmHg, $p<0.01$) or in the group C (from 123±2 mmHg to 138±4 mmHg, $p<0.01$) within 6 days. In the group B the pressure continued to rise reaching value of 164±2 mmHg by day 9 and 172±4 by day 24. In the group C SBP reached value of 145±1 mmHg by day 9 and remained unchanged by the end of the experiment ($p<0.01$ as compared to the subsequent values from group B). There were no significant changes in SBP in control group (A) throughout the entire experiment. SBP in the groups A, B and C during entire time of the experiment is presented in Figure1. Forty eight hours after clipping renal artery PRA was significantly greater in the group B compared with the group C ($p<0.05$). In both experimental groups (B and C) PRA was significantly higher compared with the control group (A) ($p<0.05$). The values of PRA in all groups are presented in *Table 1.*

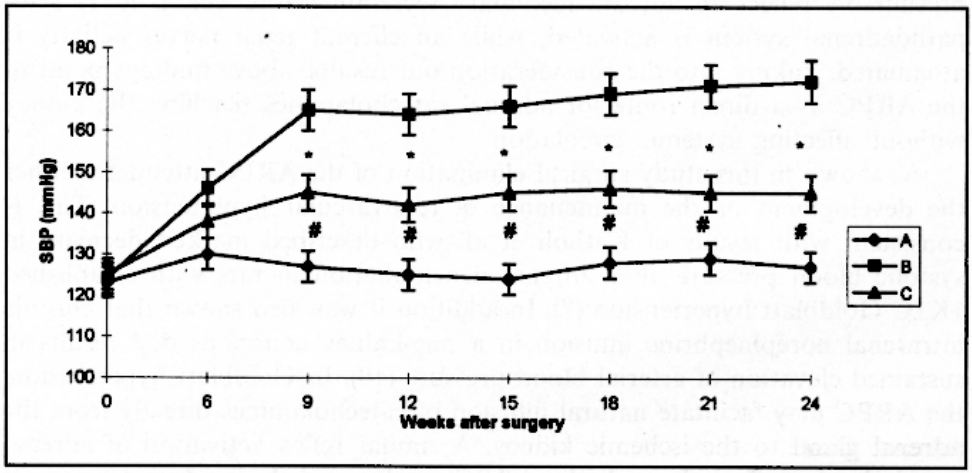

Fig. 1. Time-course of the systolic blood pressure (SBP) during entire experiment in the all group. A — control group, B — experimental group with intact ARPC, C — experimental group with elimination of ARPC. Values are mean ± standard error of means (SEM). # $p < 0.01$ as compared to group B and C. * $p < 0.01$ as compared to group C.

Table 1. The values of plasma renin activity (PRA) 48 hour after surgery in the all groups. A — control group, B — experimental group with intact ARPC, C — experimental group with elimination of ARPC. * $p < 0.01$ as compared to group A. # $p < 0.05$ as compared to group C.

Groups	PRA (mmol/l/min)
A	2.0 ± 1.6
B	39.0 ± 1.4 *#
C	31.2 ± 2.8 *

DISCUSSION

Fink and Brody (8) reported attenuation of the efferent sympathetic control of the renal vascular resistance in the clipped kidney. The mechanism of this selective decrease in the efferent sympathetic control of the renal vascular resistance in 1K1C Goldblatt hypertension in which there is an increased systemic sympathetic activity is not known. On the other hand Więcek et al. described in patients with renovascular hypertension significantly greater plasma levels of adrenaline and noradrenaline in the renal venous blood of the ischemic kidney than in the arterial blood and blood from the inferior vena cava. Plasma adrenaline levels in renal venous blood of the ischemic kidney were higher about 600% and of noradrenaline about 30% than in plasma of the „normal" kidney (15). It is well known that venous levels of noradrenaline represent contributions from various sources, while levels of adrenaline presumably reflect an adrenal medullary secretion. Moreover in RVH sympathoadrenal system is activated, while an efferent renal nerves activity is attenuated. Taking into the consideration our results, above findings point to the ARPC as a direct route for adrenal catecholamines reaching the kidney without affecting systemic circulation.

As shown in this study surgical elimination of the ARPC attenuates either the development or the maintenance of renovascular hypertension. This is consistent with results of Katholi et al. who described marked decrease in systolic blood pressure after adrenal demedullation in rats with established 1K1C Goldblatt hypertension (7). In addition it was also shown that chronic intrarenal norepinephrine infusion in a one-kidney conscious dog results in sustained elevation of arterial blood pressure (19). In Goldblatt hypertension, the ARPC may facilitate natural infusion of catecholamines directly from the adrenal gland to the ischemic kidney. A similar reflex activation of adrenal catecholamines flow through the ARPC is observed during hypotension. It results either in marked decreases in a glomerular filtration rate and urinary sodium excretion or in decrease in renal blood flow and it is abolished by administration of phentolamine or ARPC elimination (12, 14, 20).

It is well accepted that development of hypertension that follows removal of one kidney with clipping of the artery of the remaining kidney is mediated by the renin-angiotensin system (5). Immediately on reducing blood flow to the kidney there is a rise in renin secretory rate, plasma renin activity, and systemic blood pressure (21). The renal renin-angiotensin system of ischemic kidney seems to be a major factor involved in the pathogenesis of renovascular hypertension (22). A significant positive correlation was found between plasma renin activity and plasma level of adrenaline in venous blood of the ischemic kidney (15). In our study elimination of the ARPC abated the rise in PRA in the acute phase of Goldblatt hypertension. The above results corresponds well with our previous study, in which the elimination of ARPC attenuated the ischemic effect occurring after clipping (16). We postulate that in the acute phase of renovascular hypertension elimination of the ARPC reduces inflow of adrenal catecholamines to the kidney and in this mechanism decreases renal renin secretion.

However, reduction in PRA in the group with lower values of blood pressure (group C) is inconsiderable, though the difference is statistically significant. Therefore it can not be only explanation for faint development of hypertension. The most important factor which preserve the full development of arterial hypertension is the cessation of chronic influence of adrenal catecholamines (discussed above) and other adrenal hormones like mineralo- and glycocorticoids (23). The changes of the excretory kidney function, renal blood flow, sympathetic and renin-angiotensin system which occur in the later phases of 1K1C Goldblatt hypertension after ARPC elimination need the further investigation.

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Author's address: Piotr Abramczyk, Department of Experimental and Clinical Physiology, Medical University of Warsaw, Krakowskie Przedmieście 26/28, 00—927 Warsaw, Poland.
e-mail: abram@amwaw.edu.pl