Influence of Castration and Testosterone Propionate on Cardiac Output, Renal Blood Flow, and Blood Volume in Mice[1] (37659)

PETER DAN BROULIK, CHARLES D. KOCHAKIAN, AND JIRI DUBOVSKY
Laboratory of Experimental Endocrinology, Medical Center, University of Alabama, Birmingham, Alabama 35294

The mouse kidney is specially responsive to the withdrawal or administration of androgens. Castration markedly reduces while androgens not only restore but can increase the kidney weight above normal (1) with concomitant changes in the epithelial cells of the convoluted tubules and the parietal cells of Bowman's capsule (1). These changes in growth are accompanied by changes in RNA and protein biosynthesis (2–4). The RNA and polysome concentrations are decreased by castration and restored by androgens (2, 5) with concomitant changes in the rate of amino acid incorporation into protein (2). Since these changes could be a reflection of changes in the availability of the respective precursors provided by the blood, the renal blood flow and also cardiac output and blood volume were determined.

Methods and Materials. The ^{86}RbCl (2.5 mCi/mg) was purchased from New England Nuclear Corporation and was neutralized to pH 7.4 with sodium bicarbonate prior to use. The [^{131}I]albumin was from Abbott Laboratories. The testosterone propionate (Searle Chemicals, Inc.) was made into cylindrical pellets (approximately 15 mg) for subcutaneous implantation (2).

Radioactivity. Radioactivity in the blood and kidneys was determined in a Model 4216 Nuclear-Chicago automatic gamma counting system.[2]

Cardiac Output. The cardiac output was determined by the method of Hamilton and associates (6) using ^{86}RbCl or [^{131}I]albumin as indicator. The mice were anesthetized with sodium pentobarbital, 0.06 mg/g body wt (7). This drug has been used in dogs (8) and monkeys (9) without any effect on cardiac output. A 0.05 mm (OD) polyethylene tube (Clay-Adams, PE-10) was inserted in the carotid artery. The indicator (0.1 ml) was injected into a tail vein within 0.5 sec. The blood samples of approximately 10 μliter each were spotted on a strip of Whatman No. 1 paper at approximately 1-sec intervals from the continuously flowing blood. The spots were cut out and the radioactivity determined. The amount of blood in each spot then was determined by extraction of the filter paper with Drabkin's solution for the determination of hemoglobin (10). The hemoglobin also was determined in exactly measured blood volumes (micropipette) and the appropriate corrections for the serial samples were made.

The concentration of radioactivity in the arterial blood was plotted on semilogarithmic paper and the cardiac output calculated by the Hamilton-Stewart formula (6, 11).

Renal Blood Flow. The uptake of ^{86}RbCl by the kidneys was determined in separate groups of mice of the same age and treatment as the above. The neutralized rubidium solution, 2 μCi in 0.1 ml, was injected into a tail vein and 20 sec later the mice were killed by cutting through the thorax. The kidneys were immediately removed, weighed, and the radioactivity determined. The renal blood flow was calculated by multiplying the cardiac output by the percent uptake of radioactivity by the kidneys (12).

Blood and Plasma Volumes. The blood and plasma volumes were measured by the method of Kalliss (13). [^{131}I]Albumin, 0.5 μCi in 0.1

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TABLE I. Effect of Castration and Testosterone Propionate on the Cardiac Output of Mice.[a]

	Castration or TP days	No. of mice	Body weight (g)	Cardiac output	
				ml/min	ml/min/kg
Normal mice		15	40	14.9	371 ± 10.8
Castrated mice	2	7	41	15.5	372 ± 14.2
	7	8	40	14.5	360 ± 16.9
	14	7	37	12.5	333 ± 5.6[b]
	21	13	39	13.0	325 ± 23.5[b]
Treated mice	2	6	36	11.8	327 ± 8.5
	7	12	41	16.6	397 ± 11.6
	14	10	40	15.1	375 ± 13.3

[a] The experimental details were as described in the text. The age of the mice was 58–99 days. The testosterone propionate pellet was implanted after 21 days of castration. [^{131}I]Albumin was used as the indicator in approximately half of the mice in each group and ^{86}RbCl for the others. The results were identical by the two isotopes. The values are the mean ± standard error.

[b] $p < 0.01$.

ml saline, was injected into the tail vein of mice anesthetized as above. After 15 min of equilibration, a blood sample was obtained by cardiac puncture. The radioactivity of duplicate aliquots of blood and plasma was determined. The blood volume was calculated as (cpm/ml of standard):(cpm/ml whole blood or plasma).

Results. Cardiac output. The cardiac output was significantly decreased 14 days after castration (Tables I, II). The subcutaneous implantation of a pellet of testosterone propionate produced no detectable change after 2 days but restored the cardiac output to normal within 7 days. No further change was observed after 14 days of androgen treatment.

Renal blood flow. Fourteen days after castration the renal uptake of ^{86}Rb in the kidney was significantly reduced and was reduced further after 21 days (Table II). Testosterone propionate did not produce any change within 2 days, but almost completely restored the uptake of ^{86}Rb within 7 days.

TABLE II. The Influence of Castration and Testosterone Propionate (TP) on the Renal Blood Flow of Mice.[a]

	Castration or TP days	No. of mice	Kidney weight (mg)	Body weight (g)	^{86}Rb uptake (%/100 mg kidney)	Cardiac output (ml/min)	Renal blood flow (ml/min /g kidney)
Normal mice		10	585	37	3.7 ± 0.23	13.9 ± 1.4	5.1 ± 0.44
Castrated mice	2	5	614	39	3.7 ± 0.28	14.5 ± 0.7	5.3 ± 0.58
	7	5	522	41	3.4 ± 0.31	14.7 ± 0.8	5.1 ± 0.60
	14	8	458	40	3.3 ± 0.52	13.6 ± 0.6	4.5 ± 0.57[b]
	21	11	380	37	3.2 ± 0.30	12.1 ± 0.8	3.9 ± 0.53[c]
TP treated mice	2	7	410	35	3.2 ± 0.13	11.3 ± 0.9	3.6 ± 0.33
	7	7	502	35	3.4 ± 0.23	14.1 ± 1.5	4.8 ± 0.61
	14	8	586	35	3.7 ± 0.32	13.0 ± 1.6	4.7 ± 0.64

[a] The experimental details were as in the text. The age of the mice was 55–99 days. The TP pellet was implanted after 21 days of castration. The values are the means ± standard error.

[b] $p < 0.05$.

[c] $p < 0.01$.

The renal blood flow (Table II) calculated from ^{86}Rb uptake and cardiac output (12), was significantly reduced after 14 days of castration. Complete restoration in renal blood flow was observed after 7 days of testosterone propionate treatment.

A major proportion of the reduced uptake of ^{86}Rb after castration was due to the reduced cardiac output (Tables I, II).

Blood volume. Twenty-one days after castration, the blood volume of the mice was decreased from 90 ± 2.6 ml/kg body weight to 82 ± 2.2 ml/kg, and was restored to normal within 7 days by testosterone propionate.

Discussion. The data presented here show that the restoration of the weight of the mouse kidney by testosterone propionate is accompanied by changes in renal circulation. Since the changes in renal blood flow and cardiac output were not observed until after 2 days of androgen treatment, they do not represent or affect any of the earliest physiological actions of androgen (2, 14). In this respect the mouse kidney is different from the uterus (15), ovary (16), and liver (17) where circulatory changes occur much earlier. The general mechanism of hormone action, however, may involve expansion of the microcirculation of the target organ, as suggested for the uterus (15).

The changes in renal blood flow and cardiac output after castration and androgen treatment are accompanied by parallel changes in volume of blood and cells (18) and also the weight of the heart (1, 19). The restoration of cardiac output may be the primary change as observed in hypophysectomized rats (20). Hypophysectomy results in a decrease of renal blood flow which is of the same order as the reduction of the cardiac output and oxygen consumption.

The degree of decrease in blood volume after castration is similar to that in the weight of the heart and may represent a general decrease in the circulatory system or possibly vasoconstriction. The liver weight also changes to the same degree as the heart. The percent change in weight of the kidney, however, is much greater than that of either the heart or the liver (1).

Summary. The cardiac output and renal blood flow has been determined in mice by the adaptation of the ^{86}Rb method of Sapirstein. Cardiac output also was determined with [^{131}I]albumin. Castration decreased the cardiac output, renal ^{86}Rb uptake and renal blood flow. Testosterone propionate was ineffective after 2 days but within 7 days had restored these values to normal. Extension of the androgen treatment did not produce any further changes. The blood volume of the mice was decreased approximately 10% by castration and restored to normal by testosterone propionate.

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