Fibrinolytic System in the Dog with Experimental Renal (Goldblatt) Hypertension

It is generally accepted that the activation of the renin-angiotensin system is one of the most important but not a unique factor in the pathogenesis of experimental kidney hypertension[1,2]. The other factors which may be involved in the pathogenesis of experimental kidney hypertension deserve investigation.

Several authors have reported that plasmin is a factor involved in the formation of bradykinin and other kinins decreasing blood pressure[3,4]. The purpose of our experiments was to evaluate the fibrinolytic system in dogs with experimental kidney hypertension produced by bilateral renal artery constriction according to the method of GOLDBLATT et al.[5].

Experiments were performed on 18 mongrel dogs. The operation was performed under general anaesthesia following a pentothal injection in doses of 30–50 mg/kg body weight. In 9 dogs the renal arteries were clamped using silk threads. The other dogs, controls, were operated on without clamping the arteries. Blood pressure was recorded on an Hg manometer by means of direct puncture of the femoral artery. The blood was drawn from tibial veins and mixed with 0.2 *M* sodium citrate (in the proportion of 9:1) before and on the 7th and 15th day after the operation. The platelet-poor citrate plasma was obtained by centrifuging blood at 3000 rpm for 10 min.

The following determinations were made: fibrinogen level, plasma and serum euglobulin fibrinolysis, plasminogen, plasminogen proactivator, and antiplasmin. Fibrinolytic activity was expressed as an index, $f = 1000/t$ min (t = clot lysis time). All the determinations were made as previously described[6,7], provided that the fibrin plate method of ASTRUP and MÜLLERTZ[8] had been used for determining plasminogen, plasminogen proactivator and antiplasmin level. The level of plasminogen, plasminogen proactivator and antiplasmin before operation was accepted as 100%. The results are summarized in Tables I and II.

Table I. The fibrinolytic system in dogs with experimental hypertension

Test	Before operation		7 days after operation			15 days after operation		
	M	SD	M	SD	*P*	M	SD	*P*
Blood pressure	128	11.1	153	22.8	< 0.02	141	29.0	$0.2 > < 0.3$
Fibrinogen mg%	298	67.7	509	88.0	< 0.001	523	122.0	$0.001 > < 0.01$
Plasma euglobulin fibrinolysis, index	25.8	14.0	6.6	3.2	$0.001 > < 0.01$	12	8.1	$0.02 > < 0.03$
Serum euglobulin fibrinolysis, index	13.2	5.2	5.9	2.5	$0.02 > < 0.05$	7	1.8	$0.001 > < 0.01$
Plasminogen, % of initial value	100	–	156	11.0	$0.001 > < 0.01$	160	27.5	< 0.001
Proactivator, % of initial value	100	–	159	58.2	$0.01 > < 0.02$	134	51.6	$0.05 > < 0.1$
Antiplasmin, % of initial value	100	–	125	34.5	$0.05 > < 0.1$	135	43.2	$0.05 > < 0.1$

M = arithmetic mean; SD = standard deviation.

Table II. The fibrinolytic system in sham operated dogs. The mean values of 9 experiments and the range of variations (values in brackets) are given

Test	Before operation	7 days after operation	15 days after operation
Blood pressure, mm Hg	133 (120–155)	133 (120–160)	125 (115–140)
Fibrinogen, mg%	262 (204–360)	378[a] (312–624)	399[a] (276–432)
Plasma euglobulin fibrinolysis, index	31.0 (16.5–67.3)	29.4 (16.5–62.0)	30.0 (19.0–67.0)
Serum euglobulin fibrinolysis, index	37.0 (24.0–55.0)	35.0 (24.0–53.0)	39.0 (30.0–59.0)
Plasminogen, % of initial value	100	100 (93–112)	94 (90–112)
Proactivator, % of initial value	100	104 (80–122)	104 (100–100)
Antiplasmin, % of initial value	100	100 (92–100)	101 (92–110)

[a] This increase of fibrinogen is statistically significant, $0.001 < p < 0.01$.

The following statistically significant changes were observed in the animals with constricted arteries: (1) elevation of arterial blood pressure on the 7th day after the operation; (2) elevation of fibrinogen level on the 7th and 15th day after the operation; (3) inhibition of the euglobulin fibrinolysis in plasma and in serum on the 7th and 15th day; (4) increase of plasminogen level on the 7th and 15th day; (5) increase of plasminogen proactivator on the 7th day. No statistically significant changes were observed as regards the antiplasmin level (Table I). No correlation between the rise in blood pressure and the extent of changes in the fibrinolytic system could be established by analysing experimental data of the individual animals. No changes in blood pressure or

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the fibrinolytic system, except an increase in the fibrinogen level, were observed in the control dogs (Table II).

It can be concluded that the fibrinolytic system is inhibited in the blood during experimental kidney hypertension. It may be postulated that kidney anoxemia impairs the biosynthesis of the plasminogen activator in the kidney. It has been demonstrated by BULUK and MAŁOFIEJEW[9] that the formation of this substance in the kidney is dependent upon the saturation of blood with oxygen. It is possible that a decrease of kinin level follows a drop in the fibrinolytic activity in the renal circulation in dogs with an anoxemic kidney. It has been found by BARRACLOUGH and MILLS[10] that bradykinin increases endogenous clearance of creatinine and secretion of sodium. According to BOOMGARD[11], there is a close correlation between the urine urokinase level and creatinine clearance in patients with kidney diseases. In many kidney diseases there is a considerable decrease in urokinase excretion and urinary kinin level[11–13].

It is known that renin[14] and urokinase[15] are produced by juxtaglomerular (JG) cells. It is of interest to emphasize that the same stimulus, i.e. the shortage of oxygen, may enhance at the same time the formation of renin in the JG cell system and depress that of urokinase. Both events may act in the same direction, i.e. increase of blood pressure. It may be suggested that the inhibition of the fibrinolytic system may be at least in part responsible for the rise in blood pressure in experimental kidney hypertension[16].

Résumé. Nous avons constaté, au cours de l'hypertension arterielle produite chez le chien d'après la technique de GOLDBLATT, l'inhibition de la fibrinolyse des euglobulines, l'augmentation considérable de fibrinogène et de plasminogène. L'intervention chirurgicale de contrôle produisit seulement une augmentation moindre de fibrinogène, sans inhibition de la fibrinolyse.

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Transplantations d'ébauches gonadiques de Souris dans la cavité coelomique de l'embryon de Poulet

Des ébauches gonadiques de Rat ont été greffées sur l'adulte, soit sous la capsule du rein (BUYSE[1]), soit sur l'épiploon (HOLYOKE[2]), soit encore dans la chambre antérieure de l'œil (TORREY[3]): il se différencia un % relativement élevé de testicules, mais peu d'ovaires.

La différenciation sexuelle des ébauches gonadiques de Souris a été obtenue in vitro (WOLFF[4], ASAYAMA et FURUSAWA[5], WENIGER[6]), mais non encore au moyen d'une méthode de greffe. C'est pourquoi nous nous y sommes employé. Nous avons aussi réalisé des transplantations de testicules, et voici pourquoi.

Aussi surprenant que cela pût paraître, le testicule embryonnaire de Souris s'était montré féminisant in vitro à l'égard du testicule embryonnaire de Poulet (WENIGER[6–8]) et il était tentant d'obtenir cette féminisation in vivo. Rappelons que SALZGEBER[9] a transplanté avec succès des ovaires embryonnaires de Souris de 12–19 jours dans la cavité cœlomique de l'embryon de Poulet: malgré la présence d'un transplant ovarien, les hôtes mâles se developpèrent normalement.

Matériel et méthode. La technique utilisée était celle des greffes cœlomiques (HAMBURGER[10]). Les souris (*Mus musculus* L.) appartenaient à la race Swiss, les œufs de Poule (*Gallus gallus* L.), à la race Leghorn blanche.

Résultats. Ils seront exposés séparément pour chacune des 2 séries d'expériences réalisées, l'une au moyen d'ébauches gonadiques morphologiquement indifférenciées de 9–11½ jours, l'autre, au moyen de testicules ou fragments de testicules d'embryon de Souris de 11½–19 jours.

(A) Transplantations d'ébauches gonadiques.

Embryons		
opérés	110	
morts avant 11 jours	16	
autopsiés vivants entre 11 et 14 jours	94	51 ♂ / 43 ♀
avec un transplant	42	
sans transplant	52	

20 des 42 transplants recouvrés étaient manifestement en mauvaise condition, la plupart gorgés de sang: ils ne furent pas examinés histologiquement. 6 des 22 transplants soumis à l'examen histologique ne comprenaient pas de partie gonadique. Des 16 transplants restants, 5 étaient testiculaires et 11 ovariens. Aucun des 5 transplants testiculaires n'était en parfaite condition: des

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