Regional vascular reactivity in rats with Guérin carcinoma (GC)

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Summary. Increased sensitivity to phenylephrin and a decreased one to isoproterenol has been found in regional vascular beds of GC implanted rats. Circulatory sympathetic reflex adaptation, alfa- and beta-adrenergic stimulation or blockade provoked a uniform response pattern: i.e. increase in vascular resistance of GC.

Parallel to the increase of tumor size prominent, newly developed vascular area can be coupled into the peripheral circulation. GC was implanted into rats and the vascular effects of increased sympathetic activity, haemorrhagic hypotension, tourniquet shock and also as stimulation or blockade of alfa- and beta-adrenergic receptors were studied in normal and neoplastic tissues.

Materials and methods. Male rats (mean weights 189–310 g) in 15 groups served as control and 15 groups of rats were implanted with GC cells into the right axillary region. Circulatory parameters were determined 12–15 days after implantation. The mean weight of the tumors varied between 31 and 44 g, except in the tourniquet group and in its control (52 and 44 g). After pentobarbital anaesthesia (40 mg/kg i.p.) blood pressure was measured in the carotid artery with a mercury manometer. Organ fractions of the cardiac output were determined by Sapirstein's isotope fractionation technique[2,3] using ^{86}Rb and ^{125}J-antipyrine;

Groups	n	Blood pressure (mm Hg)	Δ%	Cardiac output (ml/min/100 g)	Δ%	TPR (10^4 dyn · sec · cm^{-5})	Δ%
Haemorrhage							
N: Control	35	116.0±1.62		25.5±0.65		37.0±0.88	23
N: 70 mm Hg	27	73.1±1.31*	−37	13.4±0.52*	−47	45.7±1.76*	12
N: 40 mm Hg	29	42.1±0.88*	−64	8.4±0.33*	−67	41.6±1.63*	
Tu: Control	25	108.4±2.91		30.4±1.07		29.3±1.22	38
Tu: 70 mm Hg	25	71.2±1.20*	−34	14.8±0.71*	−51	40.5±1.88*	22
Tu: 40 mm Hg	25	41.0±0.41*	−62	9.5±0.39*	−69	35.7±1.29*	
Tourniquet shock							
N: Control	13	117.7±2.69		26.0±1.22	−45	37.0±1.80	
N: Tourniquet	15	86.0±2.14*	−27	14.3±1.23*		52.9±4.35*	43
Tu: Control	15	101.7±4.13		33.0±1.95	−59	26.0±2.07	
Tu: Tourniquet	14	72.5±3.00*	−29	13.5±1.13*		45.9±3.00*	76
Phenylephrine (μg/100 g i.v.)							
N: Control	13	118.5±2.22		20.7±0.90		46.7±2.28	
N: 1.0 μg	8	151.9±5.58*	28	24.0±1.79	16	52.6±4.56	13
N: 3.0 μg	8	167.5±8.96*	41	25.7±1.76*	24	56.7±4.51*	21
Tu: Control	9	104.4±2.94		35.1±2.52		25.3±2.84	
Tu: 1.0 μg	6	150.0±6.45*	44	32.2±3.05	− 8	39.4±4.90*	56
Tu: 3.0 μg	7	163.6±4.46*	57	36.5±3.12	4	37.5±3.30*	48
Phenoxybenzamine (mg/100 g i.v.)							
N: Control	30	116.5±1.65		23.7±0.71		40.4±1.40	
N: 1.0 mg	26	93.7±2.41*	−20	26.9±1.19*	14	29.0±1.29*	−28
Tu: Control	27	107.8±2.55		27.1±0.76		32.4±1.20	
Tu: 1.0 mg	31	82.4±2.17*	−24	27.8±1.34	3	25.1±1.20*	−23
Isoproterenol (μg/100 g/min)							
N: Control	13	118.5±2.22		20.7±0.90		46.7±2.28	−21
N: 0.01 μg	8	100.0±7.15*	−16	21.9±1.68	6	36.9±1.84*	−50
N: 0.03 μg	8	84.4±8.10*	−29	31.3±2.83*	51	23.4±3.83*	−49
N: 0.10 μg	8	86.9±7.96*	−27	29.6±2.31*	43	23.8±2.09*	−64
N: 0.30 μg	9	63.3±5.20*	−47	34.2±4.42*	65	16.7±2.45*	
Tu: Control	9	104.4±2.94		35.1±2.52		25.3±2.84	14
Tu: 0.01 μg	7	108.6±5.20	4	30.8±2.21	−12	28.8±1.76	−19
Tu: 0.03 μg	8	92.5±5.67	−11	37.5±2.41	7	20.5±1.98	−10
Tu: 0.10 μg	8	93.8±7.95	−10	36.1±4.63	3	22.7±3.09	−16
Tu: 0.30 μg	7	83.6±9.80*	−20	35.1±3.72	0	21.3±4.63	
Propranolol (mg/100 g i.v.)							
N: Control	30	116.5±1.65		23.7±0.71		40.4±1.40	
N: 0.20 mg	21	111.2±3.40	− 5	20.7±0.79*	−13	43.7±1.59	8
Tu: Control	27	107.8±2.55		27.1±0.76		32.4±1.20	
Tu: 0.20 mg	20	101.7±3.58	− 6	23.0±0.97*	−15	36.8±2.23	14

the cardiac output was measured with Evans blue dilution[4,5]. Blood flow in GC or in other tumors can be properly detected by accumulation of ^{86}Rb[5,6]. Interventions: a) Arterial blood pressure was lowered by bleeding to 70 or 40 mm Hg for 10–20 min; b) tourniquet shock was applied on both hind limbs for 2.5 h, determinations started 1.5 h after its release. Treatments: 1. Phenylephrine, 1.0 and 3.0 µg/100 g/min for 5 min i.v. 2. Phenoxybenzamine, 1 mg/100 g 3–4 h prior to the experiments i.v. 3. Isoproterenol, 0.01–0.03–0.10–0.30 µg/100 g/min for 5 min i.v. 4. Propranolol, 0.2 mg/100 g i.v. 20 min before the experiments. Differences were evaluated by Student's t-test.

Results and discussion. According to our previous experiments[5], parallel to the increase of GC, characteristic alterations in the systemic circulation of rats can be found: cardiac index progressively increased, arterial blood pressure, TPR and vascular resistance in different organs decreased. Circulatory adaptation of GC bearing rats during haemorrhagic hypotension or tourniquet does not differ essentially from that in the normal rats table. Phenylephrine in a larger dose caused a greater increase in TPR and vascular resistance in the kidney, intestine, skin and carcass in the GC group than in the control rats. On the contrary, vasodilation caused by isoproterenol was observed only in normal rats but not in GC ones. Increased sensitivity to alfa-adrenergic stimulation and a decreased one to beta agonists can be explained on the basis of the general vasodilation found in GC rats[5].

In response to circulatory adaption, alfa or beta stimulation or blockade, the vascular bed of the GC showed a uniform response pattern: vasoconstriction i.e. increase in resistance. Vasoconstriction was generally higher in the GC than in the organs. The resistance vessels of the GC, like the vessels of other tumor types[7,8], seem to be extremely sensitive to circulating vasoactive agents.

It is clear that there are qualitative and quantitative differ-

Regional resistances (10^4 dyn · sec · cm^{-5})													
Brain	Δ%	Heart	Δ%	Kidney	Δ%	Gut	Δ%	Skin	Δ%	Carcass	Δ%	Tumor	Δ%
33.6±1.42		9.5±0.41		2.6±0.11		11.8±0.36		82.5±3.55		58.1±1.82			
36.0±3.35	7	9.6±0.67	1	3.6±0.25*	40	14.2±0.78*	20	117.0±6.61*	42	69.8±3.87*	20		
27.8±2.42*	−17	7.3±0.36*	−23	3.8±0.18*	48	12.5±0.57	6	103.0±5.36*	25	60.8±2.40	4		
27.9±1.49		6.6±0.28		2.2±0.10		10.5±0.68		47.0±2.20		43.3±2.23		45.6± 3.07	
24.7±1.13	−12	7.9±0.36*	21	3.2±0.17*	44	13.0±0.92*	24	83.1±5.80*	77	54.7±2.92*	26	114.2±11.00*	150
19.3±0.73*	−31	6.0±0.23	−9	3.2±0.15*	43	9.7±0.46	−8	76.9±3.80*	64	42,4±1.65	−2	167.2±18.00*	267
31.9±3.46		7.0±0.66		2.5±0.15		11.3±0.68		68.6±4.39		57.3±3.59			
35.8±3.67	12	7.3±0.74	4	4.3±0.34*	72	15.7±1.26*	40	121.9±9.97*	78	86.1±8.61*	50		
23.7±2.61		5.0±0.54		1.9±0.15		7.3±0.74		43.2±3.70		39.6±3.49		42.4± 4.42	
31.2±2.51*	32	8.2±0.86*	64	3.7±0.20*	95	10.9±1.03*	49	99.8±8.89*	131	61.5±5.73*	55	129.9±17.12*	206
45.5±3.67		8.1±0.58		3.2±0.17		17.8±2.08		88.6±3.99		72.6±3.78			
45.1±3.18	−1	8.7±1.43	7	3.3±0.32	4	18.3±2.49	3	106.9±18.90	21	90.2±8.21*	24		
40.4±2.99	−11	6.5±0.36*	−20	3.7±0.52	16	19.8±2.18	11	110.8±13.14	25	95.2±9.69*	31		
29.2±4.81		5.9±0.52		1.9±0.25		8.6±0.90		43.6±8.30		37.9±4.44		34.3± 3.33	
29.9±1.95	2	6.6±0.84	12	3.4±0.53*	72	13.2±1.93*	54	58.2±4.93	33	64.0±9.12*	69	70.8±14.93*	106
23.3±2.78	−20	4.7±0.33	−20	2.8±0.25*	44	13.2±2.03*	54	72.8±7.72*	67	58.9±5.59*	55	83.9±15.40*	146
31.5±1.51		8.6±0.33		2.8±0.11		14.7±0.52		77.9±4.02		61.0±2.25			
25.3±1.22*	−20	6.4±0.48*	−25	3.0±0.19	8	13.1±0.68	−11	69.7±4.63	−10	36.3±2.09*	−40		
25.9±1.16		6.6±0.27		2.4±0.15		11.7±0.52		53.8±2.52		47.2±2.08		47.3± 2.16	
20.9±1.58*	−19	5.0±0.33*	−23	2.6±0.13	8	8.8±0.57*	−25	44.8±2.60*	−17	30.5±1.72*	−35	58.2± 3.59*	23
45.5±3.67		8.1±0.58		3.2±0.17		17.8±2.08		88.6±3.99		72.7±3.78			
48.6±5.92*	7	6.2±0.31*	−24	2.6±0.09*	−19	12.9±0.34*	−28	73.0±3.61*	−18	56.3±4.18	−23		
31.5±4.56*	−31	3.8±0.64*	−53	2.0±0.20*	−37	9.8±1.54*	−45	56.0±7.34*	−37	30.2±5.87*	−58		
29.2±1.77*	−36	3.0±0.26*	−63	2.9±0.48	−9	9.1±1.00*	−49	57.1±5.24*	−36	31.3±2.93*	−57		
22.9±2.97*	−50	3.0±0.53*	−64	2.1±0.27*	−34	6.0±1.09*		45.4±6.80*	−49	22.3±3.59*	−69		
29.2±4.81		5.9±0.52		2.0±0.25		8.6±0.90		43.6±8.30		37.9±4.44		34.3± 3.33	
30.7±1.97	5	5.5±0.54	−7	2.3±0.21	20	10.0±0.68	16	52.4±6.76	20	40.0±2.72	6	49.2± 4.68*	41
21.0±1.87	−28	4.6±0.66	−22	1.8±0.18	−8	7.8±0.84	−9	35.6±3.76	−18	26.0±3.22*	−31	43.0± 6.37	25
23.4±2.66	−20	4.3±0.74	−28	2.0±0.19	3	8.7±1.53	1	41.7±4.59	−4	29.1±5.08	−23	47.1± 4.86*	37
22.5±4.20	−23	4.4±1.19	−26	2.0±0.28	4	6.9±1.75	−19	39.0±6.89	−11	29.6±8.01	−22	45.3± 4.41	32
31.5±1.51		8.6±0.33		2.8±0.11		14.7±0.52		77.9±4.02		61.0±2.25			
29.5±1.37	−6	10.6±0.45*	24	3.1±0.11	11	15.5±0.76	5	88.4±4.59	13	64.8±2.91	6		
25.9±1.16		6.6±0.27		2.4±0.15		11.7±0.52		53.8±2.52		47.2±2.08		47.3± 2.16	
24.4±1.91	−6	9.6±0.72*	46	2.7±0.16	12	13.9±1.56	19	57.6±5.03	7	50.8±3.15	8	71.3± 5.61*	51

Effect of sympathetic reflex adaptation, alfa- and beta-agonists or blockers on systemic circulation and on regional vascular resistances of normal and Guérin carcinoma implanted rats (mean ± SEM). N: normal groups, Tu: GC implanted groups, TPR: total peripheral resistance, n: number of rats, %: differences from control in percent, * difference from control, $p < 0.05$.

ences between the vascular reactions observed in the GC and in the organs. Supposing that the resistance vessels of the tumor have a low alfa constrictor and a significant beta dilator tone as compared to the organs, one would expect vasoconstriction provoked either reflexly or by phenylephrine or propranolol. It is possible that a secondary so called passive vasoconstriction could ensue following decrease in the arterial blood pressure during phenoxybenzamine or isoproterenol. The peculiar effect of isoproterenol in larger dose - no change in arterial pressure accompanied by an increase in the resistance of tumor vessels - cannot be explained even on the basis of the previous assumptions. Differences in vascular reactions of the organs and tumors might have some practical implications.

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Nuclear localization of aldosterone in rat brain cells assessed by autoradiography[1]

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Summary. Autoradiographic studies with ^{3}H aldosterone demonstrate nuclear concentration of hormone in neurons of the hippocampus, septum, allocortical regions and brain stem reticular formation and motor nuclei of cranial nerves and in the meninges. The results suggest that mineralocorticoids have wide ranging effects on different parts of the central nervous system.

It is now well established that cell nuclei of the central nervous system are capable of binding steroid hormones and that the sites of localization vary, depending on the molecular structure of the steroid[2,3]. 2 examples may be cited. 1. Dihydrotestosterone, an androgenic metabolite of testosterone incapable of aromatizing to estradiol, binds to nuclei of motor neurons in contrast to estradiol for which sensory neurons are target sites[2,4,5]. 2. Nuclear binding of androgen and estradiol to cells contained in the hippocampal formation, while distinct, is less pronounced than the binding to cell nuclei of specific areas in the hypothalamus[6,7]; in contrast, corticosterone, an adrenal steroid hormone classified as a glucocorticoid because it primarily effects carbohydrate metabolism, localizes in cell nuclei of the hippocampal formation, but no such nuclear localization within any of the cell aggregates of the hypothalamus has as yet become evident by radioautographic techniques[2,8,9]. We have studied the nuclear localization of aldosterone, the most potent representative of the 2nd group of adrenocortical steroid hormones, classified as mineralocorticoids because they alter electrolyte and water balance and conclude that it also has a characteristic distribution pattern, differing from that of estradiol but overlapping in part with that of dihydrotestosterone and resembling that of corticosterone, although with aldosterone a more intense localization in rudimentary as compared to postcommissural hippocampal structures and a marked concentration in cell nuclei of the arachnoid are noted.

Materials and methods. 5 weanling female Wistar rats were adrenalectomized and maintained on 0.9% saline and food *ad libitum* for 3 days prior to i.v. administration (1 µg/100 g b.wt) of 1, 2, 6, 7-^{3}H aldosterone (N.E.N., sp. act. 90 Ci/mmole). 2 animals were injected with radioinert aldosterone (100 µg/100 g b.wt) 5 min before administration of the tritiated compound. 1 h after injection of radioactive steroid the rats were decapitated and the brains frozen in liquid propane[10]. Sections of 4 µm were thaw-mounted onto slides coated with photographic emulsion, Kodak NTB 3, then exposed for 2 months prior to development in Kodak D19 and staining with methylgreen pyronin. The relative concentrations of radioactive material in

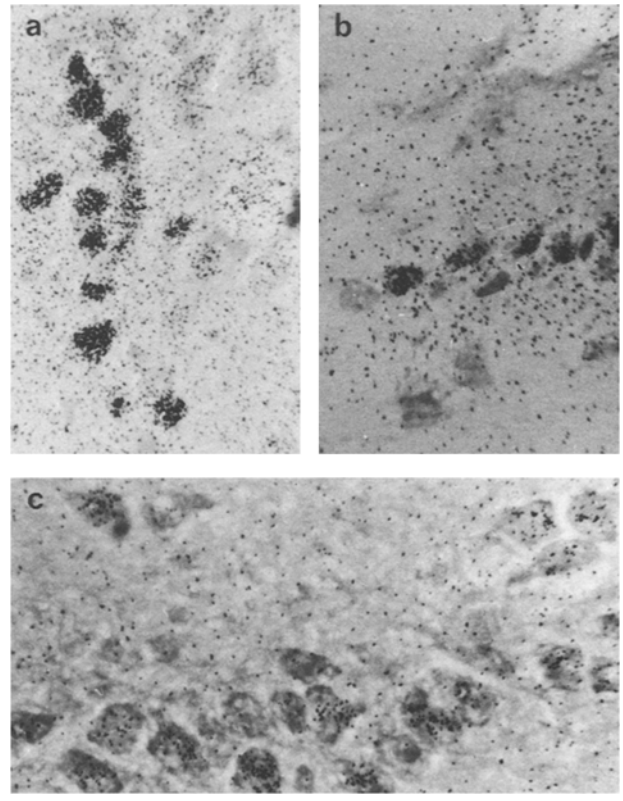

Fig. 1. Autoradiogram showing nuclear localization of radioactivity, after i.v. injection of tritiated aldosterone, in neurons of the hippocampus anterior (a), indusium griseum (b), and postcommissural hippocampus, area CA 1 (c). Exposure time 60 days, magnification × 560.