CHANGES IN SYSTEMIC ARTERIAL PRESSURE IN TUMOR-BEARING ANIMALS INDUCED BY HYPERTENSIVE AGENTS

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In individuals with tumors an increasing reduction in the intensity of the local blood flow (ILBF) is observed at a distance from the tumor, and has been demonstrated in relation to organs and tissues such as the liver, skeletal muscles, ciliary body of the eye, skin, mammary glands, concha auriculae, the ocular part of the conjuctiva, kidney, etc. [1, 2, 4, 7, 8, 12, 13, 15]. However, the mechanisms of this generalized fall of ILBF in tumor-bearing animals require further research. The problem arises of the state of the central hemodynamics and, in particular, the systemic arterial pressure (SAP), for as we know a close connection exists between SAP and ILBF. The level of SAP in individuals with tumors is not completely clear. Some workers have observed hypotension in cancer patients, especially in the late stages of development of the disease [3, 11]; according to others, SAP is only very slightly reduced in patients with tumors [6], or is completely unchanged [9]. The study of SAP and its changes during tumor growth under the influence of various procedures is interesting also because many workers have stated that blood pressure changes in response to the action of certain vasoactive compounds, notably adrenalin (the adrenalin test), are paradoxical in character in tumor-bearers [10, 11]. The evolution of these inappropriate responses of SAP at different stages of development of the neoplastic process, as well as their immediate mechanisms, likewise remain unexplained.

The aim of this investigation was to study SAP in tumor-bearing animals during growth of a neoplasm and under the influence of pressor substances: adrenalin and angiotensin. To determine correlation between the total peripheral resistance (TPR) and changes in SAP, the state of the lumen of the resistive arteries of the animals was studied at the same stages of tumor progression.

EXPERIMENTAL METHOD

Experiments were carried out on mature mice of a mixed population and of pure lines (BALB/c and CBA), anesthesized with urethane (subcutaneously, 1.3 g/kg body weight). SAP was measured in the common carotid artery in the upper part of the neck by means of a thin polyethylene catheter, connected to a Mingograf-34 electromanometer (Elema, West Germany). SAP was determined under normal conditions and on the 7th-9th and 14th-16th days after subcutaneous transplantation of the tumor (Ehrlich's carcinoma) into the region of the left thigh. At later (terminal) stages of tumor growth SAP could not be measured, for the animals died as a result of experimental manipulations. In all cases the level of SAP was judged from the mean arterial pressure. Material for transplantation (ascites fluid) was always taken in the same volume (0.2 ml). Adrenalin and angiotensin were injected intramuscularly in a dose of 0.4 mg/kg. The maximal response took place at the 2nd minute after injection. Mean values were deduced from maximal values of the parameters. The diameter of the arterioles was measured in the mammary glands, mesentery, and skeletal muscles (quadriceps femoris muscle) after removal of the overlying skin, biomicroscopically by means of a TM-1-television capillaroscope, by determination of its value on the screen of a video amplifier, using a special grid or ruler. The diameter of the arterioles also was measured on photographic nega-

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TABLE 1. Diameter of Arterioles of Various Organs of BALB/c Mice under Normal Conditions and at Various Times after Transplantation of Ehrlich's Carcinoma

Statistical parameter	Diameter of arterioles, μ								
	skeletal muscle			mammary glands			mesentery		
	normal cond.	7th-9th day after transplan.	14th-16th day after transplan.	normal cond.	7th-9th day after transplan.	14th-16th day after transplan.	normal cond.	7th-9th day after transplan.	14th-16th day after transplan.
	(n=30)			(n=30)			(n=45)		
$M \pm m$	20,1±0,5	23,8±0,6	23,2±0,5	20,5±0,9	24,4±0,5	23,0±1,2	20,8±0,4	24,0±0,4	22,0±0,4
$\pm\sigma$	2,86	3,55	2,61	4,67	2,82	3,52	2,89	2,87	2,87
	$t=4,73$	$p<0,001$	—	$t=3,91$	$p<0,001$	—	$t=5,71$	$p<0,001$	—
	$t=4,38$	—	$p<0,001$	$t=1,7$	—	$p<0,05$	$t=2,14$	—	$p<0,05$

Legend. n) Number of animals.

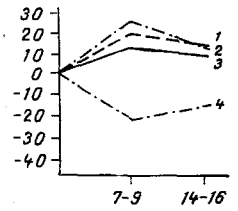

Fig. 1. Changes in lumen of resistive arteries (in %) of skeletal muscles (1), mammary glands (2), mesentery (3), and SAP (4) in tumor-bearing mice (BALB/c) at different stages of tumor development. Abscissa, time after transplantation (in days).

tives, obtained from the screen of the video amplifier by transfer of the image by means of a photographic enlarger on to paper ruled with squares of a definite scale. The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

SAP of healthy BALB/c mice was 14.7 ±0.32 kPa (110 ± 2.4 mm Hg), but on the 7th-9th day after transplantation of the tumor the mean SAP fell to 11.8 ± 0.61 kPa (88± 4.6 mm Hg, $p < 0.01$). By the 14th-16th day after transplantation of the tumor SAP rose to 12.7 ± 0.5 kPa (95 ± 4.0 mm Hg), which, however, can be regarded only as a tendency to rise ($p > 0.1$).

What causes the fall of SAP in tumor-bearing animals? It is clear that there are two possibilities to consider initially: reduction of the cardiac output and lowering of TPR. The first of these evidently not only does not decrease in the presence of tumor growth, but actually increases [14]. Meanwhile there are indications [9, 14] that in malignant disease peripheral dilatation with a fall of TPR is present, although admittedly, the evidence is more indirect in character and cannot be recorded objectively. Our observations showed that the lumen of the resistive arteries in organs such as the mammary glands, mesentery, and skeletal muscles, increases in size during tumor growth (mice of a mixed population and of the BALB/c and CBA lines) (Table 1), and, moreover, the increase is synchronized. Meanwhile the peak of the dilatation curves coincided with the peak of the pressure drop curve, but apparently in the opposite direction (Fig. 1). This high degree of correlation is evidence that the time course of the change in SAP is directly dependent on that of TPR.

Under the influence of adrenalin, in the healthy mice the mean SAP increased to 17.6 ± 0.7 kPa (132 ± 5.3 mm Hg; $p < 0.01$). In the tumor-bearing mice on the 7th-9th day after transplantation of the tumor adrenalin caused a distinctly opposite response: a fall of SAP to 8.1 ± 0.9 kPa (61± 6.6 mm Hg; $p < 0.01$), but on the 14th-16th day after transplantation, injection of adrenalin caused virtually no change in SAP compared with the background level in normal animals.

We can now begin to understand the intimate mechanisms of changes in SAP in tumor-bearing animals treated and not treated with adrenalin: a previous [1, 5] pharmacologic analysis of responses of small arteries in the mesentery of tumor-bearing rats to adrenalin showed

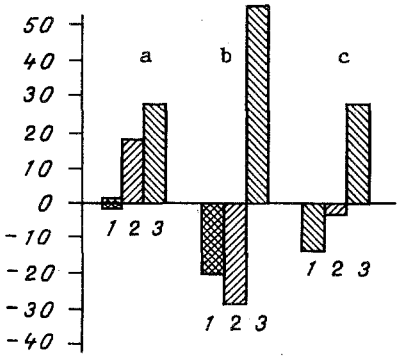

Fig. 2. Changes (in %) in SAP of intact mice and mice with tumors (BALB/c) at different stages of tumor development, untreated (1) and treated with adrenalin (2) and angiotensin (3). a) SAP in intact mice, b) 7th-9th day after tumor transplantation, c) 14th-16th day after tumor transplantation.

that in the initial period of tumor growth the function of the predominantly vascular α-adrenoreceptors is sharply depressed (dilatation of resistive arteries, fall of TPR, fall of SAP, reversed response to adrenalin), to which is added later exhaustion of β-receptor function (a tendency toward normalization of the changes mentioned above). A similar picture can be observed in the mammary glands and skeletal muscles. This steady diminution of the sensitivity of the vascular adrenoreceptors in the ciliary body of tumor-bearing rabbits was described previously [5].

The importance of this depression of adrenoreceptor function in the observations described above is confirmed by experiments with angiotensin. In healthy mice angiotensin increased SAP to 18.4 ±0.6 kPa (138 ± 4.2 mm Hg; $p < 0.01$). By the 7th-9th day after transplantation not only was the response preserved, but it was actually intensified (arteries dilated as a result of loss of α-receptor function give a hyper-reaction to angiotensin). On the 14th-16th day after transplantation SAP also rose sharply, although by a lesser degree than at the previous time. The main conclusion which follows from these data and which is of particular interest in connection with our own observations is that changes in vascular tone in tumor-bearers are connected with disturbance of the function of vascular adrenoreceptor structures, and not with depression of the contractile properties of the myocytes. The particular features of changes in SAP in tumor-bearing animals treated with adrenalin or angiotensin, and untreated, are shown in Fig. 2.

Thus the lowering of ILBF at a distance from the tumor, that is characteristic of neoplastic disease, is connected primarily, especially at the beginning of tumor growth, with a fall of SAP, which must give rise to a decrease in the longitudinal pressure gradient and the linear velocity of the blood flow in the system of the regional circulation and microcirculation. At later stages of tumor progression the SAP lowering factor begins to play a steadily diminishing role, or SAP rises a little whereas ILBF continues to fall steadily down to very low values. Consequently, other mechanisms are brought into play in this case [4, 8]. It will also be evident that the trend of changes in SAP in tumor-bearing animals reflects the character and sequence of changes in sensitivity of the vascular α- and β-receptors, whose causes are still a matter for conjecture.

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MECHANISMS OF DEVELOPMENT OF THIORIDAZINE RETINOPATHY

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KEY WORDS: retina; thioridazine; lipid peroxidation.

Several drugs (amiodarone, gentamicin, perhexiline, deferoxamine), while differing in their therapeutic action, may have side effects on the retina. This list of drugs also includes others widely used in clinical practice: the antimalarial and antirheumatoid preparation chloroquine and the psychotropic drug thioridazine (Melleril, Sonapax) which, on long-term administration gives rise to retinopathy in man [5, 7, 9, 11]. Despite much research into the study of chloroquine and thioridazine retinopathy, the mechanism of development of these pathological processes is not yet clear. The writers' previous ultrastructural investigations of degenerative processes in the retina [2, 10], reproduced by injection of chloroquine and thioridazine, showed that under the influence of these drugs the most damage is sustained by the outer segment (OS) of the photoreceptors, which are extremely sensitive to lipid peroxidation (LPO) due to their high content of polyunsaturated fatty acids. Considering the existing view that one of the leading mechanisms of destruction of photoreceptor membranes is LPO [4], it was natural to suggest that the preparation may have a damaging action on the retina through a mechanism of peroxidation. However, in relation to chloroquine, we showed [3] that LPO is not the initiating mechanism in the development of the retinopathy induced by this drug. As regards thioridazine, no definite information on the effect of this drug on LPO processes could be found in the literature.

The aim of this investigation was to study the effect of thioridazine on LPO processes in the retina of experimental animals. Comparative electron-microscopic, electrophysiological, and biochemical investigations were carried out on the retina in vivo (rats and rabbits) and in vitro (on model systems).

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