Jpn. J. Cancer Res. 85, 556–562, May 1994

Effects of Intravenous Infusion of Dopamine on Tumor Blood Flow in Rat Subcutis

Shigeru Tanda,[1] Katsuyoshi Hori, Sachiko Saito, Qiu-Hang Zhang, Hao-Chuan Li and Maroh Suzuki

Department of Tumor Microcirculation, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980

To determine the effects of intravenous administration of dopamine hydrochloride (DA) on tumor blood flow (TBF), we measured the blood flow of normal subcutaneous tissue and subcutaneous tumor (LY-80, a variant of Yoshida sarcoma) in enflurane-anesthetized male Donryu rats using a hydrogen clearance method. Measurements were made before and during intravenous infusion of DA at a rate of 5 μg/kg/min, while recording the mean arterial blood pressure of the rats. Under mild hypertension induced by DA, the blood flow of normal subcutis decreased and TBF increased significantly. SCH-23390, an antagonist of the DA_1 receptor, inhibited the enhancement of TBF by DA; while domperidone, an antagonist of the DA_2 receptor, did not modify the effects of DA. In experimental chemotherapy against the tumor using adriamycin (ADM) 5 mg/kg i.v., only the combination of DA and ADM significantly inhibited the tumor growth. Moreover, DA reduced the weight loss caused by ADM. These results indicate that DA could have a role in increasing TBF and possibly enhance drug delivery to tumors. Moreover, it appears that the DA_1 receptor contributes, at least in part, to the enhanced blood flow in rat subcutaneous tumor following DA administration.

Key words: Arterial blood pressure — Hydrogen clearance method — Doxorubicin — Tumor perfusion — Dopaminergic receptor

Tumor blood flow (TBF) plays an important role in tumor pathophysiology, influencing both the diagnosis and therapy of cancer.[1,2] Many researchers have tried to modify TBF with pharmacological agents; some catecholamines (noradrenaline, adrenaline and isoproterenol) have been examined extensively, and are known to decrease TBF in general.[3,4] On the contrary, a vasoactive peptide, angiotensin II (AII), has been shown in some studies to increase TBF.[5–8] It has been used in a variety of applications in clinical oncology.[9–12] In particular, "induced hypertension chemotherapy" with intravenously infused AII has achieved successful results experimentally and clinically for more than 10 years.[5,10,13,14] Because AII improves TBF as a secondary consequence of its constriction of normal vessels,[6,15,16] it is important to establish if other vasoconstrictive agents are capable of increasing TBF effectively and safely. The endogenous catecholamine, dopamine (DA), is a potent vasoactive drug used for therapy of cardiogenic and hypovolemic shock in clinical medicine, and some work has been done on applications in oncology.[17–19] There is, however, no report discussing the effects of DA on TBF except following intra-arterial administration.[20,21]

The purpose of the present study was to evaluate the effects of intravenously administered DA on TBF. Because TBF shows temporal and spatial heterogeneity even within an individual tumor,[22,23] repeated measurements in the same position are appropriate to estimate the pharmacological effects on TBF. To measure TBF we chose a hydrogen clearance method, that allows *in situ* determination of regional blood flow before and after drug administration.[24,25] Moreover, we extended our study to verify the influence of DA_1 and DA_2 receptor antagonists on the effects of DA by using SCH-23390 and domperidone, respectively. We also performed experimental chemotherapy to evaluate the therapeutic importance of DA infusion. If DA is capable of increasing TBF and drug delivery to tumor tissue effectively and safely, it could contribute to cancer diagnosis, chemotherapy, irradiation, antibody therapy, and photodynamic therapy.

MATERIALS AND METHODS

Animals and tumor Male Donryu rats (Charles River Japan, Inc., Yokohama), each weighing 350–450 g at inoculation, were used. They received a standard pellet diet and tap water *ad libitum*. The tumor used was LY-80 (established in 1966 by Dr. Hiroshi Satoh), a variant of Yoshida sarcoma, which has been maintained in our laboratory by successive intraperitoneal transplantation.

[1] To whom correspondence should be addressed. Present address: Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA.

Cells (2×10^6) in 0.1 ml were injected subcutaneously into the lower back of each rat. Solid tumors that grew to 2.5–5.0 cm in diameter at 11–21 days after the inoculation were examined. Tumors of such size did not seem to affect the activity of these mature rats, although some rats showed palpable inguinal lymph node metastasis. Almost all the experiments were performed in the "daytime" (10:00 a.m. to 4:00 p.m.).[26] The present study was approved by the Committee on Animal Experimentation of our Institute.

Chemicals Pentobarbital sodium and enflurane were purchased from Dainippon Pharmaceutical Co., Ltd., Osaka. Dopamine hydrochloride (DA, INOVAN™, 20 mg/ml DA in water with 0.5 mg/ml sodium pyrosulfite) and adriamycin (ADM) were purchased from Kyowa Hakko Kogyo Co., Ltd., Tokyo. SCH-23390 and domperidone were purchased from Research Biochemicals Inc., Natick, MA. DA, ADM and SCH-23390 were made up to a volume of 5 mg/ml, 10 mg/ml and 0.5 mg/ml, respectively, with physiological saline just before the experiment. Domperidone was dissolved in lactic acid and made up to volume with physiological saline to 0.6 mg/ml just before the experiment. Because the vehicle of domperidone was very acidic, we preferred subcutaneous injection to intravenous injection, after confirming that subcutaneous injection of the vehicle did not affect mean arterial blood pressure (MABP) or TBF. Rats were given continuous infusion via a tail vein by an infusion pump (Type 235, Atom Co., Tokyo). The doses and concentrations were determined on the basis of preliminary experiments.

Blood pressure monitoring The Donryu rats (350–500 g at measurement) were anesthetized with pentobarbital sodium (25 mg/kg, subcutaneously injected and supplemented as required) and enflurane (0.8–1.0% in the inhaled air at 1.0 liter/min) and placed on a heated stage at 34°C. The concentration of enflurane was maintained at a constant level by an anesthetic apparatus for small animals designed in our laboratory.[23] The MABP was measured with a pressure transducer (TNF-R, Spectramed Medical Products, Singapore) connected to a cannula inserted into the right femoral artery.[23] During cannulation, the rat was anesthetized with ethyl ether.

Measurement of tissue blood flow A detailed description of our method, modified from that of Aukland *et al.*[27] has appeared.[26,28] In brief, after saturation of the tissue with hydrogen following the inhalation of 9% hydrogen in the inhaled air (at 1.0 liter/min), the tissue blood flow (in ml/min per 100 g tissue) was calculated from the clearance curve. In the present research, the value reflected the average flow over 2–3 min. Two electrodes (UHE-201C, Unique Medical Co., Tokyo), 0.08 mm in diameter, were inserted into the normal subcutis in normal rats or into one tumor at least 2 cm apart.

Effects of 5 μg/kg/min DA i.v. on blood flow in the normal subcutis In ten rats without tumor, MABP and tissue blood flow of the normal subcutis were measured before infusion and at 2 and 15 min after the beginning of the increase of MABP with DA intravenous infusion at a rate of 5 μg/kg/min (0.06 ml/kg/h). Infusion of physiological saline at a rate of 0.06 ml/kg/h did not affect MABP or subcutaneous blood flow for over one hour in preliminary experiments.

Effects of 5 μg/kg/min DA i.v. on TBF Continuous infusion of DA at a rate of 5 μg/kg/min was performed; MABP and TBF were measured before the administration and at 2 and 15 min after the beginning of the increase of MABP with DA infusion. Ten rats were used.

Effect of DA_1 receptor blockage on MABP and TBF Ten rats were used to determine the influence of pretreatment with SCH-23390 on the effects of DA. After measuring the baseline MABP and TBF, SCH-23390 was administered as a bolus of 50 μg/kg (0.1 ml/kg) followed by an infusion at a dose of 10 μg/kg/min (1.2 ml/kg/h) from the tail vein until the end of the experiment. At 15 min after the start of SCH-23390 infusion, MABP and TBF were measured to determine the effects of SCH-23390 alone on the values. After the measurement, DA infusion started at a rate of 5 μg/kg/min (0.06 ml/kg/h) from the other tail vein until the end of the experiment. When MABP reached a constant value with infusion of SCH-23390 and DA, MABP and TBF were measured to determine the influence of DA_1 receptor blockade on the effects of DA. A bolus injection of 0.1 ml/kg and infusion at the rate of 1.26 ml/kg/h of physiological saline did not affect MABP or TBF in preliminary experiments.

Effect of DA_2 receptor blockage on MABP and TBF Ten rats were used to determine the influence of pretreatment with domperidone on the effects of DA. After the measurement of baseline MABP and TBF, domperidone solution of 0.3 mg/kg (0.5 ml/kg) was subcutaneously injected into the upper back of the rat. At 15 min after this injection, MABP and TBF were measured to determine the effects of domperidone alone. After the measurement, DA infusion began at a rate of 5 μg/kg/min from the tail vein until the termination of the experiment. When the MABP stabilized, MABP and TBF were investigated. In preliminary experiments, the dose of domperidone completely antagonized the hypotensive effects of quinpirole (30 μg/kg i.v.), an agonist of the DA_2 receptor.

Experimental chemotherapy Nineteen rats with the tumor at the 12th day after inoculation were divided at random into three groups; a control group (n=5), an ADM alone group (n=7) and a DA plus ADM group (n=7). In the DA plus ADM group, rats were injected with 5 mg/kg ADM (0.5 ml/kg) into the tail vein over 3 min after MABP had stabilized with a DA infusion rate

of 5 mg/kg/min (0.06 ml/kg/h) ino the other tail vein under the anesthetic conditions mentioned above. Immediately after completion of ADM infusion, infusion of DA was stopped. Almost all these experiments ended within 10 min after the beginning of DA infusion. In the ADM alone group, the same dosage of ADM was given from the tail vein over 3 min, while saline was infused at a rate of 0.06 ml/kg/h for 10 min into the other tail vein under the same anesthetic conditions. In the control group, rats were given saline at the same rate for 10 min from the tail vein under the same anesthetic conditions. The "tumor size" (defined as the sum of the long axis and the short axis of the tumor) was measured with calipers. Tumor size and body weight of the rat were investigated every day for one week after the treatment. The initial value of tumor size and body weight were taken as unity in each rat; the treatment day was defined as day 0.

Data analysis Results concerning MABP, blood flow, tumor size, and body weight of the rat are expressed as means±standard deviations. Differences were evaluated by use of the Kruskal-Wallis test, followed by Scheffé's comparison for identifying significant factors as required. Probability levels of less than 5% ($P<0.05$) were considered significant in the present study. Data were analyzed with StatView for the Macintosh™ version 4.0 (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Effects of 5 μg/kg/min DA i.v. on blood flow in the normal subcutis MABP was increased significantly from the base line value of 106.7±8.1 mmHg to 132.9±8.7 and 125.0±9.4 mmHg at 2 and 15 min, respectively, after the start of MABP increase. Tissue blood flow in normal subcutis was significantly reduced with 5 μg/kg/min DA (n=20, $P<0.0001$) from 12.8±4.5 ml/min/100 g tissue to 6.9±2.3 and 7.9±2.7 ml/min/100 g tissue at 2 and 15 min.

Effects of 5 μg/kg/min DA i.v. on TBF MABP increased from 105.8±9.0 mmHg to 120.9±7.9 and 125.0±9.3 mmHg at 2 and 15 min (n=10, $P<0.0005$). TBF rose from 23.9±17.4 ml/min/100 g tissue to 35.7±21.6 and 46.0±27.4 ml/min/100 g tissue (n=20, $P<0.01$).

Effect of DA_1 receptor blockage on MABP and TBF Administration of agents increased MABP from the base line value of 102.3±10.0 to 101.8±10.8 mmHg with SCH-23390 alone and 153.3±17.1 mmHg with SCH-23390 plus DA (n=10, $P<0.0001$). TBF did not change significantly, being reduced from 14.5±6.1 to 11.4±5.4 and 10.6±7.4 ml/min/100 g tissue (n=20). Thus, SCH-23390 completely suppressed the increase in TBF caused by DA.

Effect of DA_2 receptor blockage on MABP and TBF Administration of domperidone increased MABP from the baseline value of 106.1±7.9 to 107.8±6.7 and 128.7±10.2 mmHg, with domperidone alone and with domperidone plus DA, respectively (n=10, $P=0.0001$). There was no significant difference between the baseline value and the domperidone alone value, but DA increased MABP significantly ($P<0.0001$) even under DA_2 receptor blockade by domperidone. TBF changed from 18.4±13.6 to 14.6±9.2 and 31.8±20.9 ml/min/100 g tissue (n=20, $P<0.005$). Thus, the blockade of DA_2 receptor did not alter the effects of DA on MABP or TBF in the present system.

Experimental chemotherapy Concerning tumor size (Fig. 1), the group with DA plus ADM showed the best results among the three groups through days 2 to 7. At day 2, tumor size differed significantly from that of the control group ($P<0.05$). On the other hand, administration of ADM alone did not affect the growth of the tumor. Regarding body weight (Fig. 2), ADM administration had significant effects from days 2 to 6. Moreover, there was a significant difference between the ADM alone group and the DA plus ADM group at day 3 and day 4. That is, DA reduced the loss of weight by ADM. In preliminary experiments, administration of DA alone (5 μg/kg/min for 10 min) did not affect either tumor growth or the body weight of the rats.

DISCUSSION

Doses of 5 μg/kg/min of DA increased TBF twofold relative to the initial flow. This is compatible with our previous results using the same system (subcutaneous

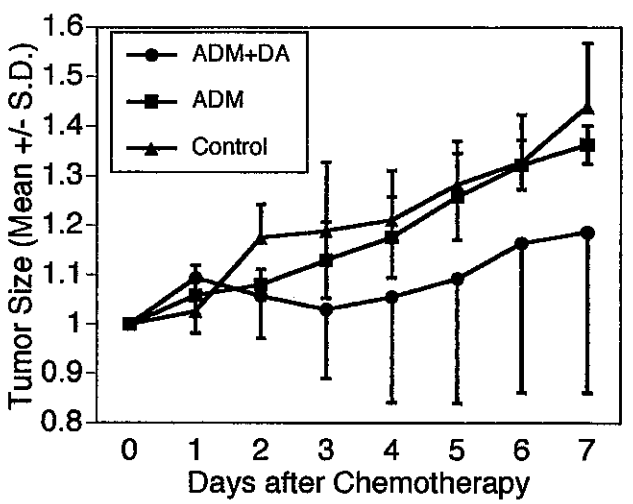

Fig. 1. Changes in tumor growth after ADM (adriamycin) treatment 5 mg/kg with or without DA 5 μg/kg/min. Each point represents the mean±standard deviation (n=7 in ADM+DA and ADM alone, n=5 in control).

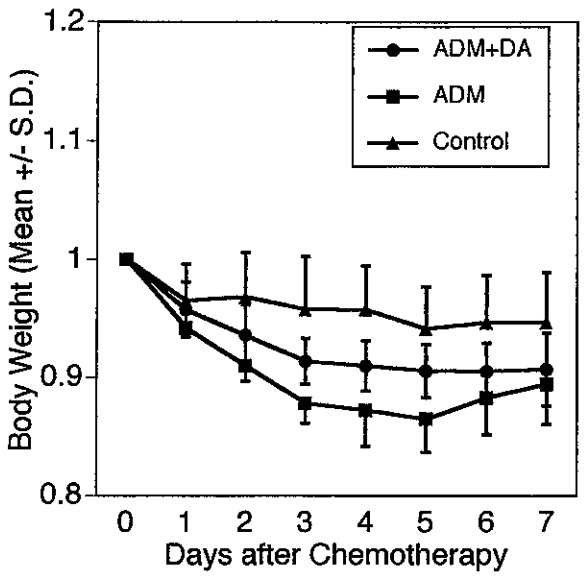

Fig. 2. Changes in body weight of the rat after ADM treatment with or without DA. Each point represents the mean± standard deviation (n=7 in ADM+DA and ADM alone, n=5 in control).

transplanted LY-80 tumor and a hydrogen clearance method) under AII-induced hypertension.[23, 26, 29] Therefore, the present study suggests that DA has potential as a tumor blood flow modifier[30] in the field of diagnosis and treatment of solid tumors.

The received wisdom is that DA is a precursor of catecholamine and should be classified as a sympathomimetic agent.[31] Adrenergic stimulants, however, constrict arterial vessels[16] and do not increase the blood flow into tumor tissue.[32] What is the reason for the difference in the effects on TBF between DA and other catecholamines? In considering this question, it is important to note that DA has specific receptors, DA_1 and DA_2, in the peripheral tissue[33]; accordingly, we performed an antagonist study.

The dose (0.3 mg/kg) of domperidone used in the present study is comparable to the dose used in previous studies in the rat *in vivo*.[34, 35] In our preliminary experiments, the subcutaneous administration of domperidone at 0.3 mg/kg was able to antagonize the hypotensive effect of quinpirole, a selective DA_2 receptor agonist. Hence, the result shows that DA could increase TBF significantly even with DA_2 blockade. This indicates that DA_2 receptors contribute little or nothing to the increasing effect of DA on rat subcutaneous TBF. On the other hand, SCH-23390 is a selective DA_1 receptor antagonist; a dose of 50 μg/kg i.v. completely abolishes the hypotensive action of fenoldopam, a selective DA_1 receptor agonist.[36] Moreover, SCH-23390 (50 μg/kg i.v. bolus; 10 μg/kg/min i.v.) produces no significant hemodynamic effect by itself, but blocks the renal effect of DA (0.5 μg/kg/min i.v.).[37] Hence, the dose of SCH-23390 used in the present study sufficiently blocked peripheral DA_1 receptors, and the enhancement of TBF by DA was antagonized entirely by SCH-23390. TBF appears to be influenced by DA_1 receptors in the present system.

DA_1 receptor stimulation leads to vasodilation, especially in the renal, mesenteric, and hindquarter vascular beds in the rat.[35] One hypothesis (intratumor receptor theory) is that DA_1 receptors are expressed specifically within the tumor and enhance TBF through their vasodilating function. An alternative hypothesis (extratumor receptor theory) is that β-stimulation by DA, at a dose of 5 μg/kg/min, increases cardiac output; moreover, α-adrenergic stimulation by DA and noradrenaline, that is, the immediate derivative of DA, might constrict normal vessels widely. Under such conditions, DA_1 stimulation could reduce vasoconstriction of arterial vessels larger than terminal arterioles and enhance blood flow into the tumor tissue. Of course, it remains to be determined where and how DA_1 receptors act in the vascular network around and within the tumor.

If the DA_1 receptor can actively modify TBF, the distribution of this receptor is important. Because the localization is dependent on the species and the organs, the effects of DA would be dependent on the species of the host and on the localization of the tumor. For example, an intra-aortic infusion of 150 μg/kg/min DA decreases the intrahepatic TBF by 30% with slightly decreased MABP in rabbits treated with pentobarbital 10–15 mg/kg i.v. and *d*-tubocurarine chloride 1 mg/kg i.m.[20] Needless to say, differences in anesthetic conditions, administration route, and infusion rate are important in the study of the effects of vasoactive agents on the systemic circulatory system and tumor microcirculation.[3] Jonsson *et al.* stated that an infusion of 95–120 μg/kg/min DA into the carotid artery increased MABP by 15–30 mmHg, but did not change TBF of subcutaneously transplanted prostatic adenocarcinoma in rats under 25 mg/kg i.p. pentobarbital.[21] Of course, the subcutaneously transplanted tumor is a very specific system.[38] Nevertheless, the first experiment showed that an increment of TBF under DA-induced hypertension was not due to the increase of blood supply to the subcutis where the tumor grew. Moreover, it has been shown that the subcutaneous system in the rat can predict changes of human TBF *in situ* with or without AII i.v.[39, 40] Therefore, we might expect an effect of DA on TBF in some human tumors. Before clinical application of DA for modification of TBF, *in situ* assessment of TBF before and during DA infusion should be done in the human body.

Fig. 1 shows that DA helped ADM to inhibit subcutaneous tumor growth in the rat. Wick reported that DA by itself has anti-tumor effects *in vitro* and *in vivo*. However, the dose (400–600 mg/kg i.p. everyday for 7 days in mice) of DA used in his study[17] was much larger than that used in our study. In preliminary experiments, DA at the dose used in the present study did not affect the tumor growth. Hence, DA might contribute to chemotherapy probably by increasing TBF and enhancing delivery of the antitumor agent to tumor tissue, as in the case of AII.[41]

DA has a vasodilating effect and increases blood flow in some organs, depending on the dose.[31, 35] It is possible that DA could increase toxicity in normal organs by enhancing delivery of anticancer agents and modifying their clearance from blood. However, some researchers have suspected that infusion of low-dose DA increases renal blood flow and diminished the renal toxicity of cisplatin, because decrement in renal blood flow and glomerular filtration rate is a significant factor in cisplatin-induced acute renal failure.[42] Nevertheless, an intravenous DA infusion (3–5 μg/kg/min for 25 h) does not influence the concentration of platinum in the kidney or in the subcutaneous tumor after cisplatin (7–12 mg/kg i.v.) in rats anesthetized with pentobarbital sodium (100 mg/kg i.p.).[18] Moreover, Umeki *et al.* reported that intravenous infusion of DA (3 μg/kg/min for 48 h) does not affect nephrotoxicity induced by cisplatin (80 mg/m^2 i.v.) in patients with lung cancer. They did not mention the therapeutic influence of DA.[19] Infusion of DA for a long time seems to enhance the washout of cisplatin from tumor tissue and blood, and so decreases the efficacy of DA as an enhancer of chemotherapy. We used the rat's body weight as an indicator of its systemic condition and the side-effects of ADM. Though the pharmacodynamic effects of DA on anticancer drugs need further investigation, DA reduced the toxicity of ADM in the present system (Fig. 2).

In conclusion, intravenous infusion of DA increased the blood flow in the rat subcutaneous tumor; DA_1 receptor plays a significant role in this effect. DA is worthy of consideration as a potential tumor perfusion enhancer in experimental and clinical oncology; other dopaminergic agents also deserve attention.

ACKNOWLEDGMENTS

We would like to thank Professor Keishi Abe, Professor Ryunosuke Kanamaru, Professor Tohru Takahashi, and Associate Professor Toshio Kudo, Tohoku University, for their critical comments; Ms. Hiroko Oikawa and Ms. Mika Sekishima for their secretarial assistance; and Mr. Takahiro Kawazoe and Mr. Tao Wu for their care of laboratory animals. This research was supported in part by Grants-in-Aid #01870102 and #04151024 from the Ministry of Education, Science and Culture of Japan.

(Received December 8, 1993/Accepted February 4, 1994)

REFERENCES

1) Jain, R. K. Determinants of tumor blood flow: a review. *Cancer Res.*, **48**, 2641–2658 (1988).
2) Vaupel, P., Kallinowski, F. and Okunieff, P. Blood flow, oxygen and nutrient supply, metabolic microenvironment of human tumors: a review. *Cancer Res.*, **49**, 6449–6465 (1989).
3) Jain, R. K. and Ward-Hartley, K. Tumor blood flow — characterization, modifications, and role in hyperthermia. *IEEE Trans. Sonics Ultrason.*, **31**, 504–526 (1984).
4) Jirtle, R. L. Chemical modification of tumour blood flow. *Int. J. Hyperthermia*, **4**, 355–371 (1988).
5) Suzuki, M., Hori, K., Abe, I., Saito, S. and Sato, H. A new approach to cancer chemotherapy: selective enhancement of tumor blood flow with angiotensin II. *J. Natl. Cancer Inst.*, **67**, 663–669 (1981).
6) Burton, M. A., Gray, B. N., Self, G. W., Heggie, J. C. and Townsend, P. S. Manipulation of experimental rat and rabbit liver tumor blood flow with angiotensin II. *Cancer Res.*, **45**, 5390–5393 (1985).
7) Trotter, M. J., Chaplin, D. J. and Olive, P. L. Effect of angiotensin-II on intermittent tumour blood flow and acute hypoxia in the murine SCCVII carcinoma. *Eur. J. Cancer*, **27**, 887–893 (1991).
8) Zlotecki, R. A., Boucher, Y., Lee, I., Baxter, L. T. and Jain, R. K. Effect of angiotensin II induced hypertension on tumor blood flow and interstitial fluid pressure. *Cancer Res.*, **53**, 2466–2468 (1993).
9) Ekelund, L. and Lunderquist, A. Pharmacoangiography with angiotensin. *Radiology*, **110**, 533–540 (1974).
10) Sato, H., Sato, K., Sato, Y., Asamura, M., Kanamaru, R., Sugiyama, Z., Kitahara, T., Mimata, Y., Wakui, A., Suzuki, M., Hori, K., Abe, I., Saito, S. and Sato, H. Induced hypertension chemotherapy of cancer patients by selective enhancement of drug delivery to tumor tissue with angiotensin II. *Sci. Rep. Res. Inst. Tohoku Univ. [Med.]*, **28**, 32–44 (1981).
11) Sasaki, Y., Imaoka, S., Hasegawa, Y., Nakano, S., Ishikawa, O., Ohigashi, H., Taniguchi, K., Koyama, H., Iwanaga, T. and Terasawa, T. Changes in distribution of hepatic blood flow induced by intra-arterial infusion of angiotensin II in human hepatic cancer. *Cancer*, **55**, 311–316 (1985).
12) Goldberg, J. A., Bradnam, M. S., Kerr, D. J., McKillop, J. H., Bessent, R. G., McArdle, C. S., Willmott, N. and

George, W. D. Single photon emission computed tomographic studies (SPECT) of hepatic arterial perfusion scintigraphy (HAPS) in patients with colorectal liver metastases: improved tumour targetting by microspheres with angiotensin II. *Nucl. Med. Commun.*, **8**, 1025–1032 (1987).
13) Sato, H., Wakui, A., Hoshi, M., Kurihara, M., Yokoyama, M. and Shimizu, H. Randomized controlled trial of induced hypertension chemotherapy (IHC) using angiotensin II human (TY-10721) in advanced gastric carcinoma (TY-10721 IHC Study Group report). *Jpn. J. Cancer Chemother.*, **18**, 451–460 (1991) (in Japanese).
14) Nakamura, M., Takahashi, T., Sato, H., Hoshi, M., Wakui, A. and Kanamaru, R. Histopathological evaluation on the effect of induced hypertension chemotherapy presurgically performed in patients with advanced carcinoma of the stomach. *Tohoku J. Exp. Med.*, **167**, 27–37 (1992).
15) Suzuki, M., Hori, K., Abe, I., Saito, S. and Sato, H. Functional characterization of the microcirculation in tumors. *Cancer Metastasis Rev.*, **3**, 115–126 (1984).
16) Hori, K., Zhang, Q.-H., Saito, S., Tanda, S., Li, H.-C. and Suzuki, M. Microvascular mechanisms of change in tumor blood flow due to angiotensin II, epinephrine, and methoxamine: a functional morphometric study. *Cancer Res.*, **53**, 5528–5534 (1993).
17) Wick, M. M. Levodopa and dopamine analogs: melanin precursors as antitumor agents in experimental human and murine leukemia. *Cancer Treat. Rep.*, **63**, 991–997 (1979).
18) Saitoh, S., Sakata, Y., Tsushima, K., Itoh, T., Sugimoto, N., Tamura, Y., Ogasawara, H., Narushima, S., Yamada, Y. and Yoshida, Y. Protective effect of dopamine against the nephrotoxicity of *cis*-diamminedichloroplatinum (II). *Hirosaki Med. J.*, **42**, 93–100 (1990).
19) Umeki, S., Yoshida, K. and Soejima, R. The use of dopamine to counter cisplatin nephrotoxicity. *Jpn. J. Cancer Clin.*, **38**, 461–465 (1992) (in Japanese).
20) Miyazaki, M. Intra-arterial infusion treatment for patients with malignant hepatic tumor — with special reference to hepatic pharmacokinetics and to combined use of vasoactive and antitumor drugs. *J. Jpn. Surg. Soc.*, **83**, 1295–1306 (1982) (in Japanese).
21) Jonsson, Ö., Widmark, A., Grankvist, K., Damber, J.-E. and Henriksson, R. Effects of clonidine-induced hypotension and dopamine-induced hypertension on blood flow in prostatic adenocarcinoma (Dunning R3327) and normal tissues. *Prostate*, **20**, 225–232 (1992).
22) Vaupel, P. Oxygenation of human tumors. *Strahlenther. Onkol.*, **166**, 377–386 (1990).
23) Hori, K., Suzuki, M., Tanda, S., Saito, S., Shinozaki, M. and Zhang, Q.-H. Fluctuations in tumor blood flow under normotension and the effect of angiotensin II-induced hypertension. *Jpn. J. Cancer Res.*, **82**, 1309–1316 (1991).
24) Suzuki, M., Hori, K., Abe, I., Saito, S. and Sato, H. Enhancement of chemotherapeutic effects by angiotensin-induced hypertension. *Jpn. J. Cancer Chemother.*, **8**, 673–680 (1981) (in Japanese).
25) Tvete, S., Elsayed, E. and Clausen, G. Effect of exogenous angiotensin-II on local blood flow in kidneys with neoplasm; experiments in the rat. *Acta Radiol. Oncol.*, **20**, 125–129 (1981).
26) Hori, K., Suzuki, M., Tanda, S., Saito, S., Shinozaki, M. and Zhang, Q.-H. Circadian variation of tumor blood flow in rat subcutaneous tumors and its alteration by angiotensin II-induced hypertension. *Cancer Res.*, **52**, 912–916 (1992).
27) Aukland, K., Bower, B. F. and Berliner, R. W. Measurement of local blood flow with hydrogen gas. *Circ. Res.*, **14**, 164–187 (1964).
28) Suzuki, M., Hori, K., Saito, S., Tanda, S., Abe, I., Sato, H. and Sato, H. Functional characteristics of tumor vessels: selective increase in tumor blood flow. *Sci. Rep. Res. Inst. Tohoku Univ. [Med.]*, **36**, 37–45 (1989).
29) Tanda, S., Hori, K., Saito, S., Shinozaki, M., Zhang, Q.-H. and Suzuki, M. Comparison of the effects of intravenously bolus-administered endothelin-1 and infused angiotensin II on the subcutaneous tumor blood flow in anesthetized rats. *Jpn. J. Cancer Res.*, **82**, 958–963 (1991).
30) Horsman, M. R., Chaplin, D. J. and Overgaard, J. The use of blood flow modifiers to improve the treatment response of solid tumors. *Radiother. Oncol.*, **20** (Suppl.), 47–52 (1991).
31) Goldberg, L. I. Cardiovascular and renal actions of dopamine: potential clinical applications. *Pharmacol. Rev.*, **24**, 1–29 (1972).
32) Li, Y., Hori, K., Saito, S., Tanda, S. and Suzuki, M. The effects of angiotensin II and other noradrenergic vasoconstrictors on the blood flow in Yoshida rat ascites hepatoma AH109A at same electrode position. *Jpn. J. Cancer Chemother.*, **17**, 548–553 (1990) (in Japanese).
33) Lokhandwala, M. F. and Hegde, S. S. Cardiovascular pharmacology of adrenergic and dopaminergic receptors: therapeutic significance in congestive heart failure. *Am. J. Med.*, **90** (Suppl. 5B), 2S–9S (1991).
34) Lefevre-Borg, F., Lorrain, J., Lechaire, J., Thiry, C., Lhoste, F., Hicks, P. E. and Cavero, I. Cardiovascular characterization of the DA_2 dopamine receptor agonist quinpirole in rats. *Fundam. Clin. Pharmacol.*, **1**, 179–200 (1987).
35) Van der Niepen, P., Dupont, A. G., Finne, E. and Six, R. O. Hypotensive and regional haemodynamic effects of fenoldopam and quinpirole in the anaesthetized rat. *J. Hypertens.*, **6**, S687–S689 (1988).
36) Sengupta, S. and Lokhandwala, M. F. Characterization of the hypotensive action of dopamine receptor agonists fenoldopam and quinpirole in anaesthetized rats. *J. Auton. Pharmacol.*, **5**, 289–294 (1985).
37) Hegde, S. S., Jadhav, A. L. and Lokhandwala, M. F. Role of kidney dopamine in the natriuretic response to volume expansion in rats. *Hypertension*, **13**, 828–834 (1989).
38) Hirst, D. G., Hirst, V. K., Shaffi, K. M., Prise, V. E. and

Joiner, B. The influence of vasoactive agents on the perfusion of tumours growing in three sites in the mouse. *Int. J. Radiat. Biol.*, **60**, 211–218 (1991).
39) Tomura, N., Saito, Y., Hirata, K., Matsudaira, N., Tamakawa, Y. and Kato, T. Tumor vascularity under angiotensin II-induced hypertension — angiographic observations. *Radiat. Med.*, **4**, 60–66 (1986).
40) Kudo, T., Abo, S., Itabashi, T., Watanabe, K., Onodera, K., Shimoma, N., Kawamura, Y., Hashimoto, M., Kato, T., Watanabe, K., Ikeda, T., Maeda, K. and Murakawa, Y. Continuous measurement of tumor blood flow under hypertension induced by angiotensin II: clinical studies with laser Doppler velocimetry. *Jpn. J. Cancer Chemother.*, **13**, 2549–2554 (1986) (in Japanese).
41) Abe, I., Hori, K., Saito, S., Tanda, S., Li, Y. and Suzuki, M. Increased intratumor concentration of fluorescein-isothiocyanate-labeled neocarzinostatin in rats under angiotensin-induced hypertension. *Jpn. J. Cancer Res.*, **79**, 874–879 (1988).
42) Winston, J. A. and Safirstein, R. Reduced renal blood flow in early cisplatin-induced acute renal failure in the rat. *Am. J. Physiol.*, **249**, F490–F496 (1985).