ROLE OF CATECHOLAMINES IN THE ANTITUMOR ACTION OF LEUKOEPHDIN AND QUERCETIN

S. M. Vermenichev, A. B. Elantsev, and O. K. Kabiev

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Development of a tumor (transplanted Pliss lymphosarcoma of rats) is accompanied by a decrease in the content of adrenalin and noradrenalin in the circulating blood. Leukoephdin and and quercetin (which possess vitamin P and antitumor properties under experimental conditions) increase the content of the hormones by 2-5.5 times and evidently stimulate the change from glycolysis to oxygen respiration by the tissues affected. A combination of leukoephdin, quercetin, and adrenalin gives a slight but statistically significant increase (up to 20%) in their antitumor action without any marked decrease in the gain in body weight of the animals. Ascorbic acid (as an adrenalin stabilizer) has no antitumor action and does not potentiate the effect of the other substances mentioned above. Adrenalin and noradrenalin themselves have weak antitumor activity.

The presence of an orthodihydroxybenzene group in the molecules of certain phenols obtained from plants gives them a structural resemblance to polyphenols and, in particular, to catecholamines of animal origin. The ability of flavonoids to slow the oxidation of adrenalin provided a basis [11, 12] for the hypothesis that the action of phenols is mediated through adrenalin.

The object of the present investigation was to study the effect of the vitamin P preparation leukoephdin and quercetin on the concentrations of adrenalin and noradrenalin in rat blood and on cytochrome oxidase activity in experiments in vivo. The antitumor properties of the catecholamines and their combined action with leukoephdin and quercetin also were investigated.

EXPERIMENTAL METHOD

Leukoephdin is a condensation product of leukopelargonidine and leukodelphinidine [7, 8] which possess vitamin P [7, 8] and antitumor [2, 4, 5] activity under experimental conditions.

TABLE 1. Effect of Leukoephdin and Quercetin on Blood Adrenalin and Noradrenalin Concentrations in Rats

Group of animals	Number of rats	Adrenalin	Noradrenalin
		in μg/g	
Intact	40	0,20±0,03	0,59±0,05
Rats with Pliss lymphosarcoma:			
control	40	0,14±0,04	0,28±0,03
leukoephdin	40	0,42±0,06	0,56±0,04
quercetin	25	0,78±0,02	0,55±0,013

The antitumor action of the preparations was tested on 318 noninbred albino rats and 377 mice with transplanted tumors: Pliss lymphosarcoma, sarcoma 45, sarcoma 180 (Crocker), and Ehrlich's solid tumor. Treatment began from the day of appearance of a probable tumor and continued for 10 days, when the animals were sacrificed. The preparations were injected intraperitoneally or given by mouth, as aqueous solutions (quercetin as a suspension) in the maximal tolerated and smaller doses.

The adrenalin and noradrenalin concentrations in the blood were determined in 40 intact rats and 105 rats with

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TABLE 2. Effect of Preparations on Growth of Transplanted Rat and Mouse Tumors

Preparations	Sessional dose (in mg/kg)	Total dose (in kg)	Inhibition of tumor growth (in percent)			
			sarcoma 45	pliss lympho-sarcoma	sarcoma 180 (Crocker)	Ehrlich's solid tumor
Adrenalin	0,5	5,0	0	10,6	16,3	9,7
	1,0	10,0	12,4	26,2	33,5	17,5
Noradrenalin	1,0	10,0	6,8	18,3	20,4	9,2
Leukoephdin	70	700	59,6	85,5	60,0	79,8
Leukoephdin + adrenalin	70	700	62,1	88,2	79,9	84,6
	1,0	10,0				
Quercetin	150	1 500	7,0	50,8	53,2	51,3
	300	3 000	—	20,6	28,6	16,3
Quercetin + adrenalin	150	1 500	—	57,7	68,2	55,8
	1,0	10,0				
Ascorbic acid	50	500	0	14,4	8,6	15,4
Leukoephdin + ascorbic acid	70	700		87,6	68,8	
	50	500	—			—

Notes: 1) mean results of two series of experiments are shown in the Table; 2) all preparations were injected intraperitoneally, except quercetin, in a total dose of 3000 mg/kg.

transplanted Pliss lymphosarcoma by Men'shikov's method [6] with a modified EF3N fluorometer. In view of the small quantity of blood available in rats, blood from several animals was taken for each analysis.

Cytomchrome oxidase activity was determined by the method of Cooperstein and Lasarov [10] in the tumor, liver, and spleen of 25 intact rats and rats with a transplanted Pliss lymphosarcoma (25 animals in each group: treated with leukoephdin and control).

These values were determined in the group of rats with Pliss lymphosarcoma treated with leukoephdin and quercetin on the 2nd day after the last administration of the preparations. Pliss lymphosarcoma was chosen as the tumor most sensitive to leukoanthocyanidins and, in particular to leukoephdin [2, 4, 5].

EXPERIMENTAL RESULTS

The results are given in Table 1. The blood levels of adrenalin and noradrenalin during tumor development were significantly reduced ($P < 0.05$). Treatment of the rats with Pliss lymphosarcoma by leukoephdin and quercetin led to an increase in the adrenalin level by 3 and 5.5 times respectively and a twofold increase in the noradrenalin level ($P < 0.001$). The adrenalin concentration was significantly higher than in intact rats ($P < 0.01$), while the noradrenalin concentration became equal to that in the animals of the control group (Table 1).

During development of the tumors a tendency was observed for the cytochrome oxidase activity to decrease in the liver and spleen tissues, but administration of leukoephdin caused it to increase slightly (although not to a statistically significant degree) in the spleen and tumor tissues.

The increase in the blood catecholamine level in the rats treated with leukoephdin and quercetin was accompanied by an inhibitory effect (to 85 and 50% respectively) on growth of the Pliss lymphosarcoma (Table 2). Adrenalin itself, in the maximal tolerated dose (1 mg/kg, 10 intraperitoneal injections) inhibited growth of the sarcoma 180 and Pliss lymphosarcoma by 26-33 % ($P < 0.05$) and noradrenalin produced similar inhibition by not more than 20 % ($P > 0.05$); both preparations were inactive against Ehrlich's solid tumor and sarcoma 45, for they inhibited growth by only 6-17% ($P > 0.1$).

To examine the role of adrenalin in the antitumor action of leukoephdin and quercetin the combined action of these agents was investigated (Table 2) and a very slight but statistically significant ($P < 0.05$) increase in this action of the preparations was observed in the experiments with sarcoma 180 (up to 20%), without any marked decrease in the gain in weight of the animals. No potentiation of the effect was observed in the experiments with other tumor strains.

Bearing in mind the stabilizing action of polyphenols on ascorbic acid [9] and the role of the latter as a stabilizer of adrenalin [3], the effect of vitamin C combined with leukoephdin was studied on Pliss lymphosarcoma and on sarcoma 180. The results of these experiments (Table 2) showed that ascorbic acid has no antitumor action and does not significantly potentiate the effect of leukoephdin.

The results can be summarized in the statement that growth of the tumor (as exemplified by transplanted Pliss lymphosarcoma) is accompanied by a decrease in the concentrations of adrenalin and noradrenalin in the circulating blood. Leukoephdin and quercetin (preparations with antitumor and vitamin P properties) increase the concentrations of these hormones and apparently stimulate the change from glycolysis to oxygen respiration in the affected tissues.

Considering the close similarity between the biological effects of phenols and catecholamines [1] it can be considered that activation of the sympathico–adrenal system, which promotes the accumulation of adrenalin, blocks the methoxylation of the catecholamines, and stabilizes adrenalin entering the blood stream, and thus exerts an adrenalin-like action, plays an important role in the antitumor action of leukoephdin and quercetin.

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