PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Impact of Preliminary Gamma-Irradiation on the Pattern of Change in Vascular Tone After Intravenous Injection of *Neisseria meningitidis* Lipopolysaccharide in Rats

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It is shown on rats that intravenous administration of the *Neisseria meningitidis* lipopolysaccharide lowers the mean arterial pressure, myocardial contractility, and vascular tone in the system of the left carotid artery. In rats exposed to gamma radiation and then to the lipopolysaccharide, the decrease in myocardial contractility and the degree of arterial hypotension were more pronounced than in those exposed to the lipopolysaccharide alone, but the vascular tone in the carotid artery system was reduced to a lesser extent.

Key Words: *lipopolysaccharide; gamma radiation; vascular tone*

The endotoxin lipopolysaccharide (LPS) elaborated by *Neisseria meningitidis* and released into the host's bloodstream in meningococcal infection causes a rise in vascular tone and leads to the development of arterial hypotension. These abnormalities result, in part, from the LPS-induced changes in the function of arterial endotheliocytes and smooth muscle cells [2]. As ionizing radiation is known to damage the structure and function of cells, including endotheliocytes [4], preliminary irradiation of the host is likely to modify the effect of LPS on vascular tone.

The purpose of this study on rats was to evaluate how their exposure to gamma radiation might affect the alterations in blood vessel tone caused by intravenously injected meningococcal LPS.

MATERIALS AND METHODS

Random-bred male white rats weighing 180-200 g were used. They were divided into four groups. Group 1 (control) rats (n=24) were injected with 0.154 M NaCl solution intravenously in a dose of 0.1 ml/100 g body weight; group 2 (n=21) were injected with *N. meningitidis* LPS at 10 mg/kg body weight 6 h before the tests; group 3 (n=19) were exposed to gamma radiation in a single dose of 3 Gy 3 days before the tests; group 4 (n=20) received an intravenous injection of the meningococcal LPS at 10 mg/kg after a single exposure to gamma radiation in the indicated dose.

Mean arterial pressure (AP) was measured with an EMT-34 (Mingograf-81) electromanometer in the left carotid artery of rats anesthetized with Nembutal (60 mg/kg). The LPS and NaCl solution were injected into the right jugular vein. Some rats were also injected with atropine (2 mg/kg) and benzohexonium (50 mg/kg) intraperitoneally and subjected to bilateral vagotomy at the cervical level to block the reflex regulation of AP.

Intraventricular pressure was measured electromanometrically *in situ* in a separate group of artificially ventilated rats with open chest [1].

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TABLE 1. Effect of Meningococcal LPS on Mean Arterial Pressure (MAP) and Heart Rate (HR) in Gamma-Irradiated (3 Gy) Rats

Group	Before benzohexonium and atropine injection and before vagotomy		After benzohexonium and atropine injection and after vagotomy	
	MAP, mm Hg	HR, beats/min	MAP, mm Hg	HR, beats/min
1: Control ($n=7$)	113.1±2.3	333±9	70.7±4.4	248±9
2: LPS ($n=6$)	48.3±4.5*	392±11*	25.5±5.0*	298±10*
3: Gamma irradiation ($n=7$)	94.4±4.5*	283±21*	56.5±4.8*	293±10*
4: Gamma irradiation+LPS ($n=7$)	37.3±3.5*	235±5*	23.3±5.0*	222±12*

Note. Here and in Tables 2 and 3: * significant difference from the control group.

The left carotid artery system was perfused with carbogen (95% O_2 and 5% CO_2)-saturated Krebs-Henseleit solution (37°C, pH 7.3-7.4) at a constant flow rate via a cannula inserted into the left common carotid artery of the isolated head of the rat placed in a thermostatically controlled chamber. Vascular tone was assessed from the perfusion pressure values recorded at volume flow rates of 3, 10, 12, and 15 ml/min.

Statistical differences between the groups were estimated by Student's *t* test.

RESULTS

Six hours after LPS injection, the mean AP in anesthetized nonirradiated rats with intact reflex AP regulation (group 2) was 57% lower than in the respective controls. In gamma-irradiated rats (group 3), the mean AP was also lowered, but only by 16.5%. As compared to the controls, the mean heart rate was 17.7% higher in group 2 and significantly lower in group 4 (235ë5 *vs.* 333ë9 beats/min; $p<0.05$) (Table 1).

The administration of atropine and benzohexonium and bilateral vagotomy led to a fall of the mean AP in all test groups - by 63.5, 19.3, and 66.7% in groups 2, 3, and 4, respectively, as compared to group 1 (control rats).

The intraventricular pressure developed by nonirradiated rats after LPS injection was 39.4% lower than in the respective controls, while the maximal rates of intraventricular pressure rise and fall were 24.5% and 24.6% lower, respectively. The intraventricular pressure developed by rats exposed to gamma radiation was significantly (by 18%) lower than in the control rats, but the maximal rates of intraventricular pressure rise and fall were only slightly lower. In group 4, exposed to the LPS and gamma radiation, the intraventricular pressure was 42% lower than in the controls and the maximal rates of its rise and fall were 26.2% and 32.3% lower, respectively (Table 2).

The mean reduction of perfusion pressure in the left carotid artery system of LPS-treated rats was 21.3% (Table 3). As is evident from this table, neither irradiation alone nor irradiation followed by LPS injection had a significant effect on the vascular tone.

The LPS caused a significant rise of the hematocrit (its mean value in the LPS-injected rats was 48.2ë1.3% *vs.* 37.2ë0.7% in the controls; $p<0.01$), whereas irradiation did not. The combined exposure to gamma radiation and LPS increased the hematocrit to 53.3ë1.4% ($p<0.01$). In addition, the rats given LPS after radiation exposure exhibited signs of pronounced enteritis.

The results presented above show that the meningococcal LPS lowered both the mean AP, myocardial contractility, and vascular tone in the left carotid artery system. The external gamma irradiation at 3 Gy altered the mean AP to a much lesser extent and did not produce a significant effect on myocardial contractility or on the tone of brain vessels. LPS injected after irradiation exerted

TABLE 2. Effect of Meningococcal LPS on Myocardial Contractility in Gamma-Irradiated (3 Gy) Rats

Group	Intraventricular pressure, mm Hg	Maximal rate of intraventricular pressure rise, mm Hg/sec	Maximal rate of intraventricular pressure fall, mm Hg/sec
1: Control ($n=11$)	93.2±5.8	4868±196	4717±216
2: LPS ($n=10$)	56.4±7.7*	3647±99*	3555±87*
3: Gamma irradiation ($n=6$)	76.4±4.2*	4634±246	4394±305
4: Gamma irradiation+LPS ($n=7$)	54.0±6.7*	3591±143*	3193±206*

TABLE 3. Effect of Meningococcal LPS on Perfusion Pressure (mm Hg) in the Left Carotid Artery System of Gamma-Irradiated (3 Gy) Rats

Group	Flow rate, ml/min			
	3	10	12	15
1: Control ($n=6$)	22.1±1.9	52.3±3.4	62.4±4.2	78.2±4.1
2: LPS ($n=5$)	15.3±0.9*	43.1±0.9*	50.6±2.0*	64.4±1.9*
3: Gamma irradiation ($n=6$)	18.1±1.1	47.8±1.6	59.3±2.5	77.5±3.4
4: Gamma irradiation+LPS ($n=6$)	17.7±3.6	51.5±5.4	60.3±7.89	76.7±8.5

a greater effect on the mean AP and myocardial contractility than on the tone of these vessels.

The effect of LPS on vascular tone is mediated, in particular, by interleukin-1 and tumor necrosis factor, which stimulate *de novo* formation of NO synthase in endotheliocytes and smooth muscle cells. This results in augmented production of nitric oxide, which is capable of reducing vascular tone and myocardial contractility [4].

The more pronounced arterial hypotension recorded for rats exposed to LPS after gamma irradiation was probably due both to a considerable inhibition of myocardial contractility and to a substantial increase in vascular permeability.

LPS injected into rats irradiated with a dose of 3 Gy, unlike that given to nonirradiated animals, failed to cause a significant reduction in the tone of brain vessels. Ionizing radiation probably impairs the LPS-induced *de novo* synthesis of NO synthase in the endothelial and smooth muscle cells of blood vessels by altering the structure and function of DNA [3]. If so, then the diminished NO production in blood vessels may explain why their tone did not decrease. Although NO itself may act as a factor reducing blood vessel tone and myocardial contractility, its intensified production in the presence of LPS is an adaptive response, given that inhibition of NO synthesis has been shown to increase mortality among animals with endotoxinemia [5].

To summarize, gamma-irradiated rats responded to the *N. meningitidis* LPS by greater decreases in the mean AP and myocardial contractility than did nonirradiated animals, although the vascular tone in the carotid artery system of irradiated animals was reduced to a lesser extent.

REFERENCES

1. F. Z. Meerson, *The Myocardium in Cardiac Hyperfunction, Hypertrophy, and Insufficiency* [in Russian], Moscow (1965).
2. V. V. Titov, *The Microcirculation in Patients with Meningococcal Infection* (Author's synopsis of doctoral dissertation) [in Russian], Moscow (1989).
3. J. L. Farber, M. E. Kyle, and J. B. Coleman, *Lab. Invest.*, **62**, 670-679 (1990).
4. S. Moncada, R. M. J. Palmer, and E. A. Higgs, *Pharmacol. Rev.*, **43**, 109-143 (1991).
5. E. Nava, R. M. J. Palmer, and S. Moncada, *J. Cardiovasc. Pharmacol.*, **20**, 132-134 (1992).