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EFFECTS OF INDOMETHACIN ON LIPOPOLYSACCHARIDE-INDUCED CHANGES IN SOME HUMORAL FACTORS OF INNATE RESISTANCE AND ACID-BASE STATUS IN RATS

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Summary

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The studies were performed on three groups of male inbred Wistar rats (5 rats in each group for each time interval) weighing 180–200 g. The effects of *Escherichia coli* 0111:B4 lipopolysaccharide (LPS), applied intraperitoneally at the dose of 1 mg/kg (group A) and of non-steroidal anti-inflammatory drug indomethacin, applied *per os* at 2.5 mg/kg 30 min prior to LPS challenge (group B) upon the factors of innate resistance (lysozyme, complement, blood proteins) and acid-base parameters were studied. The animals of group C (controls) received intraperitoneally only 1 ml 0.9% NaCl. Studied parameters were followed out at baseline, at hours 2, 4, 6, 24 and days 3, 6, 10 and 15 after the LPS administration.

The independent LPS challenge resulted in statistically significant increase in lysozyme activities as early as 4 hours later with a peak at day 6. The haemolytic activity of complement (HC), participating both in innate systemic resistance and the course of immunological processes, was the highest at day 10. LPS-induced changes in serum proteins were the most important for albumin fraction and were manifested by decrease as early as post challenge hour 24. This tendency was present up to day 6, when a minimum was reached. Afterwards albumin concentrations began to increase but reached values upper than the initial ones at day 10. The α_2- and γ-globulins were lower than baseline values during the whole period of the study (hour 2–day 15).

LPS-induced changes in lysozyme, complement and blood proteins were observed at the background of a decompensated metabolic acidosis.

Indomethacin, applied prior to LPS challenge prevented the negative effects of the agent to a certain extent. This drug influenced favourably the humoral factors of innate resistance - lysozyme, complement but could not restore the impaired liver function. Through its regulatory effect upon the respiratory component of acid-base status, it had some positive effect on LPS-induced decompensated metabolic acidosis.

Key words: acid-base status, indomethacin, lipopolysaccharide, rats

INTRODUCTION

The principal pathogen of Gram-negative bacteria is lipopolysaccharide (LPS) (Kass and Wolf, 1973; Nikaido and Nakae, 1979). The first barrier of defense, triggered by the organisms against this agent are the elements of innate immunity. The complement, lysozyme, proteins, interferons etc. determine the activity of cell components - phagocytes and are of primary importance for the issue of the infec-

tion. Grondahl et al. (1997) observed a significant reduction in phagocytosis with complement inactivation and Bernoco et al. (1987), Hietala and Ardans (1987) evidenced that the neutrophil activity was directly dependent on humoral factors.

The antibacterial properties of lysozyme are well-known (Paape et al., 1985) but Diluzio (1979) emphasized on his possible indirect role as immune modulator.

The studies of Sartorelli et al. (1999), Kask et al. (1999) confirmed the existence of regulatory interactions between metabolism and the activity of elements of innate immunity.

The fact that cytokine secretion is a pH-sensitive process (Jensen et al., 1990), supporting the suggestion for a direct correlation between acid-base and immune systemic status, must be considered as well. In patients with Gram-negative infections, the acid-base disorders could significantly alter the issue of the disease (Elisaf et al., 1993).

The new aspects in the treatment of coliform infection are related to attempts for pharmacological modulation of cytokine activity allowing the elimination of several negative LPS effects (Lo et al., 1992). For instance, Revhaug et al. (1988), Langhans et al. (1989), Uehara et al. (1989), Johnson and Borell (1994) have prevented LPS-induced anorexia, fever, adynamia with the non-steroidal anti-inflammatory drug (NSAID) indomethacin. The latter ceases the prostaglandin synthesis (Bottoms et al., 1982) via cyclooxigenase inhibition (Shen and Winter, 1977; Hansbrough et al., 1984). The effect of indomethacin upon lipopolysaccharide-induced prostaglandin E_2 (PGE_2) concentrations and the clinically manifested systemic disorders in experimental endotoxaemia were subject of previous studies of ours (Andonova et al., 1998). The pharmacokinetics of indomethacin is known (Cristofol et al., 1996) as well as its effects on the gastrointestinal tract, the secretion of chlorides, the stabilization of lysozome membranes and the production of free radicals (Wallace, 1992). Data about the relationship between NSAIDs and the humoral factors of innate resistance are however incomplete. The follow out of parameters, providing information for changes in humoral elements after LPS challenge and the haematological, metabolic, hormonal studies would allow the extension of the possibilitites for pathogenetical interpretation of LPS-induced systemic changes occurring at the same time. The early changes in parameters of innate immunity increase their diagnostical value and permit the early preclinical detection of systemic resistance disorders.

The aim of the present investigation was to study the dynamics of LPS induced changes in complement, lysozyme and blood proteins as prinicipal humoral factors of defense as well as the changes in acid-base status as an early indicator of occurring metabolic disorders and furthermore, to follow out the effects of indomethacin on all those parameters.

MATERIALS AND METHODS

Animals

The experiments were performed on 135 male inbred Wistar rats, weighing 180-200 g (from the Experimental Base of the Bulgarian Academy of Sciences, Slivnitsa, Bulgaria). They were housed in cages in groups of five and allowed to accommodate to environmental conditions – mixed light regimen, 50–60% air humidity, 20–22 ^{o}C ambient temperature, free access to food (combined granulated forage

for rats, Agrozooengineering, Russe) and water.

Experimental design

The animals were divided into three groups:

Group A (n=45) – rats treated intraperitoneally (*i.p.*) with *E.coli* 0111:B4 LPS (Sigma Aldrich Chemie GmbH) dissolved in 1 ml 0.9% NaCl and applied at a dose of 1 mg/kg;

Group B (n=45) – rats treated with LPS and indomethacin (Pharmachim, Bulgaria). Thirty minutes prior to the *i.p.* administration of endotoxin, all rats from group B received indomethacin *per os* at a dose rate of 2.5 mg/kg via an esophageal tube (Haupner). Indomethacin was dissolved in 1 ml 1% carboxymethylcellulose;

Group C (n=45) – controls treated *i.p.* with 1 ml 0.9% NaCl.

The dynamics of studied parameters was followed out prior to the challenge (baseline), at post challenge hours 2, 4, 6, 24 and at post challenge days 3, 6, 10, 15. Five animals were used to obtain blood and blood serum at each of these intervals.

Specimens and parameters

Blood samples were anaerobically obtained from the venous retrobulbar plexus after a light ether anaesthesia (to ease the pain and stress of the manipulation). Then the animals were decapitated and blood (4-5 ml) was collected in tubes for recovering blood serum. Blood samples were immediately analysed on a blood gas analyser (ABL-3, Radiometer, Copenhagen, Denmark). The following acid-base and blood gas parameters were determined: blood pH, partial pressure of carbon dioxide – pCO_2, partial pressure of oxygen – pO_2, bicarbonates – HCO_3^-, actual base excess – ABE.

The serum obtained after the decapitation served for determination of the humoral factors of innate resistance – complement, lysozyme and protein fractions. The haemolytic complement activity (HC) was measured in 50% haemolytic units (CH_{50}) by the method of Stelzner and Stein (1971) and lysozyme concentrations – by the method of Lie (1985). Serum proteins were determined via agar microelecrophoresis and the percentages were calculated on the basis of total protein readings in g/l.

For elimination of any circadian cycles influence, all samples were collected in the period 7.30–8.00 *a.m.*

Statistical analysis

Data were analyzed using two-way ANOVA with repeated measures (treatment × time). *Post hoc* comparisons of individual group means were carried out by the Tukey's test. The differences were considered as significant at the $p<0.05$ level.

RESULTS

The changes in humoral factors of defense (lysozyme, complement) in rats from control (C) and experimental (A, B) groups are presented on Figs. 1 and 2.

Lysozyme. In controls, lysozyme activity was not considerably changed compared to initial values (Fig. 1). However, the rats treated with *E. coli* LPS (group A) showed significantly higher lysozyme activities vs baseline ($p<0.001$) as early as the post challenge hour 4 and reached a peak of 1.38 ± 0.06 μg/ml at day 6. The same tendency was observed in group B

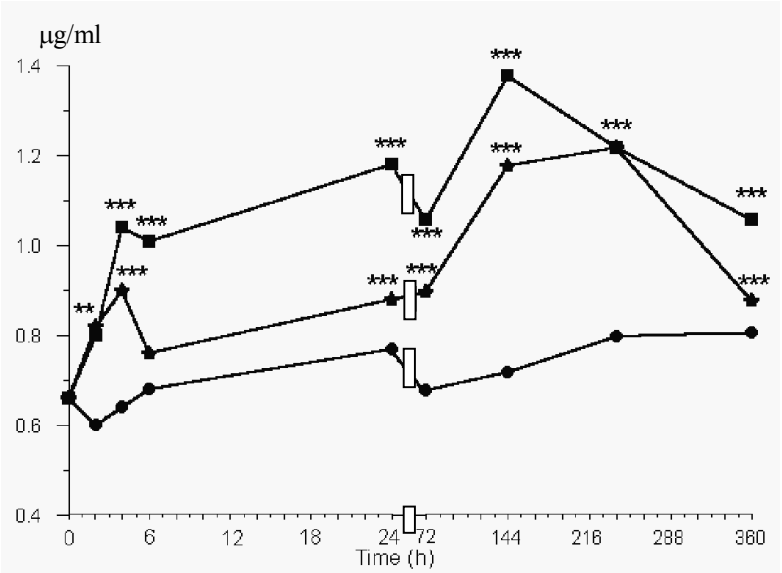

Fig. 1. Kinetics of lyzozyme activity in rats treated with *E.coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group A); indomethacin *p.o.* at 2.5 mg/kg + *E. coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group B) and untreated controls (group C). * $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs baseline (hour 0).

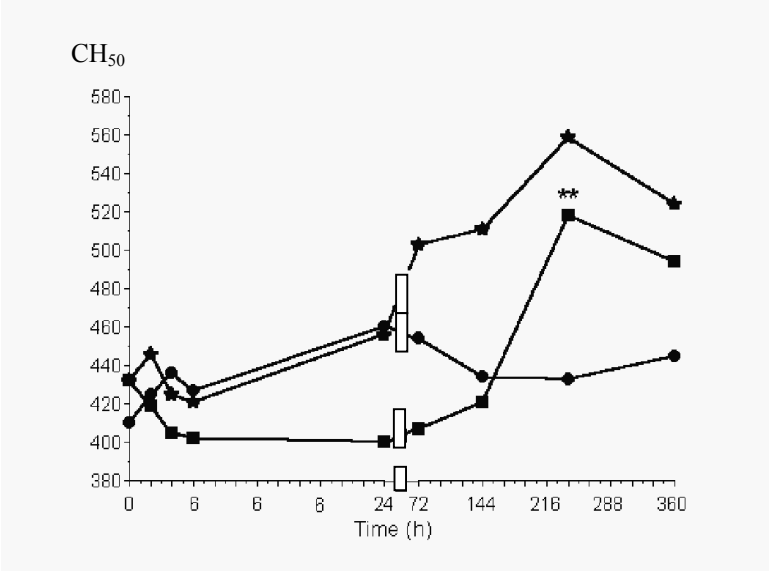

Fig. 2. Dynamics of haemolytic activity of complement in rats treated with *E.coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group A); indomethacin *p.o.* at 2.5 mg/kg + *E. coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group B) and untreated controls (group C). * $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs baseline (hour 0).

but lysozyme activities were lower compared to group A until the end of the study. The peak of 1.22 ± 0.04 μg/ml was observed at day 10. The differences were statistically significant compared to hour 0 at each time interval ($p<0.001$).

Complement. In the early period of the experiment (hour 2-24) there were no statistically significant changes in haemolytic activities of complement in all three group (Fig. 2). In group A, haemolytic complement activity increased significantly at day 10 ($p<0.01$) while in group B the elevation was noticed earlier (days 3–6), the peak was reached at day 10 and its height was superior.

Serum proteins. The results, presented in Table 1, evidenced the presence of changes in the albumin, alpha$_2$- and gamma-globulin fractions. Both LPS and indomethacin treatments influenced significantly albumins, that decreased significantly as early as post challenge hour 2 in group A ($p<0.01$) and group B ($p<0.05$) vs baseline.

Although in LPS-treated rats albumin concentrations were higher at hour 4, the tendency towards decrease vs baseline was predominating. Thus, at post challenge hour 6 a statistically significant decrease was observed in both groups ($p<0.01$), afterwards albumin levels began to increase but became higher than baseline only at day 10 ($p<0.05$). Indomethacin-treated rats showed higher values compared to group A in this period of the experiment.

In LPS-treated rats, α_2-globulins decreased at hour 4 ($p<0.001$) and day 10 ($p<0.01$) while in group B the decrease at

Table 1. Serum proteins in rats, treated with *E.coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group A) or with indomethacin *p.o.* at 2.5 mg/kg + *E. coli* 0111:B4 LPS *i.p.* at 1 mg/kg (group B)

	Group	Albumins, g/l	α_1-globulins, g/l	α_2-globulins, g/l	β-globulins, g/l	γ-globulins g/l
Baseline		20.84 ± 2.40	12.71 ± 1.20	9.07 ± 1.50	12.71 ± 2.18	15.27 ± 1.55
Hours after the LPS challenge						
2	A	13.71 ± 1.04[b]	10.71 ± 1.46	7.62 ± 0.50	10.32 ± 1.11	13.75 ± 0.86
	B	15.88 ± 1.21[a]	10.16 ± 1.23	8.10 ± 1.20	12.47 ± 1.32	11.59 ± 1.23[a]
4	A	18.33 ± 1.09	9.58 ± 0.27	4.31 ± 0.40[c]	8.63 ± 0.42	10.62 ± 1.31[a]
	B	13.22 ± 2.05[b]	9.68 ± 1.69	8.99 ± 2.94	9.73 ± 0.01	8.73 ± 0.93[c]
6	A	13.61 ± 2.16[b]	11.97 ± 0.73	6.79 ± 0.39	9.54 ± 0.51	13.20 ± 1.09
	B	13.54 ± 1.34[b]	9.62 ± 0.53	6.52 ± 0.86	9.43 ± 1.16	10.07 ± 1.01[b]
24	A	16.82 ± 0.94	9.73 ± 0.59	6.83 ± 0.56	9.46 ± 0.54	12.74 ± 1.48
	B	19.53 ± 1.14	10.87 ± 1.24	6.30 ± 1.00	13.61 ± 0.83	9.42 ± 0.80[c]
Days after the LPS challenge						
3	A	17.87 ± 1.01	10.39 ± 0.50	6.83 ± 0.56	10.54 ± 0.84	14.17 ± 1.74
	B	21.31 ± 1.67	11.68 ± 0.73	6.30 ± 1.00	9.81 ± 1.54	11.86 ± 1.49
6	A	16.81 ± 1.28	12.48 ± 1.08	8.08 ± 1.61	11.13 ± 2.05	17.45 ± 1.24
	B	20.27 ± 2.45	12.05 ± 0.80	9.27 ± 1.11	10.12 ± 0.84	12.38 ± 1.10
10	A	25.29 ± 1.21[a]	10.70 ± 1.97	5.64 ± 0.63[b]	10.86 ± 0.51	13.83 ± 1.01
	B	26.17 ± 1.23[a]	12.61 ± 1.80	5.88 ± 0.72[a]	10.36 ± 0.73	16.80 ± 0.92
15	A	19.72 ± 1.63	11.33 ± 0.91	8.57 ± 0.72	13.83 ± 1.01	16.13 ± 1.71
	B	24.34 ± 0.47	13.18 ± 0.34	6.44 ± 0.05	16.80 ± 0.92	11.61 ± 0.95[a]

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$ vs baseline (hour 0).

Table 2. Changes in acid-base parameters in venous blood in rats from groups A, B and C (5 animals in each group for each time interval). Data are presented as mean ± SEM

Intervals after LPS challenge	Parameters			
	pH	pCO_2, kPa	HCO_3, mol/l	ABE, mmol/l
Group C (untreated controls)				
hour 0	7.391 ± 0.013	6.76 ± 0.34	29.58 ± 1.36	4.46 ± 1.12
hour 2	7.382 ± 0.050	6.78 ± 0.20	30.46 ± 0.52	4.68 ± 0.24
hour 4	7.381 ± 0.040	7.00 ± 0.20	30.50 ± 0.32	5.14 ± 0.09
hour 6	7.380 ± 0.015	6.72 ± 0.16	29.36 ± 0.48	4.82 ± 0.38
hour 24	7.379 ± 0.009	7.10 ± 0.30	30.18 ± 1.01	4.92 ± 0.92
day 3	7.377 ± 0.003	6.84 ± 0.22	29.68 ± 0.68	5.08 ± 0.46
day 6	7.383 ± 0.013	6.95 ± 0.39	30.16 ± 0.67	4.52 ± 0.50
day 10	7.378 ± 0.004	7.13 ± 0.25	30.56 ± 0.85	5.04 ± 0.75
day 15	7.385 ± 0.011	6.81 ± 0.18	29.38 ± 0.79	4.92 ± 0.20
Group A (treated with *E.coli* 0111:B4 LPS *i.p.* at 1 mg/kg)				
hour 0	7.391 ± 0.013	6.76 ± 0.34	29.58 ± 1.36	4.46 ± 1.12
hour 2	7.143 ± 0.024[c]	6.60 ± 0.13	15.82 ± 0.74[c]	-12.92 ± 1.32[c]
hour 4	7.180 ± 0.017[c]	6.96 ± 0.48	18.14 ± 1.99[c]	-10.78 ± 1.23[c]
hour 6	7.173 ± 0.033[c]	7.07 ± 0.72	16.74 ± 0.73[c]	-10.08 ± 1.65[c]
hour 24	7.307 ± 0.035[a]	7.96 ± 0.74[a]	28.38 ± 1.16	0.68 ± 1.19
day 3	7.288 ± 0.014[a]	6.48 ± 0.50	22.40 ± 1.18[b]	-4.26 ± 0.68[c]
day 6	7.270 ± 0.014[b]	6.96 ± 0.30	23.30 ± 1.07[b]	-3.82 ± 1.57[b]
day 10	7.145 ± 0.046[b]	5.58 ± 0.44[a]	19.00 ± 1.24[c]	-7.72 ± 1.02[c]
day 15	7.385 ± 0.011[c]	8.94 ± 1.01[b]	20.98 ± 2.60[c]	-10.42 ± 3.45[c]
Group B (treated with indomethacin *p.o.* at 2.5 mg/kg + *E. coli* 0111:B4 LPS *i.p.* at 1 mg/kg)				
hour 0	7.391 ± 0.013	6.76 ± 0.34	29.58 ± 1.36	4.46 ± 1.12
hour 2	7.296 ± 0.019[a]	4.62 ± 0.06[b]	16.30 ± 0.72[c]	-8.66 ± 1.13[c]
hour 4	7.318 ± 0.025	3.70 ± 0.13[c]	13.86 ± 0.94[c]	-10.34 ± 1.29[c]
hour 6	7.308 ± 0.038	3.38 ± 0.30[c]	17.84 ± 0.34[c]	-6.44 ± 0.78[c]
hour 24	7.314 ± 0.042	7.38 ± 0.84	26.48 ± 0.66	-0.20 ± 1.06
day 3	7.284 ± 0.016[a]	7.41 ± 0.41	25.64 ± 1.02	-1.80 ± 0.87[a]
day 6	7.283 ± 0.017[a]	7.64 ± 0.34	26.22 ± 1.56	-1.04 ± 1.54[a]
day 10	7.224 ± 0.065[c]	6.04 ± 0.32	19.08 ± 3.22[c]	-9.24 ± 4.32[c]
day 15	7.232 ± 0.019[a]	6.72 ± 0.64	20.72 ± 2.23[c]	-7.30 ± 1.55[c]

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$ vs baseline (hour 0).

day 10 was lower ($p<0.05$).

The γ-globulin levels remained lower than baseline during the whole period of the study in both treated groups.

Acid-base status. The changes occurring in pH, pCO_2, HCO_3^-, ABE in control (C) and experimental (A, B) groups are shown in Table 2.

In controls, all parameters varied insignificantly. pH ranged between 7.377 ± 0.003 and 7.391 ± 0.013; pCO_2 – between 6.72 ± 0.16 and 7.13 + 0.25 kPa; HCO_3^- – between 29.36 ± 0.48 and 30.56 ± 0.85 mmol/l and ABE varied from 4.46 ± 1.12 and 5.14 ± 0.09 mmol/l.

The effects of LPS (group A) upon the acid-base status are presented in Table 2. As early as the initial hours (2–6), the *i.p.* administration of the agent resulted in significant decrease in pH (minimum at the 2nd hour: 7.143 ± 0.024). During the whole period of the study pH was statistically lower than baseline. At day 10, it was 7.145 ± 0.046.

The pCO_2 changes consisted in increased levels after the 2nd hour with significant ($p<0.05$) increase at hour 24. Then, pCO_2 values decreased up to day 10 when a minimum of 5.58 ± 0.44 kPa ($p<0.05$) was recorded. Afterwards (at day 15), a peak of 8.94 ± 1.01 kPa ($p<0.01$) was measured.

The combined indomethacin and LPS application in group B (Table 2) resulted in statistically significant lower pH vs baseline at hour 2 and within the interval between days 3 and 15. No statistically signifcant difference was present between hours 4 and 24 although pH was lower than the initial one. The minimum for this group was at day 10 (7.224 ± 0.065, $p<0.001$) and was higher than the pH minimum in group A. The bicarbonates and ABE in group B were lower than the initial values during the whole period of the study. The respiratory component of the acid-base status (pCO_2) in this group was statistically decreased only within the period hour 2–hour 6.

DISCUSSION

LPS-induced systemic disorders affect almost all systems: cardiovascular (Perkowski et al., 1996), nervous, alimentary (Gregory and Wings, 1998; Saitoh et al., 1999), immune and endocrine (Yu et al., 1998).

The components of innate immunity ensuring the early phase of defense and including a complex of standard reactions and mechanisms induced by the challenging agent, are among the foremost ones, reacting to the challenge (Wonderling et al., 1996; Grunwald et al., 1996).

The results of the studies showed that among humoral factors of innate resistance, lysozyme reacted with a statistically significant increase as early as hour 4 after the *i.p.* LPS treatment (group A, Fig. 1). It varied however insignificantly in controls (group C). So, the lysozyme elevation could be undoubtedly attributed to LPS effect. In our experiment, we used inbred male Wistar rats with a similar body mass, thus eliminating the possible influence of genetic, gender and age factors on this parameter, reported by Sotirov (1990). Leukocytes could also be a possible source of lysozyme. The changes in leukocyte counts (leukopenia occurring 2 hours after LPS challenge) observed in previous studies of ours (Andonova et al., 1998) support fully this suggestion. Gordon et al. (1974) consider lysozyme as a parameter of the functional status of circulating neutrophils but Goranov (1978) determines the *in vitro* presence of lysozyme (muramidase) activity only in neutrophils from peripheral blood of laboratory (rats, mice, rabbits, guinea pigs) but not in domestic animals.

The rats from group B, treated with indomethacin, showed the same tendency as those treated only with LPS, but the values were lower (Fig. 1). They could be

explained by the effects of indomethacin upon lysozomal membrane stability (Weiss and Hait, 1977). Therefore, the administered drug did probably not inhibit but corrected lysozyme activity as a component of innate systemic mechanisms of defense.

Studying indomethacin pharmacokinetics, Yesair et al. (1970) and Cristofol et al. (1996) report that following its absorption, it binds to plasma proteins and remains in low concentrations for a long period. Our electrophoretical studies (Table 1) showing a significant reduction in albumins and α_2-globulins following *i.p.* LPS challenge (group A) are clearly evidencing the detrimental effect of this agent on liver. The increase in albumins from 13.71 ± 1.04 g/l at hour 2 to 18.33 ± 1.09 g/l at hour 4 was statistically insignificant, but is intriguing in rats from group A. This event was not observed in group B. The fever, developing during this period (hours 2-4) in group A and its suppression by the antipyretic activity of indomethacin suggest that the impaired protein metabolism, accompanying fever, is probably one of the basic features of observed phenomenon.

The increase in the haemolytic activity of complement to a higher degree in group B after the 3rd day proved the involvment of this component of innate resistance in the realization of systemic immunological processes. It must be emphasized that in the early period (hours 2–24) no significant changes occurred. This fact could not be interpreted as a manifestation of the later involvement of complement in systemic defense, but was rather due to the method of determination that registered only the activity of the classical but not that of alternative pathway of complement activation. The studies of Galanos et al. (1971), Morrison and Kline (1977), Cooper and Morrison (1978) showed that LPS activates both pathways of complement cascade. Indomethacin, administered in rats from group B, influenced favourably the complement system, as proved by the higher values in this group (Fig. 2).

The LPS-induced changes in humoral factors of innate resistance – lysozyme, complement, blood proteins (group A) and the changes influenced by the administered indomethacin (group B) were realized at the background of significant changes in one of the important systemic biological constants – the acid-base status (ABS). Acid-base parameters measured in controls (Table 2), did not differ from those reported by other authors in venous blood (Chang et al., 1987). This allowed their comparison to changes occuring after LPS or LPS + indomethacin treatments.

The LPS challenge resulted in decompensated metabolic acidosis in group A (Table 2), manifested by the low values of pH and the metabolic parameters (HCO_3^-, ABE). The data of Von Sluijs et al. (1983), Griffith et al. (1983), Carverth et al. (1984), Lachmann et al. (1989) support this suggestion, evidencing a high correlation among the metabolic parameters of arterial and venous blood (the latter being used in our experiment).

A general rule in ABS compensations is that primary metabolic disorders are compensated by respiratory, and the respiratory ones – by metabolic (Naris and Emmett, 1980). This rule was not observed in group A. An evidence for this assumption was the high pCO_2 values between hours 6 and 24 after the LPS challenge. Hurtado et al. (1992) reported tussue hypoxia as an important factor in the mechanism of acidosis during *E.coli* endotoxaemia while Okusawa et al. (1988) explained in details the pulmonary injuries following a LPS challenge.

Within this period, high lactate concentrations were also measured (unpublished data). Similar facts are reported also by Jarvinen and Sankari (1996). As consequence of hypoxia, they observed high lactate concentrations, indicating activation of anaerobic glycolysis.

The application of the NSAID indomethacin in rats from group B influenced the respiratory ABS component (Table 2) that was statistically significantly decreased in the period between hours 2 and 6 in contrast to the absence of changes in group A. Although the data about the effects of indomethacin on acid-base parameters following LPS challenge are limited (Andonova et al., 1996), it could be suggested that the favourable effect of indomethacin upon pCO_2 was particularly due to its ability to block prostaglandin synthesis. Prostaglandins are those that influence the centre of thermoregulation and participate in the mechanism of fever, observed after LPS challenge too (Andonova et al., 1998). The bidirectional interactions among cortical structures, limbic system, hypothalamus, connecting neurons and respiratory center probably explain why the influence on one of these structures (here, the centre of thermoregulation) could have an impact upon other related structures.

In conclusion, the results of our study suggested that indomethacin, applied prior to the LPS challenge could prevent the negative effects of LPS to a certain extent. This drug influenced favourably the humoral factors of innate resistance - lysozyme, complement but could not restore the impaired liver function. It regulated the respiratory component of ABS leading to a certain positive effect on LPS-induced decompensated metabolic acidosis.

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