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THE ROLE OF IL-1β IN THE DEVELOPMENT OF DIABETES MELLITUS

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Abstract

Background. Currently, diabetes mellitus is the most common of all endocrine diseases with increasing tendency. **The purpose** of our research was to study the dynamics of serum levels of proinflammatory cytokine-IL-1β in streptozotocin-induced diabetes. **Materials and methods.** The experiments were performed on 88 white male Wistar rats weighing 170-210 g. Animals were divided into three groups: 1 - intact; 2 - control; 3 - experimental with a model of diabetes mellitus, which was reproduced by intraperitoneal injection of streptozotocin by “Sigma" company (USA), diluted in 0.1 M citrate buffer with a pH of 4.5, at a rate of 60 mg/kg body weight. The control group of animals received an intraperitoneal injection with an equivalent dose of 0.1 M citrate buffer solution with a pH of 4.5.

All studies were performed under thiopental-sodium anesthesia at a rate of 60 mg/kg body weight. Serum levels of IL-1β were determined by enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, USA) according to the manufacturer's instructions 14, 28, 42 and 70 days after streptozotocin injection. The STATISTICA 10 program was used for statistical processing of the obtained results. **Results.** Conducted biochemical analysis showed that in animals with streptozotocin-induced diabetes there was an increase in the content of proinflammatory cytokine IL-1β compared with similar indicators in the control group of animals at

all stages of the experiment: after 14 days by 22.5%, after 28 days by 40.2%, after 42 days by 72.8% and after 70 days by 107.2%. **Conclusion.** The obtained results suggest that pro-inflammatory cytokine interleukin-1β plays one of the leading roles in the pathogenesis of streptozotocin-induced diabetes, as indicated by a significant increase in serum of this cytokine at all stages of the experiment.

Key words: streptozotocin-induced diabetes, interleukin-1β.

INTRODUCTION

Nowadays, diabetes mellitus (DM) is the most common of all endocrine diseases with increasing tendency [1, 2, 17, 28, 29]. According to the International Diabetes Federation (IDF), the number of people with diabetes will increase to 629 million by 2045 worldwide [19, 25, 30]. In recent years, the prevalence of diabetes has increased due to a large number of patients with type 2 diabetes [6, 10, 15, 16].

Lately, increasing attention has been paid to establishing the pathogenetic role of cytokines in various diseases, including DM [3, 18, 20, 31]. It is known that cytokines are regulators of intercellular and intersystemic interactions, and ensure the coherence of the endocrine, immune, and nervous systems both under normal conditions and in response to pathogenetic factors. To date, it has been established that among many cytokines, a special role in the development of diabetes belongs to proinflammatory interleukin-1β (IL-1β) [8, 21, 24, 32, 34].

Major sources of IL-1β include tissue macrophages, blood monocytes, and dendritic cells [7, 14]. According to the literature data, IL-1β is a key proinflammatory cytokine that inhibits insulin secretion and stimulates the expression of a gene encoding inducible nitric oxide synthase. The latter leads to the synthesis of NO and the death of β-cells of the pancreas due to necrosis or apoptosis in experimental animals with spontaneous autoimmune diabetes [11]. The cytotoxic effect of IL-1β on β-cells of the islets of Langerhans is indicated by many other authors [4, 5, 22, 26, 33].

However, the role of proinflammatory cytokines in diabetes remains unclear.

The aim of our research was to study the dynamics of serum levels of proinflammatory cytokine-IL-1β in streptozotocin-induced diabetes.

MATERIALS AND METHODS

The experiments were performed on 88 white male Wistar rats weighing 170-210 g, which were kept on a standard diet with free access to water. Animals were divided into three groups: 1 - intact (n = 10); 2 - control (n = 40); 3 - experimental (n = 38) with a model of diabetes mellitus, which was reproduced by intraperitoneal injection of streptozotocin by “Sigma" company (USA), diluted in 0.1 M citrate buffer with a pH of 4.5, at a rate of 60 mg/kg body weight. The control group of animals received an intraperitoneal injection with an equivalent dose of 0.1 M citrate buffer solution with a pH of 4.5.

Animal husbandry and research were conducted in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), the Law of Ukraine on the "Protection of Animals from Cruelty" (2006) and the "General Ethical Principles of Experiments on Animals" approved by the Fifth National Congress on Bioethics (Kyiv, 2013). All studies were performed under thiopental-sodium anesthesia at a rate of 60 mg/kg body weight.

Serum IL-1β levels were determined by enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, USA) according to the manufacturer's instructions 14, 28, 42 and 70 days after streptozotocin injection.

The STATISTICA 10 program was used for statistical processing of the obtained results. Using the possibilities of descriptive statistics, all the quantitative data obtained in the study were first checked for the type of their distribution by the Shapiro-Wilk test. Since the vast majority of these data were

consistent with Gauss's normal law, the arithmetic mean ± standard error of mean (M±m) was chosen to describe the central trend, and a parametric t-test (Student's test) was chosen to assess the reliability of differences in the results obtained in the comparison groups (experimental and control) and to test the null hypothesis. To assess the reliability of data changes in the dynamics (14, 28, 42, 70 days) within each of the comparison groups we used a non-parametric method for three or more comparison groups – Friedman's test and Kendall's coefficient of concordance (Friedman ANOVA and Kenall Coef. of Concordance).

RESULTS AND DISCUSSION

Conducted studies showed that in animals with streptozotocin-induced diabetes there was an increase in the content of proinflammatory cytokine IL-1β compared with the similar indicators of the control group of animals at all stages of the experiment (Table 1 and Figure 1).

Table 1

The content of IL-1β (pg / mL) in the serum of white rats in experimental diabetes mellitus.

Group	14 days		28 days		42 days		70 days		p_2
	M	±m	M	±m	M	±m	M	±m	
Experiment	115,9 *	0,63	130,5 *	0,58	164,5 *	1,40	194,4 *	1,05	<0,001
Control	94,6	0,68	93,1	0,63	94,8	0,63	93,6	0,64	>0,05
p_1	<0,001		<0,001		<0,001		<0,001		x
Intact	94,8±0,70								

Notes: p_1 – the reliability of the difference between the data of the experimental and control groups;

p_2 – reliability of data within the group in the dynamics;

* – reliability of the data difference compared to the intact group.

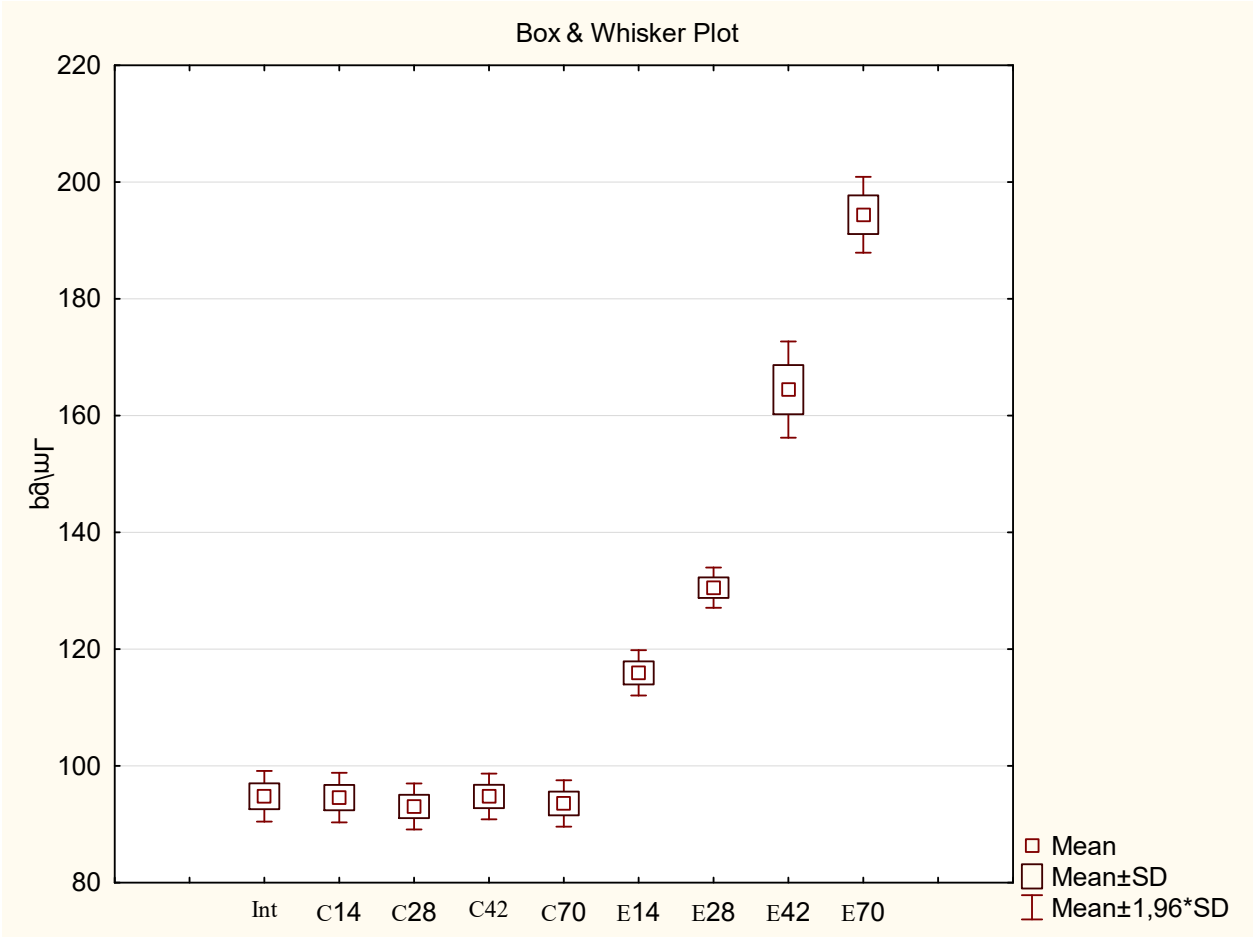

Fig. 1. Dynamics of IL-1β content (pg/mL) in the serum of white rats in experimental diabetes mellitus.

Notes: groups of animals: Int – intact; C – control; E – experimental.

14, 28, 42, 70 – days of the experiment

It was found that 14 days after the start of the experiment, the level of IL-1β in the serum significantly exceeded the control group of animals by 22.5% ($p<0.001$). With increasing study duration (28 days) there was an increase in serum proinflammatory cytokine IL-1β by 40.2% ($p<0.001$) compared with the control group of animals. 42 days after the experiment, a further increase in the level of IL-1β in the serum was determined. It was found that the value of IL-1β in the serum exceeded that of the control group of animals by 72.8% ($p<0.001$).

The study of the serum content of IL-1β after 70 days in the conditions of simulated diabetes showed a further increase in this indicator. In particular, it was found that the serum level of IL-1β at that period of the study exceeded similar indicator of the control group of animals by 107.2% ($p<0.001$).

The results of the conducted studies showed that in the conditions of simulated diabetes the serum level of proinflammatory cytokine IL-1β increased by 22.5%, 40.2%, 72.8% and 107.2%, respectively, on 14, 28, 42 and 70 days after the start of experiment. It was found that the maximum increase in IL-1β was observed 70 days after modelling of diabetes relative to the control group of animals ($p<0.001$) and differed significantly from the value of IL-1β in previous observation periods.

The results of our study are consistent with the data of other researchers, who also indicated a significant increase in serum proinflammatory cytokine IL-1β in diabetes [9, 20, 23, 27]. The production of significant amounts of IL-1β can lead to large the number of pullo-proliferative cells and their changes may be proportional to the degree of damage. IL-1β induces a wide range of biological effects on both systemic level and at the site of localization of the inflammatory response. Activating the cells of innate and acquired parts of the immune system, IL-1β promotes vessel expansion, production of acute phase proteins, and antibody synthesis [12, 13]. According to the literature data, proinflammatory cytokine IL-1β induces the migration of proinflammatory cells to the islets of Langerhans of the pancreas, mediates cytokine-induced apoptosis of β-cells, has cytotoxic properties on β-cells and thus promotes development of diabetes mellitus [4, 22].

CONCLUSION

The obtained results suggest that pro-inflammatory interleukin-1β plays one of the leading roles in the pathogenesis of streptozotocin-induced diabetes,

as indicated by a significant increase in serum of this cytokine at all stages of the experiment.

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