The Effect of Chronic Intoxication with 2-Chloroethanol on Immune Responses, Function of Th1 and Th2 Lymphocytes and Blood Cytokine Concentrations

Abstract

Experiments on Wistar rats showed that chronic intoxication of 2-chloroethanol (0.05 DL_{50} daily for 60 days) causes reduction of parameters humoral and cellular immune responses, decrease of function Th1 and Th2 lymphocytes to the same extent and contents in blood of IFN-γ, interleukins IL-2, IL-4, pro-inflammatory cytokines (TNF-α, IL-6), anti-inflammatory cytokines (IL-10, IL-13).

Keywords: 2-chloroethanol; Immune responses; Th1, Th2 lymphocytes; Immunotoxicity; Cytokines

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Zabrodskii PF*

Saratov Medical University "REAVIZ", Russia

***Corresponding author:** Pavel Franzevich Zabrodskii, Saratov Medical University "REAVIZ", Saratov, Russian Federation, Tel: (845-2) 22-76-25; Email: pfzabrodsky@gmail.com

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Introduction

2-chloroethanol (CE, ethylene chlorohydrin, chloroethyl alcohol, ethylene glycol chlorohydrin) is a highly toxic chemical compound of general toxic effect; colorless viscous liquid with a weak ether odor; Is readily soluble in water, ethanol, acetone, 1,2-dichloroethane, chloroform. It is used as a solvent for inorganic salts, in organic synthesis (dissolves acetyl cellulose). Used to produce ethylene oxide, thiodiglycol, some dyes, pesticides and pharmaceuticals [1-3]. In emergency situations, violation of safety precautions CE can induce inhalation, oral poisoning, easily penetrates through skin. After intoxication of CE are amazed the central nervous system, cardiovascular system, kidneys, liver and other organs [1-4]. There are reasons to believe that CE metabolites can cause mutagenic, carcinogenic, and teratogenic and immunotoxic effects [3]. Dysfunctions of immune system, synthesis of lymphocytes and other blood cells of cytokines with chronic intoxication of CE with purpose of targeted correction of immune homeostasis for prevention of infectious complications and disease have not been studied [1-6]. The aim of the study was to assess the chronic effect of CE (60 days, daily subcutaneously 0.05 LD_{50}) on immune responses, the function of Th1 and Th2 lymphocytes, as well as on the content of IFN-γ, interleukins IL-2, IL-4, pro-inflammatory (TNF-α, IL-6) and anti-inflammatory cytokines (IL-10, IL-13).

Materials and Methods

The experiments were carried out on Wistar rats of both sexes weighing 180-240 g. CE (Sigma-Aldrich) was administered subcutaneously at a dose of 0.05 LD_{50} in aqueous solution (0.5 ml) for 60 days (total dose 3.0 LD_{50}). LD_{50} CE with subcutaneous administration was 45±4 mg/kg. Control animals received a subcutaneous equal volume of water. The indices of the immunity system were evaluated after 60 days after the first injection of CE (reaction of delayed-type hypersensitivity-DTH-after 61 days) by conventional methods in experimental immuno-toxicology and immunology [7,8]. The humoral immune response to the T-dependent antigen (red sheep blood cells- RSBC), which characterizes the ability of Th1 cells to participate in production of B cells (plasmocytes) IgM, was determined from the number of antibody-forming cells (AFC) in the spleen 4 days after immunization (peak production of IgM), which was administered intraperitoneally at a dose of 2×10^8 RSBC after 56 days after the first administration of the toxicant. Similarly, the humoral immune response to the T-independent typhoid Vi-antigen (Vi-Ag), reflecting the synthesis of IgM B-cells in the spleen of rats, was evaluated. Immunization of Vi-Ag rats at a dose of 8μg/kg was performed 56 days after the first injection of CE. The reaction of DTH was evaluated after 1 day.

The function of Th2 lymphocytes was investigated from the number of AFC synthesizing IgG to RSBC in the spleen by indirect local hemolysis in the gel at 7 days after immunization with RSBC [7,8], which was administered intraperitoneally at a dose of 2×10^8 RSBC after 53 days after the first injection of CE. The activity of natural killer cells (NK) was evaluated by spectrophotometric method [7,8]. The concentration of IFN-γ(#MBS824935), interleukins IL-2(#MBS2885949), IL-4(#MBS2883072), proinflammatory cytokines TNF-α(#MBS175904), IL-6(#MBS2885203) and anti-inflammatory cytokines IL-10 (#MBS2087187), IL-13 (#MBS495243) [7,8] have been tested in rat blood serum using the enzyme-linked immunosorbent assay (ELISA) method using kits (ELISA Kits MyBioSoure) according to the manufacturer's instructions. At that, the content of cytokines in the blood was determined 4 days after immunization with RSBC, which was performed intraperitoneally at a dose of 2×10^8 RSBC after 56 days after the first injection of CE. The data obtained were processed statistically using the Student's t-test. Differences between the parameters were considered reliable at $p < 0.05$.

Results

After chronic intoxication CE (60 days, daily subcutaneously 0.05 LD_{50}) indices of T-dependent humoral immune response - AFC to RSBC; IgM (function of Th1 and B lymphocytes), AFC to

RSBC (IgG) (function of Th2 and B-lymphocytes), T-independent humoral immune response (B lymphocytes function) - AFC to Vi-Ag (IgM), reaction DTH (function of Th1 lymphocytes) [7,8], NK activity decreased respectively by 45.5; 42.9; 40.0; 47.3 and 48.5% ($p<0.05$) [Table 1]. The mean activity of Th1 cells (AFC to RSBC - IgM, DTH) and Th2 lymphocytes (AOK to RSBC - IgG) [7,8] after chronic intoxication of CE decreased almost the same - respectively, by 46.4 and 42.9%. Suppression of the main parameters of the immunity system is due to the action on them of both the toxicant molecule and its more toxic metabolites formed as a result of the oxidation of CE by alcohol dehydrogenase and aldehyde dehydrogenase, respectively, to chloroacetaldehyde and chloroacetic acid [1-9], which inhibit the cycle tricarboxylic acids in mitochondria of lymphocytes and other blood cells [4,5].

Table 1: Effect of chronic intoxication CE (60 days, daily subcutaneously 0.05 LD50) on parameters of immunity system of Wistar rats (M ± m, n = 9-11).

Parameters	Control	CE
AFC to RSBC (IgM), 10^3	45.7±4.6	24.9±2.5*
AFC to RSBC (IgG), 10^3	54.6±5.5	31.2±3.4*
AFC to Vi-Ag (IgM), 10^3	29.0±3.3	17.4±2.2*
DTG, %	37.4±3.9	19.7±2.3*
NK activity, %	24.1±2.7	12.4±2.0*

*- $p<0.05$ compared with the control.

The effect of CE (Table 2) led to decrease of concentration in blood of IFN-γ, interleukins IL-2, IL-4, respectively, by 37.9; 40.9; 44.4% ($p<0.05$), pro-inflammatory cytokines TNF-α, IL-6 – by 36.7 and 33.3% ($p<0.05$) respectively, anti-inflammatory cytokines IL-10, IL-13, respectively by 30.1 and 28.4% ($p<0.05$). The ratio of IFN-γ/IL-4 after chronic intoxication of CE in the control was 6.8±1.1 and after action of the toxicant was 7.6±0.9. This confirms the obtained data indicating that under the influence of CE on Th1 and Th2 lymphocytes are equally affected [7,8]. The data obtained suggest that decrease of concentrations in blood of cytokine IFN-γ is due to the damage of CE Th1 lymphocytes, as well as NK and cytotoxic T lymphocytes [10]. Decrease in blood of IL-2 after intoxication of CE probably indicates the suppression of its production by T cells, including Th0 and Th1 type lymphocytes, reduction of T and B cells proliferation, and NK activity [11]. Reduction in blood of IL-4, apparently, occurs due to defeat of predominantly Th2 lymphocytes [7-12] by the toxicant and its metabolism products [3-9], and reduction of pro-inflammatory cytokine TNF-α and IL-6 characterizes decrease of their synthesis by macrophages, monocytes and lymphoid dendritic cells, as well as (in relation to IL-6)-Th0, Th2 lymphocytes and fibroblasts [7-13]. Reduction of concentration of anti-inflammatory cytokine IL-10 in blood is due to decrease in its production of Th2-, B lymphocytes, cells of monocyte-macrophage system, and IL-13 by Th2 lymphocytes [7-15].

Thus, chronic intoxication of CE (60 days, daily subcutaneously 0.05 LD50) causes suppression of humoral and cellular immune responses, activity of Th1 and Th2 lymphocytes (equally), production of lymphocytes and other cells of IFN-γ, interleukins IL-2 and IL-4, pro-inflammatory (TNF-α, IL-6) and anti-inflammatory (IL-10, IL-13) cytokines. These changes are mainly due to products of its biotransformation (chloroacetaldehyde and chloroacetic acid) that are more toxic than CE [3-9]. The main mechanisms for reducing the function of lymphocytes and other cells of the immunity system under influence of CE are apparently inhibition of tricarboxylic acid cycle in mitochondria of immune system cells [5] and initiation of lipid peroxidation of blood cell membranes [4-8].

Table 2: Effect of chronic intoxication CE (60 days, daily subcutaneously 0.05 LD50) on the cytokine content in blood of Wistar rats, pg/ml (M ± m, n= 6-8).

Cytokines	Control	CE
IFN-γ	1352±140	840±94*
IL-2	930±115	550±70*
IL-4	198±22	110±14*
IFN-γ / IL-4	6.8±1.1	7.6±0.9
TNF-α	60±8	38±5*
IL-6	93±10	62±9*
IL-10	710±80	496±52*
IL-13	141±14	101±12*

*- $p<0.05$ compared with the control.

Acknowledgment

None.

Conflict of Interest

None.

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