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CARBON MONOXIDE SUPPRESSES PRODUCTION OF PRO-INFLAMMATORY CYTOKINES DURING ISCHEMIA-REPERFUSION

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The endogenously produced gaseous transmitter carbon monoxide (CO) affects the cardiovascular system. Enzymes responsible for CO synthesis have been found in endothelial cells and smooth muscle. The mechanism of physiological action of CO is similar to that of nitric oxide. CO is formed from heme, which is part of the heme-containing proteins under the influence of heme oxygenase enzymes. Inducible heme oxygenase has a very important role in the adaptation of body cells and tissues to stress conditions. Ischemic-reperfusion injury accompanies cardiovascular diseases. When exposed to ischemia, mast cell macrophages are activated. After that, the production of pro-inflammatory cytokines increases. Elevated levels of these cytokines attract leukocytes and initiate inflammation in ischemic-damaged tissue.

Myocardial ischemia-reperfusion was modelled in vivo in Wistar rats, and a polypropylene ligature was applied to the left coronary artery. Two groups were formed: experimental and control. In animals from both groups, a 30-minute ischemia followed by a 90-minute reperfusion was performed. Animals in the experimental group, before surgery, received CO inhalation at a dose of 250 ppm for 1 hour before ischemia-reperfusion of the heart. Blood samples were collected from each animal. In blood serum obtained 3, 6, 12, and 24 hours after reperfusion, we measured the mRNA for cyclooxygenase (COX)-2, inducible nitric oxide synthase, and the levels of cytokines IL-1β, IFN-α, IL-6, and TNF-α.

Analysis of the obtained results showed that CO inhalation at a low dose and short exposure reduces the production of pro-inflammatory cytokines after ischemia-reperfusion. The level of IL-6 and IL-1β was reduced up to 3 hours after ischemia in the group of animals that received low concentrations of CO. mRNA expression for iNOS and COX-2 was also reduced in animals given a low dose of CO for up to 3 hours. TNF-α levels in blood serum decrease after exposure to inhaled CO for up to 6 hours after exposure to ischemia. 12 hours after reperfusion, mRNA expression for iNOS increased significantly. IL-1β after 5 hours recorded an increase in this cytokine.

Key words: *ischemia-reperfusion, carbon monoxide, pro-inflammatory cytokines, myocardium.*

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МОНООКСИД ВУГЛЕЦЮ ПРИГНІЧУЄ ПРОДУКЦІЮ ПРОЗАПАЛЬНИХ ЦИТОКІНІВ ПІСЛЯ ІШЕМІЇ-РЕПЕРФУЗІЇ

Відомо, що ендогенний газотрансмітер монооксид вуглецю (СО) здатен впливати на функціонування серцево-судинної системи. Ферменти, які відповідають за його синтез, було виявлено в ендотеліальних клітинах і гладенькій мускулатурі. Механізм фізіологічної дії СО подібний до дії оксиду азоту. СО під впливом ферментів-гемоксигеназ утворюється з гему, який входить до складу гем-вмісних білків. Індуцибельна гемоксигеназа має велике значення в адаптації клітин та тканин організму до умов стресу. Безсумнівно, що ішемічно-реперфузійне ушкодження супроводжує серцево-судинні захворювання. Під впливом ішемії активуються макрофаги та тучні клітини. Після цього спостерігається підвищення

продукції прозапальних цитокінів. Підвищення рівня цих цитокінів є хемоатрактантом для лейкоцитів та ініціює запалення в ішемічно-ушкодженій тканині.

У даному дослідженні моделювали ішемію-реперфузію міокарда in vivo у щурів лінії Wistar шляхом накладання поліпропіленової лігатури на ліву коронарну артерію. Було сформовано дві групи: експериментальну та контрольну. У тварин обох груп виконували 30-хвилинну ішемію з наступною 90-хвилинною реперфузією. Тварини експериментальної групи перед операцією отримували інгаляцію CO у дозі 250 ppm протягом 1 години до ішемії серця. По завершенню реперфузії збирали зразки крові від кожної тварини. Визначили мРНК для циклоксигенази (COX-2), індуцибельної синтази оксиду азоту, рівень цитокінів IL-1β, IFN-α, IL-6, TNF-α у сироватці крові, отриманої через 3, 6, 12 та 24 години після реперфузії.

Аналіз отриманих результатів показав, що інгаляції CO в низькій дозі та нетривалій експозиції знижує продукцію прозапальних цитокінів після ішемії-реперфузії. Рівень IL-6 та IL-1β був знижений до 3-х годин після ішемії у групі тварин, які отримували CO у низькій концентрації. Експресія mRNA для iNOS та COX-2 також була знижена в період до 3 годин у тварин, які піддавалися інгаляції CO. Рівень TNF-α у сироватці крові після дії інгаляцій CO знижується в період до 6 годин після реперфузії. Проте, через 12 годин після реперфузії експресія mRNA для iNOS значно зросла. Щось подібне спостерігали у випадку IL-1β, рівень якого через 5 годин почав підвищуватися.

Ключові слова: *ішемія-реперфузія, монооксид вуглецю, прозапальні цитокіни, міокард.*

Carbon monoxide (CO) is classified as an endogenously produced gas signalling molecule (gas transmitter). CO is an essential component of regulation; it influences the contraction of smooth muscle cells, which make up the walls of blood vessels. Enzymes that are responsible for the synthesis of the gasotransmitter have been found in the smooth muscle cells themselves and endothelial cells. The mechanisms of physiological action of CO are similar to those of nitric oxide. CO is formed from heme, which is part of various heme-containing proteins (hemoglobin, myoglobin, cytochromes, catalase, and peroxidase) under the action of heme oxygenase (HO) enzymes [16].

Heme oxygenase catalyzes reactions leading to the cleavage of the heme tetrapyrrole ring to form carbon monoxide and biliverdin. The inducible isoenzyme HO-1 plays an important role in the adaptation of cells and tissues of the body under stress [22].

The problem of ischemic damage is still very important [6]. Short-term ischemia is always associated with an increase in the number of cardiovascular diseases and organ transplantation. A particularly dangerous phenomenon after exposure to ischemia is the activation of chemical mediators and enzymes. Significant cell damage leads to the activation of macrophages and other cells of the immune system. As a consequence, the production of inflammatory mediators (e.g., TNF, IL-1, and IL-6) is increased. The appearance of these mediators attracts leukocytes and initiates the inflammatory process [9, 21].

The ischemia-reperfusion syndrome is the leading cause of early organ dysfunction after resection or transplantation. Oxidative stress, impaired oxygen transport mechanisms, inflammation, and mitochondrial dysfunction are the most important mechanisms of liver damage after ischemia, which lead to organ cell death by apoptosis or necrosis [18].

Recently, data have appeared on the prospects of using CO as a pharmacological agent for the treatment of various pathological conditions, especially lung diseases, systemic inflammation, and cardiovascular diseases [3]. The anti-inflammatory effect of CO is the most intriguing and promising use of this gas in the future, since inflammation underlies the development of many diseases of the cardiovascular system, including diabetes, cancer, and obesity, as well as the body's response to external pathogenic factors. A number of cell culture studies have shown that CO reduces the production of pro-inflammatory cytokines and stimulates the release of interleukin-10 [16]. A similar effect was observed in experiments on animals with induced inflammation, during

transplantation, or under the influence of allergens such as albumin [17]. In experiments on rats, it was found that CO inhalations had a protective effect in hyperoxic injuries; CO not only reduced inflammation caused by allergens in asthmatic mice but also protected against transplantation, pulmonary hypertension, and oxidative stress [2, 7].

Thus, the aim of this study was to determine the effect of carbon monoxide on the expression of pro-inflammatory cytokines after ischemia-reperfusion.

MATERIALS AND METHODS

Modeling of myocardial ischemia-reperfusion *in vivo*. The experiments were carried out on Wistar rats weighing 250–350 g, anesthetized with chloral hydrate at a dose of 460 mg/kg, under artificial lung ventilation through a tracheostomy (respiratory rate 60/min, tidal volume 3 ml/100 g body weight). Access to the heart was made by thoracotomy in the fourth intercostal space on the left. The pericardium was opened, the left coronary artery was identified, and a thin polypropylene ligature was inserted using an atraumatic needle. The experimental protocol included two groups: 1) sham-operated animals (n=6) — a ligature was applied under the left coronary artery, but ischemia was not induced with subsequent reperfusion (control); 2) ischemia-reperfusion (n=6) — a 30-minute ischemia followed by a 90-minute reperfusion was performed.

Blood was taken from the carotid artery for analysis in animals after summing up the ligature in the group of sham-operated animals or after the completion of the reperfusion period. Because induced I/R injury involves strong inflammatory responses, the use of CO to mitigate I/R injury is a straightforward application. In a series of experiments on rodents in our laboratory, exposure of the recipient to CO at a dose of 250 ppm for 1 hour before cardiac I/R.

Collection and storage of whole blood samples. Whole blood preparations from the carotid artery were collected (obtained 3, 6, 12, and 24 hours after reperfusion*)* in test tubes with ethylenediaminetetraacetic acid, immediately mixed with an equal volume of the Trizol (Invitrogen) reagent, frozen in liquid nitrogen, and stored at a temperature not exceeding –80°C.

SYBR green Real-time RT-PCR. mRNA for cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) was quantified in duplicate using SYBR Green. Cytokine levels of IL-1β, IFN-α (Elabscience, USA), IL-6 (Fine Test, China), in sera were determined by ELISA (BD Pharmingen), per the manufacturer's instructions.

Statistical analysis of the results was carried out using the «Statistica 10» program. The validity of the differences was determined according to the Man-Whitney and Wilcoxon criteria. Changes were considered likely under P<0.05. The research has been carried out under Directive 2010/63/EU on the protection of animals used for scientific purposes.

RESULTS AND DISCUSSION

CO exposure before ischemia-reperfusion affected the level of pro-inflammatory cytokines after ischemia-reperfusion. A decrease in the level of pro-inflammatory cytokines occurred within 3 hours after reperfusion. Of particular note is the level of IL-1β, which after six hours after reperfusion increased in the group that received inhaled CO (Fig. 1-B).

The inflammatory role of IL-1β is manifested by an increase in the mobility of neutrophils, stimulation of cell activity in the focus of inflammation, and an increase in the activity of other cytokines. Interleukin-1 beta is involved in the temperature reaction due to its effect on the hypothalamus, and an increase in its production is manifested by fever. It stimulates the production of acute-phase proteins in the liver.
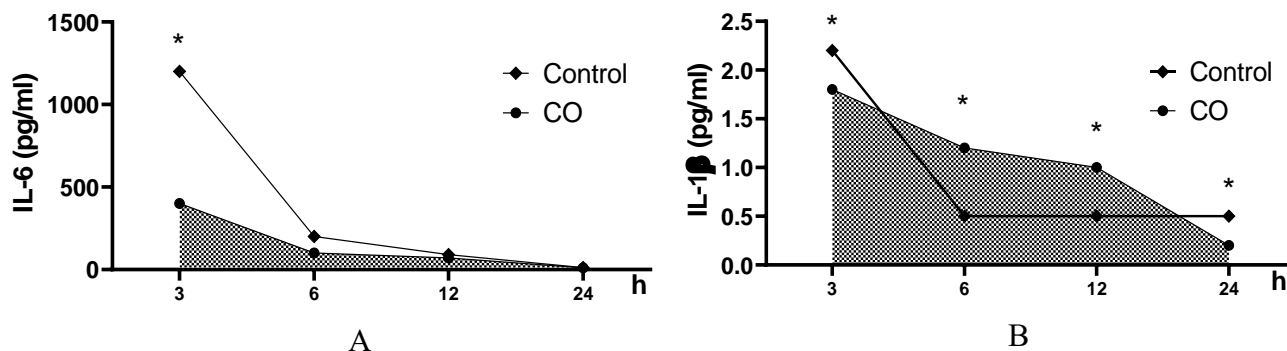
Fig. 1. Dynamics of the level of IL-6 (A) and IL-1β(B) in blood serum after ischemia-reperfusion of the coronary artery
*Notes: * P<0.05 compared to control values*

Interleukin-6 is a pro-inflammatory cytokine that has a wide range of effects on the body's organs and systems, including the blood, liver, immune and endocrine systems, and metabolism. It turned out that in the group of animals that received inhaled CO after exposure to ischemia, the level of IL-6 was reduced in comparison with the control (Fig. 1-A). The dynamics of IL-1β indices were different - CO exposure slightly reduced their level. However, three hours after ischemia, its increase was observed to be two or more times greater than the control (fig. 1-B).
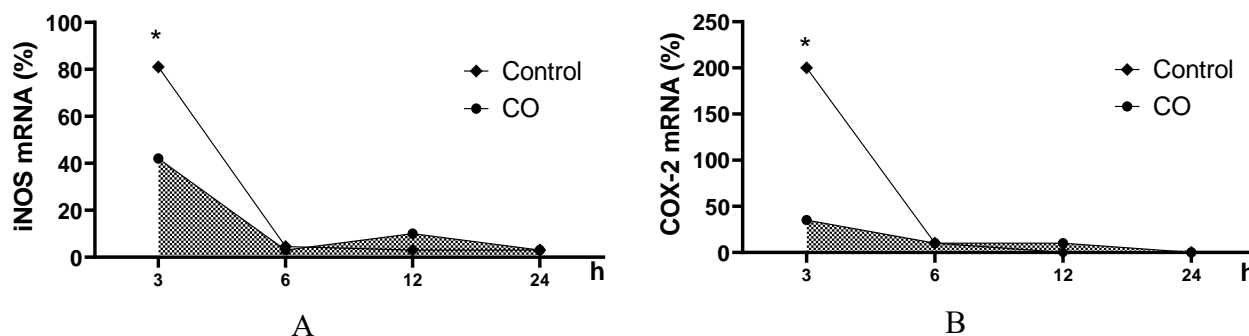

Fig. 2. Expression of mRNA iNOS (A) and COX-2(B) in the blood of the study groups
*Notes: * P<0.05 compared to control values*

Expression of mRNK iNOS in the CO group was reduced up to 3 hours after ischemia. After 3 hours, it did not significantly differ from the control. Even 12 hours after ischemia, there was an increase in mRNK iNOS expression in the CO group (fig. 2-A). mRNK COX-2 expression was also reduced 3 hours after ischemia. After this period, no significant differences from the control were observed (Fig. 2-B).

TNF-α is regarded as an important component of the complex cytokine system [14]. The presence of TNF-α in most atherosclerotic damaged vessels and its absence in normal vessels suggests that this cytokine plays a role in atherogenesis, most likely through the activation of growth factors, cytokines, chemoattractants, and stimulation of adhesion molecule formation. TNF-α overexpression in patients with myocardial ischemia predicts a high risk of vascular complications. TNF-α levels were lower in the group that received inhaled CO up to 6 hours after ischemia (when compared to the control). In the control group, which did not receive CO inhalation, the level of this cytokine was increased (Fig. 3).
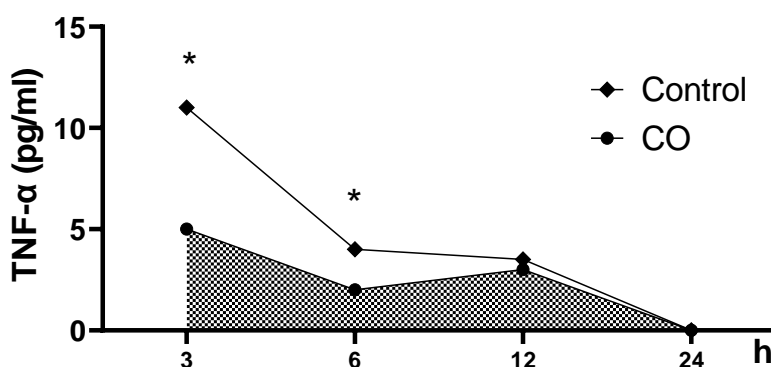
Fig. 3. The dynamics of TNF- α in blood serum after coronary artery ischemia-reperfusion

*Notes: * P<0.05 compared to control values*

These results indicate that CO can be used to reduce the risk of ischemia-reperfusion complications. Excess TNF-α production is known to cause hemodynamic disorders (reduces myocardial contractility, minute blood volume, and diffusely increases capillary permeability) as well as cytotoxicity in body cells [8, 11].

The obtained results indicate that the inhalation of air that contained a low concentration of CO had a beneficial effect on the cardiovascular system after ischemia-reperfusion. These results are consistent with the results obtained by researchers who studied the effect of CO on recovery processes after organ transplantation [15].

As is known, IL-6 is synthesised by activated monocytes and macrophages, fibroblasts, and endothelial cells during inflammation, trauma, hypoxia, and bacterial infections. The biological role of IL-6, first of all, is to induce repair mechanisms and activate immune defences (activation and differentiation of T-cells, maturation of B-cells, synthesis of C-reactive protein in the liver, increased hematopoiesis). This cytokine is a marker of acute systemic inflammation. Excessive production of interleukin-6 causes tissue damage due to an autoimmune reaction [5].

After comparing the level of IL-6, some features were clarified: CO at a low dose affected the bodies of experimental animals. The level of IL-6 β was reduced up to 3 hours after ischemia in the group of animals that received low concentrations of CO. A negative phenomenon was that an increase in the level of this cytokine was observed after. Exposure to low CO concentrations also reduced the level of mRNA expression for iNOS. Also, as in the case of IL-6 β, an increase in mRNA expression for iNOS was observed. Accordingly, the formation of peroxynitrite increased in the experimental group. As is known, increased production of peroxynitrite is associated with inflammation.

Expression of mRNA COX-2 was reduced up to 3 hours after ischemia in animals that received CO. However, other recent evidence suggests that prostacyclins as well as COX-2 may also play a role in preventing gastric injury in response to stroke, especially ischemia. Prostaglandins produced by COX-1/2 play an important role in normal physiology and development. Chronic use of a popular specific COX-2 inhibitor increases the risk of heart disease [1, 10].

One such large retrospective study was able to show a class effect, according to which increasingly selective inhibition of COX-2 led to an increase in cardiovascular risk [1]. Although these results provide a significant impetus for research on the role of COX-2 in cardiac pathology, they provide little information about potential mechanisms. After all, aspirin has long been prescribed to prevent cardiovascular disease, and aspirin inhibits both COX-2 and COX-1 [20].

Known studies have demonstrated COX-2 staining in cardiomyocytes near the site of infarction in 39% of patients with myocardial ischemia. This COX-2 staining has been associated with myocyte apoptosis, an enlarged heart, and symptomatic heart failure. However, a limitation of

this study was its small size, with a total of 23 such patients. Another small study found COX-2 immunostaining near areas of fibrosis in heart myocytes from patients with heart failure but not in control hearts [10].

Interestingly, widespread COX-2 staining has been observed in myocytes in the hearts of patients with sepsis. This finding highlights the extent to which inflammatory stimuli can induce COX-2, and even stress as severe as heart failure can only induce localized COX-2 expression. On a more physiological level, some authors have observed that COX-2 inhibition blocked serotonin-induced coronary contracture in patients undergoing cardiac surgery, but only after the onset of ischemia. This study highlights the role that COX-2 may play outside of cardiomyocytes in the heart. COX-2 in endothelial cells, cardiofibroblasts, or other types of interstitial cells may have the ability to influence vascular biology and cardiac remodeling, which may be of paramount importance during acute myocardial ischemia or heart failure.

Sticial cells may have the ability to influence vascular biology and cardiac remodeling, which may be of paramount importance during acute myocardial ischemia or heart failure [20]. A selective COX-2 inhibitor has been shown to improve the functional aspects (wall thickness and partial shortening) of rat hearts with heart failure secondary to coronary artery ligation. Similar results were obtained in a study on mice.

Importantly, the serum level of TNF- in animals given CO decreases (when compared to the control group) up to 6 hours after ischemia. Studies have shown a correlation between the severity of heart failure and levels of the pro-inflammatory cytokine TNF-α and one of its secondary mediators, interleukin-6 (IL-6), suggesting their potential as biomarkers. One of the key pro-inflammatory cytokines that has been extensively studied, including its use in therapeutic strategies and as a potential biomarker associated with heart failure, is TNF-α [4, 8, 13, 21].

One of the key mediators of TNF-α signalling in cells is NF-κB, again reflecting the dual role that TNF-α plays in cardiac physiology and pathology [19]. Despite the complexities of TNF-α signaling, multiple studies have shown that specific expression of TNF-α in cardiomyocytes results in a dose-dependent depression of cardiac function [11, 12].

CONCLUSIONS

The experiment showed that CO at a low dose affected the bodies of the experimental animals. The level of IL-6 was reduced up to 3 hours after ischemia in the group of animals that received low concentrations of CO. In comparison to the control group, the level of IL-1 was reduced for up to 3 hours. After 5 hours, on the contrary, an increase in this cytokine was recorded. mRNA expression for iNOS in animals that received a low dose of CO was reduced for up to 3 hours. But after 12 hours of ischemia, the opposite was observed: mRNA expression of iNOS significantly increased. Expression of mRNA COX-2 was reduced up to 3 hours after ischemia in animals that received CO. TNF- levels in the blood serum of animals given CO decrease (in comparison to the control group) for up to 6 hours after ischemia.

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