к предъявленному стрессу у быстрых метаболизеров по сравнению с медленными. Особенно интересно разнонаправленные изменения между содержанием цитохрома Р450 и уровнем активности изоформ CYP3A. Следует обратить внимание на вовлеченность CYP3A-зависимого монооксигенирования в регуляцию стресса за счет их участие в метаболизме глюкокортикоидов. В таких случаях возможна селективная «up- регуляция» CYP3A активности, имеющая цитокин-зависимый характер. Ранее ее наличие было продемонстрировано в экспериментах на крысах с введением рекомбинантного IL-1β (Сибиряк С.В. и соавт., 2004). В этих исследованиях снижалась активность изоформ CYP1A1 и CYP2B1/2 в ответ на введение препарата беталейкина. Но при этом был повышен уровень CYP3A-зависимого монооксигенирования на фоне повышенного содержания кортикостерона. Аналогия между полученными нами результатами и данными С.В.Сибиряка и соавторов становится понятной- если учесть, что при однодневной и трехдневной гипокинезии наблюдалось повышение содержания провоспалительных цитокинов, таких как IL-1, IL-6 ,TNF.

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NITRIC OXIDE STORES IN CORONARY BLOOD VESSELS OF DOGS WITH METABOLIC SYNDROME

Barlow M,A.,[*] Caffrey J.L.,[*] Downey H.F.,[*] Manukhina E.B.[,**]*

[*] *University of North Texas Health Science Center, Fort Worth, USA*

[**] *Institute for General Pathology and Pathophysiology, Moscow, Russia*

Introduction. Nitric oxide (NO) is a highly reactive substance which can be bound into complexes (NO stores) used for transport and intracellular storage of NO. S-Nitrosothiols (RS-NO) and dinitrosyl iron complexes (DNIC) are the main forms of NO storage and transport [4]. Both RS-NO and DNIC exist in two forms---high molecular weight, i.e. bound to thiol groups in proteins, and low molecular weight, i.e. attached to crystalloid thiols such as cysteine or glutathione. The high molecular weight complexes are much more stable than the low molecular weight ones, and they are considered to be the primary intracellular NO stores [4].

NO stores are formed after any increase in NO irrespective of the cause. NO stores in blood vessel walls can be revealed using low-molecular thiols which penetrate cells and extract vasoactive NO from protein-bound DNIC. This reaction releases NO and induces vasodilation in proportion to the size of the NO stores [3]. A key function of NO stores is defense against NO toxicity after its overproduction. Efficiency of NO store formation determines the extent of this defense [5].

Efficiency of NO storage in the vascular wall can be indexed by the maximum amount of NO stores which can be potentially accumulated. This determines the extent of NO store defense. During NO overproduction, a part of the excessive NO binds to the NO store, whereas the unbound part of NO affects target organs. When the efficiency of NO storage is high, the volume of NO stores is large, and potentially detrimental effects on target organs are smaller [3].

Metabolic syndrome (MS) is associated with NO overproduction. Zahedi et al. [6] reported that the concentration of nitric oxide metabolites is significantly higher in both male and female subjects with metabolic syndrome. This NO overproduction is detrimental for insulin-dependent metabolic processes [6] and endothelial function [2].

The aim of our study was to evaluate the ability of coronary blood vessels to store NO in dogs with MS.

Materials and methods. Studies were conducted in control and chronically high-fat-fed (6 weeks on diet comprised of 22.8% protein, ~44.3% fat, 32.9% carbohydrate) dogs. Dogs consuming the fat diet developed MS, which was demonstrated by weight gain, insulin resistance, tachycardia and lower femoral blood flow.

Hearts were excised and immersed in cold (4°C) lactated Ringer solution. Left circumflex coronary arteries (LCA) were dissected from the hearts and cleaned of periadventitial fat. Arteries were cut into 5-mm rings and mounted in organ baths for isometric tension studies at passive tension about 4.0 g.

Experiment 1. Measuring the existing NO stores. Rings were precontracted with U-46619 (thromboxane A_2 mimetic, 625 nmol/l). When the contraction reached a plateau, N-acetylcysteine (NAC, 10^{-3} M) was added to the organ bath. Existing NO stores were revealed by the relaxation response to NAC. The relaxation magnitude was expressed as a percent of the contraction induced by U-46619.

Experiment 2. Measuring the potential capacity of NO stores. To determine the “capacity” of NO stores, LCA was incubated with a NO donor, dinitrosyl iron complex (10^{-5} M) for 20 min. After washout LCA was precontracted with U46619 and NAC was added to release NO from the accumulated NO stores.

For both experiments, size of NO stores was estimated as the magnitude of NAC-induced relaxation of LCA.

Results and Discussion. In preliminary experiments, detection of NO stores was done in the presence of the NO synthase inhibitor, N^{ω}-nitro-L-arginine (LNNA). This prevented any contribution of de novo synthesized NO

to the relaxation response. As no effect of LNNA on the LCA response to NAC was observed, further experiments were performed without LNNA.

Small NO stores were revealed in control LCA (6.3±1.4%) (Fig. 1). NAC-induced relaxation of LCA from dogs with MS was larger than in control LCA (11.0%±1.6, $p<0.05$). Since the size of NO stores indirectly reflects the level of free NO in the body [5], this result suggests NO overproduction in dogs with MS.

After incubation of LCA with excess of the NO donor, DNIC, relaxation of LCA from control animals was significantly greater than that of LCA from dogs with MS (70.8±11.9% vs. 40.1±5.9%, respectively) (Fig. 2). This result shows that the "capacity" of NO stores is considerably reduced in coronary arteries from dogs with MS; therefore, their ability to bind excessive NO is much lower than in control.

MS is a clinical condition characterized by a combination of classic cardiovascular risk factors, including hypertension, insulin resistance, hyperglycemia, and dyslipidemia [1]. Endothelium-dependent relaxation is impaired in blood vessels from animals with MS due to peroxynitrite generated in the vessel walls as a result of NO overproduction [2].

Formation of NO stores is an important mechanism of blood vessel adaptation to changes in NO production, particularly to NO overproduction. Normally, efficiency of NO storage increases under conditions of long-term increase in plasma NO level and decreases in NO-deficient states [5].

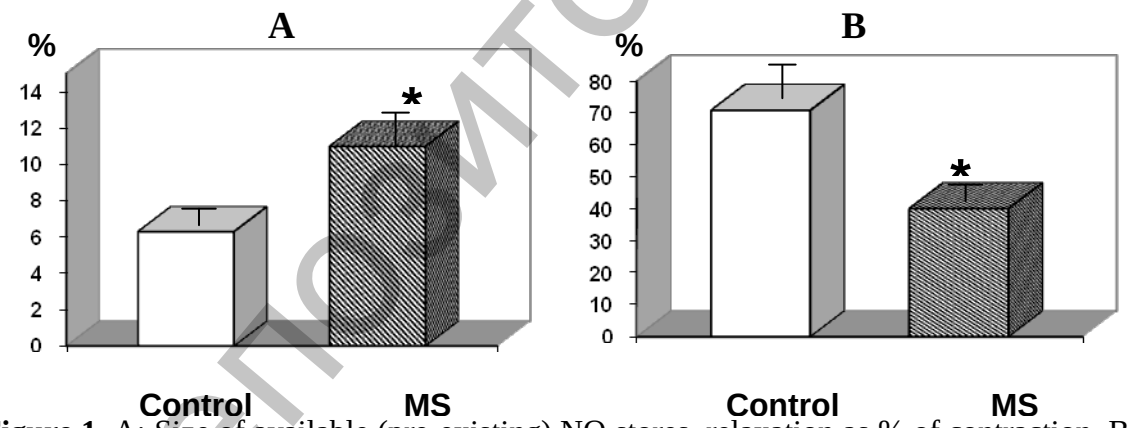

Figure 1. A: Size of available (pre-existing) NO stores, relaxation as % of contraction. B: Potential capacity of NO stores, relaxation as % of contraction.

The increase in NO storage efficiency during adaptation to high NO level protects vessels against cytotoxic and hypotensive effect of excessive NO. In dogs with MS, we observed failure of this adaptive mechanism, since incubation with an NO donor produced smaller NO stores in coronary vessels.

Therefore, the excessive NO produced during metabolic syndrome is detrimental to blood vessels and endothelial function. The reduced ability to bind NO to NO stores aggravates these disturbances in MS. Thus, it may be clinically important to develop means for modulation of NO storage in MS and other conditions.

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PYRUVATE MODULATION OF NRF2 AND HO-1 IN H_2O_2-CHALLENGED BOVINE BRAIN ENDOTHELIAL CELLS: IMPLICATIONS FOR NEUROVASCULAR ISCHEMIA/REPERFUSION INJURY

Scott GF, Ryou M-G, Awasthi YC, Mallet RT
Departments of Integrative Physiology and Pharmacology and Neuroscience
University of North Texas Health Science Center, Fort Worth, Texas, USA

Introduction. Cardiac arrest imposes severe energy depletion, Ca^{2+} overload and oxidative stress that damages the brain, leaving survivors prone to cognitive impairment, dementia, and seizures. Aside from hypothermia, no treatment after cardiopulmonary resuscitation and return of spontaneous circulation has been found capable of reducing cognitive deficits. The significance of endothelial cell damage as a pivotal step in brain I/R injury stems from those cells' position in the "neurovascular unit," an integrated entity of functionally coordinated microvessels, pericytes, extravascular basal lamina, astrocytes whose 'end-feet' encircle 95% of brain microvessels, and neurons (Figure 1).The tight junctions linking the cerebrovascular endothelial cells represent the principal permeability barrier to the indiscriminate diffusion of molecules between the circulation and the highly specialized environment of the cerebral interstitium. Disruption of the cerebrovascular endothelium is a pivotal event in the progression of post-ischemic brain injury, yet also a potential target for neuroprotective interventions.

Based on prior reports of pyruvate-induced protection ofcultured neuroblastoma cells[1]and *in situ* rat cerebrum [2] challenged by ischemia-reperfusion,