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Chapter 1 : Get Pathophysiology and Clinical Applications of Nitric Oxide PDF - Kezdolap Books

Research on the key mediator nitric oxide has increased exponentially over the last ten years. It is now clear that, in addition to its role within the cardiovascular system, this mediator is also implicated in the normal physiological function and disease pathology of several organs and systems.

The Therapeutic Uses of Nitric Oxide Published on February 7, Large clinical trials are needed to determine the efficacy and safety of this treatment method. Primary, or unexplained, pulmonary hypertension is a rare lung disorder in which the blood pressure in the pulmonary artery rises above normal levels because of derangements in either small pulmonary arteries or veins in the absence of underlying cardiac or pulmonary disease. Normal mean pulmonary-artery pressure is approximately 14 mm Hg at rest. In the primary pulmonary hypertension patient, the mean pulmonary artery pressure is more than 25 mm Hg at rest and more than 30 mm Hg during exercise. This abnormally high pressure is associated with changes in the small blood vessels of the lungs, resulting in an increased resistance to blood flow through the vessels. Over time, the right ventricle will enlarge and, eventually, fail. Histopathologically, several lesions have been described in primary pulmonary hypertension: These lesions are not specific to primary pulmonary hypertension; they are recognized in several secondary forms of pulmonary hypertension. ETIOLOGY Researchers believe that one of the ways that primary pulmonary hypertension starts is injury to the layer of endothelial cells that lines the small blood vessels of the pulmonary system. This injury, which occurs for unknown reasons, may bring about changes in the way that the endothelial cells interact with the smooth muscle cells in the vessel wall. As a result, the smooth muscle contracts more than normal, thereby narrowing the vessels. This process eventually results in the development of extra amounts of tissue in the walls of the pulmonary arteries. The amount of muscle increases in some arteries, and muscle appears in the walls of arteries that normally have no muscle. With time, scarring, or fibrosis, of the arteries takes place, and they become stiff as well as thickened. Some vessels may become completely blocked. There is also a tendency for blood clots to form within the smaller arteries. In response to the extra demands placed on it by primary pulmonary hypertension, the heart muscle in the right ventricle becomes hypertrophied. Overworked and enlarged, the right ventricle gradually becomes weak and loses its ability to pump enough blood to the lungs. Eventually, the right side of the heart may fail completely, resulting in death. In some patients, the disease progresses fairly rapidly. The first symptom is frequently tiredness, with many patients and their physicians thinking that they tire easily because they are simply out of shape. Dyspnea, dizziness, syncope, edema in the ankles, cyanosis, and angina are among the symptoms of the disease. Oral vasodilators, such as calcium channel-blocking agents, may lead to reductions in pulmonary artery pressure and, therefore, improvement in right ventricular function. In patients who are responsive to calcium channel blockers, survival is markedly enhanced. For the remainder of patients, other options are needed. Prostacylin is a good mediator. It maintains pulmonary blood vessels in a relaxed and nonproliferative state. It has been shown3 that chronic intravenous infusion of prostacyclin has beneficial effects in primary pulmonary hypertension patients. In most patients, chronic prostacyclin use results in improved exercise tolerance and decreased signs of right ventricular failure. In addition, pulmonary arterial pressures may gradually decrease, independently from the acute effects of the drug. This slow improvement in pulmonary hypertension suggests that epoprostenol sodium may cause other beneficial changes within the pulmonary vasculature, such as preventing platelet aggregation or inhibiting the detrimental remodeling thickening of the vessel wall seen in primary pulmonary hypertension. Unfortunately, chronic prostacyclin has several drawbacks. It is a systemic vasodilator associated with numerous widespread adverse effects, including diarrhea, dizziness, rash, leg and foot pain, jaw pain, and hypotension. In addition, the central venous catheter may become infected, requiring antibiotic therapy or, in many cases, removal of the catheter. Therefore, a safer, more convenient treatment for primary pulmonary hypertension is needed. Nitric oxide may meet that need. In , Furchgott and Zawadski reported that the intact endothelium plays a critical role in vascular

relaxation. Using isolated strips of arteries, they discovered that when acetylcholine interacts with the endothelial cells of these vessels, substances are released that cause relaxation of vascular smooth muscle. One of these substances was later termed the endothelium-derived relaxing factor EDRF. Furchgott and Zawadski discovered that sections of the aorta would relax in response to agonists only if the inner linings of endothelial cells were intact. Aortic rings with no endothelial cells, however, could not relax. Endothelial cells thus released an agent that relaxed vascular smooth muscle; within several years, it was discovered that this EDRF was nitric oxide. Whether EDRF is identical to nitric oxide gas or a nitric-oxide-containing compound is still under investigation. The nitric oxide gas then diffuses into the adjacent smooth muscle cells, where it activates guanylate cyclase. When nitric oxide crosses into the intravascular space, it rapidly binds with hemoglobin, forming nitrosylhemoglobin which is metabolized to methemoglobin. This rapid transformation, along with the short biological half-life of nitric oxide 0. Recent reports8 confirm the role of endogenous nitric oxide as a modulator of vascular tone in the pulmonary circulation. Nitric oxide is an unusual messenger. It is a small molecule composed of one atom each of nitrogen and oxygen, not to be confused with nitrous oxide two atoms of nitrogen and one of oxygen , an inhalational anesthetic gas. Nitric oxide is an uncharged molecule with an unpaired electron. These characteristics of nitric oxide make it an ideal messenger molecule: With an unpaired electron, it is called a radical molecule, which is highly reactive having a half-life of 2 to 30 seconds ; after transmitting a signal spontaneously, it decays into nitrite. The tiny nitric oxide molecule, a reactive gas, functions both as a signaling molecule in endothelial and nerve cells and as a killer molecule in activated immune cells-and it can be used as a new medicine through inhalation. Small, simple, and highly toxic, nitric oxide seems an unlikely biological jack-of-all-trades. This previously elusive and obscure chemical is proving to be of vital physiological significance. Nitric oxide may be the first of a novel class of neurotransmitters. Endothelial cells continuously release small amounts of nitric oxide, producing a basal level of vascular smooth muscle relaxation. When inhibitors of nitric oxide are infused into animals or humans, nitric oxide production is inhibited, vascular smooth muscle contracts, and blood pressure increases. In the presence of oxygen, it exists for about 6 to 10 seconds and then is converted into nitrate and nitrite and nitrogen dioxide. It was shown2 that inhaled nitric oxide at very low doses 5 to 20 ppm completely reversed hypoxia-induced pulmonary vasoconstriction. Moreover, no hemodynamic effect occurred, probably because of the inactivation of nitric oxide by hemoglobin in the circulation. Thus, inhaled nitric oxide appears to be the first selective pulmonary vasodilator. Subsequently, numerous reports2 confirmed the acute pulmonary vasodilating effects of inhaled nitric oxide in primary and secondary forms of pulmonary hypertension. In patients with reactive pulmonary vessels, a decrease in pulmonary arterial pressures is noted within seconds of the inhalation of nitric oxide. Given the acute effects of inhaled nitric oxide in pulmonary hypertension, the possibility of chronic therapeutic use emerges. To date, chronic inhaled nitric oxide, delivered via nasal cannula, has been used for up to 3 years in primary pulmonary hypertension patients. The basis of the delivery system is a commercially available oxygen-pulsing device that delivers gas via nasal cannula for a set length of time at the onset of each inspiration. The device is demand-activated, responding to negative inspiratory pressure. The source concentration of nitric oxide delivered with each pulse is ppm. The duration of each pulse and the flow rate were constant. A dose-response relationship was determined at a specific pulse setting to produce The actual concentration of nitric oxide delivered to the alveoli is less than the source concentration of ppm. The amount of nitric oxide exhaled into the environment is minimal because the pulsed nitric oxide is delivered during the initial inspiratory phase. Using this system, several patients with primary pulmonary hypertension and one patient with idiopathic pulmonary fibrosis IPF have been given chronic inhaled nitric oxide. Twelve weeks after therapy began, repeat cardiac catheterizations demonstrated improvement in 4 of 7 patients. One patient, who has continued on nitric oxide for 3 years, has had complete resolution of pulmonary hypertension. The patient with IPF had acute improvement in Pao2 when given inhaled nitric oxide. Improvement in hypoxemia was accompanied by an acute decrease in pulmonary arterial pressure. This patient demonstrates the benefits of using a selective pulmonary vasodilator for patients with pulmonary hypertension and

parenchymal lung disease. A systemic dilator might, in fact, worsen oxygenation in such a patient by increasing shunting through poorly ventilated lung zones. Inhaled nitric oxide, as evidenced by the response seen in patients with adult respiratory distress syndrome, generally decreases intrapulmonary shunting. The results of chronic delivery of nitric oxide to patients with pulmonary hypertension patients are preliminary. Clearly, large preferably randomized clinical trials are needed to determine the efficacy and safety of chronically inhaled nitric oxide. We now have, however, a basic biological rationale, animal data, and preliminary human data to give us great optimism regarding the future applications of this simple, but potent, molecule. National Institutes of Health. Improvement in pulmonary hypertension and hypoxemia. Respir Crit Care Med. The biology of nitrogen oxides in the airways. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension.

Chapter 2 : Endothelial Health

Hypercoagulation of blood, thrombosis, clotting disorders Renal Failure Metabolic Syndrome- abdominal obesity, hypertension, insulin resistance Sleep Apnea as a cause of endothelial dysfunction Glaucoma Given that a wide body of research has established the role of the endothelium and nitric oxide in the overall health of the human body, the importance of understanding how the endothelium becomes damaged, and how to prevent that damage, becomes clear. Aside from genetic mutations, which may contribute to endothelial dysfunction, various studies and clinical trials have helped establish at least some of the causes of endothelial damage, as well as suggest some preventative measures. Additionally, to counteract toxin exposure, our bodies contain efficient systems for removing waste. For example, our liver, kidneys and lymphatic system all work to remove toxins from our bodies. However, our increasing understanding of the endothelium has allowed us to identify potential sources of damage, and to suggest likely preventative measures. Potential Causes of endothelial dysfunction Oxidative stress Our bodies constantly react with oxygen as we breathe and as our cells produce energy. However, our use of oxygen is a double-edged sword: Free radicals are atoms or molecules with electrons which have lost their partner electron, often as a result of our respiratory or metabolic process, or from outside influences. Free radicals can disrupt the balance of NO, damage the endothelium and leave it overly permeable, allowing toxins to pass into our tissues9. In most instances, our body has an adequate supply of antioxidants obtained from food to neutralize these free radicals, but if the body is depleted, or if there are too many coexistent factors, injury to the endothelium and a change in the balance of NO may occur. Factors which can increase the number of free radicals in our bodies include: Smoking reduces nitric oxide in the blood vessels and causes an increase in ADMA, the modified amino acid which puts strain on the heart. Nicotine also causes vessels to narrow, so that less oxygen is delivered to the heart. Platelets become stickier, and therefore clot formation is increased. Additionally, smoking raises the level of carbon monoxide in the blood, which increases the risk of injury to endothelial cells11 Metals exposure, including mercury and cadmium12 Air pollution, especially diesel exhaust13 Arsenic and chlorine14 which can sometimes be found in drinking water Eating Bad fats Some fats are not good for our bodies and should be avoided. Heavily saturated animal and dairy fats, trans fats, hydrogenated fats and chemically-altered fats from vegetable shortening and oils can all damage the endothelium Stress Cortisol, the hormone released into the body when we are under acute stress, impairs endothelial production Sleep deprivation Lack of restful sleep, due to obstructive sleep apnea or, potentially, oxygen deprived sleep , or not enough time in bed, may create endothelial dysfunction and constricted blood flow Acute Bacterial infections Chlamydia pneumonia, Lyme disease, Sepsis, Staph - all of these infections can become chronic as the endothelium is weakened, and bacteria may enter body tissues, compromising or impairing the immune system Low Vitamin D levels A lack of sunshine and dietary vitamin D has been shown to be harmful to the endothelium Low Vitamin B12 levels Low vitamin B12 creates high levels of homocysteine in the blood a sulfur containing amino acid which damages the endothelium. An unbalanced diet, a strict vegetarian diet that excludes all meat, fish, dairy and eggs diet, or a diet overly reliant on processed foods, could all lead to low vitamin B12 levels, potentially damaging the endothelium High glucose intake Ingesting too much glucose in the form of simple sugars increases endothelial cell death and increases oxidative stress Sedentary Lifestyle Lack of physical exertion, especially cardio-vascular exercise, damages the endothelium Preserving and enhancing Endothelial health Research suggests several methods for restoring the endothelium to its healthy natural state, potentially relieving inflammation, normalizing blood pressure, and minimizing the harmful effects of C-Reactive protein or various antigens that may cross the blood brain barrier. Healthy endothelium

is largely impermeable to unnecessary breaches of the blood brain barrier, thus protecting central nervous system tissue. Endothelial health is not achieved through a single pill or a simple cure. The process of endothelial restoration is multifaceted, and takes discipline and dedication. Again, please note that this information is purely informational â€" all dietary or nutritional decisions should be made in conjunction with your physician or medical professional. Physical Activity Physical activity has been shown to stop endothelial dysfunction, especially cardiovascular exercise. Inactivity increases the breakdown of the blood vessels. A sedentary lifestyle is not beneficial to the endothelium; daily moderate exercise is recommended Stress reduction Reducing stress through lifestyle changes can reduce endothelial damaging cortisol. While no single stress reduction technique works for everyone, common options include meditation, visualization, exercise, mindful communication, prayer for those of faith , and intentional breathing practices such as tai chi and yoga. This substance, which actually consists of a group of compounds called flavonolignans, helps repair liver cells damaged by toxic substances. Silymarin also helps prevent new liver cells from being destroyed by toxins, reduces inflammation, and has potent antioxidant effects. Sylmarin has been shown to protect the endothelium Promote vitamin D intake Given that vitamin D is derived from sunlight, spend time outdoors. Because of sunscreen and our indoor lives, many people are not receiving enough of this potent vitamin. Vitamin D acts as a hormone in our bodies, working with the parathyroid to keep proper levels of calcium in our blood. It can also be taken as a supplement. Research on the efficacy of various types of vitamin D supplements is still on-going; we encourage anyone interested in vitamin D supplements to investigate current recommendations with their physician. The effects of laughter lasted for 45 minutes after the movie had finished. Nutrition and supplements eat healthy food; avoid processed foods Avoid processed foods whenever possible. Not only do processed foods often contain high levels of salt, which is linked to vascular problems, preservatives and various chemicals for coloring and flavoring, but recent research has shown a strong correlation between production and consumption of processed foods and MS Eating a diet of whole foods unprocessed foods; foods that retain the natural state provide ample levels of nutrition and antioxidants, supplements can also be taken to help our body reach optimal nutritional levels. Antioxidants bind with free radicals to minimize the damage they cause to the endothelium. Vitamin A and carotenoids are found in carrots, squash, broccoli, sweet potatoes, tomatoes, kale, collards, cantaloupe, peaches and apricots brightly-colored fruits and vegetables Vitamin B is common in fish, meat and dairy products. Vitamin B12 is frequently used in combination with other B vitamins in a vitamin B complex formulation. This helps maintain healthy nerve cells and red blood cells and is also needed to make DNA, the genetic material in all cells. Vitamin C is found in citrus fruits like oranges and limes, green peppers, broccoli, green leafy vegetables, strawberries and tomatoes. Flavonoids, a specific kind of antioxidants from plant pigments, reduce inflammation and improve vascular health. Quercetin, found in apple skin, red onion, red grapes, as well as ECGC found in green tea , also contain important antioxidants and nutrients. Healthy fats Salmon, trout, herring, avocados, olives, walnuts, and olive oil all contain healthy fats. An omega-3 fish oil supplement is important, particularly if you do not have fish in your diet. Current research suggests that the most important fish oil fatty acid is docosahexaenoic acid DHA. We have long known that fish is healthy, but it is now proven that the omega-3s in fish fat improve endothelial function by enhancing nitrec oxide production, increasing HDL good cholesterol levels, and reducing LDL bad cholesterol and triglyceride levels. Further, fish oils have been shown to reduce production of free radicals and substances that cause inflammation in the body Healthy Proteins Reducing red meat proteins in your diet and replacing them with vegetable and soy proteins will help the endothelium. Animal proteins contain mixtures of amino acids that produce more of the amino acid methionine, which is the precursor for homocysteine, which can damage the endothelium. Vegetable proteins are healthier because they contain no saturated fat and less methionine. Vegetable proteins also have more fiber and nutrients called phytonutrients. Soy proteins produce a mixture of amino acids that have more L-arginine. L-arginine is essential for the production of NO. Soy proteins also contain other phytochemicals - the biochemical products of plants - which are healthy for the endothelium. Other L-arginine sources include

fish, nuts, legumes, beans and chicken Probiotics Probiotics are live microorganisms in most cases, bacteria that are similar to beneficial microorganisms found in the human gut. They are also called "friendly bacteria" or "good bacteria. Essential Minerals Studies have shown that magnesium, zinc, and calcium are all important to preserving endothelial health28, Look for supplements which contain all three of these minerals in balance. Antithrombic and Anti-inflammatory Herbs Curcumin, Salvia, Ginko, and Garlic are all shown to decrease inflammation and regulate blood viscosity, preventing hypercoagulation. Proteolytic Enzymes, both serrapeptase and nattokinase, are enzymes which reduce inflammation and pain and help blood viscosity by regulating clotting. Bromelain, found in pineapple, is one of the best anti-inflammatory substances known. Periventricular Lesions on Mlutiple Sclerosis: Current Neurovascular Research, 6 2 ; Kolb, H. Nitric oxide in autoimmune disease: Retrieved March 12, , from http: Clinical Chemistry, 55, Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor s. American Journal of Physiology. Papaioannou, PhD, Paraskevi Th. Acute smoking induces endothelium dysfunction Journal of the American College of Nutrition, Vol. The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. Alternative Therapies in Health and Medicine, 13 2: Mills, Manuel Gonzalez, Mark R. Graziano, Ahsan Habibul Association between arsenic exposure from drinking water and plasma levels of soluble cell adhesion molecules. Environmental Health Perspectives Cholesterol-independent endothelial dysfunction in virgin and pregnant rats fed a diet high in saturated fat. The Journal of Physiology, Volume 2 , pp. Jones and Michael P. Journal of the American College of Cardiology, El Solh Ali A. Endothelial cell apoptosis in obstructive sleep apnea: A link to endothelial dysfunction. American journal of respiratory and critical care medicine, 11 , Effect of vitamin D replacement on endothelial function and oxidative stress in vitamin D deficient subjects. Homocysteine, Folic Acid and Cardiovascular Disease. Retrieved 29 June, , from http:

Chapter 3 : Inhaled Nitric Oxide :Basic Biology and Clinical Applications | Anesthesiology | ASA Publication

Extra resources for Pathophysiology and Clinical Applications of Nitric Oxide (Endothelial Cell Research) Example text. Download PDF sample.

Published online Feb Received Sep 30; Accepted Jan The use, distribution or reproduction in other forums is permitted, provided the original author s or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. This article has been cited by other articles in PMC. Abstract Metabolic syndrome MS is a cluster of metabolic disorders that collectively increase the risk of cardiovascular disease. Nitric oxide NO plays a crucial role in the pathogeneses of MS components and is involved in different mitochondrial signaling pathways that control respiration and apoptosis. The present review summarizes the recent information regarding the interrelations of mitochondria and NO in MS. Changes in the activities of different NO synthase isoforms lead to the formation of metabolic disorders and therefore are highlighted here. Reduced endothelial NOS activity and NO bioavailability, as the main factors underlying the endothelial dysfunction that occurs in MS, are discussed in this review in relation to mitochondrial dysfunction. We also focus on potential therapeutic strategies involving NO signaling pathways that can be used to treat patients with metabolic disorders associated with mitochondrial dysfunction. The article may help researchers develop new approaches for the diagnosis, prevention and treatment of MS. Mitochondria play central roles in energy metabolism, signaling and apoptosis and its alterations may contribute to the development of metabolic disorders Peinado et al. It has been recently found that mitochondrial biogenesis and function are enhanced by nitric oxide NO , which is a key signaling molecule in vascular homeostasis. This finding indicates that changes in the production of NO bioavailability and MS may be associated with the mitochondria. However, the link between NO signaling components and mitochondria in MS in different tissues is still not clear. Today, mitochondria remains an attractive target for the prevention and therapy of MS and its complications Sorriento et al. Understanding the mechanisms that lead to decreased mitochondrial activity in insulin-sensitive tissues is important for developing therapies to reverse insulin resistance. A deeper understanding of the role of NO pathway components in this process opens up new opportunities for applied research in this area. Metabolic syndrome and mitochondrial dysfunction Mitochondrial dysfunction is closely associated with obesity, metabolic syndrome and type 2 diabetes mellitus T2DM Lowell and Shulman, ; Agrawal and Prakash, Changes in the mitochondrial membrane potential, a reduction in the ATP level, the inhibition of mitochondrial oxygen consumption and reduced mitochondrial biogenesis Ren et al. The underlying mechanism of mitochondrial dysfunction is very complex, which includes genetic factors from both nuclear and mitochondrial genome and numerous environmental factors Lee et al. Dismutation of superoxide produces hydrogen peroxide, which in turn may be partially reduced to hydroxyl radical causing more damage to various mitochondrial and cellular components Turrens, Free radical damage to mitochondria may lead to decreased affinity of mitochondrial proteins for substrates or coenzymes Liu et al. The centerpiece of the pathophysiologic mechanism of MS is insulin resistance. The interplay between mitochondrial dysfunction and insulin resistance was first discovered in Laguens and Bianchi, Kitt Falk Petersen et al. It is still unclear whether mitochondrial dysfunction results from or causes insulin resistance Martin and McGee, One of the key pathophysiological factors underlying the formation of insulin resistance may be the dysregulation of energy metabolism in insulin-sensitive tissues such as skeletal muscle, liver, and adipose Litvinova et al. Particularly, in skeletal muscle, decreased mitochondrial respiration capacity, reduced ATP production, and increased ROS levels lead to reduced fatty acid oxidation and increased cytosolic free fatty acid levels, resulting in insulin resistance and T2DM Pagel-Langenickel et al. As regards liver, there are findings that strongly support that non-alcoholic fatty liver disease can be considered as the hepatic representation of MS Paschos and Paletas, Insulin resistance is a key pathogenic factor in both

pathologic states. Recent findings suggests that reduced SIRT3 activity in fatty liver may result in hyperacetylation of mitochondrial proteins that contributes to mitochondrial dysfunction Kendrick et al. Nitrosative stress in non-alcoholic fatty liver disease also contributes to the development of mitochondrial dysfunction that is mediated by the oxidative modifications of mitochondrial DNA mtDNA , lipids and proteins Song et al. Moreover, high-fat diet-induced mtDNA damage correlates with increased oxidative stress in skeletal muscle and liver, which is associated with the induction of markers of endoplasmic reticulum stress, protein degradation and apoptosis Yuzefovych et al. In adipose tissue, mitochondria provide key intermediates for the synthesis of triglycerides and are critical for lipogenesis. Adipose mitochondria are also important for lipolysis through the oxidation of fatty acids, which constitutes an important source of ATP to supply cells with energy Serra et al. The study of M. The authors show that reduction of adiposity via mitochondrial uncoupling in white fat not only reflects increased energy expenditure, but also decreased in situ lipogenesis. Therefore, various studies suggest that modulation of mitochondrial function including oxidative phosphorylation, ATP synthesis and ROS generation in above-mentioned tissues may in turn may affect the development of insulin resistance and obesity. It has been demonstrated in mice with adipocytes deficient in mitochondrial transcription factor A that isolated mitochondrial dysfunction in adipose tissue can cause lipodystrophy and lead to MS and chronic inflammation Vernochet et al. Thus, mitochondrial alterations that occur during insulin resistance trigger a cascade of pathological processes in different tissues and form a vicious cycle between chronic inflammation and mitochondrial oxidative stress that eventually contributes to cardiovascular pathologies and T2DM. Mitochondrial DNA as a molecular marker of metabolic syndrome MtDNA is a bp, circular, double-stranded molecule that harbors 37 genes involved in the energy production that takes place in the ETC. This gene set includes 13 structural genes that code for subunits of oxidative phosphorylation complexes as well as genes encoding 22 tRNAs and 2 rRNAs that are involved in the protein synthesis that occurs directly within mitochondria Smits et al. According to current estimates, the human genome incorporates approximately mitochondrial protein-encoding genes; however, only fewer than of these proteins have been identified in isolated mitochondria Jiang and Wang, The TC mutation in mtDNA has been shown to be associated with MS in a large Caucasian family, and a common mtDNA variant, TC, has been shown to be associated with a lower body mass index at birth, insulin resistance, dilated cardiomyopathy and an increased susceptibility to MS in a Chinese population Palmieri et al. Our results showing a reduced number of mtDNA copies in peripheral blood and samples of adipose tissue obtained from different locations from patients with MS Mozhey et al. The administration of pioglitazone, which is a mainstay drug for the treatment of T2DM, leads to an increase in the number of mtDNA copies in subcutaneous adipocytes in vitro Bogacka et al. As previously mentioned, mtDNA levels may vary in different organs. However, experiments performed in rats have shown that changes in mtDNA copy number in peripheral blood leukocytes reflect similar processes in muscle tissue and hepatocytes. Thus, we can assume that the level of mtDNA in human peripheral blood cells is an indicator of various metabolic disorders. Moreover, the quantitative estimation of mtDNA in various biological samples might become a tool for the prognosis and estimation of treatment efficiency of MS. Interconnections between mitochondria and nitric oxide production in different tissues NO is a relatively stable gas that belongs to a family of gas transmitters with similar inherent intracellular effects. NO is a regulator of many physiological processes. It is synthesized by vascular endothelial cells, is responsible for vasodilatation and is involved in various processes in the nervous, reproductive and immune systems. In addition to its participation in the regulation of vascular smooth muscle tone, NO directly affects mitochondrial respiration Lee, Its inhibition of ETC enzymes may also be one of the causes of the decrease in oxygen consumption by cardiomyocytes. NO plays important roles in the development of MS components, such as insulin resistance, endothelial dysfunction, hypertriglyceridemia and chronic adipose tissue inflammation. NO is formed from L-arginine, when in the presence of oxygen, by isoenzymes of nitric oxide synthases NOS , which depend on the cell type. Inducible NOS iNOS , which is a calcium-independent form of NOS, is localized to macrophages, neutrophils, and micro- and astroglial cells and is expressed under the

influence of factors such as cytokines and bacterial lipopolysaccharide Yang et al. Impaired NOS activity is closely associated with insulin resistance Kashyap et al. Experiments with homozygous eNOS knockout mice have definitively proven the relationship between NO and insulin sensitivity because these mice show increased blood pressure and insulin resistance Shankar et al. Endothelial dysfunction, which is defined by a decrease in flow-mediated vasodilatation and vascular insulin resistance, represents an established vascular abnormality in diabetic patients Montagnani et al. However, studies in animal models and in humans have assumed that T2DM and atherosclerosis are not necessarily associated with reductions in total eNOS Felaco et al. Several mechanisms leading to endothelial dysfunction, such as a lack of enzymatic cofactors for eNOS Mangge et al. Peroxynitrite, in turn, has been shown to uncouple endothelial nitric oxide synthase eNOS , thereby converting an antiatherosclerotic NO-producing enzyme into an enzyme that may accelerate the atherosclerotic process by producing superoxide Schulz et al. It should be noted that these mechanisms are not mutually exclusive and can occur simultaneously. The studies of Youn et al.

Chapter 4 : Improve Nitric Oxide Levels in Endothelial (vessels), Neurons (brain), Immune Cells

Pathophysiology and Clinical Applications of Nitric Oxide Part B The Endothelial Cell Research Series A series of significant reviews of basic and clinical research related to the endothelium.

NO biosynthesis[edit] Platelet -derived factors, shear stress , acetylcholine , and cytokines stimulate the production of NO by endothelial nitric oxide synthase eNOS. NO production by eNOS is dependent on calcium - calmodulin and other cofactors. Three isoforms are known for the NOS enzyme: The neuronal enzyme NOS-1 and the endothelial isoform NOS-3 are calcium-dependent and produce low levels of this gas as a cell signaling molecule. The inducible isoform NOS-2 is calcium-independent and produces large amounts of gas that can be cytotoxic. NOS oxidizes the guanidine group of L-arginine in a process that consumes five electrons and results in the formation of NO with stoichiometric formation of L-citrulline. The transformation occurs at a catalytic site adjacent to a specific binding site of L-arginine. These include vascular smooth muscle relaxation, resulting in arterial vasodilation and increasing blood flow. NO also partially mediates macrophage cytotoxicity against microbes and tumor cells. Besides mediating normal functions, NO is implicated in pathophysiologic states as diverse as septic shock, hypertension, stroke, and neurodegenerative diseases. Nitroglycerin and amyl nitrite serve as vasodilators because they are converted to nitric oxide in the body. Likewise, Sildenafil citrate , popularly known by the trade name Viagra, stimulates erections primarily by enhancing signaling through the nitric oxide pathway. Green, leafy vegetables and some root vegetables such as beetroot have high concentrations of nitrate. The purpose of this mechanism to create NO is thought to be both sterilization of swallowed food, to prevent food poisoning, and to maintain gastric mucosal blood flow. A rise in salivary levels is indicative of diets rich in leafy vegetables which are often abundant in anti-hypertensive diets such as the DASH diet. In alternative fashion, nitrite anions on sun-exposed skin may be photolyzed to free nitric oxide radicals by UVA in sunlight. In this way, the immune system may regulate the armamentarium of phagocytes that play a role in inflammation and immune responses. In vitro studies indicate that phagocyte-dependent generation of NO at concentrations greater than NM triggers apoptosis in nearby cells and that this effect may act in a manner similar to Specialized pro-resolving mediators to dampen and reverse inflammatory responses by neutralizing and then speeding the clearance of pro-inflammatory cells from inflamed tissues. Reduced levels of exhaled NO have been associated with exposure to air pollution in cyclists and smokers, but, in general, increased levels of exhaled NO are associated with exposure to air pollution. S-nitrosation of thiols[edit] S-nitrosation involves the reversible conversion of thiol groups, including cysteine residues in proteins, to form S-nitrosothiols RSNOs. S- Nitrosation is a mechanism for dynamic, post-translational regulation of most or all major classes of protein. Typical cases involve the nitrosylation of heme proteins like cytochromes, thereby disabling the normal enzymatic activity of the enzyme. Nitrosylated ferrous iron is particularly stable. Hemoglobin is a prominent example of a heme protein that may be modified by NO by both direct attack by NO and, independently, via attack by S-nitrosothiols, involving NO transfer from S to Fe. Guanylate cyclase is a key component of the famous smooth-muscle relaxing properties of NO. It is a heme-containing enzyme that is acted on by NO, which binds to the heme.

DOWNLOAD PDF PATHOPHYSIOLOGY AND CLINICAL APPLICATIONS OF NITRIC OXIDE (ENDOTHELIAL CELL RESEARCH)

Chapter 5 : Pathophysiology and Clinical Applications of Nitric Oxide : Gabor M. Rubanyi :

It is now clear that in addition to its role within the cardiovascular system, the key mediator nitric oxide is also implicated in the normal physiological function and disease pathology of several.

These observations opened the way to unprecedented research activity in the early s which led to new insights into the physiology and pathophysiology of numerous biological and disease processes. Research on NO has continued at a high pace in the past 5 years and it is by now clear that in addition to the cardiovascular system, NO is implicated in the function and disease of several other organs and systems as well e. It is also evident that we are entering into a new phase of NO research: Selective inhibitors of nitric oxide synthase isoforms are being discovered, novel NO-donors are being developed and the first reports on gene therapy approaches have been publishedâ€”just to name a few examples which illustrate the point. Athough some excellent books have been published in the past about NO research, this work is the first that summarizes the quantum leap from basic sciences to clinical applications of novel therapeutic principles emerging from this decade-long research activity. The book is divided into two parts. Part A starts with a historical perspective written by Dr Robert Furchgott. His cornerstone observation in about the essential role of the endothelium in acetylcholineinduced vasorelaxation undoubtedly represented the start of this whole field. Leading experts give state-of-theart overviews of various aspects of this theme, including the description of NOS function and regulation, the biological actions of NO, and the functional consequences of NOS gene knock-out in mice. The second section of Part B summarizes the recent progress achieved with therapeutic applications of NO. This section describes, among other topics, the discovery and therapeutic application of new NO donors, the therapeutic use of NO inhalation, selective inhibitors of NOS isoforms, and gene therapy approaches with both the constitutive and inducible forms of NOS. Based on the scope, the excellent contributions by the leading experts, and the very efficient and professional work of the publisher, I believe this book on the pathophysiology and clinical application of nitric oxide is a one-of-a-kind work which will be of interest and benefit to both the experts working in the field and interested professionals of a wide variety of disciplines. In vascular hemostasis, NO is important for preventing platelet activation, adhesion, and aggregation. NO may play a role in the development of hemostatic disorders that occur when NO availability is altered. In this chapter, we discuss the importance of NO in the hemostatic response with particular emphasis on the pathogenesis of thrombotic and hemorrhagic diatheses. A poorly controlled or excessive hemostatic response, however, can be manifested as hemorrhage or thrombosis, respectively. The primary hemostatic response is dependent upon platelets and products of the endothelium that modulate platelet function. One mediator that has been shown to have antiplatelet activity is nitric oxide NO. Under resting conditions the endothelium is stimulated by flow to produce NO, which can regulate platelet adhesion and aggregation Pohl and Busse, ; Cooke et al. The production of NO leads to activation of soluble guanylyl cyclase with a concomitant increase in cGMP, which is a principal mediator of the effects of NO. NO can inhibit platelet adhesion and aggregation, and can also induce disaggregation of previously aggregated platelets Radomski and Moncada, a,b; Radomski et al. The platelet response may also be modulated in patients with cardiovascular disease who use organic nitrates, such as nitroglycerin, which act as NO donors. While lack of NO may lead to thrombosis, an excess of NO may be detrimental such that platelet aggregation is impaired and a bleeding diathesis results. In this chapter we will provide evidence for the importance of NO in regulating platelet function and hemostasis, and illustrate hemostatic disorders that arise when NO production or bioactivity is altered. In arteries, a thrombus may occlude the vessel resulting in decreased or absent blood flow to tissues, potentially leading to ischemia or infarction. These laminae are arranged such that a gradient exists within the vessel, with the greatest velocities found in the laminae closest to the center of the vessel and the lowest velocities found near the vessel wall. Because of cell size and charge properties, the laminae in the center of the vessel are enriched in red blood cells while the laminae closest to the vessel wall are enriched in platelets. Since the blood velocity is

relatively low in the vicinity of the vessel wall, platelets have a long residence time in that domain, thereby allowing for rapid activation should the vessel become damaged. Another hemodynamic factor that is important for understanding the hemostatic function of platelets is shear rate defined as the product of blood viscosity and shear stress , which is determined by the velocity gradient in the vessel. Thus, blood velocity is highest in those vessels that have the smallest crossectional area, such as the aorta. Capillaries have the largest crossectional area, and, therefore, the lowest velocities. Large vessels with high velocities have higher rates of shear than do small vessels with low velocities. Increases in the shear rate lead to an increase in platelet deposition, while low shear rates are associated with preferential fibrin deposition Loscalzo, Under normal circumstances, platelet activation is suppressed. There are three known endothelial products that inhibit platelet activation: Prostacyclin has been shown to inhibit platelet aggregation Radomski et al. The ecto-nucleotidases metabolize ADP to AMP and adenosine, resulting in a decrease in platelet recruitment and activity by the dinucleotide agonist Marcus et al. The role of NO as an inhibitor of platelet aggregation will be elucidated next. A simplified scheme of the hemostatic response. Platelet Adhesion Adhesion of platelets to the subendothelial matrix following vascular injury or contact with foreign surfaces in the blood is the initial event in the process of thrombosis. Binding interactions occur between glycoproteins found on the platelet surface and the connective tissue of the subendothelium. Some of these glycoproteins include: Adhesion is mediated by von Willebrand factor vWF , which links the platelet integrin to collagen in the subendothelium Vaughan, After these components come into contact, vWF undergoes a conformational change that is essential for the platelet and subendothelium to remain in contact. Representation of the normal pathways of coagulation. At the same time, the eicosanoid thromboxane A2 TxA2 is formed from arachidonic acid via membrane-bound phospholipase C. Its ligand, fibrinogen, has two different sequences that can directly interact with platelets, including two RGD sequences in the a chain and a dodecapeptide sequence near the carboxyterminus of the chain Hawiger et al. Simultaneously, the platelet aggregate activates the coagulation cascade via the assembly of prothrombinase on the platelet surface. This series of reactions leads to further platelet aggregation by the production of yet another platelet agonist, thrombin Loscalzo, Thrombin is produced by cleavage of its inactive precursor prothrombin in the common pathway of the coagulation cascade Figure 13â€”2. This reaction occurs through the action of activated factor X Xa and activated factor V Va along with calcium and phospholipid cofactors. Factor X activation can occur through either the intrinsic or extrinsic pathways. The intrinsic pathway is activated by contact of the blood with subendothelial structures like collagen or basement membrane components in areas of vessel damage. Factor VII undergoes a conformational change to expose its active site, which converts the zymogen prekallikrein to kallikrein and converts factor XI to activated factor XI XIa. Tissue factor activates factor VII directly, which then activates factor X of the common pathway as described above Wilcox et al. In recent years, the exclusivity of the intrinsic and extrinsic coagulation pathways has been questioned. Crosstalk between early events in these pathways has been identified that both complicates our understanding of clotting mechanisms and adds yet another level of redundancy to hemostatic defense. The platelet plug that forms in response to vascular injury is not stable. The fibrin meshwork formed by the action of thrombin on fibrinogen is required in order to add stability. Fibrin is produced when the serine protease thrombin cleaves the A and B chains of fibrinogen. Fibrin can then be further stabilized through transamidation reactions by factor XIIIa, which itself is generated by the action of thrombin on factor XIII Loscalzo, Endothelial Defense Mechanisms If the hemostatic response were to occur inappropriately or without proper regulation, pathological thrombosis could result. The endothelium and the platelet itself release mediators that attenuate the hemostatic response, providing a mechanism of defense against unbridled hemostasis and thrombus formation. Two such mediators are prostacyclin and nitric oxide. Prostacyclin has been shown to inhibit platelet activation through cAMP-dependent mechanisms, while NO impairs platelet adhesion and activation, in part, by an increase in cGMP Moncada et al. The endothelium itself is also able to regulate thrombosis by degrading any prothrombotic vasoactive amines present in the blood, inactivating thrombin, and inducing expression of

thrombomodulin, a thrombinbinding surface protein that facilitates thrombin-dependent activation of protein C, a naturally occurring anticoagulant that degrades factors Va and VIIIa Esmon et al. The fluidity of the blood is also maintained by endothelial surface glycosaminoglycans that catalyze the binding of the anticoagulant serine protease inhibitors serpins , antithrombin III and heparin cofactor II, to specific coagulation proteins, such as thrombin, thereby attenuating coagulation and platelet activation Rosenberg et al. The endothelium also contributes to thrombus dissolution by producing molecules essential for fibrinolysis, including plasminogen activators. Fibrinolysis Plasmin, the fibrinolytic counterpart to thrombin, is the principal mediator of fibrinolysis. This enzyme is converted from its plasma zymogen plasminogen by plasminogen activators, including tissue-type plasminogen activator t-PA and the urokinase-type plasminogen activators, all of which are serine proteases. Plasmin, once formed, cleaves fibrin leading to the dissolution of the fibrin clot or the thrombus. The mechanism by which platelets regulate fibrinolysis has not been established. Platelets can directly bind plasminogen and t-PA, leading to enhanced activity of plasminogen Adelman et al. Platelet granules contain a myriad of substances that can regulate the fibrinolytic response, including plasminogen activator inhibitor-1 PAI-1 , 2-antiplasmin, Cl esterase inhibitor, and 2-macroglobulin, all of which are inhibitors of fibrinolysis Ouimet and Loscalzo, Figure 13â€”3. Molecules involved in plasminogen activation and its subsequent conversion to plasmin. Solid lines indicate activation; dashed lines indicate inhibition. Plasmin has been shown to have the ability both to activate and inhibit platelets Niewiarowski et al. High concentrations of plasmin can act as a platelet agonist, yet low concentrations of plasmin lead to inhibition of platelet aggregation. At very high concentrations, plasmin modifies the platelet GPIIIa fibrinogenbinding domain leading to impaired fibrinogen binding and platelet aggregation, thus providing an explanation for the dichotomous actions of plasmin on platelet functional responses Pasche et al. In addition to the endothelial and fibrinolytic systems discussed above, other systems also exist to limit the extent of thrombosis. Heparin and endothelial heparan sulfate potentiate the anticoagulant actions of antithrombin III by catalyzing the binding of this serpin to these serine proteases Bjork et al. Proteins C and S provide another mechanism of anticoagulation. Protein C is activated by the thrombomodulin-thrombin complex, and in its active form is able to inactivate factors Va and VIIIa Clouse et al. Protein S is a cofactor for activated protein C, which has the added ability to potentiate fibrinolysis by complexing to plasminogen activator inhibitor -1 and enhancing plasminogen activation by t-PA. NO is produced when the terminal guanidino nitrogen of L-arginine undergoes a 5-electron oxidation to form L-citrulline and NO Palmer et al. This reaction is catalyzed by the nitric oxide synthase NOS family of enzymes. The differences between these isoforms are shown in Table 13â€”1. Characterization of inducible a nd constitutive nitric acid synthases. Diagram of nitric oxide synthesis by nitric oxide synthase NOS. Inducible NOS has been found in many cell types including the macrophage, and the neutrophil Marietta et al. Inducible NOS is stimulated by exposure to bacterial endotoxin or cytokines Drapier et al. The mechanism of activation of NO synthase in the endothelial cell has not been elucidated. NO binds to the heme moiety of guanyly cyclase and induces a conformational change that displaces the iron out of the plane of the porphyrin ring Ignarro, Cyclic GMP-dependent protein kinase phosphorylates intracellular enzyme targets that are responsible for regulation of intracellular calcium levels. Regulation of calcium level in platelets has been suggested as one mechanism of action of guanylyl cyclase. Cyclic GMP itself inhibits receptor-mediated calcium influx in platelets. An inhibitor of guanylyl cyclase, 1H- 1,2,4 oxadiazolo 4,3-a quinoxalin1-one, blocks these cGMP-dependent effects resulting in an increase in platelet aggregation Moro et al. Inhibition of cGMP-mediated platelet responses can also occur through cyclic nucleotide phosphodiesterases, which can degrade cGMP. The molecular size of this constitutively expressed NOS was found to be 80 kDa in contrast to the kDa protein found in endothelial cells, which could represent either differential splicing of the Nos3-like transcript or be the result of post-translational processing.

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Chapter 6 : The Therapeutic Uses of Nitric Oxide - RT: For Decision Makers in Respiratory Care

Pathophysiology and Clinical Applications of Nitric Oxide by Gabor M. Rubanyi, , available at Book Depository with free delivery worldwide.

I cannot say enough about Flavay! When I stop taking it, the pain comes right back. The simple things work better. I feel a general sense of wellbeing with Flavay. I feel it does the job! Flavay shrank the protruding disk so I could stand up straight again. When I stopped taking it for a couple of weeks, my neuropathy and arthritis pain come raging back. So I started again on Flavay and the pain is almost completely gone. Oh my gosh this Flavay is great! Now I take Flavay as much for the benefits to my skin as for joint pain. I skeptically ordered two bottles And low and behold, it works. I read that I could take more than 2 that some people had to take 4 or 5 at a time, so I did, hoping and praying, and my prayers were answered. To say thank-you is an understatement, and I have been able to stop all other pain meds. I honestly was on a one way road to nowhere, now I am free again.. Both of my clients have raved about the product. One of my clients has a problem with circulation and she said Flavay really works for her. She has heart problems and taking 2 Flavay per day she has so much energy again and her color is better too. I love the Flavay, I really like it! Now I need to start again. I will continue to take it daily. The medication affects my brain badly. I want to control asthma instead of it controlling me. Flavay is a big help, I am so happy! I was so skeptical of your product at first and really had a negative attitude when I started taking it. I am a 40 yr old female with anxiety, mild ADHD and a host of arthritis and inflammation issues. It was a struggle for me to get out of bed everyday and focus on what needed to be done. I had no focus, no attention span, no energy, and no desire to do anything. About a week into taking Flavay and Flavay Plus, I started noticing that I could think a little clearer. I never thought I would feel like my old self again. I think there is definitely something in your formulas that stop inflammation and get your body in balance and healing itself. It seems to have a positive effect on my lymph system. We do not compensate for our endorsements and testimonials. We do not consider paid testimonials to be nearly as valuable as comments from customers who were not compensated and yet liked the products so much they gave their testimonials anyway. These products are not intended to diagnose, treat, cure, or prevent any disease.

Chapter 7 : Biological functions of nitric oxide - Wikipedia

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Chapter 8 : Pathophysiology and Clinical Applications of Nitric Oxide - PDF Free Download

The benefits of nitric oxide include its ability to dilate blood vessels and enable white blood cells to kill tumor cells and bacteria. 2 Nitric oxide is formed, on demand, in a generator cell (such as an endothelial cell), and it acts on target cells nearby (such as vascular smooth muscle cells). Nitric oxide is an unusual messenger.

Chapter 9 : Nitric oxide and mitochondria in metabolic syndrome

Because nitric oxide is short-lived and can travel only a short distance, glial cells must migrate to and position themselves near the target cells with which glial nitric oxide primarily interacts.