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ENDOTHELIUM AND ENDOTHELIAL DYSFUNCTION - HEALTH IMPLICATIONS AND RISK FOR CARDIOVASCULAR DISEASES

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The endothelium forms the lining of tunica intima, a single cell layer at the interface between the blood and the extravascular fluid spaces. Not many years ago ther endothelium was considered a simple structural barrier that merely modulated permeation through the vessel wall by providing pores of appropriate size. Largely as a result of progress in tissue culture technology, we now know that endothelial cells accomplish a long list of metabolic functions.

Key words: Endothelium, endothelial cells as endocrine organ, vascular system, NO, prostacyclin, endothelium dysfunction, atherosclerosis, cardiovascular diseases.

In a number of diseases, endothelial dysfunction is associated with the subendothelial accumulation of blood-borne materials [1]. For example, the accretion of lipid beneath the endothelium in atherosclerotic lession reflects the failure of the endothelium to serve as an effective barrier between tissue and plasma. Thus, a modern view of endothelium holds that the metabolic and endocrine functions of its cells play a critical role in disease. The normal endothelium maintains a continuous release of nitric oxide (NO), which is formed from L-arginine through the action of the enzyme nitric oxide synthase [2, 3]. The production of NO can be stimulated by a variety of endothelial agonists, including acetylcholine, bradykinin, histamine and thrombin. Shear stress resulting from an increase in blood flow or blood pressure also stimulates NO production and vessel relaxation. NO also inhibit platelet aggregation and secretion of platelet contents, many of which cause vasoconstriction. The fact, that nitric oxide is released into the vessel lumen (to inactive platelets) and away from the lumen (to relax smooth muscle) suggests that it protects against both thrombosis and vasoconstriction [3]. The major cause of insuficient coronary flow leading to a heart attack is the presence of atherosclerosis in these vessels. Cardiovascular diseases (CVD) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD. Endothelial dysfunctions leads to a variety CVD with platelet hyperaggregability, coagulation abnormalities, hypertension or diabetes. They are as important risk factors for life-threatening complications such as coronary artery diseases, atherothrombosis, heart failure and stroke, end-stage renal disease, diseases associated with serious cardiovascular and renal co-morbidity and with substantial a lot of social and economic costs [4].

Introduction

Endothelial control of Vasodilatation and Vasoconstriction

The endothelium, which lies between the blood and the vascular smooth muscle, serves as a physical barrier for vasoactive substances that circulate in the blood. Once

thought to be nothing more than a single layer of cells that line blood vessels, it is now known that the endothelium plays an active role in controlling vascular function. In cappilaries, which are composed of a single layer of endothelial cells, the endothelium is active in transporting cell nutrients and wastes. In addition to its function in cappilary transport, the endothelium removes vasoactive agents such as norepinephrine from the blood, and it produces enzymes that convert precursor molecules to active products (e.g., angiotensin I to angiotensin II in lung vessels) [2, 3, 5, 6]. One of the important functions of the normal endothelium is to synthesize and release factors that control vessel dilation. Of particular importance was the discovery first reported in early 1980s, that the intact endothelium was able to produce a factor that caused relaxation of vascular smooth muscle. This factor was originally named: *Endothelium-Derived Relaxing Factor /EDRF/* and is now known to be nitric oxide (NO). Many other cells types produce nitric oxide by means of similar enzymes. In these tissues, nitric oxide affords other functions, including modulation of nerve activity in the nervous system [3, 6]. The normal endothelium maintains a continuous release of nitric oxide, which is formed from L-arginine through the action of the enzyme nitric oxide synthase. The production of nitric oxide can be stimulated by a variety of endothelial agonists, including acetylcholine, bradykinin, histamine and thrombin. Shear stress resulting from an increase in blood flow or blood pressure also stimulates nitric oxide production and vessel relaxation. Nitric oxide (NO) also inhibit platelet aggregation and secretion of platelet contents, many of which cause vasoconstriction. The fact that nitric oxide is released into the vessel lumen (to inactive platelets) and away from the lumen (to relax smooth muscle) suggests that it protects against both thrombosis and vasoconstriction [3, 6]. In addition to nitric oxide, the endothelium also produces other vasodilating substances such as the prostaglandin, prostacyclin, which produces vasodilatation and inhibits platelet aggregation. It has been suggested that the tendency to vasoconstriction that characterizes atherosclerotic vessels may be related to impaired vasodilator function due to disruption of the vessel endothelial layer. *NO is a key mediator in both the normal and pathological control of blood pressure.* The endothelium also produces a number of vasoconstrictor substances, including angiotensin II., vasoconstrictor prostaglandins, and a family of peptides called *endothelins.* There are at least three endothelins. Endothelin-1 made by human endohelial cells, is the most potent endogeneous vasocontrictor known [3, 7].

Endothelial cells and platelet aggregation. Thrombosis is also an important event in any situation in which endothelial injury and function are lost, or blood flow is obstructed. The aggregation of platelets and the activation of the clotting cascade are exquisitely sensitive to alterations in the microenvironment. Activated platelets, in turn release factors that initiate clotting, resulting in the formation of complex thrombus on the vessel wall. For thrombosis to occur, endothelial continuity must be disrupted or the endothelial cell surface must change from an anticoagulant to a procoagulant surface. The most common denuding endothelial injury is the progressive endothelial disruption of an andvancing atherosclerotic lesion. Denuding endothelial injury has also been described in homocysteinemia, as a response to the injection of radiologic contrast dyes, and in hypoxia and endotoxemia. In addition, the interactions of a thrombus with the underlying subendothelium may cause a further disturbance of endothelial integrity. The simplest view is that subendothelial thrombogenic molecules are covered by a nonthrombogenic cell layer – endothelium. The endothelium plays an active rather than a passive role in the control of thrombosis. Endothelial cells also synthesize plasminogen activators, and thus may dissolve some clots as they form. In addition, endothelial cells at the site of thrombosis may take up vasoactive amines released from platelets. The presence of these antithrombotic mechanisms on the endothelial surface has raised the intriguing possibility that endothelial dysfunction might lead to thrombosis in vivo [8].

Atherosclerosis. Cardiovascular diseases (CVD) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD. Hypertension and coagulation changes are more frequent in patients with diabetes compared with patients without the disease. The major cause of insuficient coronary flow leading to a heart attack is the presence of atherosclerosis in these vessels. Atherosclerosis (sometimes called „hardening of the arteries“) is disease characterized by a thickening of the arterial wall with large numbers of abnormal smooth-muscle cells and deposits of cholesterol and other substances in the portion of the vessel wall closest to the lumen [9]. The mechanisms

that initiate the thickening are not clear, but it is known that cigarette smoking, high plasme cholesterol concentration, hypertension, diabetes, and several other factors increase the incidence and the severity of the atherosclerotic process. The mechanism by which atherosclerosis reduces coronary blood flow is quite simple: The extra muscle cells and various deposits in the wall bulge into the lumen of the vessel and increase resistance to flow. This is usually progressive, often leading ultimately to complete occlussion. Acute coronary occlussion may occur because of : (I) sudden formation of a blood clot on the roughened vessel surface, (2) the breaking off of a fragment of blood clot or fatty deposit that then lodges downstream, completely blocking a smaller vessel, or (3) a profound spasm of the vesselr's smooth muscle. If the coronary occlussion is gradual, the heart may remain uninjurred because, over time new accessory vessels supplying the same area of myocardium develop [7, 10]. The question of whether regular excercise is protective against heart attacks is still contraversial, although more and more circumstantial evidence favors this view. Certainly, modest excercise programs induce a variety of changes consistent with a protective effect: (I) increased diameter of coronary arteries, (2) decreased severity of hypertension and diabetes, which are risk factors for atherosclerosis, (3) decreased plasma cholesterol concentration (yet another risk factor) whith simultaneous increase in the plasma concentration of a cholesterol-carrying lipoprotein thought to be protective against atherosclerosis and (4) improved ability to dissolve clots. Finally, the results of long-term studies that evaluated the effects of excercise on evidence of atherosclerosis are also suggestive of some degree of protection. In a number of diseases, endothelial dysfunction is associated with the subendothelial accumulation of blood-borne materials. For example, the accretion of lipid beneath the endothelium in atherosclerotic lession reflects the failure of the endothelium to serve as an effective barrier between tissue and plasma. Thus, a modern view of endothelium holds that the metabolic and endocrine functions of its cells play a critical role in disease. The extent and severity of atherosclerosis is increased by diabetes. Significant atherosclerosis is rarely found in healthy premenopausal women, but diabetes predisposes them to its early appearance. Thus myocardial and cerebral infarcts are extremely common complications of diabetes. Indeed, atherosclerotic coronary heart disease is the major cause of death among adults with diabetes. Platelet aggregation an important contributory event in atherosclerosis at sites of endothelial cell injury, appears to be altered in the diabetics. A partial explanation is the observation that the synthesis of the prostaglandin thromboxane A_2 is inreased while the counterbalancing effects of the prostacyclins are reduced. The superimposed effects of the individualr's genetic predisposition to vascular disease and such risk factors as smoking and the use of oral contraceptives are obviously also important. Whatever the complex of pathophysiologic abnormalities that results in occlusive vascular disease, such disease is a major cause of morbidity and mortality among diabetic patients [9, 11].

Conclusions

Important functions of the normal endothelium is to synthesize and release factors that can control vessel dilation and platelets activity. Endothelial dysfunctions with lower liberation of vasodilatatory active substances play important roles in accelerating of many pathological changes leading to a variety cardiovascular disorders with vasoconstriction and in subsequent hypertension, with platelet hyperaggregability and coagulation abnormalities. They are very important risk factors for life-threatening complications such as coronary artery diseases, atherothrombosis, heart failure and stroke as well as risk factors of nephrological disorders with end-stage renal disease, diseases associated with serious cardiovascular and renal co-morbidity.

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Резюме

ЭНДОТЕЛИЙ И ДИСФУНКЦИЯ ЭНДОТЕЛИЯ — ПОСЛЕДСТВИЯ ДЛЯ ЗДОРОВЬЯ И РИСК СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

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Эндотелий — однослойный пласт плоских клеток мезенхимного происхождения, выстилающий внутреннюю поверхность кровеносных и лимфатических сосудов, сердечных полостей. Еще недавно эндотелий считался простым структурным барьером, который просто модулировал проникновение веществ через стенку сосуда, обеспечивая поры соответствующего размера. Во многом в результате прогресса в технологии культивирования тканей, в настоящее время показано, что эндотелиальные клетки осуществляют многочисленные метаболические функции.

Ключевые слова: Эндотелий, эндотелиальные клетки, эндокринный орган, сосудистая система, NO, простациклин, дисфункция эндотелия, атеросклероз, сердечно-сосудистые заболевания.

Резюме

ЕНДОТЕЛІЮ І ДИСФУНКЦІЯ ЕНДОТЕЛІЮ - НАСЛІДКИ ДЛЯ ЗДОРОВ'Я І РИЗИК СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАНЬ

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Ендотелій - одношаровий пласт плоских клітин мезенхимного походження, що вистилає внутрішню поверхню кровоносних і лімфатичних судин, серцевих порожнин. Ще недавно ендотелій вважався простим структурним бар'єром, який просто модулював проникнення речовин через стінку сосуду, забезпечуючи пори відповідного розміру. Багато в чому в результаті прогресу в технології культивування тканин, в даний час показано, що ендотеліальні клітини здійснюють численні метаболічні функції.

Ключові слова: Ендотелій, ендотеліальні клітини, ендокринний орган, судинна система, NO, простациклін, дисфункція ендотелію, атеросклероз, серцево-судинні захворювання.

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ОСОБЕННОСТИ УГЛЕВОДНОГО И НУКЛЕОТИДНОГО ОБМЕНОВ ПРИ РАЗЛИЧНОЙ ЭКСПРЕССИИ CD 34 В АДЕНОКАРЦИНОМЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

Шатова О.П., Хилько Д.А., Хомутов Е.В., Зинкович И.И., Седаков И.Е., Скоробогатова З.М.

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В данном исследовании изучена взаимосвязь между уровнем экспрессии CD 34 в опухоли молочной железы и активностью ферментов обмена углеводов и нуклеотидов. Установлена статистически значимая связь между активностью тимидинфосфорилазы в сыворотке крови и показателем экспрессии CD 34 в аденокарциноме молочной железы. Тимидинфосфорилаза и CD 34 участвуют в неоангиогенезе и взаимосвязаны со степенью лимфогенного метастазирования.

Ключевые слова: рак молочной железы, CD 34, обмен углеводов и нуклеотидов.