Molecular and Cellular Mechanisms of Endothelin Regulating Cardiovascular Function Based on Non-linear Method

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Abstract: Endothelin (ET) is a potent vasoconstrictor released by vascular endothelial cells. ET, as vasoconstrictor peptide, growth factor, neuropeptide and hormone regulatory peptide, participates in the regulation of physiological function. A method of evaluating cardiovascular sub-health status based on non-linear parameters is proposed. Through quantitative evaluation of cardiovascular system function, the sub-health status of human body can be effectively evaluated in order to prevent and prevent as early as possible. The structure-activity relationship of endothelin (ET) and its receptor and receptor subtypes, the possible mechanisms by which ET regulates vascular tone and myocardial contraction, and ET as a potent vasoconstrictor and positive muscle are described at the cellular and molecular levels. The possible role of force substances in the occurrence and development of cardiovascular diseases such as hypertension, coronary heart disease and heart failure. The effect and mechanism of endothelial cell ET on cardiovascular function in suiTable intensity exercise training, and explore its significance in sports health and exercise rehabilitation.

1. Introduction

Endothelin (ET) is a bioactive substance composed of 21 amino acids. Endothelin precursor is produced by the hydrolysis of endothelin precursor by peptidase, and then endothelin is produced by the action of endothelin converting enzyme [1]. There are three isomers: ET-1, ET-2 and ET-3. ET-1 is a powerful vasoconstrictor, which is mainly produced in the vascular wall. Endothelin, as one of the cytokines, exists in many organs and tissues of the body. Endothelin is secreted by body cells in the form of autocrine or paracrine, and partially mediated by specific receptors of endothelin [2]. In the cardiovascular system, vascular endothelial cells and endocardium are the main sites of ET synthesis and release, regulating cardiovascular function in a para/autocrine manner [3]. Endothelin This polypeptide plays important biological functions in various physiological systems in mammals, such as the gastrointestinal tract, central nervous system, respiratory system, cardiovascular system and genitourinary system. ET is the strongest vasoconstrictor active substance found in the body so far, which plays an important role in regulating local blood flow and maintaining environmental stability in the body [4]. This article describes the research progress of ET on the molecular and cellular levels of cardiovascular function regulation and disease pathogenesis.

2. The Relationship Between Molecular Structure and Biological Effects of ET and its Receptors

The three groups of human genes were cloned and sequenced, including ET-1, ET-2 and ET-3 codes, respectively. The nucleotide sequence was concentrated in the 21 encoded amino acid residues of these ETs. Named ET-1, ET-2, and ET-3 [5]. This distribution shows its functional diversity in the central nervous system. ET is also present in neurons such as choline acetate, somatostatin and neuropeptide Y, which may be coexisting transmitters or neuromodulators. Radiation autoradiography studies have shown that ET receptors are widely distributed in the central and peripheral nervous systems, mainly in the brainstem and cerebellum, and the

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distribution density along the nerve axis toward the head is lower [6]. From the point of view of structure-activity relationship, the difference of action intensity of ETs may be due to the genetic heterogeneity of ET amino acid sequence. Half-substituted amino acids containing amino terminal in ET molecule can affect the bioactivity of ET. As cardiovascular regulatory peptide, growth factor, neuropeptide and hormone regulatory peptide, it participates in the regulation of physiological activities of the body. In the initial experiments, it was observed that ET-1 has a very long time of vasoconstriction and 10 times stronger than angiotensin II, thus rapidly establishing its important position in regulating blood pressure. Ischemia, hypoxia and injury of body tissues, especially skeletal muscle and myocardium, can also lead to increased ET secretion.

Statistical analysis and discriminant analysis are carried out on the obtained non-linear parameters. The discriminant formulas are composed of the effective parameters with significant statistical differences, as shown in the following formulas:

$$Y = a_1 X_1 + a_2 X_2 + \Lambda + \mathrm{a}_n X_n \tag{1}$$

Where: Xi(i=1, 2, 3, ..., n) represents the ith effective parameter; ai(i=1, 2, 3, ..., n) represents the corresponding discriminant coefficient.

According to the distribution trend of the discriminant value of the two groups from small to large, as shown in Figure 1, this paper selects the power function as the basic function to establish the scoring formula. The formula of the percentile system established in this paper is:

$$S_{\mathrm{j}} = \frac{1}{\sum_{i=1}^{n}(S_r)}, (0 < (S_{\mathrm{j}}) \le 1) \tag{2}$$

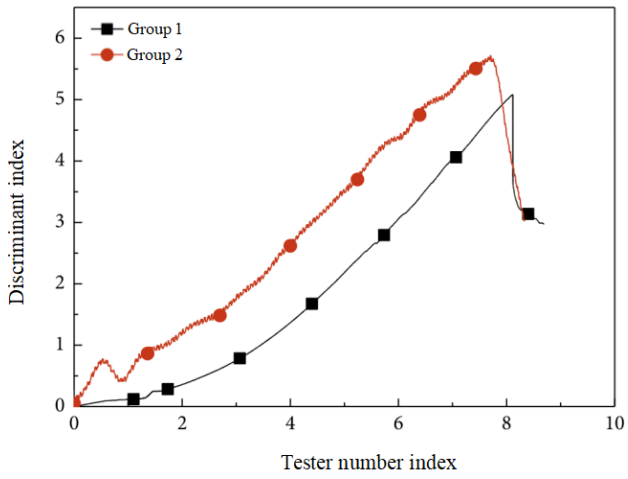

Fig.1. Distribution trend of scores in two groups

The role of endothelin in maintaining normal blood pressure is uncertain, and the onset of essential hypertension is not well understood. Endothelin levels were significantly increased in salt-sensitive hypertensive animal disease models. Removal of tryptophan at the base of the ET molecule may reduce receptor binding activity and reduce ET vasoconstriction to one thousandth. Endothelin has a strong mitogenic proliferation effect on smooth muscle cells of animals, and excessive blood vessel growth leads to hypertension. This may be a pathological mechanism in which exercise-induced myocardial damage occurs. The increase of plasma ET content during acute exercise may be a compensatory response under stress in the body [7]. At present, three complementary DNA clones of ET receptors, called ETA, ETB and ETc, have been isolated and distributed in different tissues in different proportions. Both of them belong to G protein-coupled receptor superfamily. Different ET isomers have different affinity with the two receptors. ETA receptor is the main receptor subtype on VSMC, and ETB receptor mainly exists in vascular endothelial cells. Similarly, bosentan, a receptor blocker of ETA/ETB, did not cause systemic pulmonary hemodynamic changes in dogs under normal anesthesia, nor did it affect pulmonary

vasoconstriction in dogs with low oxygen content. However, if the secretion of ET increases abnormally, the blood vessel contracts strongly, aggravating myocardial ischemia and hypoxia, it is of great significance to promote the pathological changes of cardiovascular system.

3. Molecular and Cellular Mechanisms of Cardio-vascular Effects of ET

ET is the strongest and longest vasoconstrictor known to date. The vasoconstrictive effect of ET may be mediated by two intracellular signal transduction systems, namely, calcium channel opening and phosphoacetase activation. Endothelin A/endothelin B receptor antagonists can normalize and decrease blood pressure in experimental hypertensive animals, suggesting that endothelin is involved in the pathophysiological process of hypertension [8]. The strong positive myodynamic effect of ET on the heart enhances myocardial contractile function, increases cardiac output, and increases oxygen pulse. At the same time, due to the enhanced vasoconstrictive function of ET, the rise of blood pressure reflex causes heart rate depression. ET stimulates phosphoacetase C activation and promotes inositol triphosphate production, which promotes Ca^{2+} release from calcium reserves to the cytoplasm. Activated ET receptors also stimulate voltage-dependent calcium channels and receptor-operated calcium channels, promoting extracellular Ca^{2+} influx, and increased intracellular free Ca^{2+} leads to vasoconstriction. In general, ET acts better on the vein than on the arteries, and on the resistance small vessels is stronger than the volumetric large vessels. In addition, different ET-isopeptides have different effects on the contraction of blood vessels. Injection of exogenous ET-1 reduces renal plasma flow, glomerular filtration rate, and increases renal vascular resistance. These effects are blocked by selective or non-selective endothelin receptor antagonists.

In actual situations, some hypertensive patients insist on taking medicine and physical exercise for a long time, while some young healthy people suffer from poor physical condition or bad living habits. Therefore, the health status of the two groups of people is not absolutely polarized, but there is some overlap, which also determines that the discriminant classification of the two groups of people in this study can not reach 100%. Table 1 below shows the non-linear parameters of the discriminant formula and their corresponding discriminant coefficients.

Table 1 Nonlinear parameters composing discriminant formula and their corresponding discriminant coefficients

Parameter	Discriminant coefficient
Post-motion approximate entropy	5.33
Relative Complexity after Motion	11.28
Scatter plot area ratio (post-motion/pre-motion)	-0.04

Studies on the cardiac effects of ET have been delayed, and it has been suggested that ET may be the most potent positive hunger substance in mammalian hearts. The binding of ET to ETB receptor on endothelial cells can promote the release of NO and PGI2 from endothelial cells, which act on smooth muscle cells to induce vasodilation. Endothelin binds to its specific receptor, resulting in an increase in intracellular Ca^{2+} concentration in cardiac myocytes, which has a direct time-varying and stress-changing effect on the heart. Atrial and ventricular contractions of endothelin are different, and atrium is more sensitive to endothelin than ventricle. The level of plasma ET has a certain relationship with exercise intensity and load mode. Not all extreme sports can lead to a significant increase in plasma ET, which increases with the increase of exercise intensity and the aggravation of hypoxia. Under the same conditions, single-cultured cardiac microvascular endothelium could not induce PPET mRNA transcription, suggesting that cardiac ET production is regulated by dynamic interaction between cardiomyocytes and adjacent microvascular endothelial cells. Studies have shown that endothelin receptors are found in a wide distribution in the gastrointestinal tract of mammals and humans, and are closely related to gastrointestinal motility and glandular secretion. In the gastrointestinal tract, endothelin causes contractile and/or diastolic responses in the esophagus, stomach, ileum, and colon. Cardiac output is reduced by endothelin and

negative for the heart. In patients with heart failure, the effects of endothelin on the hemodynamics of isolated hearts, myocardium, and whole animals are consistent.

4. Progress in Molecular and Cellular Mechanisms of ET Participation in Cardiovascular Disease and Its Therapeutic Measures

Under physiological conditions, there is a complete set of ET expression and regulation system to maintain the basic or physiological level of ET expression and release. Increased endothelin levels increase vascular resistance, which directly contributes to the progression of heart failure and plays an important role in the pathogenesis of heart failure. Appropriate intensity exercise training can reduce the concentration of Ca^{2+} and the response of coronary artery smooth muscle to sub-extreme ET, reduce the vasoconstriction effect on sub-polar ET concentration, and reduce the pathological changes of coronary vessels. Under the pathological condition, the expression of ET in the body regulates the abnormal state of ET and leads to the abnormal expression and release of ET. ET may be an endogenous pathogenic factor and participate in the occurrence and development of the following diseases.

4.1 High blood pressure

Recently, there is more direct evidence for ET-induced hypertension: 2 patients with malignant hemangioendotheloma have increased blood pressure and plasma ET-1 levels, and plasma ET-1 levels and blood pressure have decreased to normal after resection of the tumor. Plasma ET-1, and blood pressure are simultaneously raised again. Studies have shown that the use of angiotensin-converting enzyme inhibitors in patients with heart failure, and endothelin antagonist Bosentan treatment, found that the entire circulatory system or lung hemodynamics have been significantly improved. Therefore, ET-1 may be involved in the formation of exercise-induced myocardial hypertrophy. SuiTable exercise training can reduce the secretion of ET-1 in hypertensive and hypertrophic cardiomyocytes, which may have positive significance in reducing the injury of ET-1 to hypertrophic heart. The possible explanation is that ET inhibits ATP-sensitive potassium channels and partially depolarizes the resting membrane potential; the number of ET receptors increases significantly and is up-regulated. ETA activation leads to relaxation of LES, while ETB activation leads to contraction of LES. It is also suggested that endothelin may play an important role in the dynamic function control of LES complex.

4.2 Coronary heart disease

ET-1 has a strong effect on coronary artery spasm. Coronary spasm induced by ergonovine is related to the promotion of PPET expression and ET release. The positive inotropic effect of ET is characterized by slow onset, about 5-15 latency, long duration, and significant increase in the maximum rate of myocardial contraction and diastole without changing the time of maximum tension. Studies have shown that angiotensin-converting enzyme inhibitors are discontinued in patients with heart failure, and treatment with endothelin antagonist Bosentan has shown a significant improvement in hemodynamics, whether in the whole circulatory system or in the lung. Due to the effect of ET on coronary artery spasm and the upregulation of ET receptor during ischemia-reperfusion, elevated plasma ET levels may aggravate coronary artery contraction and myocardial ischemia-reperfusion injury, and expand the infarct size. Thereby, the transcription of ET receptors on cardiomyocytes and vascular endothelial cells can be stimulated, and the circulating blood ET content is increased. Basic research shows that ET can cause strong contraction of various blood vessels, and the most sensitive coronary artery, animal experiments prove that ET can make the single coronary artery of the pig contraction strongly, and also have direct damage to myocardial cells. However, in animals, cell migration occurs first in vascular remodeling, or cell phenotypic change occurs first. Whether it is consistent with in vitro studies, it is worthy of research and discussion, which will provide a new idea for the prevention and treatment of coronary heart disease.

4.3 Heart failure

The level of plasma ET increased in patients with congestive heart failure and dogs with congestive heart failure induced by rapid ventricular pacing, and the increase was positively correlated with the degree of heart failure. After treatment, the level of plasma ET decreased. ET can increase coronary perfusion pressure and reduce coronary blood flow in a dose-dependent manner, while high-dose ET can lead to coronary spasm, which can lead to arrhythmia, cardiac contracture and even ischemic necrosis. Therefore, the direct effect of ET on myocardium is often concealed. In the experimental model, endothelin is a strong factor of coronary artery contraction. Intravenous infusion of endothelin-1 can reduce coronary artery blood flow by 92%. The experimental animal model of distal ligation of coronary artery found that the level of endothelin increased significantly. However, too high ET may increase vascular resistance and overload Ca^{2+} in cardiomyocytes, thereby damaging cardiomyocytes and aggravating heart failure. The study found that suiTable exercise training can reduce the response of Ca^{2+} to sub-polar ET, reduce the contraction response of sub-extreme ET concentration to blood vessels, and reduce the sensitivity of blood vessels to ET contraction response. The involvement of ET in or exacerbates the process of myocardial ischemia, leading to myocardial necrosis, so we believe that the increase in ET at AMI will affect the development and prognosis of AMI to a certain extent.

5. Conclusion

The close relationship between ET and cardiovascular disease has been widely accepted by the medical community. Modern medicine and traditional medicine have made great progress in their clinical research. However, compared with modern medical clinical research, traditional medicine still has a big gap. Appropriate intensity exercise training has been applied to the prevention of heart disease and exercise rehabilitation. However, in exercise rehabilitation, the exercise load should be appropriately arranged according to the patient's condition to prevent excessive exercise load from aggravating the condition. Endothelin is an important pathogenic factor of cardiovascular diseases. Its antagonism is beneficial to the treatment of cardiovascular diseases. Therefore, endothelin can be used as a target for rehabilitation intervention of cardiovascular diseases. With the establishment and improvement of different ET isomers, different ET receptor subtypes and ET converting enzyme deficient animals, and the discovery and application of new ET receptor specific antagonists, the biological function of ET and its role in disease occurrence and prevention will be gradually clarified.

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