Comparison of Inflammatory Mechanisms and Model Replication Methods in the Pathogenesis of Atherosclerosis

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Abstract: Atherosclerosis (AS) is the most common and important disease in arteriosclerotic vascular disease, and it is the main pathological basis of ischemic diseases such as coronary heart disease and cerebrovascular disease. Atherosclerosis is an important pathological basis for the occurrence of serious adverse vascular events such as myocardial infarction and stroke, and its essence is a kind of chronic inflammatory disease of blood vessels, which is caused by a variety of stimuli and involved in a variety of factors. The study of pathogenesis and treatment of AS has become a hot topic in medical research, which is an important condition for the study of pathogenesis and treatment of AS to select the right animal model. Considering that rats have strong anti AS characteristics, and their physiological anatomy is similar to that of human beings, so we regard them as experimental animals of AS model. In this paper, we review the development of inflammation mechanism and model replication methods of atherosclerosis..

1. Introduction

Atherosclerosis (AS) is a kind of disease that endangers human health and the number one killer leading to human death. Therefore, the medical circles at home and abroad pay more and more attention to as. AS is a systemic disease, mainly involving large and medium-sized arteries. The basic pathological changes are lipid deposition, focal fibrosis and proliferation of smooth muscle cells and connective tissue [1-2]. It can cause focal fibrous thickening of intima and formation of atheromatous plaque, hardening of arterial wall, stenosis of lumen, and secondary lesions, especially ischemic lesions of heart, cerebrovascular and other organs. In recent years, the results of basic research and clinical research suggest that AS inflammatory theory should be paid more attention [3-4]. There is sufficient evidence to show that in different clinical manifestations of AS diseases, inflammation participates in all aspects of its occurrence and development.

At present, there is no perfect animal model of human AS. The commonly used experimental animals are: pig, monkey, rabbit, quail, chicken, rat, etc. the phylogeny and diet structure of monkey and pig are similar to that of human, and they can produce spontaneous AS, which are ideal animals model for studying human AS [5]. However, due to the high cost of purchase and feeding of these two kinds of animals, their large-scale application AS model animals is limited. Although quail has the advantages of small size, strong strength, less consumption of drugs and easy to raise, its arterial lesions are similar to those of early human plaques, mainly limited in the arterial bifurcation. Rabbit is not easy to produce as spontaneously, but it is particularly sensitive to high-fat diet, so it has been used as an AS model. However, the damage caused by high-fat diet in rabbits is similar to xanthomatosis, which is different from human AS. Although rats have strong anti AS properties, as experimental animals, they have the characteristics of convenient feeding, low cost, strong viability, low mortality and wide range of application [6-7]. Moreover, they are omnivorous animals, and their physiological anatomy is similar to that of human beings. So people still regard it AS the experimental animal of AS model, and continue to explore to establish mature rat AS model Therefore, this paper makes a brief review of AS model established by rats.

2. Risk Factors of Atherosclerosis and Chronic Inflammation

2.1 Hyperlipidemia

Hyperlipidemia generally refers to the high cholesterol or triglycerides in the body. Cholesterol and triglycerides do not exist alone in the blood, but are combined into lipoproteins, which are mainly high-density lipoproteins and low-density lipoproteins. HDL is to transport cholesterol from the peripheral to the liver for metabolism, which can reduce the cholesterol in the peripheral blood vessels, thus protecting the heart and brain vessels. Known as "good cholesterol", low-density lipoprotein transports the cholesterol of the liver to the peripheral blood vessels, accumulates under the vascular endothelial cells, destroys the normal vascular endothelial cells, and eventually leads to the formation of plaque, which is the root of heart disease, stroke, peripheral vascular disease and other problems, so it is called "bad cholesterol".

2.2 Hypertension

Among the risk factors of AS, hypertension has been recognized as the main risk factor. Inflammation may be the bridge between hypertension and AS. In the animal model of hypertension, it was also found that the infiltration of inflammatory cells and the expression of inflammatory factors in the resistant arteries such as aorta and mesenteric artery increased significantly. However, the infiltration of inflammatory cells in vascular tissue and the synthesis and release of a large number of inflammatory related factors in inflammatory response can lead to pathophysiological changes such as endothelial cell function damage, vascular stiffness increase, vascular smooth muscle cell abnormal proliferation and so on. In addition, the study of endothelin-1 AS another important mediator of chronic inflammation of vascular wall has also made new progress, which means that the inflammatory mechanism is an important participant in the pathophysiological process of hypertension related cardiovascular diseases, including AS [9]. The disease caused by atherosclerosis is shown in Figure 1.
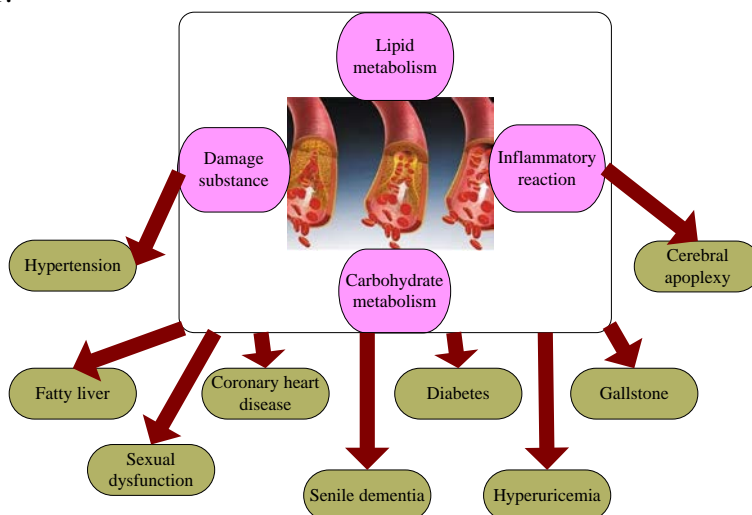

Figure 1 Atherosclerosis caused by the disease

2.3 Microbial infection

Some microbial infections in human body may participate in the occurrence and development of AS, because infection can cause the rise of various proinflammatory factors and acute phase proteins, thus changing the function of endothelial cells. It is known that the microorganisms causing as inflammation include Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, EB virus and herpesvirus. May et al. introduced the fluorescent labeled macrophages into healthy mice [10]. The results showed that the macrophages infected with CPN had stronger adhesion to carotid artery than those uninfected, and the expression of some adhesion factors, chemokines, growth factors and so on increased after the vascular endothelial cells infected with CPN, which could promote the occurrence

of AS. In conclusion, infection can aggravate inflammatory stimulation and promote the formation of AS.

3. Replication of Atherosclerosis Model in Rats

3.1 Hyperlipidemia and AS in Rats

AS is the result of lipid deposition in the arterial intima and stimulation of connective tissue proliferation. Therefore, most AS models are based on high-fat food, but due to the lack of gallbladder and less absorption of cholesterol and other lipids in rats, only high-fat diet can produce lipid deposition. It is difficult to induce the formation of AS in rats Studies have shown that feeding high-fat diet with drugs to inhibit thyroid function can cause hyperlipidemia and early atherosclerotic changes.

A large number of experiments and clinical data show that hyperlipidemia is the main risk factor of as Cheng Chunying et al established the hyperlipidemia model of Wistar rats by gavage with hyperlipidemia mixture. On the 48th day of the experiment, there were obvious lipid deposition and early atheromatous plaque formation in the arteries, and the lesions were mostly seen in the middle and small vessels. The intima was thickened in varying degrees, and the lumen was narrow Wang Occasionally, mononuclear cells adhered to the intima, and a small amount of foam cells infiltrated beneath the intima. It is suggested that L-methionine can cause significant changes in blood lipid, hyperlipidemia and early atherosclerotic changes in animals, suggesting that the occurrence of AS is a complex process of multifactor interaction. There was significant difference between the experimental group and the control group after modeling, as shown in Table 1 and table 2.

Table 1 Levels of TC, TG, LDL and FBG in each group

Group		n	TC(mmol/L)	TG(mmol/L)	LDL-C(mmol/L)	Fbg(g/L)
Experience group	Before modeling	30	1.75	0.78	1.46	262.22
	After molding	28	28.7	1.69	22.52	470.65
Control group		30	1.86	0.78	1.46	260.75

Table 2 Test results before and after molding

Group		n	TXB2(ng/L)	6-Keto-PGFl(ng/L)	ET-1(ng/L)	No(umol/L)	ICAM-1(ng/L)
Experience group	Before modeling	30	54.64	414.88	42.45	11.6	5.14
	After molding	28	280.75	113.82	165.92	6.57	46.86
Control group		30	55.39	421.42	43.42	11.98	4.98

3.2 High Fat Diet + Calcium Overload and As in Rats

Studies have shown that calcification of arterial wall and lipid deposition on arterial wall are the most significant characteristics of AS. It is known that the content of calcium apatite in the sediments of human AS can be as high as 71%, which is positively correlated with the pathological degree of AS. At present, vitamin D3 (VD3) has been found to cause the increase of blood calcium, which can damage endothelial cells in the early stage of arterial disease, and secondary local proliferation reaction of vascular wall in the later stage, such as focal proliferation of vascular smooth muscle cells and deposition of calcium salt in the arterial wall. Therefore, some scholars think that VD3 may

induce atherosclerosis by damaging the integrity of the arterial wall endothelium, which is conducive to the invasion and damage of plasma lipids to the wall of the artery and the formation of AS. Kramsch et al found that in the process of AS formation, the migration and proliferation of smooth muscle cells, as well as the secretion of extracellular matrix, need calcium AS a second messenger So many studies use high dose VD3 as inducer to establish AS model, but the specific dose, application way and experimental period of VD3 are different.

Some scholars think that high-dose VD3 or high cholesterol diet alone can not form typical AS. When rats are fed with high-fat diet and high-dose VD3 at the same time, atheromatous plaque and calcification appear on the arterial wall of rats. Shen Li et al. used high-fat diet, VD3 (400000 u, 200000 U) and high-fat feed, respectively, to explore and verify AS modeling and summarize. The results showed that the method of establishing AS model of calcium overload in rats by high fat diet for 9 weeks was successful. But fed with high-fat diet for 9 weeks can only produce hyperlipidemia in rats, and can not form a real AS model. After 6 weeks, the intima of the lesion was obviously thickened, the vascular endothelial cells were not completely arranged, smooth muscle cells proliferated significantly in the intima, and formed typical AS plaque with a large number of foam cells. Wen et al. fed rats with vd3.7 million IU / kg by gavage and high-fat diet to establish a rapid AS model. 24 days later, the serum cholesterol and triglyceride levels of rats increased significantly, plaque like processes appeared in the hyperplasia of arterial intimal cells, and obvious calcification, smooth muscle cell proliferation and foam like cells were found in the middle membrane, but no similar changes were found in the corresponding control group. It is concluded that AS can be induced rapidly by high fat diet and high dose VD3.

4. Conclusion

There are many kinds of animals used in clinical trials of atherosclerosis. Researchers can choose different experimental animals according to their own research purposes and get their own ideal experimental results. At present, the most commonly used atherosclerosis model in clinic is still rats, but even the more widely used mice are different from the human body in vascular structure and pathogenesis. Other animals are limited in their application due to various reasons. As a model animal for AS research, rats show their unique advantages. With the deepening of people's understanding of the pathogenesis of AS, the establishment of AS model will continue to improve. In the future, a more accurate rat model will be established to simulate human pathophysiology in a short time. Inflammation runs through the development of AS. From the beginning of AS disease, i.e. lipid streaks, plaque formation and clinical events, it can be considered as the inflammatory effect of blood vessels on injury. Although there are many shortcomings and deficiencies in animal model clinical trials, but through these clinical animal trials on the pathogenesis, drug efficacy and pathological mechanism of research, to solve many clinical difficulties that can not be explained and solved, for the next step in-depth study of the occurrence, development and clinical outcome of the disease provides a large number of data support.

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