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EXPERIMENTAL ATHEROSCLEROSIS IN DIFFERENT ANIMAL MODELS

KAYASTH D* AND KAKADIYA J

Department of Pharmacology, Parul Institute of Pharmacy and Research, Parul University, Limda, Waghodia, Vadodra-396710, Gujarat, India

***Corresponding Author: Mr. Deep Kayasth: E Mail: deepkayasth@gmail.com**

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ABSTRACT

Atherosclerosis affects large and medium-sized blood vessels which are affected by the illness known as atherosclerosis, This causes endothelial dysfunction, vascular inflammation, and an accumulation of lipids, cholesterol, calcium, and cell waste in the intima of the arterial wall. Plaque development, acute and chronic luminal blockage, vascular remodeling, irregular flow of blood, reduced oxygen delivery to the favoured organs are all consequences of this buildup. Vasomotor activity, the blood vessel wall's propensity for thrombosis, the coagulation cascade's level of activation, Cellular inflammation, migration and proliferation of smooth muscle cells, and the fibrinolytic system are all intricately linked biological processes that lead to atherogenesis and the clinical symptoms of atherosclerosis. Low-density lipoprotein cholesterol levels that are too high in the blood overpower the protective antioxidant functions of the healthy endothelium causing this lipid moiety's and endothelium metabolism behave abnormally. Numerous toxic effects and dysfunctions of the cell and vessel walls caused by oxidized low-density lipoprotein are regularly and distinctly linked to the emergence of atherosclerosis. It is possible to research atherosclerosis in detail utilizing a variety of animal models. Various types of animals, including mice, rats, rabbits, squils, hamsters, and guinea pigs, are frequently used in screening procedures. There are several animal models, including transgenic models, hereditary hyperlipidemic models, hereditary hypercholestermic models, and hypolipidemic models. These models are employed to evaluate the effects of medications on atherosclerotic animals.

Keywords: Atherosclerosis, Animal Models, preclinical models

1. INTRODUCTION

Atherosclerosis is Severe human diseases that can cause this type of disease, like ischemic heart disease, myocardial infarction, and stroke, are all caused by atherosclerosis, which also contributes significantly to worldwide morbidity and mortality. Any artery in the body can be affected by this condition, but the carotid and coronary arteries, which are particularly large and critical vessels, are particularly problematic. Atherosclerotic plaque formation is more likely to occur in certain blood vessel segments that bend or split **[1]**.

Growing atherosclerotic plaque alone has the potential to diminish vessel volume, which can have negative pathological effects on the fed organ or tissue. The hazard lies in thrombotic events that take place at the surface of so-called unstable plaques. Many incidences of sudden cardiac mortality are caused by thrombosis linked to atherosclerotic plaque degradation or rupture, which results stop a stoppage of normal blood flow, an increase in plasma cholesterol, triglycerides, low density lipoprotein (LDL), and a lowering the level of good cholesterol (HDL). Several studies show that the preclinical models used for the study of the atherogenic effect in rats are their severity is determined experimentally and determines the incidence of the disease **[2]**.

1. List of Animal models of Atherosclerosis

Sr No	Inducer	Animal	Route of Administration	Days	References
1	Fructose	Wistar rat	Po (60% wt/wt fructose in drinking water)	10 weeks	[1,6,11]
2	TritonWR1339	Albino-wistar rats	IP /400mg/kg	2 days	[2,8]
3	Cholesterol	Wistar rats	Po (for 8 weeks, either conventional chow or laboratory chow with 2% cholesterol)	21 days	[2,3,4]
4	Propylthiouracil (PTU)	Wistar rats	p.o. 10 mg/kg body weight	7 days	[2 3]
5	HFD (high fat diet)	Wistar rats	Po (cholesterol pwoder & vegetable oil, cholic acid mix in diet)	4-8 week	[2,3,5,10]
6	Angiotensin 2	ApoE or LDLr mice	Ang 2 was SQ and chronically infused in mice(ApoE)	28 days	[7]

2. Animal Model of atherosclerosis

2.1 Fructose Induced Hyperlipidemia [1, 6, 11]

2.1.1 Principle

Fructose can be absorbed and broken down quickly by the human liver. For countless years, people consumed 16–20 grams of fructose(sugar)per day, more from fresh fruits. A typical adult consumes 85–100 grams of added sugar every day as a result of westernization's significant increases in added fructose. When the liver is exposed to a lot of fructose, that experiences rapid

lipogenesis and TG accumulation, that may lead to hepatic insulin resistance, decreased insulin sensitivity, and glucose intolerance. Due to fructose's unfavorable consequences, the metabolism of fructose has attracted a lot of scientific attention. The impact of glucose loading on blood sugar can be reduced and tolerance to glucose can be improved by tiny catalytic amounts of fructose, it turns out. Additionally, These outcomes are observed in the absence of any modifications to insulin responses.

2.1.2 Procedure

We used male Wistar rats that were five months old, weighing in at about 250 & 300 g. They were housed separately in cages and kept in a regular laboratory environment (22 +/- 2 C, 12 hr cycle of darkness and light). Water and food were freely available to all animals. The Institute Animal Ethics Committee authorised all experimental methods. Ten rats each were apportioned at random to one of four various test groups. The regular mouse food was combined with 60% weight/weight fructose to create the fructose-rich diet. Diet and treatment plan groups. Rats were provided regular rodent food for the entire 10-week experiment as the control group. Rats in the fructose group received a diet containing 60% fructose throughout the course of the 10-week experiment.

2.2 Triton Induced Hyperlipidemia [2, 8]

Using adult rats with TritonWR1339 (isooctyl polyoxy ethylene phenol), which is administered parenterally.

2.2.1 Principle

Triton-induced hyperlipidemic rats are used as a model to provide an in vivo approach for detecting antihyperlipidemic action. A non-ionic surfactant called Triton X-100 speeds up the synthesis of liver cholesterol as well as improves emulsification-mediated intestinal lipid absorption.

2.2.2 Procedure

Testing hyperlipidemic activity in vivo can be done using albino Wistar rats (160–200 g). The animals are housed in polypropylene cages a 25 °C temperature with a 12-hour light-to-dark cycle in a well-ventilated setting. Filtered tap water and common pellet feed should be provided for the duration of the trial. Three groups of twelve rats each are formed from the rat population. All rats are given 400 mg/kg of triton, which is dissolved to a 5 percent concentration in ordinary saline, before being given to the control group. Blood samples from rats are taken through the retro-orbital plexus. Last but not least, LDL, VLDL, total cholesterol, and triglyceride levels in the blood are determined using conventional diagnostic kits.

3.3 Cholesterol Induced Hyperlipidemia [2, 3, 4]

3.3.1 Principle:-

cholesterol diet fed to rats for 21 days that will induce hyperlipidemia in rats.

3.3.2 Procedure

In a space that has 12-hour light to dark cycles and is always 23 °C, (18 weeks old) male Wistar rats were given either ordinary lab food or grub for 8 weeks, 2% more cholesterol was added to the food. The HFD is made up of 45% commercial rat food, 4% cholesterol, and 1% choline. It is given for 21 days while driving. LDL, VLDL, total cholesterol, and triglyceride levels in the blood were measured after the course of treatment.

4.4 PTU- Induced Hyperlipidemia In Rats [2, 3]

4.4.1 Principle:-

This process only requires a small length of time. PTU can causes hyperlipidemia. PTU is a treatment for hyperthyroidism. Elevated levels of triglycerides, LDL, and VDL cholesterol are symptoms of hypothyroidism, which is caused by this.

4.4.2 Procedure:-

Ahead of total cholesterol, VLDL, and LDL six hours levels are assessed, a significant amount of cholesterol is supplied to each group. There are five groups of 32 rats needed in total. PTU is given to every group but 10 mg/kg of rat body weight was administered to the control group daily for 7 days. Propylthiouracil is given seven days in a row at a dosage of 0.01%. The final step is to measure the total cholesterol concentrations in the liver extract, stool, and serum.

5.5 High Fat Diet Induced Hyperlipidemia (HFD) [2, 3, 5, 10]

5.5.1 Principle:-

The food for 20 days consists of well-pulverized mixtures of cholesterol (2%), cholic acid (1%), peanut oil (10%), sugar (40%) and conventional laboratory diet (47%). These are the criteria that have been established through the use of several blood collection techniques, including retro-orbital and tail vein collection. Total cholesterol (TC), triglycerides, high-density lipids(HDL), cholesterol, and low-density lipids (LDL) make up the lipid profile. This formula for detecting the atherogenic index of plasma includes the markers myopathy marker, creatine kinase marker, and log (triglyceride/HDL-cholesterol). CPK, or phosphokinase. CRP, TNF, interleukin-6, adiponactin mRNA, and RB-4 are examples of C-reactive proteins.

5.5.2 Procedure:-

The animals were chosen, weighed, and then given unique identification markings. In this experiment, Rats had unrestricted access to the food for a 20-day period while being administered an atherogenic diet that was mixed with a standard pellet diet. All of the

groups continued to receive the same dosage of the atherogenic diet during these days. The hyperlipidemic meal and the vehicle were given to the control animals. The animals were used to evaluate several biochemical parameters after the treatment period. Under ether anaesthesia, blood was drawn from a rat's orbital plexus and centrifuged for 30 minutes at 2000 rpm to get serum.

6.6 Angiotensin 2 [7]

6.6.1 Principle:-

Angiotensin II induces plaque vulnerability in part by 1) downregulating vascular expression of anti-atherosclerotic genes and/or upregulating expression of pro-atherosclerotic genes and 2) tilting the systemic lymphocyte Th1/Th2 balance towards a pro-inflammatory Th1 response in the early disease phase. Direct evidence for this claim comes from experimental studies in hypercholesterolemic mouse models with high circulating levels of angiotensin II.

6.6.2 Procedure:-

Using osmotic pumps, Daugherty et al. started investigations in which ApoE-/- mice were persistently and subcutaneously injected with angiotensin II for a period of 28 days. The region of the atherosclerotic- lesion into thoracic aorta was noticeably increased by angiotensin II, and the lesions were primarily rich in lymphocytes and macrophages that were lipid-laden., there is no significant variation between mice given angiotensin II injections at increasing levels (500 v/s 1000 ng/min/kg). Mice unpredictably also acquired a sizable aneurysm of the abdominal aorta. These angiotensin II-induced arterial effects did not increase blood pressure or alter plasma lipid levels. Additionally, demonstrated such subcutaneous hypertension brought on by angiotensin II infusion (8 weeks) selectively an expanded plaque in the thoracic and abdominal aorta and increased macrophage infiltration in ApoE-/- mice receiving regular an atherogenic diet or fast food. In mice lacking ApolipoprotienE deficient this is the first to provide evidence of plaque susceptibility in reaction to angiotensin II infusion. According to the authors, plaque size was enhanced in Apolipoprotien E deficient mice after angiotensin II injection. corroborated earlier discoveries, and encouraged atherosclerotic plaque change to an even weakened composition.

7. CONCLUSION

The review provides a thought analysis of various chemical agents and their effectiveness in animal models. Researchers are able to assess prospective treatment strategies and gain a better understanding of the pathogenesis of atherosclerosis by using diverse animal models. These medications'

drawbacks have also been explored, which can direct further study and drug development. Overall, this analysis advances our knowledge and comprehension of atherosclerosis. It is emphasized how crucial it is to use animal models in preclinical research because it enables scientists to evaluate particular components of the illness and perhaps even discover novel treatments that could be used in clinical settings. It's heartening to see that research is ongoing and that there is a focused effort to identify novel and efficient treatments for atherosclerosis.

This review paper, in my opinion, is highly beneficial for anyone looking to learn more about atherosclerosis in animals. It provides valuable information about the use of different chemicals in different animal models. This can open the door for more improvements in the comprehension and treatment of this disorder. In the end, having this knowledge may result in better patient outcomes and a higher standard of living.

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