A Review Article on Recent Advancements in the cardiovascular Drug Carriers and Animal Models Used in Treatment of Hypertension

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***Abstract*—cardiovascular diseases the infection that influences the cardiovascular system, regardless of all advances in pharmacological and clinical treatment, heart failure is a main reason for morbid ness and mortality around the world. many new therapeutic advance strategies, including cell transplantation, gene delivery or therapy, and cytokines or other small molecules, have been research to treat heart failure. The principal point of this review article is to focus on nano carriers' advancement and resolving the issues related with old and present-day therapeutics such as nonspecific effects and poor stability. Experimental animal models of hypertension have turned into a significant instrument for giving data on etiology, pathophysiology, and complications of the disease and on the adequacy and mechanism of action of different medications and compounds utilized in treatment. An animal model has been developed to study hypertension for several reasons because of multiple factors. Compared to human models, an animal model is easily manageable. Blood vessels and cardiac tissue samples can be taken for detailed experimental and biomolecular examination. In conclusion, animal models for hypertension and atherosclerosis are invaluable in improving our understanding of cardiovascular disease and developing new pharmacological therapies**

***Index Terms*—cardiovascular disease, gene therapy, nanotechnological approaches, Nanoparticle, animal model, hypertension**

I. INTRODUCTION

Cardiovascular disease (also called heart disease) is that class of diseases which involves either one or both of the heart and blood vessels. here are many causes of cardiovascular disease but Hypertension are the most common. with increasing age, a number of physiological and morphological changes modify cardiovascular function and lead to an increased risk of cardiovascular disease in the later years, even in healthy symptomless individuals. Research animals are valuable tools for understanding the pathophysiology and in developing therapeutic interventions for a disease. Various animals have been reported as useful models in studying diseases afflicting humans and animals. Research animals include mice, rats, rabbits, guinea pigs, sheep, goats, cattle, pigs, primates, dogs, cats, birds, fish, and frogs. Careful consideration should be given in choosing the most appropriate animal model to answer the specific research question of the study. With increasing awareness of animal welfare and research ethics, it is important to obtain accurate results using suitable models while reducing wastage of animals used for testing

II. RECENT THERAPEUTIC STRATEGIES FOR CARDIOVASCULAR DISEASES

heart failure is a leading cause of morbidity and mortality worldwide. Many new and advanced therapeutic strategies, including cell transplantation, gene delivery or therapy, and cytokines or other small molecules have been researched to treat heart failure (HF). Recent advancement in the study of those molecules that regulate the cardiac functions shows that they are key molecules to treating heart failure. Furthermore, a theory of the paracrine mechanism, which comes under the Gene transfer therapy means delivery of genetic materials into cells to attain desired therapeutic effects. Recently, gene therapy in the cardiovascular system has seen great improvement and clinical research on several new therapeutic target genes has begun, with some desired good results already achieved.

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III. TABLETS

The conventional regular tablet or its novel liquid spray by sublingual or lingual administration is quickly absorbed. Specified oral tablets or transdermal patches, maintain longtime absorption via slow absorption through the digestive tract and skin. Some of the drugs have different types of tablets for attaining different pharmacodynamics. Several types of medicine can be used to help control high blood pressure: ACE inhibitors, Angiotensin-2 receptor blockers (ARBs), Calcium channel blockers, Diuretics, Beta blockers. However, some common side effects associated with these therapies include: Cough, Diarrhea or constipation, Dizziness or lightheadedness, feeling tired, weak, drowsy, or a lack of energy, Headache, Nausea or vomiting. Considering all of these adverse effects of ablets and the very slow absorption of sublingual tablets, nanoparticles are found to be the better and advanced approach towards curing of angina pectoris instantly, by direct intravenous administration into the patient's body.

IV. LIPOSOME

An ideal drug delivery vehicle should be biocompatible, non-toxic, non-immunogenic, and biodegradable and should avoid recognition by the host's defense mechanisms. Liposomes are made up of phospholipids and may comprise small amounts of other molecules. Liposomes can vary in the size from a low micrometer range to tens of micrometers in range. Unilamellar liposomes are in the lower size range with various other targeting ligands to their surface, which allows for their surface-attachments and accumulation in pathological areas for treatment of disease. Liposomes are non-hemolytic, non-toxic, non-immunogenic, biocompatible and biodegradable in nature and could be designed to avoid clearance mechanisms such as chemical or enzymatic inactivation, renal clearance etc. Liposomes supply both a lipophilic environment and aqueous environment in one system and are therefore suitable for the delivery of hydrophobic, amphipathic and hydrophilic drugs. Liposomes can be formulated as a suspension, or in a semisolid form such as cream, gel and lotion, or they can be administered through most routes of administration including ocular, pulmonary, nasal, oral, intramuscular, or through the vein. Liposomes reduce toxicity and increase the stability of the entrapped drug through encapsulation. Liposomes also increase the efficacy and the therapeutic index of some drugs. hey have the flexibility to couple with site-specific ligands to achieve active targeting. One of the main disadvantages in the use of liposomes is their very fast elimination from the blood and the capture of the liposomal formulations by the cells of the reticuloendothelial system, mostly in the liver. There have been a few improvements meant to decrease this problem.

V. IMMUNOLIPOSOME

IgG class immunoglobulins and their fragments are the most widely used targeting moieties for liposomes, which could be attached to the liposomes without disturbing liposomal integrity or liposomal antibody properties. The majority of the immunoliposomes gather in the liver as a consequence of inadequate time for the communication between the target and directed liposome.

VII. LONG CIRCULATING LIPOSOME

The use of improved liposomes with specific monoclonal antibodies against some components is a major characteristic of the cardiovascular system and tumor vascular system. e. When designing immune liposomes, antibodies work conjugated either to the liposomal surface or with the distal end of the liposomal PEG. There are some ultrasound parameters for enhancing the delivery of therapy-loaded echogenic immunoliposomes into the arterial wall for the treatment of atherosclerosis in an ex vivo mouse aorta model. This is done by using anti ICAM-targeted echogenic liposomes and following the 1-MHz wave ultrasound. There is greater adherence of the targeted liposomes to the vascular endothelium and greater passage across the vessel wall. Targeting the liposomes to ICAM-1, fibrin, VCAM-1, fibrinogen, and TF, in addition to targeted enhancement in the vessel walls 5 min after intravenous administration of targeted liposome.

VIII. NANOPARTICLES

Nanoparticles range in size from 1 nm to 100 nm. Because of their small size, they hold some unique properties compared to their larger matching counterparts. They are capable of easily crossing through the human body, cells and tissues. These systems have very important applications for the delivery of poorly soluble drugs or the delivery of drugs with high toxicity to target areas, therefore alleviating possible side effects. Nanotechnology deals with four areas, in which cardiovascular diseases can be better battled with immediate impact. nanoparticles are characteristically clear as the particles with diameter ranging from 1 to 100 nm, and have been exploited for both diagnostic and therapeutic purposes Nanoparticles can achieve controlled release of drugs, targeting and bioavailability of many diagnostic or beneficial therapeutic agents.

IX. DENDRIMERS

Dendrimers are the smallest of the nanocarriers, which have their own multiple end groups appropriate for high degree of link targeting or the active agents. Dendrimers are typically very even in size, and can attain very high molecular masses beyond 1,000 kD. Because of their extremely branched structure, they tend to accept a sphere-shaped geometry. Dendrimers with a very low intrinsic viscosity and the very high surface-to-volume ratio, as related to linear polymers of the same molecular weight. Dendrimers are also polymer-based drug delivery vehicles. Dendrimers have a core that branches out in regular intervals to produce a spherical, small, and very dense nanocarrier.

X. ARTIFICIAL DNA NANOSTRUCTURES

These methods use the DNA as a chemical material and do not make use of its biological role as the carrier of genetic DNA information. Nucleic acid logic circuits that can be used as the core of the system which helps to release the drug only in response to a stimulus like a specific mRNA have been demonstrated. In addition, the DNA “box” with a controllable lid has been formulated by using the origami method. This structure can encapsulate the drug in the closed state, and open to release it only in the response to the required stimulus.

XI. ULTRASOUND-MEDIATED DRUG DELIVERY

Ultrasound has been industrialized as both a valuable analytic tool and a potent promoter of valuable tissue for the management and treatment of cardiovascular disease oscillating micro bubbles can generate stresses directly on nearby tissue and induce fluid effects which result in drug penetration into vascular tissue, lyse thrombi and deliver drugs straight to the optimal sites for distribution.

XII. PULSATILE DRUG DELIVERY SYSTEMS

The pulsatile drug delivery system is cast off, which releases the drug on a planned pattern that is at a suitable time and at a suitable site of action. Pulsatile drug delivery systems are essentially time-controlled drug delivery systems in which the system controls the lag time self-governing of environmental factors such as pH, gastro-intestinal enzymes, motility etc. pulsatile drug delivery systems delivered via the oral route could be divided into two separate types, namely time-controlled delivery systems and site-specific delivery systems. In the recent pharmaceutical applications including pulsatile delivery, multi particulate dosage forms (e.g. pellets) are attaining much favor over single-unit dosage forms. pulsatile drug delivery will improve the patient compliance, promote ideal drug delivery to the target side and decrease the undesired effects. The benefits of the pulsatile drug delivery system are improved patient compliance, reduced side effects, reduction in dose size, dosage frequency, extended daytime or night time activity, reduction in the daily cost for the patient, protection of mucosa from irritating drugs, prohibition of drug loss by the extensive first pass metabolism, targetability of the drug to specific sites like the colon, and adaptability of the drug to suit circadian rhythms of body functions.

XIII. NANOGELS

Nanogels are based on the cross-linked hydrophilic materials, developing insoluble gels that swell in water due to the hydrophilic nature of the inner volume and structural components. the main necessity for any cardiovascular nano carrier is biocompatibility, which means they could be injected intravenously without the toxicity and side-effects including the stimulation of platelets, leukocytes, coagulation, complement, and kinins.

XIV. ANIMAL MODELS IN TREATMENT OF HYPERTENSION

Animals are used in biomedical research for the following reasons.

1.) Feasibility: - They are relatively easy to manage, as compounding effects of dietary intake and environmental factors including temperature and lighting can be controlled. Animals typically have a shorter life span than humans. Hence, they make good models, as they can be studied over their whole life cycle or even across several generations.

2.) Similarities to Human: - Many animals are suitable due to their similarity in anatomical basis and physiological functions with humans. For example, chimpanzees and mice share about 99% and 98% of DNA with humans respectively.

3.) Drug Safety: - Preclinical toxicity testing, pharmacodynamics, and pharmacokinetics profile of drugs may be investigated on animals before the compounds or drugs are used in humans. This is vital, as prior to testing on humans, the effectiveness of a drug as potential treatment needs to be carried out on animals.

XV. ANIMAL MODELS FOR HYPERTENSION

A.) Main Genetic Models of Hypertension: -

In the 1970s, Lewis Dahl discovered that some rats became hypertensive when given a normal salt diet and selectively bred them to produce the Dahl salt-sensitive (Dahl SS) rat and its control strain the Dahl salt-resistant. At around the same time, Schlager and colleagues developed BP high (BPH), BP low (BPL) and a normotensive blood pressure normal (BPN) strains of mice in the late 1970s by crossing eight normotensive strains of mice. These strains of mice have firmly established themselves as the leading genetic strain of hypertension in the mouse and parallels the hypertension in SHR with both models developing elevated BP at a very early age.

B.) Main Induced Models of Hypertension

Figure 1, Indicates Induced models originate from dietary manipulation (e.g., high salt or fat) and the use of pharmacological agents and/or surgery. Inappropriate regulation of the renin angiotensin-aldosterone system (RAAS) in primary hypertension has made the Ang II rodent model a reliable model to study hypertension. Different doses of Ang II have been used, usually ranging from 200 ng·kg−1·min−1 to 1440 ng·kg−1·min−1 over a period of 14–28 days, and the effects on BP vary. At higher Ang II doses (e.g., >1000 ng·kg−1·min−1), a rapid increase in BP is observed due to the immediate increase in peripheral resistance.

Another induced model is the deoxycorticosterone (DOCA)-salt model. Sprague–Dawley rats, Wistar rats and C57BL/6J mice are rodent strains often used for DOCA-salt interventions. The administration of DOCA varies from 40 to 65 mg·kg−1 combined with 0.9–1.7% NaCl in drinking solution and a uni nephrectomy. The control group receives the same treatment, with the only difference being a placebo tablet instead of DOCA. The time of intervention ranges from two to six weeks after the surgery.

nitric oxide (NO) is an endothelium-derived vasodilator produced by NO synthase (NOS) which can be inhibited using L-NG-nitro arginine methyl ester (L-NAME) (Ribeiro et al., 1992). A chronic infusion of L-NAME results in a volume-dependent increase in BP as a result of systemic and renal vasoconstriction.

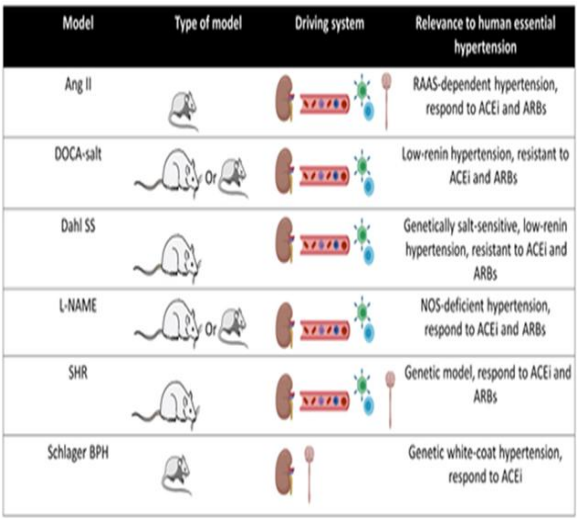

Fig. 1

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