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INDUCTION OF HYPERTENSION BY VARIOUS ANIMAL MODELS

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ABSTRACT

Blood pressure is the pressure of the blood flowing through our blood vessels against vessel walls. It depends on the blood pumped from the heart and elasticity of the blood vessels and varies with age and activity. Hypertension is defined as a diastolic blood pressure of 90mm Hg or higher and systolic blood pressure of 140mm hg or higher. Experimental models of human disease are used to study pathophysiological factors involved in hypertension and assess antihypertensive agents. Today different strains of rats with genetic hypertension are available and in most laboratories, therapeutic studies on hypertension are carried out on these models.

KEYWORDS: blood pressure, hypertension, experimental models.

Introduction

Hypertension is the most common cardiovascular disease and is a major public health issue in developed as well as developing countries. Although it is common and readily detectable, but if left untreated it can often lead to lethal complications. Because of its high incidence and morbidity, various classes of drugs and regimens have been proposed for the control of hypertension. Despite the large armamentaria of drugs being available for the treatment of hypertension, the last two decades have witnessed the introduction of a number of new antihypertensive drugs. Recent research during this period has also added considerably to our knowledge of the mechanisms involved in the pathogenesis of hypertension.

The animal models of hypertension share many features which are common to human hypertension. Many of these models have been developed by utilizing the etiological factors that are presumed to be responsible for human hypertension such as excessive salt intake, hyperactivity of renin angiotensin- aldosterone system (RAAS) and genetic factors. These models are also used in the pharmacological screening of potential antihypertensive agents. In the past, hypertensive animal models have been used infrequently for testing antihypertensive potential of drugs. As new molecules are being synthesized in a large number, the use of animal models is increasing for testing these molecules. New animal models of hypertension are being developed as new insights in to the pathogenesis of hypertension are revealed.

DIFFERENT MODELS OF INDUCING HYPERTENSION IN RODENTS:

The various types of animal models of hypertension are:

1. Renovascular hypertension
2. Dietary hypertension
3. Endocrine hypertension
4. Neurogenic hypertension
5. Psychogenic hypertension
6. Genetic hypertension
7. Other models

RENOVASCULAR HYPERTENSION:

Goldblatt method[1]: It was reported that a partial constriction of renal arteries in dogs produced hypertension. This type of hypertension has also

been induced in rabbits, rats and monkeys. A U-shaped silver ribbon clip is used to constrict the renal arteries in rabbits and rats.

1. ***Three types of hypertension are produced by Goldblatt method:***

• ***Two kidney one clip (2K1C) hypertension*** [1, 2, 3] The renal artery is constricted on only one side with the other artery (or kidney) left untouched which causes sustained increase in BP due to increased plasma renin activity (PRA), which in turn increases circulating angiotensin-II, a potent vasoconstrictor. However, there is no salt and water retention because of the other normal kidney being intact. Therefore, the resultant hypertension at this stage is renin-angiotensin dependent. After about 6 weeks, the increased angiotensin-II releases aldosterone from adrenal cortex leading to a gradual retention of salt and water. Decreased renin production is because of the retention of salt and water. From this stage onwards, hypertension is volume dependent. This clearly shows that salt and water balance is critically involved in the pathogenesis of renovascular hypertension. Increased BP and increased renin activity returns to normal by unclipping or removal of the affected kidney.

• ***One kidney one clip (1K1C) hypertension*** [1, 2, 3] Constriction of renal artery is done on one side and the contralateral kidney is removed. BP rises within few hours. As there is no other kidney, there is no pressure diuresis and natriuresis, so rapid salt and water retention is there. Plasma renin activity is usually normal. Hypertension soon becomes volume dependent

• ***Two kidney two clip (2K2C) hypertension***[2]: Constriction of aorta or both renal arteries is done. There is a patchy ischemic kidney tissue, which secretes renin causing increased BP. The remaining kidney tissue retains salt and water. In fact, one of the most common causes of renal hypertension in human beings is such a patchy ischemic kidney disease.

2. ***Hypertension induced by external compression of renal parenchyma*****:** This type of hypertension is produced in dogs, rabbits and rats. The following methods are used to produce this type of hypertension:

• ***Page hypertension***[3, 4, 5] : A sheet of cellophane is covered around the kidney and held in place by silk sutures tied loosely around the renal hilus. Both kidneys are wrapped or one kidney is wrapped and other is removed. A fibrocollagenous shell is formed around the kidney in 3-5 days because of reaction of the tissue to the foreign material. Renal vascular pressure is decreased due to the shell compressing renal parenchyma. This expands the extracellular volume leading to increased peripheral resistance and hence increased BP.

• ***Grollman hypertension***[6] : In this method, kidney tissue is compressed by securing a 'figure of 8' ligature around the kidney. The ligature around the kidney forms a figure resembling number 8. This type of hypertension can be produced in dogs, rabbits and rats. It is of two types:

1. Two kidney one ligature (2K1L)
2. One kidney one ligature (1k1L)

3. ***Coarctation of aorta***[7, 8, 9] : Renal blood flow can be decreased by compressing the aorta. Coarctation can be done just above the renal arteries, between renal arteries and superior mesenteric arteries or between two renal arteries with the right artery above and the left artery below the site of coarctation. An increase in BP similar to 2K1C model can be produced by applying a rubber band to abdominal aorta along with constriction of right renal artery for 8 weeks. Coarctation can be followed by unilateral nephrectomy to produce this type of hypertension.

4. ***Reduced renal mass***[10] : Reducing renal tissue to five-sixth (5/6th) by renal mass ablation produces hypertension. The right kidney is removed and 2 or 3 branches of left renal artery are ligated to produce infarction of approximately 2/3rd of the left kidney in this method.

DIETARY HYPERTENSION:

1. ***Increased salt intake***[11] **:** Physiologically, normal kidney has the ability to excrete easily the daily salt load without allowing a marked rise in

extracellular volume. Excess salt intake produces hypertension in rats, which mimics human hypertension. High salt intake hypertension has been produced in rats, rabbits and chicks by replacing drinking water with 1-2% sodium chloride for 9-12 months.

ENDOCRINE HYPERTENSION:

1. ***Mineralocorticoid induced hypertension***[11, 12, 13, 14, 15] : It was first demonstrated that deoxycorticosterone acetate (DOCA) produces hypertension in rats. Increased blood volume and hence increased BP is due to increased DOCA-induced reabsorption of salt and water. Vasopressin secretion is increased leading to water retention and vasoconstriction. Additionally, altered activity of RAAS leads to increased sympathetic activity. Rats are prone to DOCA-salt induced hypertension. This type of hypertension can also be produced in dogs and pigs. Other mineralocorticoids (e.g., aldosterone) and glucocorticoids can also produce this type of hypertension.

2. ***Adrenal regeneration hypertension***[16] : Hypertension is produced in rats by unilateral nephrectomy followed by removal of right adrenal gland and enucleation of left adrenal gland. Enucleation is carried out by making a small incision in the capsule of adrenal gland through which the bulk of glandular tissue is extruded by gentle application of pressure with curved forceps. Drinking water is replaced with 1% saline. Hypertension develops during regeneration of adrenal glands in about 2 weeks.

NEUROGENIC HYPERTENSION

1. ***Denervation of sinoaortic baroreceptors***[2, 16, 17]: This is the most often used neurogenic model of hypertension. In dogs, cardioaortic nerve is located at the junction of superior laryngeal and vagus nerve and runs in the form of several fine strands. These strands unite and may be traced back as a white band lying within the vagal sheath alongside the cervical sympathetic nerve. Following bilateral vagotomy and carotid sinus denervation, the region is painted with 5% phenol and then alcohol to ensure complete denervation of the carotid sinus. There is sudden increase in BP. The dog is allowed to equilibrate for approximately 30 min and a bolus of the test compound can be given by intravenous administration. BP returns to normal within about 2 days because the response of vasomotor center to the absent baroreceptors signals fades away, which is called "resetting of baroreceptors". Thus, this is only an acute type of hypertension.

PSYCHOGENIC HYPERTENSION[18, 19, 20]

Reports depict that elevation of BP resulting from repeated exposure to stressful situation may lead to a state of persistent hypertension. Borderline hypertensive rats (BHR) are useful for psychogenic hypertension. BHRs that were exposed to daily sessions of either short (20 min) or long (120 min) duration air-jet stimulation developed hypertension within 2 weeks in comparison to home cage controls. Animals exposed to 120 min stress sessions had significantly higher systolic BP relative to the 20 minute group.

GENETIC HYPERTENSION[21, 22, 23, 24]

In 1963, Okamoto and Aoki introduced a new model of experimental hypertension that required no physiological, pharmacological or surgical intervention. The so called 'spontaneous hypertensive rat (SHR)' was developed by meticulous genetic inbreeding that uniformly resulted in 100% of the progeny having naturally occurring hypertension.

OTHER MODELS:

1. Obesity related hypertension[25] **:** Wistar fatty rats (WFR) derived from cross between obese Zucker and Wistar Kyoto rats show persistent hyperinsulinemia and hypertension after 16 weeks of age and may be a good model to elucidate the relationship between hyperinsulinemia and hypertension.

2.Hypertension induced by cholinomimetic agents[26, 27]**:** Physostigmine (10-80 µg/kg, *i.v.*), a cholinesterase inhibitor, and oxotremorine (20-40

µg/kg, *i.v.*), a direct muscarinic cholinergic agonist, cause a dose-dependent increase in BP. The cholinomimetic-induced hypertension has been shown to be elicited through activation of central cholinergic mechanism and mediated peripherally through sympathetic nervous system.

3.Angiotensin-II induced hypertension[28, 29] : Subcutaneous infusion of angiotensin-II (0.7 mg/kg/day) using mini pump elicits hypertension in 4-8 weeks.

4.Hypertension induced by cadmium[12]: Hypertension is produced by the chronic administration of CdCl (1 mg/kg/day, i.p. for 2 wk). CdCl-induced hypertension might be due to the fact that the metal ion might mimic Ca2+ ion as a partial agonist and produce a direct contractile effect on vascular smooth muscle.

5.Chronic nitric oxide inhibition-induced hypertension:

•L-NAME model of inducing hypertension:

The endothelium is a single-cell layer that lines all arteries and veins. It contributes to the tone of vascular smooth muscle (VSM) and mediates vasodilation in response to various stimuli including shear stress and the neurotransmitter, acetylcholine (ACh).[30] ACh binds to muscarinic cholinergic receptors located in the endothelial cell membrane which initiates the synthesis and release of the autocoid, nitric oxide (NO). Since cell membranes are permeable to small, gaseous molecules, NO readily diffuses into the adjacent VSM cells resulting in relaxation. This relaxation is achieved through the cGMP second messenger system that leads to activation of calcium pumps embedded in the plasma membrane and sarcoplasmic reticulum. The calcium pumps effectively lower the intracellular calcium concentration causing relaxation of VSM and dilation of the blood vessels.[31]

NO is produced in the body by endothelial cells as well as by activated macrophages and neutrophils. NO is synthesized by the enzyme, nitric oxide synthase (NOS), through the deamination of the amino acid, L-arginine.[32] After NO is synthesized, this small, hydrophobic molecule diffuses into neighbouring cells. Due to its short half-life (5 to 10 seconds), it acts only locally because it is converted to nitrates and nitrites by oxygen and water in the extracellular space.[33] Once NO reaches the VSM cell cytosol, it reacts with iron in the active site of the enzyme guanylyl cyclase. This stimulates the production of the intracellular mediator cGMP which greatly amplifies the signal.[34]

The endothelium synthesizes NO incorporating the terminal guanidino nitrogen of L-arginine. Synthesis of NO is an enantiomer-specific reaction and is inhibited in vitro by Nω-monomethyl-L-arginine (L-NMMA), but not its D-enantiomer.[35] Other experiments showed NOS is also inhibited by N-iminoethyl-L-ornithine (L-NIO) and Nω-nitro-Larginine methyl ester (L-NAME) in the adrenal gland[36] and brain.[37]

eNOS is inhibited by guanidino substituted analogues of L-arginine such as L-NMMA, L-NIO and L-NAME. These analogues, both in vivo and in vitro, compete with L-arginine for binding sites on eNOS, resulting in inhibition of NO synthesis.[38] Administration of L-NAME results in hypertension and serves as an excellent model for in vivo study because it is orally active. Aside from the action of L-NAME to competitively inhibit eNOS, other L-NAME actions may influence blood pressure (BP). L-NAME may limit NO production by acting as a muscarinic receptor antagonist.[39]

Conclusion:

The present review opens vista for the induction of hypertension in various animal models.

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