HYPERTENSION

An elevated arterial pressure is probably one of the most important public health problem in developed countries-being common, asymptomatic, readily detectable, usually easily treatable, and often leading to lethal complications if left untreated *(Williams, 1998)*.

Definition of hypertension:

The Joint National Committee on Prevention, Detection Evaluation, and Treatment of high blood pressure (JNC) defines hypertension as systolic blood pressure equal or greater than 140 mmHg and/or diastolic blood pressure equal or greater than 90 mmHg. It should be emphasized that blood pressure is extremely variable. Raised blood pressure values should be confirmed by repeated measurements over several weeks and possibly months *(Black, 1999)*.

Classification of hypertension:

Hypertension can be classified by two manners either according to blood pressure level or according to the extent of organ damage.

According to blood pressure level, the sixth report of the JNC classified blood pressure as shown by the following table:

Table (I) :Classification of hypertension according to blood pressure level. Classification is for adults age 18 years and older.

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	< 130	< 85
High normal	130-139	85-89
Hypertension		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	> 210	> 120

Quoted from *(JNC VI, 1997)*

According to the extent of organ damage, hypertension is classified by the World Health Organization ***(WHO/ISH, 1999)*** into: stage I, stage II and stage III as shown in the following table:

Table (II): Classification of hypertension according to extent of organ damage.

Stage	Organ damage
I	No objective of organic changes.
II	At least one of the following signs of organ involvement : 1. Left ventricular hypertrophy. 2. Generalized and focal narrowing of the retinal arteries. 3. Proteinuria and/or slight elevation of plasma creatinine concentration (106-177 µmol/L) or both. 4. Ultrasound or radiologic evidence of atherosclerotic plaque (carotid arteries, aorta, iliac and femoral arteries).
III	Both symptoms and signs have appeared as a result of organ damage. These include the following : - Heart : Angina pectoris, myocardial infarction, heart failure. - Brain : Transient ischaemic attacks, stroke, hypertensive encephalopathy. - Optic fundi : Retinal haemorrhages and exudates with or without papilloedema. - Kidney : Plasma creatinine concentration above 20 mg/dL, renal failure.

Quoted from ***(WHO/ISH,1999)***

Complications of hypertension:

The higher the level of blood pressure, the more likely that various cardiovascular diseases will develop prematurely through acceleration of atherosclerosis, the pathological hallmark of uncontrolled hypertension ***(Barker et al., 1998).*** If untreated, about 50 percent of hypertensive patients die of coronary heart disease or congestive failure, about 33 percent of stroke, and 10 to 15 percent die more frequently of renal

failure *(Berlowitz et al., 1998).* It is easy to underestimate the role of hypertension in producing the underlying vascular damage that leads to these cardiovascular catastrophes. Death is usually attributed to stroke or myocardial infarction instead of the hypertension that was largely responsible. Moreover, hypertension may not persist after a myocardial infarction or stroke *(Haider et al., 1997).*

1. Effect on the heart:

Hypertension was reported to have direct and indirect effects on the heart. Direct effects accounted for the presence of left ventricular hypertrophy (LVH) and the resultant hypertensive heart disease *(O'Donnell and Kannel, 1998).* LVH was the consequence of the increased peripheral resistance that is usually present in hypertension. It represented the adaptive mechanism of the heart to systolic overload of the left ventricle *(Kahan, 1998).* Nevertheless, over a period of time, the presence of LVH played a role in the appearance of the following complications: left ventricular dysfunction, which may lead to the appearance of congestive heart failure *(Vasan and Levy, 1996),* myocardial ischemia without stenosis of epicardial coronary arteries, which may be explained by the increased oxygen uptake and decreased coronary reserve *(Verdecchia et al., 1998);* and the presence of cardiac arrhythmias of supraventricular and ventricular origin *(Bayes-Genis et al., 1995).*

The indirect effects of hypertension on the heart usually appeared late in the follow-up and were linked to evidence that hypertension was one of the most important risk factors of atherosclerosis. Through these indirect effects, it was clear that hypertension may also induce cardiac arrhythmias and may be involved in the multifactorial problem of sudden death *(Bayes Genis et al., 1995).*

2-Vascular effects of hypertension:-

In general, the vascular complications of hypertension can be considered as either " hypertensive" or "atherosclerotic". The former are more directly caused by the increased blood pressure per se and can be prevented by lowering this level; the latter have more multiple causations. Although hypertension may represent the most significant of the known risk factors for atherosclerosis in quantitative terms, lowering blood pressure may not by itself halt the atherosclerotic process ***(Safar, 1994; Kaplan, 2001).***

The path from hypertension to vascular disease probably involves three interrelated processes: pulsatile flow, endothelial cell dysfunction, and smooth muscle cell hypertrophy ***(Williams, 1998).*** Higher systolic pressure are probably more responsible for these changes which provides an explanation for the closer approximation of cardiovascular risk to systolic pressure and pulse pressure.

These three interrelated processes are probably responsible for the arteriolar and arterial sclerosis that is the usual consequence of longstanding hypertension. Large vessels such as the aorta may be directly affected and may be at risk for aneurysms and dissection ***(Kaplan, 2001).***

3. Renal effects:

Arteriosclerotic lesions of the afferent and efferent arterioles and the glomerular capillary tufts are the most common renal vascular lesion in hypertension and results in decreased glomerular filtration rate and tubular dysfunction. Proteinuria and microscopic haematuria occur because of glomerular lesions, and approximately 10% of the deaths

secondary to hypertension result from renal failure *(Pedrinelli et al., 1994; Nishijo et al., 1999)*.

On the other hand, accelerated nephrosclerosis associated with malignant hypertension is a dramatic complication of all forms of hypertension. The renal lesions of malignant hypertension include peticheal haemorrhage of the cortical surface, fibrinoid necrosis of the afferent arterioles, a hyperplastic arterioles of the interlobular and arcuate arteries and severe ischaemic atrophy or infarction distal to the abnormal vessels *(Klag et al., 1997)*.

4. Effect on blood lipids:

Atheroma deposition is accelerated by hypertension, and causes the most numerous of the complications of coronary artery disease; it is responsible for most of the cases of stroke *(Grundy, 1997)*.

Epidemiological studies indicate that there are biological interrelationships between blood pressure and blood lipids, as the production of active oxygen species and cellular damage by oxidized lipids are believed to be important factor in the pathogenesis of hypertension and other cardiovascular disease *(Kaplan, 2001)*.

The altered lipoproteins trigger cellular responses contributing to the pathogenesis of metabolic functions in endothelial cells and differentiating monocytes and cytotoxicity *(Haberland and Fogelman, 1987)*.

Oxidized LDL-cholesterol are involved in the formation of lipid laden foam cell (macrophages), by producing massive deposition of

cholesteryl esters in lipid droplets within the cytoplasm. The major portion of this cholesterol is derived from lipoproteins. Internalization (i.e. entry) of both cholesterol rich lipoproteins and modified LDL-cholesterol is mediated by scavenger cell receptors which are selectively present in monocytes and macrophages that participate in the atherosclerotic lesion. The LDL-cholesterol subfraction that is responsible for the above process is the LDL-IIIA which is smaller, denser with increased cholesterol to protein content and thus has more atherogenic potential. Expression of LDL-IIIA dominant allel is age dependent ***(Krauss, 1987; Weisser et al., 1993)***.

Another role of oxidatively LDL-cholesterol (ox-LDL-C) is that it cause vasoconstriction, while the native LDL-cholesterol had no influence on vascular tone ***(Galle et al., 1993)***.

Also, LDL-cholesterol cause amplification of serotonin-induced platelet aggregation particularly at sites of vascular injury and atherosclerotic plaques, resulting in progression of thrombotic events and atherosclerosis ***(Krauss, 1987)***.

HDL-cholesterol plays important role by interacting with arterial cells in removing unesterified cholesterol (presumably the first step in "reverse cholesterol transport"). HDL-cholesterol has antiatherogenic (particularly at sites of vascular injury and atherosclerotic plaques) and thus, reduce thrombotic events ***(Bierman and Oram, 1987)***.

5. Effect on central nervous system:

Occipital headache, most often in the morning are among the most prominent early symptoms of hypertension. Dizziness, vertigo, tinitus and

syncope may also be observed, but the more serious manifestations are haemorrhage or encephalopathy due to vascular occlusion. *(Braunwald et al., 1991)*.

Cerebral infarction is secondary to the increased atherosclerosis observed in hypertensive patients, while cerebral haemorrhage is the result of both the elevated arterial pressure and the development of cerebral vascular microaneurysms *(Chalmers et al., 1989; Davis et al., 1998).*

Hypertensive encephalopathy manifestations such as: complex severe hypertension, disordered consciousness, increased intracranial pressure, retinopathy with papilledema and seizures. The pathogenesis is uncertain but probably not related to arteriolar spasm or cerebral edema *(Vidt et al., 1984)*.

Focal neurologic signs are infrequent, and if present suggest that infarction, haemorrhage or transient ischaemic attacks are more likely diagnosed *(Cuneo and Caronna, 1987)*.

Pharmacological management of hypertension:

The purpose of treating hypertension is to reduce the incidence of hypertensive complications, particularly coronary heart disease and stroke. The ideal antihypertensive drug should have a predictable dose-response curve, an acceptable, recognised side effect profile, as well as a long half-life to provide 24-hours control of blood pressure. Furthermore, it should have trial evidence to prove effectiveness in prevention of complications *(Spencer and lip, 1999)*.

The main classes of antihypertensive drugs:

Diuretics:

Thiazide diuretics reduce the reabsorption of sodium and chloride in the early part of the distal convoluted tubule of the kidney. This results in the delivery of increased amounts of sodium to the distal tubule, where some of it is exchanged for potassium. The net result is increased excretion of sodium, potassium and water. Circulating volume is diminished, reducing preload on the heart and, thus, cardiac output and blood pressure with long-term therapy, autoregulation by the body's own compensatory mechanisms results in vasodilatation, reduction of peripheral vascular resistance and return of the cardiac output to normal. Thiazides also have some direct vasodilatory properties ***(Brater, 2000).***

Thiazide diuretics may cause hypokalaemia due to potassium wasting. Hypokalaemia may give rise to ventricular arrythmias and cause adverse drug effects in patients taking digoxin ***(Kaplan, 2000).***

Thiazides can also increase serum LDL-cholesterol and triglyceride levels, impair glucose tolerance and increase insulin resistance. Thus, thiazides probably should be avoided as first-line drugs in patients with diabetes and those with hyperlipidaemia ***(Brown, 2001)***.

Loop diuretics act on the ascending limb of the loop of Henle and inhibit the reabsorption of chloride, sodium and potassium. They produce a brisk but short-lived diuresis and are thus unsuitable as first-line agents for hypertension, as they do not provide 24-hour control. However, they do have a role in patients with impaired renal function in whom thiazides are ineffective, and in patients with

hypertension resistant to multiple drug therapy, who are often fluid overloaded *(Puschett, 2000).*

Potassium-sparing diuretics produce little reduction in blood pressure themselves. They may be useful in combination with other diuretics to prevent hypokalaemia *(Brater, 2000)*.

Adrenoceptor-blockers:

Beta (β)-blockers:

β-blockers act by blocking the action of adrenaline at β-adrenoceptors throughout the circulatory system and elsewhere. Their major effect is to slow the heart rate and reduce its force of contraction. β-blockers also cause some reduction in renin release and central sympathetic tone *(Staessen et al., 1999)*.

Lipid soluble β-blockers, cross the blood brain barrier more readily and are associated with a higher incidence of central side effects like, of insomnia, nightmares and fatigue. Some of them, have intrinsic sympathomimetic activity. They, therefore, cause less bradycardia and possibly fewer problems with cold extremities than conventional β-bolockers *(Spencer and Lip, 1999).* Like diuretics, β-blockers can worsen glucose intolerance and hyperlipidaemia *(Oparil, 1999).*

β-blockers are useful as first-line antihypertensive agents, although they tend to be less effective in the elderly and black hypertensives *(White, 2000)*

Labetalol and carvedilol have both α-and β_1-blocking properties, causing a reduction in peripheral vascular resistance, as well as slowing

the heart rate *(Michelson and Frishman, 1983)*. In addition to its β_1-blocking properties, carvedilol also has antioxidant effects, which give it theoretical advantages in reducing endothelial damage and lowing levels of highly atherogenic oxidised LDL-cholesterol *(Weber et al., 1998)*.

Alpha (α_1)- adrenoceptor blockers:

α_1-adrenoceptor blockers produce vasodilatation by blocking the action of noradrenaline at post-synaptic α_1 receptors in both arteries and veins. This results in a fall in peripheral resistance, without a compensatory rise in cardiac output. The prototype α_1-blocker prazosin is short acting and tends to produce precipitous falls in blood pressure, but the longer acting doxazosin combines the advantage of a more gentle reduction in blood pressure with once daily dosing *(Spencer and Lip 1999).*

α_1-blockers are, on the whole, well tolerated. Their main side effect is postural hypotension, which is more commonly caused by shorter-acting agents. In women, α_1-blockers may cause urinary incontinence *(Brown, 2001)*. In men, they may improve the symptoms of benign prostatic hypertrophy *(Cooper et al., 1999)*.

Calcium channel Antagonists:

There are three subclasses of calcium channel antagonists: the phenylalkylamine derivatives (e.g. verapamil), the benzothiazepines (e.g. diltiazem), and the dihydropyridines (e.g. nifedipine). All three subclasses are efficaious at reducing blood pressure as single agents. They modify calcium entry into cells by interacting with specific binding sites on the α_1 subunit of the L-type voltage-dependent calcium channel. There

are other calcium channels like the T and N types, so the actions of these drugs only partially modify total calcium transport into cells ***(Spencer and Lip 1999).***

The relative specificity of each agent stems from the fact that each class has a unique binding site on the α_1 subunit, and these sites are variably expressed in different tissues. Thus, while agents from all three subclasses cause vasodilatation, usually only dihydropyridines produce reflex tachycardia. Diltiazem and verapamil can both slow atrioventricular conduction, a feature not observed with the dihydropyridines ***(Hansson et al., 2000).***

The main, and most troublesome, side effect of calcium channel blockers is ankle oedema. This is caused by vasodilatation, which also causes headache, flushing and palpitation, especially with short-acting dihydropyridines ***(Opie et al., 1995)***.

Angiotensin converting enzyme (ACE) inhibitors:

ACE inhibitors have become increasingly popular over the past decade. They work by blocking the renin-angiotensin system, inhibiting the conversion of the inactive angiotensin I to the powerful vasoconstrictor and stimulator of aldosterone release, angiotensin II. This result in decreased peripheral vascular resistance and also a reduction in the levels of the sodium-retaining hormone aldosterone ***(Ferreira, 2000).***

ACE inhibitors also reduce the breakdown of the vasodilator bradykinin, which may enhance their action. Furthermore, they may improve endothelial function and reduce central adrenergic tone ***(Grassi et al., 1998)***. ACE inhibitors also have beneficial effects on renal

haemodynamics, reducing intraglomerular hypertension, resulting in improvements in proteinuric renal disease ***(Mackenzie et al., 1999; Ma and Fogo, 2001)***.

ACE inhibitors are effective as single agents in hypertension. ***(Hansson et al., 1999)***. There is useful synergism between the ACE inhibitors and diuretics and between ACE inhibitors and calcium channel blockers ***(Chalmers, 1999)***.

The most common side effect of ACE inhibitors is cough, caused by the inhibition of bradykinin breakdown ***(Mackay et al., 1999).*** The far more serious, but rare, side effect is angioedema ***(Guo and Dick, 1999)***. Dramatic deterioration in renal function can occur in patients with bilateral renal artery stenosis. Serum urea and creatinine should, therefore, be checked before and a few weeks after starting an ACE inhibitor ***(Bakris and Weir, 2000)***. The ACE inhibitors can cause hyperkalaemia because they reduce aldosterone and, thus, potassium excretion. Rare side effects include rash, taste disturbance, blood dyscrasias and a symptom complex that includes fever and vasculitis ***(Spencer and Lip, 1999).***

Angiotensin II Antagonists:

Like the ACE inhibitors, these drugs act on the renin-angiotensin system, blocking the action of angiotensin II antagonists at its peripheral receptors. They do not inhibit the breakdown of bradykinin ***(Mimran and Ribstein, 1999)***. Angiotensin II antagonists have similar physiological effect to ACE inhibitors and produce similar falls in blood pressure. There is synergism of antihypertensive effect with thiazide diuretics

(Chalmers, 1999). There is also evidence that they may regress LVH and improve proteinuria *(Burnier and Brunne, 2000).*

The main advantage of the angiotensin II antagonists is their apparent lack of side effects. Like the ACE inhibitors, they may cause hyperkalaemia, renal impairment and hypotension but, otherwise, they are almost as well tolerated as placebo. Nevertheless, cases of angioedema have been reported with some of these agents *(Oparil, 2000).*

CENTRALLY ACTING ANTIHYPERTENSIVE DRUGS

Numerous experimental drugs have been demonstrated to lower blood pressure, in particular when elevated, via primarily central nervous mechanisms, involving catecholaminergic, imidazoline-ergic, cholinergic, GABA-ergic, serotonergic, and other neuronal pathways and their associated receptors *(Van Zwieten, 1996)*. Although all of these receptors could theoretically be thought of as targets for centrally acting antihypertensive agents, in clinical practice only three categories of this large variety of receptors are indeed the targets of clinically useful antihypertensive drugs, alpha 2 (α_2)-adrenoceptors, I_1-imidazoline receptors, and serotonergic receptors *(Van Zweiten and Peters, 1999)*.

Central pathways regulating blood pressure:

The nucleus tractus solitarii (NTS) has long been known to be critically important in mediating the arterial baroreceptor reflex. The neuronal network between the NTS and the origin of the sympathetic neurons in the spinal cord has been established in recent years *(Van Zwieten, 1997)*. The afferent fibers from the arterial baroreceptors of the carotid sinus and the aortic arch terminate in the NTS, probably involving the excitatory amino acid L-glutamate as a neurotransmitter *(Arnolda et al., 1992; Chalmers et al., 1992)*.

Stimulation of the NTS causes a depressor response, involving the caudal ventrolateral medulla, also, using L-glutamate as its primary neurotransmitter. The depressor response is assumed to be triggered via a short inhibitory projection to the rostral ventral medulla, which is the

main pressor region in the brain stem *(Chalmers and Pilowsky, 1991)*. Descending sympathoexcitatory pathways from the brain stem originate from two separate and discrete areas in the rostral medulla. Firstly, the rostral ventrolateral medulla coincides with the C_1 group of adrenaline-containing neurons. Secondly, the rostral ventromedial medulla coincides with the B_3 group of serotonin-containing neurons *(Van Zwieten, 1996)*. Accordingly, centrally acting antihypertensives such as clonidine and α- methyl dopa act via both adrenergic and serotonergic neuronal pathways *(Minson et al., 1989)*.

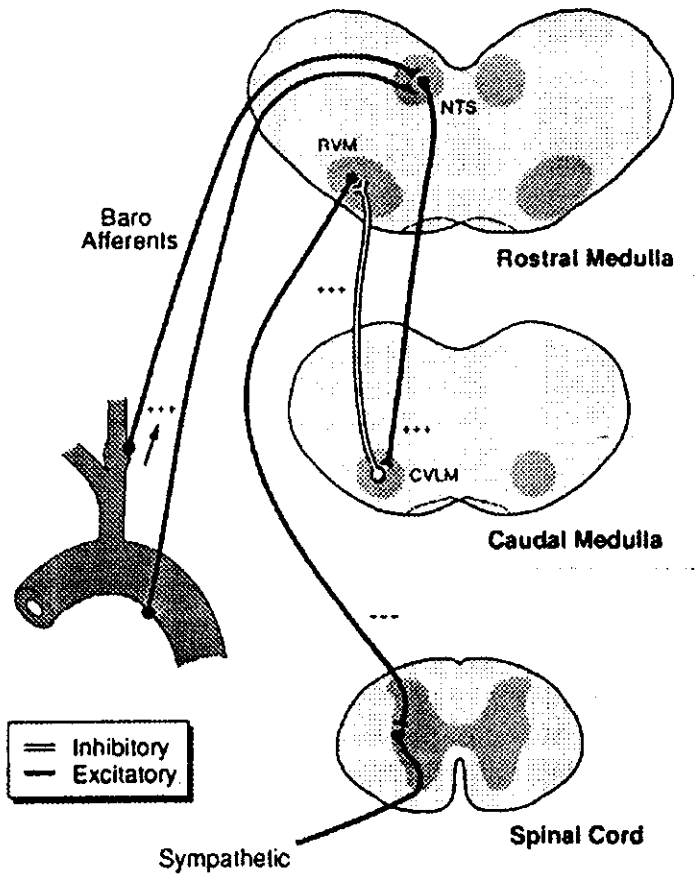

Figure (1): Schematic representation of neurons involved in the central regulation of blood pressure *(Van Zwieten and Chalmers, 1994)*.

The major receptor subtypes that are the targets of centrally acting antihypertensives are assumed to be located within the aforementioned neuronal networks involved in the central regulation of the cardiovascular system via the autonomic nervous system ***(Esler, 2000)***.

Different types of centrally acting antihypertensive drugs:

Clinically developed centrally acting antihypertensive drugs may be subdivided into 3 categories, based on the receptor targets in the central nervous system which mediate their antihypertensive actions ***(Van Zwieten, 1999)***.

1- α_2-adrenoceptors agonists:

α_2-adrenoceptors in the brain stem are the initial targets of classical drugs such as clonidine, guanfacine and α-methyl-DOPA (via its active metabolite α-methylnoradrenaline). These drugs were introduced in the management of hypertensive disease in the 1960s. they have been widely used in clinical practice in the 1970s and 1980s ***(Van Zwieten, 1997)***. These drugs are effective antihypertensives with an attractive hemodynamic profile. However, they have lost a great deal of their clinical relevance because of their unfavourable profile of adverse reactions, such as sedation, dry mouth and sexual impotence. For such reasons these drugs can hardly compete with newer antihypertensives, such as low-dose diuretics, β-blockers, calcium antagonists, ACE-inhibitors or angiotensin II-receptor antagonists ***(Van Zwieten and Chalmers, 1994)***.

Mode of action and Hemodynamicprofile:

The exact location and the specific receptors responsible for the central hypotensive action of α_2-adrenoceptor agonists are not known. Involvement of postsynaptic α_2- adrenoceptors and I_1-imidazoline receptors in the brainstem have been suggested ***(Bousquet and Feldman, 1999)***. Although the role of imidazoline receptors have been questioned ***(Guyenet, 1997; Kuzmin et al., 2000)***. The mechanism of action of different centrally acting antihypertensives is illustrated in figure (II).

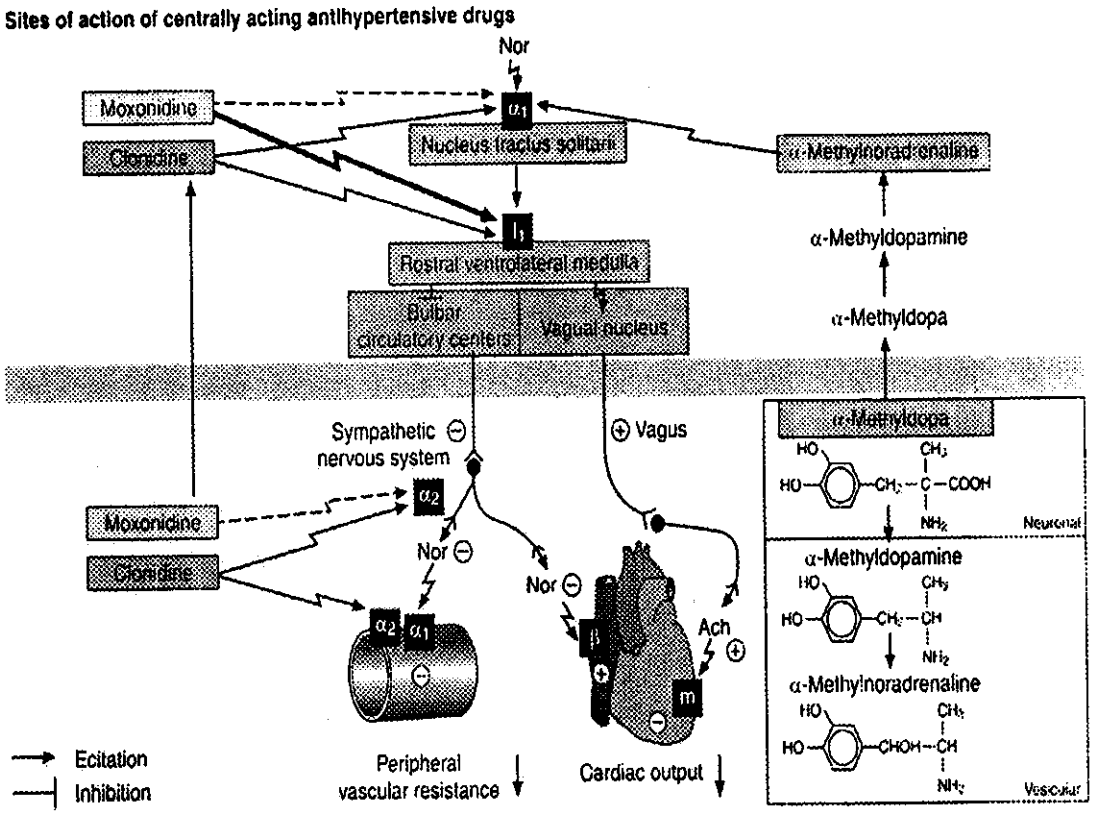

Figure (II): Central antihypertensive mechanisms of various types of centrally acting antihypertensive drugs. Note the different targets of α_2-adrenoceptors but not by I_1- imidazoline receptors. NTS, nucleus tractus solitarii; RVLM, rostral ventrolateral medulla. ***(Van Zwieten, 1997)***

α_2-adrenoceptor stimulation not only lowers the baseline blood pressure values but also lowers the set point around which arterial blood pressure is regulated. Thus, the baroreceptor reflex is not abolished but only re-set at a lower level ***(Grassi et al., 2001).*** The α_2- adrenoceptor agonist clonidine is only capable of decreasing blood pressure that is dependent on sympathetic tone and, thus, has little effect on blood pressure in normotensive individuals ***(Maze and Tranquilli, 1991)***

A considerable portion of the central hypotensive activity of α-methyl-DOPA is mediated by the modulation of central serotonergic pathways ***(Chalmers et al., 1992)***.

It is important to emphasise that inhibition of central sympathetic output by α_2- adrenoceptor stimulation might be deleterious especially in patients in which sympathetic activity is essential for maintenance of circulatory function (e.g chronic valvular disease). However, in contrast to the effect of beta receptor blocking agents and ganglion blockers clonidine neither alters catecholamine metabolism nor does it block ganglion transmission or adrenergic receptors. Thus, the protective reflexes triggered by a reduction in blood pressure are still functional and vasoactive and inotropic drugs still remain effective despite prior administration of α_2-adrenoceptor agonists ***(Van Zwieten, 1999).***

Intravenous administration of α_2- adrenoceptor agonists frequently lead to an initial increase in arterial blood pressure and systemic vascular resistance and a secondary decrease in heart rate resulting in a transient reduction of cardiac output ***(Khan et al., 1999).*** These effects are probably due to the activation of α_1-receptors and postjunctional vascular α_2- adrenoceptors located on vascular smooth muscles. This first short

period of increase in blood pressure is within minutes followed by a longer period characterised by a decrease in heart rate and arterial blood pressure due to a centrally mediated decrease in sympathetic tone ***(Prichard and Graham 2000).*** The reduction in sympathetic tone and increased vagal activity result in a reduction of heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. The results of these effects is a net decrease in myocardial oxygen consumption which most probably explains the positive effects seen with α_2- adrenoceptor agonists in the treatment of angina pectoris ***(Khan et al., 1999).***

The effect of α_2- adrenoceptor agonists on coronary vasculature in human is not yet known ***(Khan et al., 1999)***, as there is considerable interspecies variation in distribution and α_2-adrenoceptor subtypes. It is known that the α_2-adrenoceptors on the endothelium release nitric oxide when activated ***(Angus et al., 1986)*** and this has been shown to be the α_{2a} subtype ***(Bockman et al., 1992)***. It has been postulated that the stimulation of α_2- adrenoceptors may lead to a postsynaptic coronary vasconstriction, which may be countered by a nitric-oxide-mediated coronary vasodilatation ***(Coughlan et al., 1992)***.

Other effects of α_2- adrenoceptor agonists:

Central nervous system effects:

The use of clonidine as an antihypertensive has been limited by its sedative effects, but offers advantages in anaesthetic practice ***(Horn et al., 1997).*** When clonidine was given in a sufficient dose to produce sleep, the EEG showed an increase in stage 1 and 2 sleep and decrease in rapid eye movement sleep ***(Bischoff et al., 1998)***

α_2-adrenoceptor agonists and benzodiazepine produce similar anxiolysis *(Frank et al., 2000).* The sedative and anxiolytic effects may be mediated by postsynaptic α_{2a}- subtype adrenoceptors located in the locus coeruleus *(Van Zwieten, 1986).* Clonidine at high doses can be anxiogenic owing to α_1- adrenoceptor activation *(Soderpalm and Engel, 1988).*

Clonidine is frequently described as enhancing memory especially in early stages of Alzheimer's disease *(Riekkinen et al., 1999).*

Renal effects:

Stimulation of α_2- adrenoceptors increase the glomerular filtration rate and promotes both diuresis and natriuresis by decreasing the secretion of antidiuretic hormone (ADH) and antagonising its action on renal tubules *(Molderings, 1995).*

α_2-adrenoceptors are also though to inhibit the release of renin *(Pettinger, 1987)* and increase the release of atrial natriuretic factor in the rat *(Chen et al., 1989).*

Respiratory system effects:

α_2-adrenoceptor agonists have minimal effects on ventilation in therapeutic doses although respiratory depression has been described following intoxication *(Olsson and Pruitt, 1983; Anderson et al., 1981).* In adults clonidine has been shown to result in a small reduction in resting minute ventilation and expired carbon dioxide concentration *(Ooi et al., 1991).* α_2- adrenoceptor agonists have no significant effect on hypercapnic or hypoxic ventilatory drive and do not potentiate the

ventilatory depression caused by opioids *(Baily et al., 1991; Jarvis et al., 1992).*

Neuroendocrine system effects:

The α_2-adrenoceptor agonists have a number of neuroendocrine effects, mainly related to their inhibition of sympathetic outflow and the decrease in plasma levels of circulating catecholamines *(Khan et al., 1999).*

Stimulation of α_2- adrenoceptors located on the β cells of the islets of langerhans can temporarily cause directed inhibition of insulin release *(Abd El-Zaher et al., 2001).* However, clinical hyperglycaemia has not proved to be a problem *(Khan et al., 1999).*

α_2-adrenocptor agonists increase the release of growth hormone *(Dhir-Ravindra et al 2002)* and inhibit adipose tissue lipolysis *(Van-den Thillart et al., 2001).* The release of stress hormones such as adrenocorticotropic hormone (ACTH) and cortisol following surgery is also modified *(Masal et al., 1985).*

Gastrointestinal system effects:

Salivary flow is reduced by α_2- adrenoceptor agonists *(Watkins 1980)* and colonic water and ion secretion is inhibited, explaining why diarrhoea successfully can be treated with α_2- adrenoceptor agonists *(Schworer et al., 1995).* Activation of prejunctional α_2-adrenergic receptors also inhibits the vagally mediated release of gastric acid from parietal cells *(Molderings et al., 1995).* However, no change in gastric

pH has been observed following α_2- adrenoceptor stimulation in humans ***(Orko et al., 1987).***

Platelet effects:

Higher doses of α_2- adrenoceptor agonists stimulate platelet aggregation ***(Grant and Scrutton, 1980)*** whereas lower doses indirectly decrease adrenaline concentrations, thus, reducing platelet aggregation. α_2-adrenoceptor stimulation also causes the release of nitric oxide, a potent platelet aggregation inhibitor ***(Radomski et al., 1987).*** However, the net effect of α_2-adrenoceptor stimulation does not appear to cause any clinically significant effect regarding platelet function.

Effect on the eye:

Topical application of clonidine significantly reduce intraocular pressure in patients with open angle glaucoma ***(Petursson et al., 1984).***

Analgesic effects of α_2-adrenoceptor agonists:

In ***1974 Paalzow*** was the first to report clonidine to be potent analgesic in animals. The anatomical site associated with this analgesic action of clonidine as well as the pharmacological mechanisms of this analgesic effect is still debated.

Descending noradrenergic antinocieptive pathways originating in the brainstem have been shown to contribute to pain control by suppression of spinal nociceptive impulses by interaction with postjunctional α_2- adrenoceptors in the dorsal horn ***(Mayer and Liebskind, 1974; Fields and Basaum, 1978)*** and is generally believed to be one of the main mechanisms of descending endogenous pain

modulation. Thus, interaction with α_2- adrenoceptors in the dorsal horn normally responsible for endogenous pain modulation might be one possible mechanism for the antinociceptive action of clonidine. However, since direct administration of clonidine into the brainstem does not produce analgesia ***(Coote, 1988; Castro and Eisenach, 1989).*** More central mechanism for the analgesic action of α_2-adrenoceptor agonists has been hypothesised. Finally, as has been mentioned above, the central analgesic action of systemic administered α_2-adrenoceptor agonists has by some critics been solely attributed to the sedative actions of α_2-adrenoceptor agonists, thereby merely decreasing the unpleasantness of the pain experience ***(Bernard et al., 1991; Bernard et al., 1995).***

Although other mechanisms are discussed the most widely accepted theory regarding the antinociceptive action of clonidine is believed to be spinal modulation ***(Eisenach et al., 1996).*** α_{2a}-adrenoceptors have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord and stimulation of these α_2- adrenoceptors inhibits the firing of nociceptive neurones stimulated by peripheral Aδ and C fibers ***(Howe et al., 1983).*** More recent evidence suggests that the antinociception produced by α_2- adrenoceptor agonists may be due in part to acetylcholine release in the spinal cord ***(Bouaziz et al., 1995; Klimscha et al., 1997).***

Systemically administered clonidine have a documented analgesic effect ***(Hall et al., 2001),*** but since the spinal cord is suggested to be the major site of analgesic action of α_2- adrenoceptor agonists ***(Eisenach et al., 1993),*** the epidural and intrathecal routes have been considered preferable to the intravenous route. This is, however, questioned by data

showing as similar effect of orally administered clonidine when compared to intrathecally applied clonidine in the context of spinal anaesthesia *(Kita et al., 2000).*

Apart from a beneficial effect in acute pain α_2- adrenoceptor agonists have also been reported to be useful in the treatment of chronic pain syndromes in both animal and human studies *(Puke and Wiesenfeld-Hallin, 1993; Yakash et al., 1995; Leiphart et al., 1995).* The epidural route has proved the most effective way of administrating clonidine in neurophatic pain *(Caroll et al., 1993),* although both intravenous and transdermal routes have been used *(Byas-Smith et al., 1995).* A combination of epidural clonidine and local anaesthetics is particulary effective in patients suffering from neurophatic pain syndromes *(Glynn and O'Sullivan, 1995).* Epidural clonidine has also been reported to be effective in treating cancer pain in patients tolerant to opioids *(Eisenach et al., 1989; Eisenach et al., 1995)* and topical clonidine has been found beneficial in the treatment of sympathetic mediated pain states *(Davies et al., 1991).*

Antihypertensive efficacy:

The antihypertensive efficacy of clonidine and α-methyl-DOPA has been confirmed in very large numbers of patients, and also analyzed in several clinical trials. The diminished interest in the practical use of these drugs is certainly not caused by insufficient antihypertensive efficacy and reliability, but clearly due to the unfavourable side-effect profile *(Van Zwieten, 1997).*

Adverse reactions:

The adverse reactions to classic α_2-adrenoceptor agonists, such as sedation, dry mouth and sexual impotence, are well known *(Van Zwieten,*

1989a; Van Zwieten and Chalmers, 1994). These side effects are not dangerous, but generally experienced as unpleasant and therefore they negatively influence patient compliance.These side-effects are mediated by α_2-adrenoceptors in other regions than those involved in the antihypertensive activity of these drugs.

The most important adverse effect of clonidine is the variable occurrence of a withdrawal syndrome when the drug is abruptly ceased *(Weber, 1980)*. This syndrome presents 18-72 h after the last dose of clonidine and is characterized by a rapid rise in blood pressure towards pretreatment values and symptoms such as headache, flushing, sweating, insomnia, tremor, nausea, and vomiting *(Whitsett, 1983)*.

The clonidine withdrawal syndrome clinically resembles withdrawal syndromes associated with opiates, alcohol and hypnosedatives, suggesting a common final pathway *(Gowing et al., 2000)*. The syndrome can be prevented by gradual withdrawal of clonidine over days to weeks and if present, controlled by reintroducing clonidine treatment or by α- and - β- adrenoceptor antagonists. *(Thoolen et al., 1983)*.

Drug interactions:

α_2-adrenoceptor agonists and opioids have some similar pharmacological effects. It is known that they have a similar distribution in the brain and that they function through the activation of the same transduction and effector mechanisms, i.e. G-proteins and coupling to potassium channels. Therefore, if α_2-adrenoceptor agonists and opioids are administered together they may exhibit a synergistic action

(Khan et al., 1999). It may also be possible to reduce the opioid dose and therefore decrease the respiratory and addictive side-effects. α_2-adrenoceptor agonists also have a synergistic action with benzodiazepines. The administration of antagonists of either class of drug does note reverse the effects of the other, i.e. atipamezole and flumazenil *(Salonen et al., 1992)*.

2-Drugs interacting with central serotonergic receptors:

A possible role of peripheral serotonin, serotonergic neurones, and receptors in the central regulation of blood pressure was repeatedly discussed in the 1980s, inspired by the antihypertensive activity of ketanserin which is the only 5-HT_2 receptor antagonist that causes an antihypertensive and vasodilator effect *(Van Zwieten and Chalmers, 1994).*

The potential role of 5-HT in central cardiovascular regulation is further emphasized by the discovery of central 5- HT_{1A} receptor stimulation as a general principle of drug - induced hypotension *(Van Zwieten et al., 1992).*

Stimulation of central 5- HT_{1A} receptors, with an appropriate agonist, will mediate peripheral sympatho inhibition and a fall in heart rate *(Ramage, 1991).*

The rostral ventrolateral medulla has been identified as the site of a action of 5- HT_{1A} receptors agonists like 8-OH- DPAT, flesinoxan and the hyprid drug urapidil *(Benedict, 1999).*

Ketanserin:

Ketanserin is a selective 5-HT_2 receptor antagonist and additionally α_1- adrenoceptor antagonist. However, the α_1- antagonistic activity is weaker than the 5-HT_2 antagonistic potency ***(Robertson et al., 1986).*** It lowers blood pressure as a result of vasodilatation and a reduction in total peripheral resistance. Heart rate remains unchanged in spite of the vasodilatation ***(Van Nueten et al., 1981).***

The details of the central hypotensive mechanism of ketanserin remain unknown, but it has to be concluded that both 5-HT_2 and α_1-adrenergic receptor antagonism are required to explain its long- term antihypertensive activity ***(Van Zwieten, 1997).***

Ketanserin is a moderately effective antihypertensive agent without particular advantages. Most of side effects, which are comparable with that of placebo, are rather unspecific like sedation, fatigue, dizziness, headache and mild gastrointestinal discomfort. They are not clearly related to 5- HT_2 or α_1-receptor blockade ***(Van Zwieten, 1999).*** In higher doses ketanserin causes prolongation of QT segment in the ECG, with the potential risk of dysrhythmia. This risk is enhanced by hypokalemia, and for this reason the combination of ketanserin and thiazide or loop diuretics should be avoided. It may be combined with potassium sparing diuretics ***(Breckenridge, 1988).***

Urapidil:

Urapidil, a derivative of uracil, is a selective α_1-adrenoceptor antagonist, and thus its mode of action is similar to that of prazosin, causing a reduction in peripheral vascualr resistance and a consequent

fall in blood pressure *(Schoetensack et al., 1983)*. Its selectivity for α_1-adrenoceptors is lower than that of prazosin, but at clinical doses the interaction of the drug with either pre-or postsynaptic α_2-adrenoceptors probably does not significantly contribute to the antihypertensive effect *(Van Zwieten, 1989b)*.

Apart from its α_1-antagonistic activity, urapidil displays significant centrally mediated antihypertensive potency, although the evidence for this mechanism is limited to animal experiments *(Van Zwieten, 1989b; Gillis et al., 1988)*. The central hypotensive mechanism of urapidil largely differs from that of clonidine, guanfacine and α-methyl-DOPA which are known as the prototypes of centrally acting drugs antihypertensive *(Van Zwieten and Chalmers, 1994)*. It does not stimulate centrally located α_2-adrenoceptors and, unlike clonidine and related drugs, its central hypotensive effect cannot be blocked by the α_2-adrenoceptor antagonist, yohimbine *(Gillis et al., 1988)*. Several studies have suggested that the central hypotensive activity of urapidil is triggered by the stimulation of central 5-HT_{1A} receptors, as concluded from radioligand binding and functional experiments *(Gross et al., 1987; Fozard et al., 1987)*.

Urapidil displays a hemodynamic profile as to be expected for a postsynaptic α_1-adrenoceptor antagonist, which means dilatation of the resistance vessels, and to a lesser degree also of the capacitance vessels. Owing to the central mechanism involving the stimulation of $5HT_{1A}$-receptors reflex tachycardia does not occur, in spite of the potent vasodilator action *(Prichard et al., 1989; Van Zwieten et al., 1992)*.

Urapidil is able to decrease elevated pulmonary vascular resistance in either chronic obstructive pulmonary disease or heart failure *(Zink et al., 2002).*

Flesinoxan is also a 5-HT_{1A} receptor stimulant with hypotensive/ vasodilator activity *(Wouters et al., 1988)*. The compound is devoid of α_1-receptor antagonistic activity, suggesting that central 5-HT_{1A} receptor stimulation is a more general principle of sympathoinhibition initiated at the level of the central nervous system *(Saxena and Villalón, 1990)*.

Clinical efficacy and tolerability:

Urapidil's clinical efficacy and tolerability are well documented in a large number of patients. Adverse reactions to urapidil, such as dizziness, headache, fatigue and gastrointestinal problems are usually mild and rather unspecific and quite different from those of the classic α_2-adrenoceptor agonists. Rebound phenomena have so far not been reported *(Dooley and Goa, 1998)*.

3-Imidazoline (I_1)-receptor agonists:

The imidazoline receptors recently have been discovered to be involved in the central nervous system control of sympathetic outflow. A new class of centrally acting antihypertensive agents, the imidazoline receptor agonists, have been developed to control blood pressure effectively without the adverse effects of sedation and mental depression that usually are associated with the first generation of centrally acting antihypertensives. This second generation is highly selective for the imidazoline receptor but has a low affinity for α_2- adrenergic receptors *(Palkhiwala et al., 2000).*

Stimulation of the central I_1- receptors by these agents causes peripheral sympathoinhibition. Similar to that induced by clonidine and related drugs ***(Bousquet, 2000; Greenwood et al., 2000)*** Moxonidine and rilmenidine are two imidazoline compounds with 30 -fold greater specificity for I_1- receptors than for α_2- adrenoceptors ***(Prichard and Graham, 2000).*** They are the prototypes of centrally acting I_1- receptor agonists ***(Van Zwieten, 2000).***

A series of pyrrolinic isosteres of rilmenidine has been prepared and their biological activity at imidazoline receptors of both types (I_1- and I_2) and α_2-adreroceptors evaluated to find new compounds selective for I_1- receptors. This isosteric replacement provided compounds which still bound to I_1- receptors but not to I_2- nor to α_2- adrenoceptors ***(Schann et al., 2001).*** One compound in this series, LNP 509 [cis-/trans-dicyclo-propylmethyl-(4,5-dimethyl-4,5-dihydro-3H-pyrrol-2-YL)-amine], had no detectable affinity at α_2-adrenoceptors yet was capable of lowering blood pressure after central administration.

These pyrrolinic analogues constitute a new chemical class of imidazoline related compounds with high selectivity for the I_1- receptors. They could be used as new tools in the study of I_1- receptors and in the conception of new centrally acting hypotensive drugs ***(Schann et al., 2001).***

Mode of action and Hemodynamic profile:

Moxonidine and rilmenidine activate I_1- receptors in the region of the rostral ventrolateral medulla (RVLM) and hence decrease the firing rate of the bulbospinal symathoexcitatory neurons, thus causing peripheral sympathoinhibition, and a fall in blood pressure ***(Szabo, 2002).***

Accordingly, the stimulation of both α_2-adrenoceptor and I_1-receptors in the central nervous system reduced activity of the peripheral sympathetic nervous system. It is very likely that in both cases the same final neuronal pathways are involved, although the initial stimulation is mediated by 2 different types of receptors ***(van Zwieten, 1999)***.

The antihypertensive activity of both moxonidine and rilmenidine is associated with arterial vasodilatation and a reduction in peripheral vascular resistance ***(Van Zwieten, 1997)*** cardiac output and heart rate are not much changed by both drugs although they can suppress tachycardic episodes ***(Head and Burke, 2000)***

The vasodilator and antihypertensive activities of both drugs are clearly caused by sympathoinhibition, as reflected by a lowering of plasma noradrenaline levels ***(Szabo et al., 2001)***. They also caused a reduction of plasma renin activity, whereas plasma concentrations of adrenaline, angiotensin II, aldosterone and atrial natriuretic peptide were not significantly diminished ***(Prichard, 1996a)***. Long-term treatment with both drugs is associated with a partial regression of left ventricular hypertrophy (LVH) ***(Eichstadt et al., 1989; Van Zwieten, 2000)***.

Antihypertensive efficacy:

The antihypertensive efficacy of these drugs has been established in a large number of patients with essential hypertension ***(De Freitas , 2000)***.

The efficacy of rilmenidine (1-2 mg daily) has been demonstrated in a large number of hypertensive patients. It is as effective in monotherapy as all other first - line classes of drugs , including diuretics,

beta-blockers, angiotensin converting enzyme inhibitors and calcium antagonists, it can be taken in combination for greater efficacy ***(Reid, 2001).***

Treatment with rilmenidine will reduce cardiac and renal sympathetic baroreceptor responses, whereas cardiac vagal baro-reflex sensitivity appears to be increased. These phenomena indicate the possibility of restoring the impaired baroreflex function known to occur in hypertensive ***(Head et al., 2001)***.

Adverse reactions:

Dry mouth, fatigue and drowsiness are the most frequently reported side-effects for the I_1-receptor stimulants moxonidine and rilmenidine. However, the incidence of these side-effects of the I_1-stimulants appears to be significantly less than that known to occur for clonidine ***(Prichard, 1996b; Webster and Koch, 1996)***. For treatment with rilmenidine it has been claimed that dry mouth and drowsiness were the same as experienced by comparable patients on placebo ***(Reid, 2000)***. In more refined psychomotor tests rilmenidine did not impair alertness ***(Morrison et al., 1990)***.

Although it seems very likely that the incidence and severity of adverse reactions to moxonidine and rilmenidine are considerably less than those of clonidine or α-methyl-DOPA, appropriately designed trials to quantitatively compare the side-effect profiles of both types of drugs remain to be performed ***(Khan et al., 1999)***.

The rebound phenomenon has never been reported for the cessation of moxonidine or rilmenidine treatment, and neither could it be evoked in

animal models where the clonidine rebound phenomenon could be demonstrated *(Sevcik and Masek, 1999)*.

Both moxonidine and rilmenidine are considered to be neutral with respect to plasma lipids, blood glucose levels are unchanged by rilmenidine treatment, whereas under certain conditions moxonidine may even lower glucose levels via a combination of central and peripheral mechanisms *(De- Freitas, 2000)*.

Both moxonidine and rilmenidine appear to be safe in patients with chronic obstructive pulmonary disease (COPD), diabetes mellitus or depression *(Prichard, 1996a; Dupuy et al., 2000)*.

IMIDAZOLINE (I) RECEPTORS

History:

In the early 1980s, ***Bousquet et al.*** proposed the existence of receptors specifically recognising the imidazoline or similar chemical structure and which were not adrenergic receptors. This was because the central hypotensive effects of *clonidine*-like drugs could not be explained by their α_2-receptor actions alone. It was suggested that these receptors might be found in the nucleus reticularis lateralis of the ventrolateral medulla, the site of the hypotensive action of these drugs ***(Bousquet et al., 1981; Bousquet et al., 1984)***. In 1987, ***Ernsberger et al.*** were the first to verify the existence of specific imidazoline binding sites in the ventrolateral medulla which were insensitive to catecholamines. Further study during the 1980's with the radiolabelled forms of *clonidine* and *idazoxan* not only substantiated the existence of these non-adrenoceptor binding sites but showed that at least two distinct populations of imidazoline binding sites existed ***(Michel and Insel, 1989)***. However, by this time several forms of nomenclature were in use utilizing (^{3}H)-*idazoxan*. For example, non-adrenergic *idazoxan* binding sites (NAIBS) ***(Michel et al., 1989)***, imidazoline-preferring receptors (IPR) ***(Hamilton et al., 1991)***, *idazoxan* receptors (IR) ***(Wikberg, 1989)*** and imidazoline-guanidinium-receptive sites (IGRS) ***(Tesson et al., 1991)***, were all described. Those non-adrenoceptor sites predominantly labelled by (^{3}H) *clonidine* or (^{3}H) *para-aminoclonidine* were termed I_1-sites, whereas those non-adrenoceptor sites predominantly labelled by (^{3}H)-*idazoxan* were termed I_2-sites. They then subdivided the I_2-site into I_{2A} (amiloride-sensitive) and I_{2B} (amiloride-insensitive) which relieved much of the confusion derived from species differences ***(Ernsberger, 1992)***.

However, as so often happens, there are examples of atypical imidazoline binding sites which appear pharmacologically distinct from the above classification *(Molderings, 1995)*. More recent studies using an immunological approach have demonstrated a family of imidazoline binding proteins with a range of masses from a range of tissue *(Bousquet et al., 2000)*.

Molecular characterization of I receptors:

Structural studies:

The fact that all ligands binding to I also bind to α_2-adrenergic receptors raises questions as to whether the two receptors differ structurally. The full I receptors has not been cloned *(Bousquet, 2001a)*. Several lines of evidence support the view that I and α_2-adrenergic receptors are very different. ***Parini et al. (1989)***, first attempted to determine whether the I receptor and α_2- adrenergic receptor of rabbit kidney were distinct entities. Using physical separation methods, they were able to separate two proteins that retained the respective binding properties of each receptor and demonstrated that the imidazoline binding site was a protein that was distinct from the adrenergic binding element. By subcellular fractionation, the receptive site was shown to be localized to the outer mitochondrial membrane in rabbit and human liver *(Tesson et al., 1991)* and rabbit kidney *(Lachaud-Pettiti et al., 1991)* and was closely linked to monoamine oxidase in that organelle. By further purification, they identified an I_2 receptor binding subunit of approximately 60 kDa that was an acidic protein and whose binding activity was regulated by H^+ concentration near a physiological pH of 7.4 *(Limon et al., 1992)*.

Using a different approach, ***Wang et al. (1992)*** isolated and partially purified proteins from bovine adrenal chromaffin cell membranes with ligand binding properties of I_2 receptors. The proteins were purified by ligand-affinity chromatography. Purification yielded a major protein component of 70 kDa, it was not glycosylated ***(Wang et al., 1992)***.

Polyclonal antibodies were raised in rabbits against this protein. The labeled antibodies, immunostained cultured chromaffin cells of cow and adrenal medulla of rat ***(Wang et al., 1993)***. This antibody has been utilized to analyze the expression and regulation of the I receptor-binding protein in rat and human brain ***(Escriba et al., 1994)*** and in human platelets. In these tissues, the antibody recognized, in addition to the 60-kDa band, heterogenous proteins with apparent molecular weights of 66, 47, and 30 kDa. The 47-and 30-kDa proteins and (^{3}H)-idazoxan binding in brain show parallel increases during aging as well as following treatment with imidazoline drugs in rats, suggesting that these proteins are the binding entity. I-receptor antibodies also recognize a 33kDa protein in human membranes, which correlates with the I_1 imidazoline sites ***(Escriba et al., 1994)***.

Bousquet et al. (1994), have isolated an imidazoline binding protein from membranes of the human ventrolateral medulla which binds both (^{3}H)-*idazoxan* and (^{3}H)-*clonidine* with high affinity. Their conclusion is that this protein may represent the binding entity of human I_1 imidazoline receptors.

Lanier et al. (1993), have developed photoaffinity probes based on the structure of *cirazoline* with which they have successfully labeled

(Raasch et al., 2002). Its role in normal brain function, however, has not yet been established, in part because of the absence of agents that selectively effect its biosynthesis or degradation *(Otake et al., 1998; Reis and Regunathan, 1998b)*.

A recent study demonstrates that *agmatine* stimulates the firing rate of locus coeruleus neurons via a nitric oxide synthase-dependet mechanism located in this nucleus *(Ruiz- Durantez et al., 2002).*

Classification, Distribution and Function:

Two subtypes of imidazoline receptors (IRs) have been isolated, I_1 and I_2 *(Ernsberger, 1992)*. Furthermore, there are reports of imidazoline receptors I_3, which appear distinct from either I_1- or I_2 sites and yet the compounds which act at these "atypical" receptors are invariably imidazolines or closely related compounds *(Bousquet, 1997)*.

Table (III): Classification and properties of I receptors.

	I_1-sties	I_2-sites
Radioligands	^{3}H-aminoclonidine, ^{3}H-clonidine.	^{3}H-idazoxan, ^{3}H-2BFI
Drug affinities	Clonidine= phentolamine= idazoxan > rilmenidine = moxonidine > efaroxan >> guanabenz >> epinephrine = rauwolscine.	Cirazoline > idazoxan = BFI > naphazoline = tolazoline > guanabenz >> clonidine >> epinephrine = rauwolscine.
Subcellular localization	Nonmitochondrial membrane	Mitochondrial and plasma membrane
G-protein coupling	Yes	No
Signal transduction	Prostaglandin release	Unknown, regulation of monoamine oxidase
Endogenous ligands	Agmatine, cCDS, ir-CDS	Agmatine, cCDS, ir-CDS
Distribution	Brainstem, kidney, chromaffin cells, PC12 cells, platelets	Cerebral cortex, astrocytes, kidney, liver, adrenal medulla, platelets, adipocytes, pancrease, prostate, placenta, urethra, vascular cells, carotid body, colon.

Quoted from *(Regulnathan and Reis, 1996)*

Imidazoline (I_1)-receptors subtype:

Location and Function:

I_1- subtype is present in the rostral ventrolateral medulla oblongata (RVLM) in the brainstem, and is involved in blood pressure regulation via central sympathetic outflow ***(Bousquet, 2001b)***. In addition, I_1-receptors are found in bovine frontal cortex ***(Ernsberger et al., 1987)*** and also in rat locus coeruleus where their activation increases spontaneous neuronal firing ***(Pineda et al., 1995)***.

In the periphery, low affinity [^{3}H]-*para-aminoclonidine* binding has been reported in rat kidney and in guinea pig kidney ***(Ernsberger et al., 1995)***, and [^{3}H]-*clonidine* binding to rat kidney membranes appears to be a pharmacological model of central I_1 receptors ***(Ernsberger et al., 1996)***. These I_1-receptors have been proposed to be functional as their activation leads to natriuresis in anaesthetized unilaterally-nephrectomised rats ***(Smyth et al., 1995)***. ***Ernsberger et al. (1995)*** has reported the existence of I_1-receptors in adrenal chromaffin cells. The existence of an I_1-receptor site on human platelets have been established ***(Piletz et al., 1991; Piletz and Sletten, 1993)*** whose density is elevated in depressed subjects ***(Piletz et al., 1996)***. Binding studies indicate that I_1-receptors are also present in pancreatic islets, along with a high density of α_2 adrenergic receptors ***(Ernsberger et al., 1995)***.

Recent studies demonstrate that the heart possesses imidazoline I_1-receptors that are up - regulated in the presence of hypertension or heart failure, which would suggest their involvement in cardiovascular regulation ***(EL- Ayoubi et al., 2002).***

Subcellular distribution:

Knowledge of the subcellular distribution of I_1 receptors is incomplete. In contrast to the I_2 receptor, which is primarily associated with mitochondria ***(Tesson et al., 1992)***, I_1 receptors have not been detected on this organelle in all tissues so far examined. In platelets and the tissue in which some subcellular analysis has been undertaken, I_1 sites have been reported to be localized to cell membranes ***(Ernsberger et al., 1995)***.

Signal transduction:

Several studies reported that binding to I_1 imidazoline sites in bovine ventrolateral medulla ***(Ernsberger et al., 1993)***, bovine adrenal medulla ***(Ernsberger et al., 1995)***, and human platelets ***(Piletz and Sletten, 1993)*** are inhibited by guanine nucleotides, suggesting that the receptor belongs to a G-protein-coupled receptor superfamily. Others have failed to detect regulation of binding of ^{3}H-*clonidine* to human brain stem membranes by GTP, indicating that G-protein coupling is not involved ***(Bricca et al., 1994)***. Proof that the I_1 receptor exists in high-and low-affinity forms and is a member of a G-protein-coupled receptor superfamily will only be established when the receptor has been cloned and can be studied in transfected cells ***(Bousquet, 2001a)***.

The intracellular signal transduction pathways coupled to the I_1 receptor are unknown. In part, efforts to define the cellular function coupled to the receptor have been complicated by the lack of defined agonists or antagonists. Moreover, not all of the actions of imidazoline drugs are receptor mediated ***(Regunathan and Reis, 1996)***.

In adrenal chromaffin cells-which express many I_2 ***(Regunathan et al., 1993b)***, fewer I_1 ***(Ernsberger et al., 1993; Molderings et al., 1993)*** and no α_2-adrenergic receptors ***(Regunathan et al., 1993b)***, exposure to appropriate ligands do not modify the content of cAMP, cGMP, and inositol phosphates ***(Regunathan et al., 1991a)***, suggesting that these second messengers are not involved. On the other hand, moderately high concentrations of *clonidine* elicit a small delayed and relatively prolonged increase in the influx of Ca^{2+} possibly related to stimulation of I_1 receptors ***(Regunathan et al., 1991a)***.

A preliminary report claims that activation of I_1 receptors increases the release of prostaglandin E_2, which would suggest coupling of the receptors to the release of arachidonic acid ***(Ernsberger et al., 1995)***.

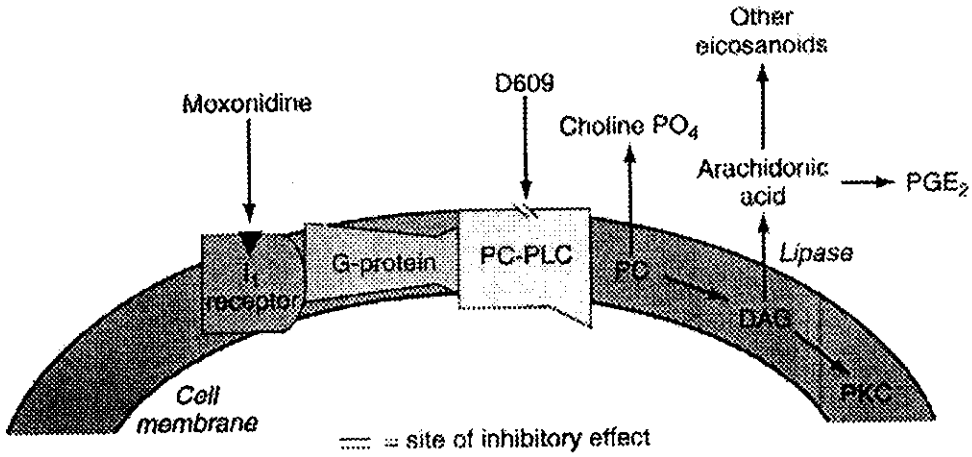

Figure (III): Hypothetical model of signalling mechanisms coupled to I_1-imidazoline receptor (I_1R) activation. PC-PLC= phosphatidyl-choline -selective phospholipase; PC = phosphatidylcholine; DAG = diacylglyceride PGE_2 =prostaglandin E_2 ***(Ernsberger et al., 1997).***

Ernsberger et al. 1997 suggest a hypothetical model for the signalling pathway activated by I_1- imidazoline receptors in PC12 cells and in the RVLM (Figure 3). Binding of the agonist to the I_1-imidazoline receptor leads to activation of phosphatidylcholine -selective phospholipase (PC-PLC), possibly through coupling to an unidentified G-protein, as suggested for other receptor systems coupled to PC-PLC. The plasma membrane enzyme PC-PLC, in turn, uses phosphatidycholine (PC) as a substrate and generates diacylglyceride (DAG) and phosphocholine. Besides the accumulation of the lipid second messenger DAG, I_1- receptor stimulation in PC12 cells elicits the release of prostaglandins and their precursor, free arachidonic acid ***(Ernsberger et al., 1997).***

Selective I_1- receptor ligands:

There are few selective I_1-receptor ligands, most having a degree of affinity for α_2-adrenoceptors; however, their I_1-over I_2-receptor selectivity is generally good. The oxazoline analogue of *clonidine*, *rilmenidine*, is an antihypertensive agent and shows selectivity for the I_1-receptor ***(Wethmar et al., 2001)***. *Rilmenidine* has been widely used as an I_1-receptor ligand, however, evidence from binding studies in rat suggests [^{3}H]-*rilmenidine* may also label an I_2-like receptor in cerebral cortex membranes ***(Bousquet and Feldman, 1999)***. *Moxonidine*, also appears to lower blood pressure via I_1-receptors in rats and binding studies with [^{3}H]-*moxonidine* have confirmed this selectivity ***(Ernsberger, 1992)***. The potent α_2-adrenoceptor antagonist *efaroxan* is also reported to be a high affinity I_1-receptor ligand with low affinity for I_2-receptors ***(Ernsberger, 2000)***. One of the most recently reported I_1-receptors ligands is benazoline, which exhibits hypertensive properties which are reversed by *rilmenidine* ***(Greney et al., 2000)***.

Imidazoline (I_2)-receptors subtype:

Location and Function:

I_2-receptors are widely distributed throughout mammalian brain and periphery. In rat brain, I_2-receptors are localized to distinct brain nuclei such as interpeduncular nucleus, arcuate and pineal gland, whereas they are more widespread in rabbit and human brain ***(Olmos et al., 1996)***. In man, brain I_2-receptor density changes in conditions such as Huntington's Chorea and Alzheimer's disease, and is also affected by mood and opiate addiction ***(Garcia-Sevilla et al., 1999)***.

I_2 receptors have been identified by ligand binding in many other tissues and cells such as astrocytes ***(Regunathan et al., 1993a)***, kidney ***(Lachaud-Pettiti et al., 1991)***, adipocytes ***(Langin et al., 1990)***, platelets ***(Michel et al., 1989)***, adrenal medulla ***(Molderings et al., 1994)***, liver ***(Zonnenchein et al., 1990)***, placenta ***(Diamant et al., 1992)***, urethra ***(Yablonsky and Dausse, 1991)***, colon ***(Senard et al., 1990)***, pancreatic cells ***(Chan et al., 1995)***, Carotid bodies ***(Youngson et al., 1995)***, prostate ***(Regunathan et al., 1996)*** and vascular smooth muscle cells ***(Regunathan et al., 1995)***.

The many functions of I_2-receptors might reflect the many subclasses of binding proteins. In rabbit kidney, I_2-receptors activation inhibits Na^+ uptake into renal tubules cells ***(Bidet et al., 1990)***. In cultured rat cerebral cortical astrocytes I_2-receptors activation leads to an increase in levels of mRNA for glial fibrillary acidic protein (GFAP) so they regulate its level. This association with GFAP is of great interest since the brain density of I_2-sites in man increases with age ***(Garcia-Sevilla et al., 1995)*** and *idazoxan's* neuroprotective effects following brain ischaemia are proposed to be mediated via I_2-sites ***(Regunathan et al., 1991b)***. An

I_2-receptors selective compound RS-45041-190 has been noted to increase food consumption in rats, which may indicate a role for I_2-receptors in appetite ***(Brown et al., 1995)***. There is also evidence for I_2-receptors-selective compounds playing a role in nociception ***(Molderings, 1995)***.

Furthermore, a down regulation of I_2- imidazoline receptors has been reported in frontal cortices of depressed suicide victims, according to I_2- radioligand binding and confirmed by western blotting ***(Piletz et la., 2000).***

Subcellular distribution:

In many tissues-including kidney ***(Limon et al., 1992)***, brain ***(Tesson and Parini, 1991)***, liver ***(Tesson et al., 1991)*** and adrenal medulla ***(Regunathan et al., 1993b)*** the receptor has been localized to mitochondria, prepondernatly to the outer mitochondrial membrane ***(Tesson et al., 1991)***.

This localization is unusual and shared only by peripheral-type benzodiazepine receptors. However, I_2 and the benzodiazepine receptor differ because, a high-affinity ligand for the latter (PK-11195), does not bind to I_2 imidazoline sites ***(Tesson et al., 1991)***. Not all tissues express I_2 receptors. For example, skeletal mucle, heart, lung and spleen fail to express I_2 receptors either in plasma membranes or in mitochondria ***(Tesson et al., 1992)***. In placenta, (^{3}H)-*idazoxan* binds to receptors only on plasma membranes ***(Diamant et al., 1992)***, indicating some organ variability with respect to subcellular localization.

Signal transduction:

Little is known of the signal transduction mechanisms coupled to I_2 receptors. The facts that ligand binding is not modified by GTP or its analogues ***(Zonnenchein et al., 1990; Bricca et al., 1993; De Vos et al., 1994)***, that the receptor is mitochondrial, and that exposure of tissues to appropriate ligands fails to increase accumulation of soluble second messengers such as cyclic nucleotides or inositol phosphates ***(Regunathan et al., 1991a)*** indicate that the receptor is not coupled to G proteins.

Treatment of adrenal chromaffin cells with a range of ligands binding to the receptor produces a slow dose-dependent increase in the influx of Ca^{2+} ***(Regunathan et al., 1991a)***. Suggesting that I receptors may regulate intracellular calcium, possibly by influencing mitochondrial storage. Other ions may also be involved such as Na^+ ***(Bidet et al., 1990)*** and K^+ ***(Atlas, 1991)***. Imidazolines are reported to regulate K_{ATP} channels in cells of pancreas ***(Dunne, 1991)***.

Selective I_2-receptor ligands:

Compounds such as *cirazoline* and *naphazoline* have high affinity for I_2-receptors and also for α_1-adrenoceptors ***(Ogidigben et al., 1999)***. The 1, 3 benzodioxan isomer of *idazoxan*, RX821029, is also reported to show 100-fold selectivity for I_2-receptors over α_2- adrenoceptors in binding studies. Some compounds containing a guanidino moiety, such as *guanoxan* and *guanabenz*, also bind with high affinity to I_2-receptors ***(Hieble and Ruffolo, 1995)***. Interestingly the structurally related diuretic *amiloride* has high affinity in tissue homogenates from rabbit and for about 50% of I_2 receptors found in rat brain. This had led to the subdivision I_{2A}-*amiloride* sensitive and I_{2B}-*amiloride* insensitive sites

(Ernsberger et al., 1992). More selective ligands with high affinity to I_2-receptors such as RS-45041-190 *(Mackinnon et al., 1995)*, and recently, the original compound,2-(3`-fluoro-4-tolyl)-imidazoline (31) *(Anastassiadou et al., 2001)*.

Imidazoline (I_3)-receptors subtype(Non-I_1,Non-I_2 receptors):

There are reports of imidazoline receptors which appear distinct from either I_1-or I_2 sites and yet the compounds which act at these a typical receptors are invariably imidazolines or closely related compounds *(Angel et al., 1995; Sjoholm et al., 1995)*. *Chan et al. (1995)* reports an imidazoline site in pancreas which enhance insulin secretion. It is *efaroxan* sensitive and could be a target for the development of compounds to treat type II diabetes. This site is also sensitive to *agmatine* and to crude preparations of CDS *(Herman, 1997)*.

An atypical imidazoline receptor which mediates inhibition of *noradrenaline* release was reported in rabbit pulmonary artery *(Gőthert and Molderings, 1991)* and in rat blood vessels *(Gőthert and Molderings, 1998)*. However, due to the fact that *noradrenaline* was also effective, they suggested that their imidazoline receptor was an allosteric site on the presynaptic α_2-drenoceptor. More recently, it has been suggested that this presynaptic imidazoline receptor shares common binding domains with cannabinoid receptors (CB_1) and that the effects of several imidazoline ligands can be blocked by (CB_1) antagonists *(Gőthert et al., 1999)*.

The molecular identity of I_3 receptors awaits further phramacological and structural characterization.