PHARMACOLOGY

- **Autacoids : Angiotensin, Plasma Kinins**

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Angiotensin, renin, angiotensin converting enzyme inhibitor, ACE, angiotensin receptor blockers, bradykinin, vasoactive intestinal peptide, neurotensin, substance P, calcitonin gene related peptide, arachidonic acid, eicosanoids, prostaglandins, prostacyclin, thromboxane, platelet activating factor,

Introduction

Autacoids are substances of diverse nature normally present in the body or may be formed there. The word autacoid is derived from the Greek word *autos (self)* and *akos (medical agent or remedy).* Thus the word autacoids was used for substances that act within restricted, local areas near their site of synthesis, unlike hormones that are produced by specific cells and then transferred by circulation to distant sites of action. Thee substances usually have a brief lifetime. Heterogeneous substances have been included as autacoids. These are:

Amine Derived	Histamine
	5 Hydroxytryptamine
Lipid derived	Prostanoids (prostaglandins, thromboxanes)
	Leukotrienes
	Platelet Derived Factor
Peptide	Angiotensin
	Kinins (Bradykinin, kallidin)
	Vasoactive intestinal Peptide
	Neurotensin
	Substance P
	Calcitonin Gene related Peptide

This grouping of substances is arbitrary as the role of these substances in the body is getting better defined and many now have multiple roles as neurotransmitters (serotonin), neuromodulators (vasoactive intestinal peptide), paracrine actions (histamine in regulation of gastric secretion). They are also being distributed by the circulation to act at distant sites (angiotensin).

Not included as yet as autacoids are a number of substances:

a) which are synthesized by specific cells and often exert their action on neighboring cells e.g. Paracrine hormones including somatostatin, gastrin.

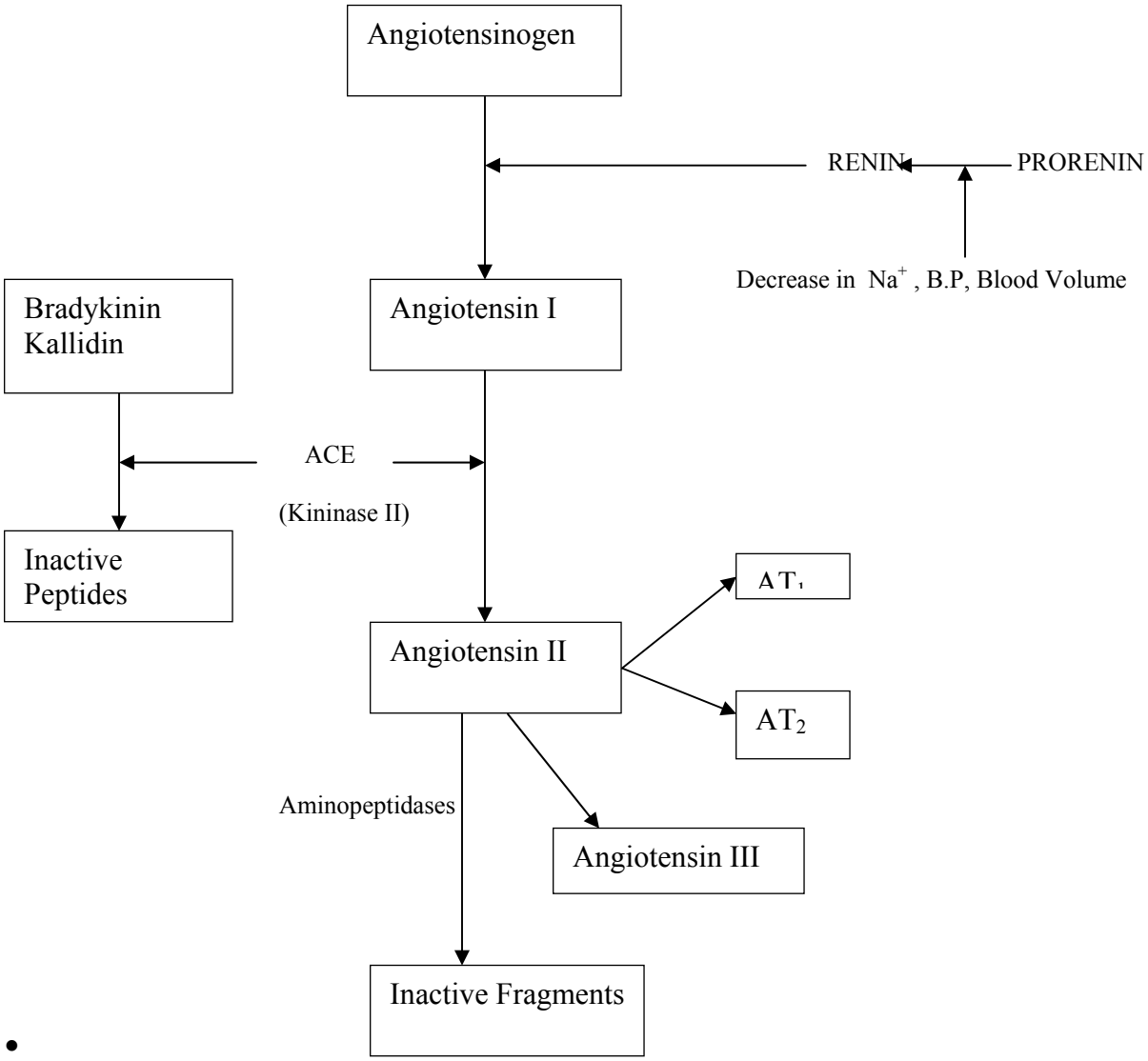
b) Substances that act locally in the inflammatory process e.g. Cytokines and lymphokines and are also involved in generation of the classic autacoids e.g. Interleukin 1 exerts pyrogenic effect by synthesis of prostaglandins.

Autacoids exert multiple actions in the body. They have a role in many physiological and pathological functions in the body. Hence pharmacological modulation of various autacoids finds many therapeutic applications.

Angiotensin

Angiotensin belongs to the family of vasoactive peptides in the body that exerts important effects on the vascular smooth muscle. It forms part of the better known "renin – angiotensin system in the body. The renin angiotensin system is amongst the major systems involved in both short term and long term regulation of blood pressure in the body. It participates significantly in the pathophysiology of major cardiovascular diseases like hypertension, congestive heart failure, myocardial infarction and diabetic nephropathy. Its pharmacological inhibition has led to major improvements in clinical outcomes of these conditions.

Biosynthesis of Angiotensin: Renin a proteolytic enzyme released from the kidneys, acts upon angiotensinogen and converts it into a decapeptide angiotensin I. Angiotensin I is acted upon by the angiotensin converting enzyme (ACE) to form the octapeptide angiotensin II. Angiotensin II then exerts its actions by binding to specific angiotensin receptors in the body. Angiotensin II is subsequently degraded by peptidases in the body (Figure-1).



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- **Figure 1: Synthesis and degradation of Angiotensin II**

Components of the Renin Angiotensin System

Renin and factors controlling its secretion: Renin is an aspartyl protease that attacks a restricted number of substrates, of which the major one is a circulating alpha 2 globulin angiotensinogen. Renin is synthesized as a preproenzyme of 406 amino acids that is processed to prorenin, an inactive form of the protein which forms the active renin. Renin is a glycoprotein containing 340 amino acids. Both renin and prorenin are synthesized and stored in juxtaglomerular cells and on release, enter the circulation. The half life of renin is about 15 minutes. The rate at which renin is secreted by the kidney is the primary determinant of the activity of the renin angiotensin system. Renin is released upon stimulation of the juxtaglomerular apparatus. Prorenin is released constitutively and its concentration is about tenfold greater than that of the active enzyme. Renin secretion is controlled by a variety of factors.

Control of renin secretion: The secretion of renin from juxtaglomerular cells is controlled by:

a) **The macula densa pathway**: The macula densa comprises of specialized columnar epithelial cells in the wall of the cortical thick ascending limb of the loop of Henle, which passes between the afferent and efferent arterioles of the glomerulus. Macula densa lies adjacent to the granular juxtaglomerular cells. Alterations in NaCl reabsorption by the macula densa results in transmission of signals to the juxtaglomerular cells that control renin release. Increase in NaCl reabsorption across the macula densa inhibit renin release and vice versa. This inhibition of renin release is mediated by adenosine and stimulation by prostaglandins. Nitric oxide and cycloxygenase 2 are probably involved in the mechanism of macula densa stimulated renin release.

b) **Intrarenal baroreceptor pathway**: Increases and decreases in blood pressure in the afferent arterioles inhibit and stimulate renin release respectively. The renal vascular receptor, responds to the degree of tension in the afferent vessels, with a reduced tension resulting in renin release. This release may be dependent on prostaglandins and the calcium concentration within the juxtaglomerular cells.

c) **Sympathetic nervous system**: This is also known as the β adrenergic receptor pathway. Local release of norepinephrine from postganglionic sympathetic nerves, results in activation of β_1 receptor on juxtaglomerular cells, which causes renin secretion. Circulating epinephrine and norepinephrine may also cause renin release by the same mechanism.

d) **Feedback control**: Increase renin secretion, results in enhanced formation of angiotensin II. Angiotensin II then acts an AT_1 receptors on juxtaglomerular cells to inhibit renin release. Angiotensin also increases arterial blood pressure by stimulating AT_1 receptor. Increase in arterial blood pressure inhibits renin release by decreasing sympathetic tone, increasing the tension within other renal vascular receptors, and by decreasing NaCl reabsorption in the proximal tubule increasing tubular delivery of NaCl to the macula densa.

e) **Physiological and biochemical variables**: A fall in blood pressure and decrease in dietary sodium can stimulate renin release and vice versa.

f) **Drugs**: A number of drugs also stimulate the release of renin. These are :

i) vasodilators (hydralazine, minoxidil, nitroprusside) and alpha adrenergic blockers (cause a fall

in arterial blood pressure),
ii) Loop diuretics and other diuretics (diuretics decrease reabsorption of NaCl and will result in increased delivery of NaCl to the macula densa),
iii) β-adrenoceptor agonists (isoproterenol) cause direct β1 receptor stimulation,
iv)Phosphodiesterase inhibitors (theophylline, milrinone), rolipram (inhibit adenosine),
v) Angiotensin converting enzyme(ACE) inhibitors and angiotensin receptor blockers (interrupt the feedback mechanisms for renin release).

Angiotensinogen
Angiotensinogen is a globular glycoprotein with a molecular weight of 57,000 that acts as a substrate for renin. Angiotensinogen is synthesized primarily in the liver as preangiotensinogen. Other sites include fat, brain and kidney. The secretion of angiotensinogen may be enhanced by inflammation, insulin, estrogens, glucocorticoids, thyroid hormone and angiotensin II. Increased levels of angiotensin may contribute to the hypertension seen in pregnancy and with the use of oral contraceptives and corticosteroids.

Angiotensin I contains the peptide sequence necessary for all the actions of the renin angiotensin system, but has little or no biologic activity. It has to be converted to angiotensin II to exert its biological actions by the action of the angiotensin converting enzyme (ACE). Angiotensin I may be acted upon by aminopeptideses to form (des-Asp^1) angiotensin I. This is converted by ACE to (des asp^1) angiotensin II, also known as angiotensin III (angiotensin 2-8)

Angiotensin converting enzyme (ACE, Kinnase II, Dipeptidyl carboxypeptidase)
ACE is an ectozyme and a glycoprotein with a molecular weight of 170,000. It is present on the luminal surface of vascular endothelial cells. ACE has a large extracellular domain, an intracellular domain and a hydrophobic region that anchors the ectoenzyme to the cell membrane. Membrane ACE may undergo proteolysis to result in the circulating ACE. The enzyme catalyzes the cleavage of dipeptide units from the carboxyl terminal of certain peptides substrates that are having only one free carboxyl group in the carboxy terminal amino acid and proline must not be the penultimate amino acid. Its most important substrates are angiotensin I which it converts into angiotensin II and bradykinin which it inactivates. ACE is the same as Kininase II. It also acts on substance P and enkephalins, but the physiological significance of this action is not established yet. It does not act on Angiotensin II, which has a penultimate prolyl residue.

Another homolog of ACE has been identified as angiotensin converting enzyme 2 (ACE2). It is expressed in the endothelial cells of the kidneys, heart and testes. It has a single catalytic site and hence removes a single amino acid from the C-terminal of angiotensin I and II forming angiotensin (1-9) and angiotensin (1-7). ACE2 does not hydrolyze bradykinin and is not inhibited by angiotensin converting enzyme inhibitors.

Angiotensin Peptides
These include Angiotensin 1, Angiotensin II, Angiotensin III [(des-Asp^1) angiotensin II or angiotensin (2-8)], angiotensin (1-9) and Angiotensin(1-7), Angiotensin(3-8). The potency of Angiotensin 1 is only 1% as that of angiotensin II on smooth muscle,heart and adrenal cortex . Angiotensin III and II cause qualitatively similar effects. Angiotensin II and III stimulate

aldosterone equally, but the potency of angiotensin III is only 25% and 10% as that of angiotensin II in elevating the blood pressure and stimulating the adrenal medulla respectively.

Angiotensin (1-7) is formed by multiple pathways. It can be formed by the action i) of aminopeptidases on angiotensin I ii) Angiotensin II can be converted to angiotensin (1-7) by the action of ACE. iii) ACE metabolizes angiotensin (1-9) to angiotensin (1-7). The levels of Angiotensin (1-7) can be increased by ACE inhibitors. Angiotensin (1-7) is different in its actions from angiotensin II. It does not cause vasoconstriction, aldosterone release or facilitation of noradrenergic neurotransmission. Instead angiotensin (1-7) causes vasodilation, natriuresis, vasopressin release, inhibition of proliferation of vascular smooth muscles. It may be acting by a specific angiotensin (1-7) receptor.

Angiotensin (3-8) is also called as angiotensin IV. It stimulates the expression of plasminogen activator inhibitor in endothelial and proximal tubular cells. It may also be involved in memory acquisition. Both angiotensin (1-7) and angiotensin (3-8) may be counteracting the effects of angiotensin II in the body.

Angiotensinases

Angiotensinases are various nonspecific peptidases that degrade and inactivate angiotensin peptides. They include aminopeptidases, endopeptidases and carboxypeptidases. They are responsible for the short half life of angiotensin I and II. Angiotensin II has a plasma half life of 15-60 seconds.

Local (Tissue) Renin-Angiotensin systems

In addition to the classical renin angiotensin system (RAS) described above, there are local (tissue) RAS. These may be extrinsic or intrinsic.

1) **Extrinsic local renin angiotensin system**: Renin of renal origin is taken up by vascular endothelial cells and other tissues. It causes conversion of hepatic angiotensinogen to angiotensin I and II within or at the surface of the blood vessel wall and not in the circulation. This is possible as ACE is present on the surface of the vascular endothelial cells.

2) **Intrinsic local renin angiotensin systems**: Various tissues express mRNAs for renin, angiotensinogen and or ACE. These include blood vessels, heart, kidney, adrenal gland, brain and pituitary and they produce renin, angiotensinogen, ACE, angiotensin I, II and III. These local systems do not contribute to a large extent to the levels of renin and angiotensins in the body.

Other pathways for angiotensin biosynthesis

Angiotensin II may be synthesized by pathways involving enzymes other than renin and angiotensin converting enzymes. These pathways would not be inhibited by ACE inhibitors.

Angiotensin Receptors

Angiotensin II exerts its actions through specific G protein coupled receptors. There are two subtypes AT_1 and AT_2. There are many differences between the two and they were identified because of their differential affinity for antagonists.

Angiotensin II binds with equal affinity to both the receptors. AT_1 receptors have a high affinity for losartan and a low affinity for PD123177, whereas AT_2 receptors have a high affinity for PD123177 and a low affinity for losartan.

Most of the known actions of angiotensin II are mediated by AT_1 receptor. It is present on vascular smooth muscle, kidney, heart, adrenal gland. The AT_2 receptors are present in high density in all tissues during fetal development. Their density is much less in adults, where they are found in adrenal medulla, reproductive tissues, vascular endothelium and parts of the brain.AT2 receptors are upregulated in pathologic conditions such as myocardial infarction and congestive heart failure. They may have a cardioprotective role.

Most of the actions of angiotensin II such as vasoconstriction, aldosterone release are mediated by AT_1 receptors. AT_2 receptors activation causes vasodilation and AT_2 receptors may exert antiproliferative effects. AT_2 receptors may also be involved in fetal tissue development. AT_2 receptor mediated vasodilation may be due to nitric oxide released via bradykinin – B_2 receptor – NO – cGMP pathway.

Angiotensin binding to the receptors activates a large array of signal transduction systems. AT_1 receptors couple to many G proteins including Gq, G12/13 and Gi. This results in activation of phospholipase C with generation of inositol triphosphate and diacylglycerol followed by eicosanoid production, activation of calcium dependent and MAP kinases and activation of nitric oxide synthases. Angiotensin also influences the expression of gene products related to cell growth and the production of extracellular matrix. It activates receptor and non receptor tyrosine kinases such as the Janus tyrosine kinase. (Jak2), inducing transcriptional regulatory factors. AT_1 receptors also stimulate the activity of a membrane bound NADH/NADPH oxidases that generates superoxide ions.

Signaling from AT_2 receptors is mediated largely by Gi proteins. This results in activation of phosphatases, potassium channels, bradykinin and nitric oxide production and inhibition of calcium channel functions.

Functions

Angiotensin II exerts important actions at vascular smooth muscle, adrenal cortex, kidney, heart and brain. Through these actions it plays a major role in regulation of blood pressure and electrolyte balance as well as in cell growth.

Blood Pressure: The renin angiotensin system is involved in short (rapid) term and long (slow) term maintenance of blood pressure in the body. Angiotensin is a potent pressor agent, 40 times more potent than norepinephrine. Whenever there is a hypotensive challenge to the body, angiotensin causes a rapid pressor response with an increase in total peripheral resistance by the following ways.

a) Direct vasoconstriction: Angiotensin II acts on AT_1 receptor on vascular smooth muscle vascular cells causing vasoconstriction

b) Angiotensin II facilitates peripheral noradrenergic neurotransmission by augmenting norepinephrine release from sympathetic nerve terminals, by inhibiting its reuptake and by

enhancing the vascular response to norepinephrine. It also stimulates the sympathetic ganglions.

c) Angiotensin II increases the central sympathetic outflow. It enhances the release of vasopressin from the neurohypopysis and adrenocorticotrophic (ACTH) hormone from adenohypophysis. Angiotensin II acts on the brain to reset the baroreceptor reflex.

d)Angiotensin stimulates the release of catecholamines from the adrenal medulla.

Angiotensin may increase cardiac contractility and heart rate. The increase in blood pressure in response to angiotensin action activates a baroreceptor reflex that decreases sympathetic tone and increases the vagal tone. Angiotensin II helps in long term stabilization of blood pressure by a slow pressor response mainly resulting from effects on renal functions.

Kidneys: Angiotensin II reduces urinary excretion of sodium and water, while increasing the excretion of potassium. Angiotensin stimulates the reabsorption of sodium in the proximal tubule by stimulating Na^+/H^+ exchange and increasing the expression of the Na^+- glucose symporter in the proximal tubule and also stimulates the Na^+- K^+ - 2Cl symporter in the thick ascending limb of loop of Henle.

Angiotensin II reduces renal blood flow by constricting the renal vascular smooth muscle directly and indirectly. Angiotensin II influences the glomerular filtration rate (GFR) variably. i)by constricting the renal afferent arterioles it reduces the GFR, ii)constriction of efferent arterioles increases intra glomerular pressure and increases GFR iii) contraction of mesangial cells tends to decrease the GFR. Normally the GFR is slightly reduced by angiotensin II, however, in renal artery hypotension, the effects of angiotensin II on the efferent arteriole predominate so the GFR increases. The effect of angiotensin II on maintaining the GFR is important in patients with bilateral renal artery stenosis and unilateral renal artery stenosis in patients with a single kidney.

Adrenal cortex: Angiotensin II stimulates the synthesis and secretion of aldosterone from the adrenal cortex directly as well as augments responses to other stimuli (ACTH and K^+). Aldosterone acts on distal and collecting tubules to cause retention of Na+ and excretion of K^+ and H^+.

Structural changes in the cardiovascular system : Angiotensin II is mitogenic for vascular and cardiac muscle cells. It may result in hypertrophy (increase in tissue mass), hyperplasia (increase in cell number) and remodeling (redistribution of mass within a structure) in cardiovascular structure, as well as increased extracellular matrix. The cells involved include vascular smooth muscle cells, cardiac myocytes and fibroblasts. Angiotensin II also exerts a variety of important effects on vascular endothelium.

Angiotensin II acts via AT_1 receptors to stimulate generation of reactive oxygen species in the blood vessels from the NAD(P)H oxidases. It also contributes to plaque formation by promoting macrophage and T- lymphocyte recruitment through the generation of adhesion molecules such as intercellular adhesion molecules-1(ICAM-1), integrins and osteopontin. Angiotensin II stimulates the production of inflammatory chemokines and cytokines that enhance migration of

inflammatory cells. Angiotensin II acts directly on cells to induce the expression of specific proto oncogenes and of genes coding for extracellular matrix proteins such as collagen, fibronectin, tenascin. Changes in preload and after load due to the action of angiotensin II also contribute to cardiac hypertrophy and remodeling.

Other effects: Angiotensin II affects development of normal kidney morphology, it also causes anorexia and weight loss

Angiotensin and Cardiovascular Disease: The role of angiotensin II has been clearly implicated in development of atherosclerosis, hypertension, congestive heart failure, left ventricular dysfunction following infarction and diabetic nephropathy. Inhibition of the renin angiotensin system with specific antagonists has shown a significant improvement in the clinical outcome in patients in large scale, randomized, controlled clinical trials.

Inhibitors of the Renin Angiotensin System

There are now available a wide variety of agents that inhibit the actions of angiotensin II. These drugs could act by inhibiting i) renin secretion ii) the enzymatic action of renin iii) the conversion of angiotensin 1 to angiotensin II iv) Angiotensin II receptors

I) **Inhibition of renin secretion:** Drugs that decrease sympathetic outflow or activity of beta receptors inhibit the secretion of renin. These include clonidine, which decreases the central sympathetic outflow. Beta blockers like propranolol inhibit the intrarenal and extrarenal beta receptors involved in the sympathetic control of renin secretion.

ii) **Inhibition of renin activity**: Drugs that inhibit renin activity did not find much use because of their low bioavailability and short duration of action. Recently a new class of nonpeptide, low molecular weight, orally active inhibitors have been developed. e.g. aliskiren. Aliskiren has produced a dose dependent reduction in plasma renin activity, angiotensin I, II and aldosterone and reduction in blood pressure. The safety of aliskiren appears to be comparable to angiotensin antagonists.

iii) **Angiotensin converting enzyme inhibitors:** These drugs inhibit the conversion of angiotensin I to angiotensin II or the conversion of (des-Asp^{1}) angiotensin I to angiotensin III. They are highly selective drugs and their effects arise mainly from suppression of angiotensin II. Since ACE acts on other substrates, inhibition of ACE may induce other effects also. ACE inhibitors increase bradykinin levels and hence bradykinin induced prostaglandin biosynthesis. These may contribute to the vasodilatory and other pharmacological effects of ACE inhibitors. ACE inhibitors increase the levels of natural stem cell regulator N-acetyl-seryl-aspartyl lysyl proline and increase renin levels by interfering with the angiotensin II feedback mechanisms. The angiotensin I will be diverted down alternate pathways
resulting in increase production of angiotensin (1-7).

Angiotensin converting Enzyme inhibitors include captopril, enalapril, lisinopril, ramipril, quinapril, moexipril, trandalopril, spirapril, perindopril and fosinopril

They may be classified chemically as:
i) Sulfhydryl containing : Captopril
ii) Dicarboxyl containing : Enalapril, lisinopril, ramipril, benazepril, trandalopril
iii) Phosphorous containing : Fosinopril

Most of the ACE inhibitors are prodrugs. They are administered as prodrugs to increase their bioavailability. The potency of these prodrugs is 100 to 1000 times lesser than the active moiety. All except enalaprilat are for oral administration. The drugs differ primarily in their pharmacokinetics and dosings. Most of the ACE inhibitors are to be administered in a once to twice a day dosing frequency.

The oral bioavailability of ACE inhibitors differs, ranging from 30% for lisinopril to 75% for captopril and perindopril. Food reduces the bioavailability of captopril, benazepril, trandalopril, quinapril, ramipril. These drugs should be given an hour before meals. The drugs are hydrolyzed by esterases in the liver to produce the active moieties. ACE inhibitors are cleared predominantly by the kidneys except for fosinopril and spirapril which are eliminated both by the liver and kidneys. Doses of most ACE inhibitors should be reduced in patients with renal dysfunction.

Enalaprilat is the active dicarboxylic acid form of enalapril. It is not absorbed orally but is available for intravenous use. Lisinopril is the lysine analogue of enalaprilat and is pharmacologically active by itself.

Dosing : ACE inhibitors are effective in wide dose ranges. They may be administered in a single or divided doses. Treatment is started with smaller doses which are gradually increased. Patients with elevated plasma renin activity will be hyper responsive to the antihypertensive action of ACE inhibitors and therefore treatment should be started with low doses in patients with high plasma renin levels. These include patients who are fluid and salt depleted (dehydration, diarrhoea, diurised patients, patients with congestive heart failure, liver cirrhoses, nephrotic syndrome, on vasodilators).

Doses: The recommended oral dose ranges of ACE inhibitors are

i)	Captopril	6.25 to 150 mg in divided doses, two to three times daily
ii)	Enalapril	2.5 to 40 mg single or divided dose
iii)	Lisinopril	5 to 80 mg daily
iv)	Benazepril	5 to 80 mg
v)	Fosinopril	10 to 80 mg
vi)	Trandalopril	1 to 8 mg
vii)	Quinapril	5 to 80 mg
viii)	Ramipril	1.25 to 20 mg
ix)	Moexipril	7.5 to 30 mg
x)	Perindopril	2 to 16 mg

Therapeutic uses of ACE inhibitors
ACE inhibitors are used in:
1) Hypertension : ACE inhibitors are amongst the first line antihypertensive drugs. ACE

inhibitors lower systemic vascular resistance and mean, diastolic and systolic blood pressures. ACE inhibitors also cause dilatation of large arteries. Cardiac output may increase slightly. There is no postural hypotension and ACE inhibitors lower blood pressure in both patients with high and normal plasma renin activity. Elderly African American patients are more resistant to the hypotensive effect of these drugs.

ACE inhibitors alone effectively control blood pressure in 50% of the patients with mild to moderate hypertension. 90% of patients will be controlled with a combination of an ACE inhibitor with other drugs. Diuretics enhance the antihypertensive response to ACE inhibitors. ACE inhibitors are the preferred anti hypertensives in i) diabetics because they slow and prevent the development of diabetic glomerulopathy and other diabetic complications, ii) in patients with ischemic heart disease because they improve endothelial dysfunction in patients iii) patients with hypertension with cardiac hypertrophy as they cause regression of hypertrophy iv) patients after myocardial infarction to improve ventricular function.

2) Congestive heart failure: ACE inhibitors decrease the afterload and preload in patients with congestive heart failure. They also potentiate the effect of diuretics in heart failure. They do this by suppressing angiotensin II and aldosterone production and decreasing sympathetic nervous system activity. The decrease in left ventricular afterload, improves the stroke volume and cardiac output. Venodilation decreases right and left ventricular filling pressures and end diastolic volumes. Angiotensin II inhibition and increased bradykinin inhibit the growth stimulating effects of angiotensin II. ACE inhibitors have been shown to improve survival in patients with overt heart failure due to ventricular systolic dysfunction.

3) Left ventricular systolic dysfunction: ACE inhibitors unless contraindicated, are recommended in all patients with impaired left ventricular systolic function. The ventricular dysfunction may range from asymptomatic to a severe impairment. ACE inhibitors in patients with systolic dysfunction prevents or delays the progression of heart failure, decrease the incidence of sudden death and myocardial infarction, decreases hospitalization and improves quality of life. ACE inhibitors do this by their hemodynamic affects as well as preventing and reversing ventricular remodeling.

4) Acute myocardial infarction: ACE inhibitors are indicated in patients with acute myocardial infarction unless contraindicated. They reduce overall mortality when treatment is begun early. In patients at high risk with large infarcts and ventricular dysfunction, ACE inhibitors should be continued for a long term.

5) In patients at high risk of cardiovascular events: ACE inhibitors improve endothelial function and produce a profibrinolytic state in patients with coronary artery diseases. ACE inhibition decreased the incidence of myocardial infarction, stroke and death in patients with risk factors for cardiovascular events such as diabetes. ACE inhibitors improve outcome in patients at risk for ischemic events.

6) Chronic Renal failure: ACE inhibition affords renal protection by reducing glomerular capillary pressure, increasing the permeability selectivity of the filtering membrane thereby decreasing the exposure of the mesangium to proteinaceous factors and attenuate mesangial cell

growth and matrix production.

7) Diabetes: ACE inhibitors increase insulin sensitivity in diabetics. They prevent or delays the progression of renal disease and decreases the albuminuria in diabetes. They also may decrease the progression of other complications of diabetes.

8) Renal Crisis of Scleroderma: ACE inhibitors improve the renal crisis in patients with scleroderma.

Adverse Effects: ACE inhibitors are well tolerated and the incidence of serious adverse effects is low. The side effects include

a) Hypotension: A severe fall in blood pressure may occur following the first dose of an ACE inhibitor. The fall may be more in patients who are salt depleted, on other antihypertensive drugs etc. The treatment should be begun with small doses of ACE inhibitors.

b) Cough : A dry cough occurs in 5-20% of patients. The incidence is more in women and is not dose related. The cough regresses on discontinuation of the ACE inhibitor. It may be due to accumulation of bradykinin.

c) Hyperkalemia: ACE inhibitors may cause hyperkalemia when administered to patients with renal insufficiency, or in patients taking potassium sparing diuretics. ACE inhibitors normally do not cause potassium retention in patients with normal renal function.

d) Acute renal failure : Since angiotensin II is needed to maintain glomerular filtration in patients in whom renal perfusion is less, ACE inhibitors can cause acute renal failure in patients with bilateral renal artery stenosis or unilateral renal artery stenosis in patients with a single kidney.

e) Fetopathic : ACE inhbitors are not teratogenic during first trimester of pregnancy. However, during second and third trimesters they cause oligohydroamnios, fetal pulmonary hypoplasia, fetal growth retardation, fetal death, neonatal anuria and death. ACE inhibitors are contraindicated during pregnancy.

f) Angioedema : A rare but a serious side effect. ACE inhibitors induce edema of the nose, mouth, throat, glottis, larynx, lips or tongue. Airway obstruction may lead to death. It is not dose related and usually occurs within the first week of therapy. The condition requires immediate cessation of the ACE inhibitors and emergency management of the respiratory obstruction. Rarely angioedema of the intestine may occur and is manifested by vomiting, diarrhoea and abdominal pain.

Other side effects include skin rash, proteinuria, dysgeusia, neutropenia, glycosuria and hepatotoxicity

Drug interactions

1. Antacids may reduce the bioavailability of ACE inhibitors
2. NSAIDs may reduce the antihypertensive effect of ACE inhibitors

3. Potassium sparing diuretics and potassium supplements may cause hyperkalemia.
4. Diuretic administration may enhance the antihypertensive effects
5. ACE inhibitors may increase plasma levels of digoxin.

Angiotensin II Receptor Antagonists

Nonpeptide orally active angiotensin II receptor antagonists (ARB) are now available. they bind to the AT_1 receptor with a high affinity and are more than 10,000 fold selective for the AT_1 receptor versus AT_2 receptor. The AT_1 receptor antagonists include candesartan, losartan, valsartan, eprosartan, irbesartan, olmesartan and telmisartan. They are competitive antagonists, but the inhibition of biological response to angiotensin II may be insurmountable. AT_1 receptor antagonists inhibit most of the biological effects of angiotensin II on the vascular smooth muscle, kidney, adrenal cortex sympathetic neurotransmission, cellular hypertrophy and hyperplasia. They differ from ACE inhibitors in that 1)they reduce activation of AT_1 receptors more effectively than ACE inhibitors. 2) they divert angiotensin II to activate AT_2 receptors 3) AT_1 receptor antagonist would not increase bradykinin levels 4) ACE inhibitors may increase angiotensin (1-7) levels more.

Therapeutic Uses

1) Hypertension
2) Congestive heart failure
3) Diabetic nephropathy

The efficacy of AT_1 receptor antagonists has been established in the above conditions. AT_1 receptor antagonists are similar to ACE inhibitors in efficacy. They are indicated in patients who cannot tolerate ACE inhibitions due to cough. Combination therapy with both an ACE inhibitor and an angiotensin receptor antagonist is being investigated for clinical use.

Adverse effects: The incidence of adverse effects is comparable to a placebo. The side effects, other precautions and contraindications are the same as with ACE inhibitors. Angioedema may be lesser with ARBs.

Summary: The renin angiotensin system plays an important role in maintenance of cardiovascular structure and function. It's over activation is implicated in the pathogenesis of hypertension, congestive heart failure, infarction, ventricular remodeling , nephropathies and diabetes. Angiotensin converting enzymes and recently angiotensin receptor blockers have improved the clinical outcome in patients suffering from the above disorders. Inhibition of the renin angiotensin system at multiple sites is being evaluated to see whether it results in enhanced benefit.

Renin Angiotensin System

Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is activated by conversion to angiotensin II in a reaction catalyzed by ACE (dipeptidyl carboxypeptidase or peptidyl kinnase II). ACE under it's designation as kinnase II also inactivates bradykinin.

Angiotensin II increases blood pressure (by peripheral vasoconstriction, augmentation of sympathetic activity centrally, release of norepinephrine, release of catecholamines from adrenal medulla)

- stimulate synthesis and secretion of aldosterone from adrenal cortex
- reduces urinary excretion of sodium and hydrogen ions and increases potassium excretion
- reduces renal blood low an may decrease or increase the glomerular filtration rate.
- is mitogenic for cardiovascular muscle cells and may result in hypertrophy, hyperplasia and remodeling

Angiotensin II is implicated in development of hypertension, congestive heart failure, left ventricular dysfunction, diabetic nephropathy, atherosclerosis.

Inhibition of renin angiotensin system with angiotensin dysfunction, acute myocardial infarction, patients at high risk of cardiovascular events, diabetic nephropathy, renal crisis of scleroderma.

Adverse effects of ACE inhibitors and angiotensin receptor blockers include hypotension, cough, hyperkalemia, acute renal failure, angioedma and are fetopathic.

Kinins

Kinins are potent vasodilator peptides that contribute to inflammatory responses in the body, by stimulating the release of potent mediators such as prostaglandins, nitric oxide or endothelium derived hyperpolarizing factor (EDHF). They are synthesized in the body by the action of enzymes known as kallikreins or kininogenases which act upon protein substrates called kininogens.

Kininogens

Are the precursors of kinins. They are present in plasma, lymph and interstitial fluid. Two kininogens are known to be present in plasma (i) high molecular weight form (HMW kininogen) and (ii) low molecular weight form (LMW kininogen). Both are derived from a single gene by alternate splicing. HMW kininogen serves as a substrate for plasma kallikrein and tissue kallikrein to yield bradykinin and kallidin and LMW kininogen for tissue kallikrein to yield kallidin only. The kininogens also inhibit cysteine proteinases, thrombin binding, and have antiadhesive and profibrinolytic properties.

Kallikreins

Are enzymes present in plasma and several tissues including the kidneys, pancreas, intestine, sweat glands and salivary glands. They convert kininogens into kinins in the body. They are of two types (i) plasma kallikrein, of 88,000 dalton molecular weight. It is activated by Hageman Factor (Factors XII), trypsin and prolylcarboxypeptidase, a lysosomal enzyme; (ii) Tissue kallikrein, is a smaller 29,000 dalton protein, synthesized as a preprotein in epithelial or secretory cells of a number of tissues, salivary glands, pancreas, distal nephron and human neutrophils. The synthesis of tissue prekallikrein is controlled by a number of factors including aldosterone in kidney and salivary glands and androgens in certain other glands. Kallikreins can convert prorenin to renin. Three kinins have been identified in mammals. These are i). Bradykinin ii) Kallidin (Lysylbradykinin) iii) Methionyllyslbradykinin.

Each is formed from kininogen by the action of a different enzyme. Bradykinin is released by plasma prekallikrein, kallidin by tissue kallikrein and methionyllyslbradykinin by pepsin and pepsin like enzymes.

Synthesis and Metabolism: Figure 2 shows the synthesis and metabolism of kinins in the body. Kallidin (decapeptide) is about as active as the nonapepetide bradykinin. The half life of kinins is only about 15 seconds and 80-90% of the kinins may be destroyed in a single passage through the pulmonary vascular bed. The main catabolizing enzyme in the lung and other vascular beds is kininase II or Angiotensin converting enzyme (ACE). A slow acting enzyme carboxypeptidase (kininase I releases the C-terminal arginine residue producing (des-Arg^{9}) bradykinin and (des-Arg ^{10}) kallidin.

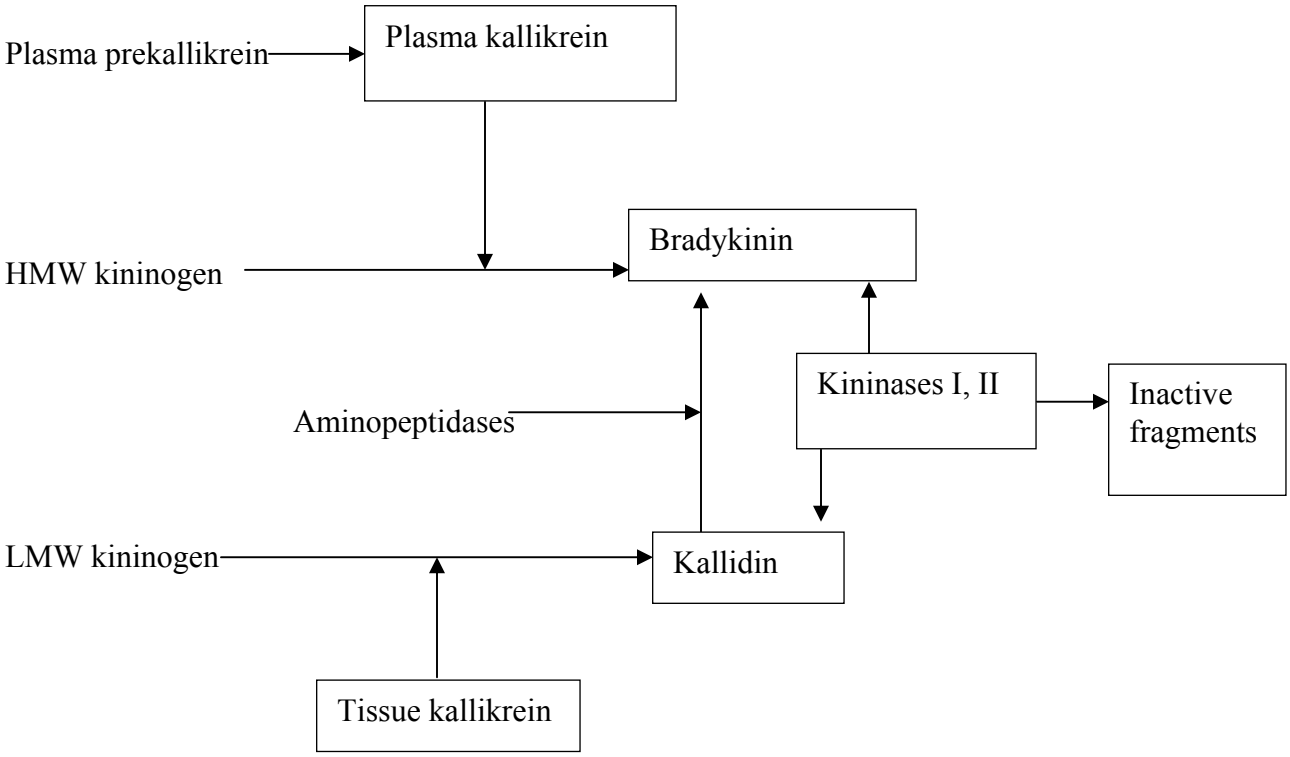


Figure 2: The kallikrein-kinin system

Bradykinin Receptors

There are at least two receptors for kinins B_1 and B_2, both are G protein coupled receptors (GPCR), with 36% amino acid sequence homology.

(i) B_2 receptor is constitutively present in most normal tissues where it selectively binds bradykinin and kallidin and mediates the majority of their effects.

(ii) B_1 receptor is absent or expressed at low levels in most tissues. It selectively binds to the des-Arg metabolites of bradykinin and kinin. Their expression is upregulated by inflammation and by cytokines, endotoxins and growth factors.

Functions of kinins

The kinins are involved in many patho-physiological functions in the body. These are:

Pain : Kinins are powerful algesic agents, when applied topically or injected intradermally. Bradykinin stimulates primary sensory neurons and provokes the release of neuropeptides such as substance P, neurokinin A and calcitonin gene related peptide.

Inflammation : Kinins play an important role in the inflammatory process and produce clinical signs of inflammation such as redness, local heat, swelling and pain. Plasma kinins increase permeability in the microcirculation by widening the intercellular spaces between the endothelial cells and leading to edema. B_1 receptors on inflammatory cells such as macrophages can elicit production of inflammatory mediators interleukin 1 and tumor necrosis factor alpha. Kinin levels are increased in a number of inflammatory conditions eg. rhinitis, gout, disseminated intravascular coagulation, inflammatory bowel disease. Kinins may also stimulate bone resorption through B_1 and possibly B_2 receptors.

Cardiovascular System: Kinins produce vasodilation in several vascular beds including the heart, kidney, intestine, skeletal muscle and liver. This may be due to a direct action on arteriolar smooth muscle or may be mediated by the release of nitric oxide or vasodilator prostaglandins such as PGE_2 and PGI_2 or hyperpolarizing epoxyeicosatrienoic acid. They can cause contraction of veins directly or by release of vasoconstrictor prostaglandins PGF_{2x}. On intravenous injection kinins produce a rapid but brief fall in blood pressure. This rapid reversibility is due to reflex increases in sympathetic activity resulting in increases in heart rate, myocardial contractility and cardiac output. Bradykinin can directly release catecholamines from the adrenal medulla and may also increase sympathetic outflow in the central nervous system. Urinary kallikrein concentrations are decreased in individuals with high blood pressure. The endogenous kallikrein kinin system may play a role in hypertensive states.

The kallikrein-kinin system appears to be cardioprotective. It contributes to the beneficial effect by preconditioning of the heart against ischemia reperfusion injury, prevents vascular smooth muscle growth and cell proliferation and stimulates tissue plasminogen activator (tPA).

Kidney: Renal kinins regulate urine volume and composition. They increase blood flow, cause natriuresis by inhibiting sodium reabsorption at the collecting duct.

Exocrine and Endocrine glands: Kinins may modulate the tone of ducts of various glands such as salivary and pancreatic glands and help regulate gastrointestinal motility. They influence the transepithelial transport of water, electrolytes, glucose and amino acids in kidney and physiologic activation of various prohormomes including proinsulin and prorenin.

Other actions: Kinins play a role in transition from fetal to neonatal circulation, for eg. dilation of fetal pulmonary artery, closure of ductus arteriosus, constriction of umbilical vessels.

Potential Therapeutic uses

A few drugs that modify the activity of kallikrein kinin system are available, although none are in wide clinical use. Antagonists of the system are expected to have considerable therapeutic potential as antiiflammatory and antinociceptive agents. Agonists may have a beneficial cardioprotective role in hypertension and myocardial hypertrophy.

Kallikrein inhibitors

Aprotinin is a kallikrein inhibitor and is a natural proteinase. It is obtained from bovine lung. It inhibits mediators of inflammatory response, fibrinolysis and thrombin generation. It is

administered to patients undergoing coronary bypass to minimize bleeding and blood requirements. Hypersensitivity reactions may occur and hence a test dose should always be given. It can interfere with activated clotting time used to determine the effectiveness of heparin anticoagulation.

Bradykinin receptor antagonists

Competitive antagonists (peptides) of both B_1 and B_2 receptors are available for use in research. These include Icatibant (a second generation B_2 receptor antagonist), FR173657 FR172357, NPC18884 S5R240612 (third generation B_2 receptor antagonist). They are being used to study their potential use in inflammation and pain. Kininase I and neural endopeptidase inhibitor omapatrilat, inhibits two kinin degrading enzymes. In clinical trials omapatrilat was found to be associated with a threefold higher incidence of angioedema as compared to an ACE inhibitor alone and has been now withdrawn from trials.

Bradykinin contributes to the blood pressure lowering effects of angiotensin converting enzyme inhibitors. Administration of bradykinin antagonists attenuates the favorable effects of ACE inhibitors on blood pressure, myocardial infarct size and ischemic preconditioning. Increased bradykinin levels may also be responsible for the adverse effects of angioedema and cough that are associated with the use of angiotensin converting enzyme inhibitors.

Summary: The kallikrein-kinin system plays a major role in inflammation in the body. Bradykinin by activating B_2 receptor is responsible for many of the beneficial cardioprotective effects of ACE inhibitors. It may have potential as a therapeutic agents in these conditions.

Peptides

There are a number of peptide substances in the body, whose role in the physiological processes in the body is still in the process of being defined. As their functions are getting elucidated, it is becoming clearer that they play multiple roles as neuromodulator, neurotransmitter, and local hormones These include vasoactive intestinal peptide, substance P, neurotensin and calcitonin gene related peptide.

Vasoactive Intestinal Peptide (VIP)

VIP is a 28 amino acid peptide. It is related structurally to glucagon and secretin. It is widely distributed in the central and peripheral nervous system in gastrointestinal tract, heart, lungs, kidneys, thyroid gland and blood vessels.

Pharmacological Effects

Central Nervous System: VIP functions as a neurotransmitter and neuromodulator, alone or as a cotransmitter. It may be involved in transmission of afferent impulses from autonomic structures in the periphery to spinal cord and higher centers It is also involved in peptidergic cotransmission in the autonomic nervous system. VIP coexists with acetylcholine in many autonomic fibers including parasympathetic fibers that innervate smooth muscle and exocrine glands, cholinergic sympathetic neurons that innervate sweat glands. Acetylcholine and VIP are stored in separate vesicle in the neurons and act synergistically. VIP exerts independent actions at postsynaptic sites, which are not blocked by anticholinergic drugs.

Gastrointestinal Tract: VIP is involved in parasympathetic responses in the gastrointestinal tract, it may facilitate sphincter relaxation and salivary secretion.

Cardiovascular system: VIP causes vasodilation in most vascular beds, which is more potent than that induced by acetylcholine. It causes coronary vasodilation and exerts positive inotropic and chronotropic effects.

Endocrine: VIP stimulates secretion of vasopressin and prolactin in the brain.

Receptors: The actions of VIP are mediated by G protein coupled receptors. There are 2 subtypes $VPAC_1$ and $VPAC_2$. Binding of VIP to the receptor is associated in activation of adenylyl cyclase and formation of cAMP. Other mediators include increase release of nitric oxide and cGMP.

Agonists and antagonists of VIP are at present available only for research use.

Neurotensin

Is a neuropeptide that functions as a neurotransmitter and neuromodulator in the central nervous system and a local hormone in the periphery. It is a tridecapeptide and is synthesized as part of a larger precursor that also contains neuromedin N (a neurotension like peptide). Processing of the precursor releases both neurotensin and neuromedin N from the nerve endings. It is present in the central nervous system, gastrointestinal tract and blood

Pharmacological Actions

Central Nervous system: There is a close association between neurotensin and dopamine systems. Neurotensin exerts antidopaminergic effects in animals. Central administration in animals results in hypothermia and antinociception. It may be involved in pathophysiology of Parkinson's disease and schizophrenia.

Vascular system : Neurotesin causes vasodilation, hypotension and increased vascular permeability.

Gastrointestinal system: It causes inhibition of gastric secretion and gastric motility.

Endocrine: Neurotensin increases secretion of anterior pituitary hormones.

Receptors: Neurotensin acts by 3 subtype of receptors NT_1, NT_2 and NT_3. NT_1 and NT_2 are G protein coupled receptors while NT_3 receptor is a single transmembrane domain protein that belongs to a family of sorting proteins.

Selective neurotensin agonists and antagonists have been developed which are being investigated in schizophrenia and Parkinson's disease.

Substance P
Substance P is a peptide, belonging to the tachykinin family of peptides. Other members of this family are neurokinin A and neurokinin B. It functions as a neurotransmitter in central nervous system and in the enteric nerve plexus.

Pharmacological Actions
Pain : Substance P is present in afferent sensory fibers in the dorsal root ganglion, in the dorsal horn of the spinal cord and is involved in transmitting painful stimuli from the periphery to the spinal cord and higher brain structures. It is present in vagal afferent fibers innervating the solitary tract nucleus and area postrema and is involved in emesis. In striatal neurons it modulates the release of dopamine. It is implicated in behavior, anxiety, depression, nausea and emesis.

Cardiovascular System: Substance P causes vasodilation and produces hypotension due to release of nitric oxide from the endothelium.

Smooth muscle: Substance P causes contraction of venous, intestinal and bronchial smooth muscle.

Kidney: Substance P causes diuresis and natriuresis.

Receptors: The actions of substance P, Neurokinin A and B are mediated by three G protein coupled receptors NK_1, NK_2, NK_3. NK_1 is the major tachykinin receptor in the brain and substance P is the preferred ligand for the NK_1 receptor.

Pathophysiological role: Neurogenic inflammation: Substance P and Neurokinin A are both involved in neurogenic inflammation. They act on mast cells, releasing histamine and other mediators and produce smooth muscle contraction and mucous secretion. Neurogenic inflammation is implicated in the pathogenesis of several inflammatory conditions including the delayed phase of asthma, allergic rhinitis, inflammatory bowel disease etc.

Antagonists
Many orally active antagonists, which are selective and have good penetration in CNS have been developed. They are being investigated for use in depression and prevention of chemotherapy induced emesis.

Aprepitant: This is a NK_1 receptor antagonist. It has antiemetic effects in delayed nausea and improves the efficacy of standard antiemetic regimens in patients receiving multiple cycles of chemotherapy. The drug is administered orally. It is extensively bound to plasma proteins (>95%). It is metabolized by hepatic CYP3A4 and is excreted in stools. Its half life is 9-13 hours. As it is metabolized by CYP3A4 the likelihood of drug interactions is very high and it should not be administered with cisapride.

Calcitonin Gene Related Peptide
Calcitonin gene related peptide (CGRP) is a member of the calcitonin family of peptides which includes calcitonin, adrenomedullin and amylin. It is synthesized along with calcitonin in

thyroid parafollicular C Cells. CGRP has 37 amino acids. It is distributed in central and peripheral nervous systems, in cardiovascular system, gastrointestinal tract and urogenital system.

Pharmacological Actions

Central nervous system: CGRP is present in afferent sensory fibers in the spinal cord and may be transmitting nociceptive stimuli from the periphery to the spinal cord and higher centers On central administration in animals it suppresses feeding and causes hypertension.

Cardiovascular system: CGRP causes hypotension and tachycardia. It is a potent vasodilator

Receptors: $CGRP_1$ and $CGRP_2$ antagonists (peptide and nonpeptide) are available for investigational use.

Pathophysiological role: Neurogenic inflammation: CGRP has been implicated in neurogenic inflammation

Migraine: The release of CGRP from trigeminal nerves plays a role in pathophysiology of migraine. The peptide is released during migraine attack.. CGRP antagonist BIBN4096BS has been shown to be effective in migraine

Peptide Autacoids

These include (VIP), Neurotensin, Substance P and calcitonin gene related peptide(CGRP).

Most peptides are synthesized as preprohormones and act through G protein coupled receptors.

Each peptide has specific actions. Most function as neurotransmitters, neuromodulators alone or as cotransmitters. VIP functions as a neurotransmitter and neuromodulator, it also causes vasodilation. Neurotensin may be involved in pathophysiology of Parkinson's disease and schizophrenia.

Substance P is involved in transmitting painful stimuli from periphery to the brain, in inflammatory process. It is involved in pathogenesis of inflammatory conditions including delayed phase of asthma, allergic rhinitis, inflammatory bowel disease etc.

CGRP has been implicated in neurogenic inflammation and pathophysiology of migraine.

Agonists and antagonists of most peptides are presently in use as investigational agents.

Lipid Derived Autacoids: Eicosanoids (Prostaglandins, Thromboxanes, Leukotrienes)

Lipid derived autacoids are synthesized from membrane lipids when stimulated by physical, chemical and hormonal stimuli. They include eicosanoids (prostaglandins, prostacyclins, thromboxanes, lipoxins, hepoxylins) and platelet activating factor.

They are not stored (except lipoxins, hepoxylins) but are produced by most cells whenever stimuli activate hydrolases that make arachidonic acid available. Platelet activating factor is present in a lesser number of cells; (leukocytes, platelets and endothelial cells). They play a major role in a number of important physiological functions and pathological processes in the body such as inflammation,hemostasis, thrombosis, parturition etc. Hence their pharmacological

modulation would be of therapeutic use.

Source: Eicosanoids are ubiquitous compounds which are derived from polyunsaturated long chain fatty acids. They are found in plants and animals. They are derived in the body by oxygenation of polyunsaturated long chain fatty acids, which include:
i)Arachidonic acid : Arachidonic acid (AA) is the most important precursor. It is an azocarbon fatty acid that contains 4 double bonds beginning at omega 6 position to yield a,5,8,11,14 eicosatetraenoic acid (C20:4-6)
ii) Homoγ linoleic acid (C20:3-6). It has 3 double bonds
iii) Eicosapentaenoic acid (C20:5-3). It has 5 double bonds

All these result in derivatives which are qualitatively different in their actions.

Synthesis: The biosynthesis of eicosanoids is dependent on the availability of AA or other polyunsaturated fatty acids.

Release of arachidonic acid : AA is present in membrane phospholipids and must be released from the cell membrane by lipases. Most important is phospholipase A_2(PLA_2). Many isoforms of PLA_2 have been characterized and these include Group IV cytosolic PLA_2 ($cPLA_2$) ii) Group IIA, Group V, Group X secretory PLA_2 ($sPLA_2$) iii) Group VI calcium independent PLA_2 ($iPLA_2$). Group IV cytosolic PLA_2 is the most dominant in acute release, but the inducible PLA_2 is active under sustained stimulation of AA release.

Oxygenation of Arachidonic acid: AA is oxygenated by different enzyme systems (figure 3). These are:
i)Cycloxygenases ii) Lipoxygenases iii) Cytochrome P450 Epoxygenases iv) Isoprostane

i)Products of Cycloxygenase Pathway
AA is metabolized to prostanoids in a step wise manner by microsomal enzymes (Figure-4). The first step is formation of prostaglandin endoperoxide (PGG_2) by the action of prostaglandin endoperoxide G/H Synthase, known as cycloxygenase (COX). There are 2 distinct COX isoforms, COX-1 and COX-2.
COX-1 is expressed constitutively in most cells. It is said to subserve housekeeping functions such as cytoprotection of gastric epithelium.
COX-2 is inducible. It's expression can be increased by cytokines, growth factor (inflammation and cancer).

However, both are involved in pathophysiologic functions in the body. COX-2 is the main source of vascular prostacyclin and in kidneys COX-2 derived prostanoids are needed for normal renal development and function. Both isoforms are expressed as dimers inserted into the endoplasmic reticular membrane. COX oxygenates AA into PGG_2 and then PGG_2 is rapidly acted upon by peroxidase moiety of COX to add 15 hydroxyl group that is essential for biological activity and the product is known as PGH_2.

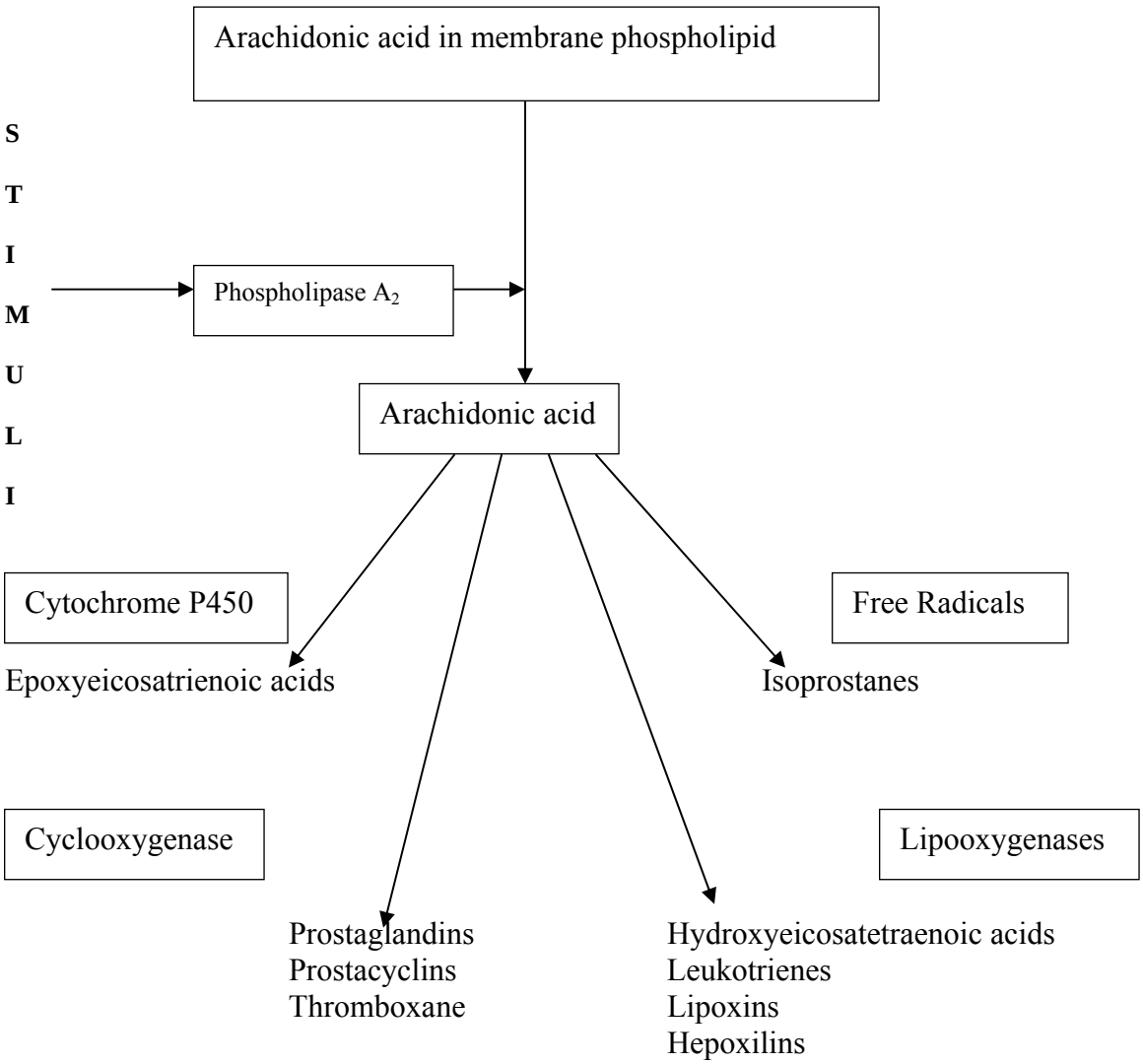
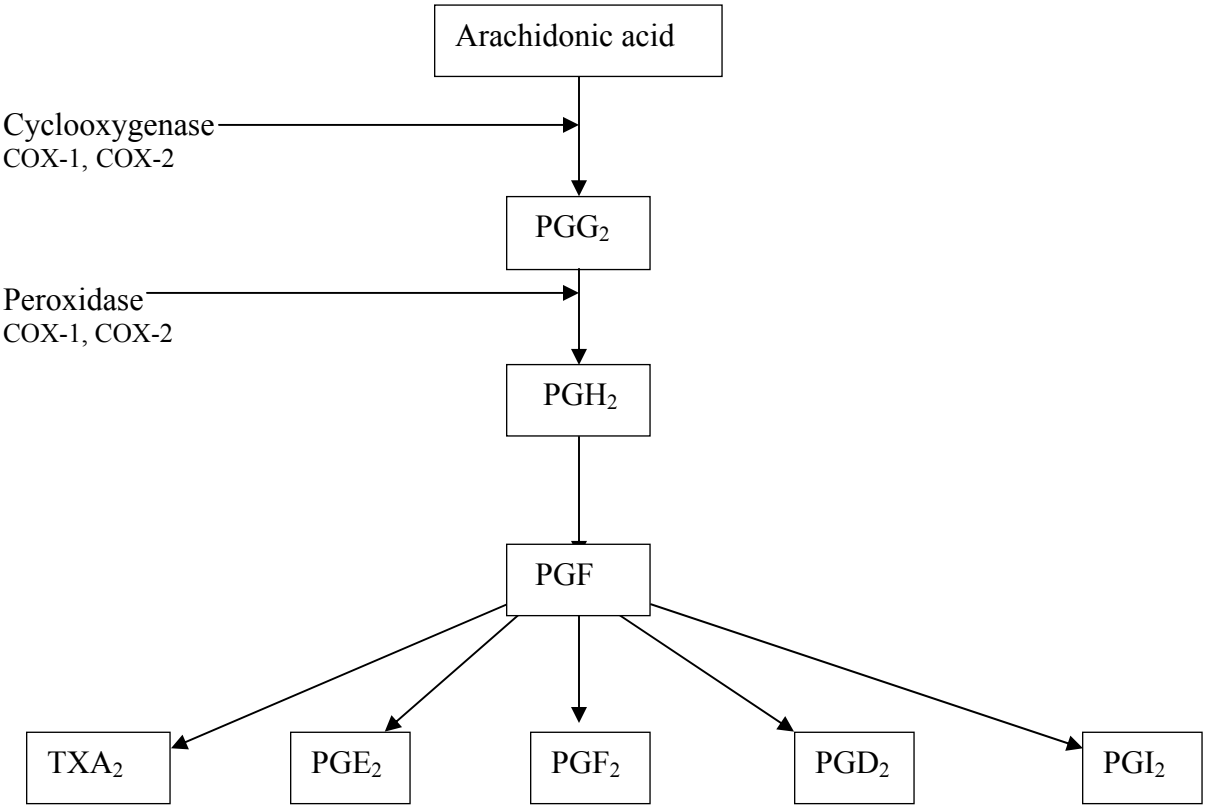


Figure 3: Pathways of Prostaglandin Synthesis from Arachidonic Acid

PGH_2 is then transformed enzymatically into prostaglandins, thromboxane, and prostacyclin by isomerases and synthases, present in specific cells. The expression of these enzymes is such, that only one or two prostanoids are made by each cell. The prostaglandins differ from each other by I) Substituents of the pentane ring indicated by the last letter E. F D etc ii) Number of double bonds in the side chains indicated by the subscript.

All these undergo rapid metabolism by beta and omega oxidation and reduction. Their levels can be measured in blood and urine by an assay for prostanoid levels.



TX Thromboxane
PG Prostaglandin
PGI Prostacyclin

Figure 4: Products of Cycloxygenases

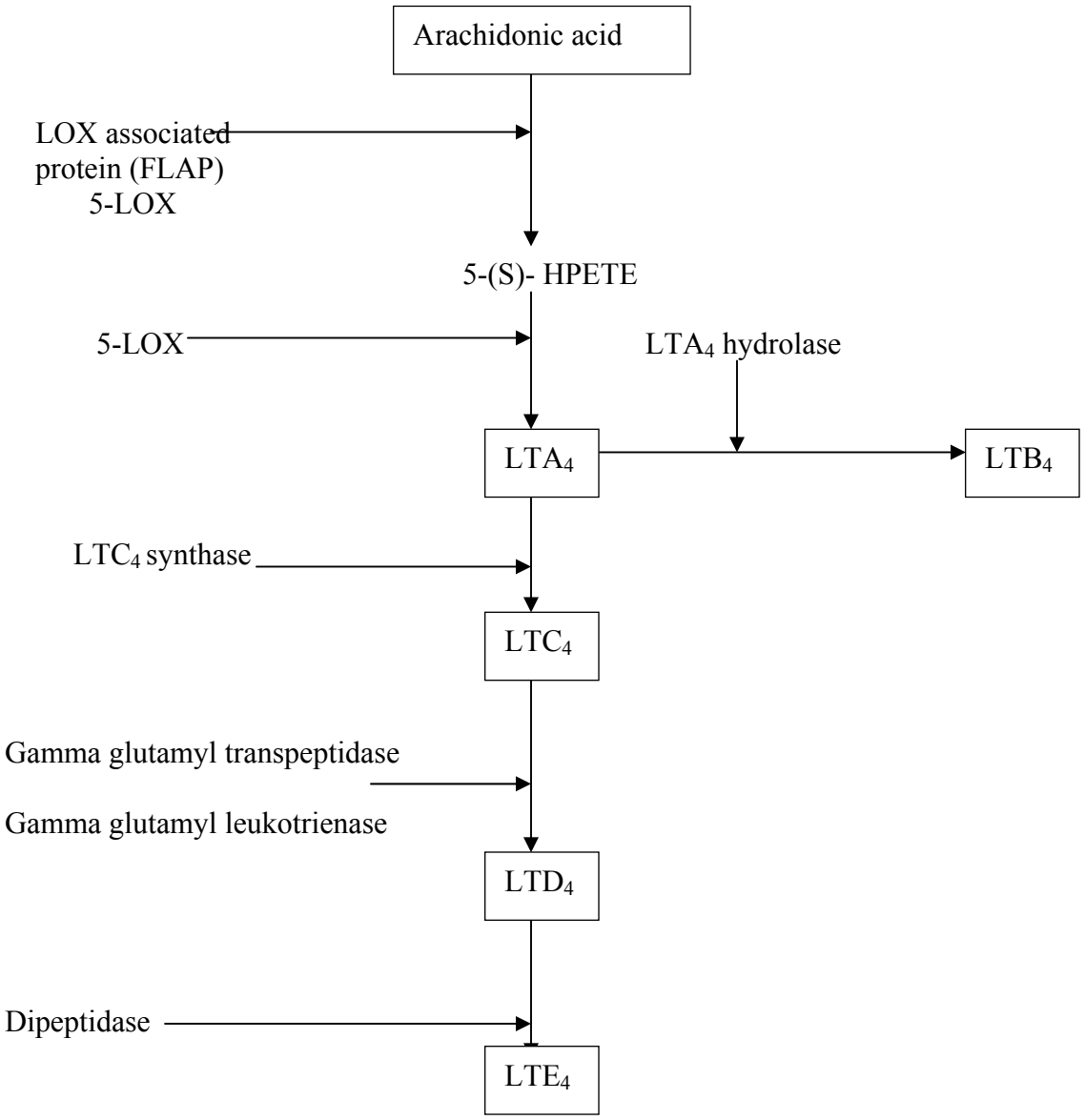
ii)Products of Lipoxygenases

Lipoxygenases (LOXs) are a family of non haem-iron containing enzymes that catalyze the oxygenation of polyenic fatty acids to corresponding lipid hydroperoxides.

There are five active human lipooxygenases. These are 5-LOX, 12(5) LOX, 12-(R) LOX, 15-LOX-1, 15-LOX-2. They are classified according to the site of hydroperoxy group insertion. Their expression is cell specific.

1)**Leukotrienes:** AA is metabolized by 5-,12- and 15 LOX forming hydroperoxyeicosatetraenoic acids (HPETEs), which are converted rapidly into hydroxy derivatives (HETEs) and leukotrienes (LTA_4, LTB_4, LTC_4, LTD_4, LTE_4) (figure-5).

The 5 LOX pathway leads to the synthesis of the leukotrienes (LTs) which play a major role in inflammation. When eosinophils, mast cells, polymorphonuclear leukocytes are activated, 5 LOX translocates to the nuclear membrane and associates with 5 LOX activating protein (FLAP). FLAP may present AA to the 5 LOX for synthesis of leukotrienes. LTC_4, LTD_4 and LTE_4 are known as cysteinyl leukotrienes and were originally known as the slow reacting substance of anaphylaxis.



HPETE Hydroperoxyeicosatetraenoic
LT Leukotiene

Figure 5: Products of Lipoxygenases

2) **Lipoxins:** LTA_4 can be converted by 12 COX in platelets to lipoxins LXA_4 and LXB_4. Lipoxins can also be formed through 5 LOX metabolism of 15 HETE.

3) Epilipoxins : (Aspirin triggered epilipoxins) 15 (R) HETE derived from aspirin-acetylated COX-2 can be transformed by 5 LOX to 15-epi-LXA_4 or 15-epi-LXB_4.

4) **Hepoxilins :** 12HETE can undergo catalyzed molecular rearrangement to form epoxyhydroxyeicosatrienoic acid.

5) **Epidermal lipooxygenases** : Lipooxygenase is also present in epidermal cells where it acts on substrates other than arachidonic acid and linoleic acid. 12(R)HETE tends to accumulate in the epidermis in psoriasis and ichthyosis.

iii)Products of Epoxygenase pathway

AA is converted by specific isozymes of microsomal cytochrome P450 monooxygenases to 4 epoxyeicosatrienoic acids (EET). These are 5,6-,8,9-,11,12- and 14,15 oxido products. These epoxides are unstable and rapidly form dihydroxyeicosatrienoic acid (DHET). Both EET and DHET can be stored in membrane phospholipids (unlike prostanoids). EETs are important modulators of cardiovascular and renal function. They are synthesized in endothelial cells and cause vasodilation in many vascular beds. They lower blood pressure. EET may function as endothelium derived hyperpolarizing factors (EDHFs).

iv)Other pathways (Isoprostanes)

Isoprostanes (isoeicosanoids) are formed nonenzymatically by direct free radical based attack on AA and related lipid substrates. These compounds are generated initially on the esterified lipid in cell membranes, from which they are cleared. Their synthesis is not inhibited by COX inhibitors. They are present in much greater amounts than COX derived PGs. It is thought that they may play a role in pathophysiology of inflammatory responses.

Inhibitors of Eicosanoid Biosynthesis : Eicosanoid biosynthesis can be inhibited at many steps. These are:

1. Decreased release of AA: By inhibitors of PLA_2 which include glucocorticoids, calcium and calmodulin inhibitors. Glucocorticoids inhibit PLA_2 by inducing the synthesis of proteins (annexins) that modulate PLA_2 activity. Glucocorticoids also decrease expression of COX-2. Calcium and calmodulin are needed for activating PLA_2, hence there inhibition would inhibit PLA_2.

2. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit COX (but not HOX, (hydroxyperoxidase) moieties of the prostaglandin G/H synthases and decrease prostanoid biosynthesis. These are nonselective, inhibit COX 1 & 2;preferentially selective, inhibit COX-2>COX-1 and selective which inhibit primarily COX-2.

3. Cysteinyl leukotriene receptor antagonists (zafirlukast, pranlukast, montelukast) antagonize the action of leukotrienes.

4. The inhibitors of other receptors and lipoxygenase pathway are investigational agents.

Actions of eicosanoids : Eicosanoid exhibit diverse functions in the body by acting on specific receptors. They activate membrane receptors close to their site of synthesis in an autocrine and paracrine fashion. All receptors are G protein coupled receptors that interact with Gs, Gi and Gq to modulate the activities of adenylyl cyclase and phospholipase C. The following receptors have been identified.

1. PGD_2 : (DP, DP_2, $CRTH_2$)
2. PGE_2 : (EP_1, EP_2, EP_{3A-D}, EP_4)

3. PGF $_{2\alpha}$: ($FP_{A,B}$)
4. PGI_2: (IP)
5. TXA_2 : (Tpx,B)
6. LTB_4 : (BLT_1, BLT_2)
7. LTC_4 :($CysLT_2$)
8. LTD_4 :($CysLT_1$, $CysLT_2$).

Signal transduction mechanisms:
1.EP_2, EP_4, IP, DP_1 activate adenylyl cyclase, resulting in increased cAMP, which activates specific protein kinases that phosphorylate internal calcium proteins. It decreases intracellular free calcium concentration.
2. EP_1, FP, TP activate phosphatidylinositol pathway with increased intracellular calcium. TP may also activate or inhibit adenylyl cyclase via Gs (TPX) or Gi (TPB) respectively and signal to membrane associated protein (MAP) kinase signaling pathways.
3. DP_2 couples with a Gi type G protein, inhibiting cAMP synthesis and increasing intracellular calcium concentrations.
4. BLT_1 activates IP_3 pathway, causing activation, degranulation and superoxide ion generation in polymorphonuclear leucocytes.
5. Cys LT1 increases intracellular calcium via Gq.

Other AA metabolites eg. isoprostanes, epoxyeicosatrienoic acids and hepoxilins have biological activities and there is evidence that they are acting through distinct receptors.

Organ System Effects: The prostaglandins and thromboxanes have many effects in the body. These are :
Cardiovascular System: Prostaglandins. PGE_2 causes vasodilation and a fall in blood pressure, vasoconstriction may also occur. This is due to an action on endothelial cells. PGD_2 causes flushing, nasal stuffiness and hypotension. PGI_2 causes vasodilation with hypotension and reflex tachycardia. It is synthesized by both smooth muscle and endothelial cells. $PGF_{2\alpha}$ and TXA_2 are vasoconstrictors. TXA_2 is also a smooth muscle mitogen. Cardiac output is increased with PGE and PGF. Increase in force of contraction and heart rate may be there due to a reflex increase in sympathetic activity.

Leukotrienes : LTC_4, LTD_4 cause hypotension due to decrease in cardiac contractility. They cause constriction of coronary and pulmonary arteries. They act on post capillary venules to cause exudation of plasma. At higher concentrations they may constrict arterioles and reduce exudation of plasma.

Isoprostanes : usually cause vasoconstriction. Isoprostane 8 – iso – $PGF_{2\alpha}$is produced in large amounts in patients with cirrhosis and may play a role in pathophysiology of hepatorenal syndrome.

Smooth muscle: PGs contract or relax many smooth muscles. The LTs contract most smooth muscles.
i. Gastrointestinal muscle **:** Most PGs and LTs stimulate gastrointestinal smooth muscle, PGE_2, $PGF_{2\alpha}$ contract the longitudinal muscle. The circular muscle contracts in response to $PGF_{2\alpha}$and

PGI_2 and relaxed by PGE_2. The prostaglandins E and F stimulate the movement of water and electrolytes into the intestine, PGI_2 prevents this. Diarrhea, cramps, nausea and vomiting are common side effects of PG administration.

Gastric and intestinal secretions : PGE_2 and PGI_2 ıncrease mucous secretion in the stomach, reduce acid secretion and reduce pepsin content by vasodilatory properties and direct effects on secretory cells.

***ii. Respiratory Tract Muscle* :** Respiratory smooth muscle is contracted by PGD_2, PGF_{2x}, TXA_2 and relaxed by PGE_2 and PGI_2. Cysteinyl leukotrienes cause bronchoconstriction and are 1000 times more potent than histamine. They also stimulate respiratory secretions and edema

iii. Uterus : The sensitivity of the uterine smooth muscle to PGs varies with the menstrual cycle, pregnancy and parturition. The uterine muscle is contracted by $PGF_{2\alpha}$, TXA_2 and low concentrations of PGE_2. PGI_2 and high concentrations of PGE_2 cause relaxation. Sensitivity to the contractile response is most prominent before menstruation, whereas relaxation is greatest at midcycle. Uterine responsiveness to PGs increase as pregnancy progress but remains smaller than the response to oxytocin.

In males PGE_1 enhances penile erection by relaxing the smooth muscle of the corpora cavernosa.

Platelets : Eicosanoids play a major role in platelet aggregation. Low concentrations of PGE_2 and TXA_2 are platelet aggregators. High concentrations of PGE_2, PGD_2 and PGI_2 inhibit platelet aggregation TXA_2 is synthesized by platelet COX-1 and is released during platelet activation and aggregation. TXA_2 also amplifies signals for other platelet agonists such as thrombin and adenosine diphosphate.

Kidney: Prostaglandins are synthesized in the cortex and medulla of the kidney. Other eicosanoid products hydroxyeicosatetraenoic acid, leukotrienes, cytochrome P 450 products and epoxides are also synthesized. PGs play a major role in maintaining renal physiology, hemodynamics, glomerular filtration and tubular function. PGE_2, PGD_2 and PGI_2 increase renin release by an action on juxtaglomerular cells. They increase renal blood flow, increase sodium and water excretion. TXA_2 causes renal vasoconstriction with a decline in renal function.
They do this by attenuating the action of antidiuretic hormone (ADH) or directly inhibiting sodium reabsorption in the distal tubule.

Eye: PGE and PGF_{2x} lower intraocular pressure by increasing the aqueous humor outflow of the eye from the anterior chamber via the uveoscleral pathway.

Central Nervous System: Fever : Fever is inducted by a number of pyrogens by releasing interleukins which promotes the synthesis and release of PGE_2.
Sleep : PGD_2 induces natural sleep by acting on arachinoid trabecular cells in the basal forebrain to increase extracellular adenosine during intracerebral administration.
Pain : PGs contribute to pain both centrally and peripherally. PGE_2 and PGI_2 sensitize the peripheral nerve endings to painful stimuli by lowering the threshold of nociceptors. LTB_4 also produces hyperalgesia.

PGE inhibit release of norepinephrine from post ganglionic sympathetic nerve endings. COX-2 has been implicated in many neurological disease such as Alzheimers, Parkinson's and epilepsy.

Endocrine: PGE_2 promotes the release of adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone, growth hormone, prolactin, gonadotropins (Follicle stimulating hormone, luetinizing hormone(LH)) and insulin. PGF_{2x} induces an oxytocin dependent decline in progesterone level in parturition. Leukotriene's LT_4 and LTD_4 stimulate luetinizing hormone releasing hormone and LH secretion. 12 HETE stimulates the release of aldosterone from the adrenal cortex.

Bone: PGs are modulators of bone metabolism. They are produced by osteoblasts and adjacent hematopoetic cells. PGE_2 increases born turnover i.e. stimulates bone resorption and formation.

Inflammation: Eicosanoids play a major role in inflammation and immune responses. LTs are generally proinflammatory, lipoxins antiinflammatory and prostanoids can be both pro and anti inflammatory. LTB_4 is a potent chemoattractant for polymorphonuclear leucocytes, eosinophils and monocytes. LTC_4 and LTD_4 are chemotactic for eosinophils. LTB_4 promotes aggregation of polymorphonuclear leukocytes, degranulation, generation of superoxide, adhesion and migration. It stimulates synthesis of cytokines from macrophages and lymphocytes. The leukotrienes and TXA_2 stimulate T cell clonal expanison by stimulating the formation of interleukin 1 and 2 as well as the expression of interleukin 2 receptors. The leukotrienes also promote interferon gamma, PGs inhibit lymphocyte function, proliferation and differentiation and suppress immunological function. PGD_2 is a chemoattractant for eosinophils. They do so by attenuating T cell clonal expansion by inhibiting interleukin 1 and 2, class II antigen expression by macrophages.

Lipoxins cause activation of monocytes and macrophages, inhibition of activation of neutrophils, eosinophils and lymphocytes. They inhibit natural killer cell cytotoxicity.

Cancer: Angiogenesis is promoted by TXA_2, PGE_2 and PGI_2 and specific COX -2 expression is associated with many tumors such as colon cancer and breast cancer.

Clinical Pharmacology of Eicosanoids

The eicosanoids play diverse and important physiological roles in the body. As a result pharmacological modulation of their functions finds many therapeutic applications. The effective use of modulators of eicosanoid synthesis and function has been made possible by 1) the development of long acting, stable, oral and parenteral PG analogs 2) development of many enzymes inhibitors and receptor antagonists (COX inhibitors and leukotriene receptor antagonists) 3) dietary manipulation to change polyunsaturated fatty acid precursor's in the cell membrane phospholipids in over the counter products and recommendations of diets with increased fish intake etc.

Reproductive system: Female :PG analogues of PGE_2 and $PGF_{2\alpha}$ which have potent oxytocic actions find use in 1) induction of abortion and 2) facilitation of labour

They are used for inducing first and second trimester abortions, for benign hydatidiform mole, for softening (priming or ripening) the cervix before abortion or induction of labour. They appear to soften the cervix by increasing proteoglycan content and changing the biophysical properties of collagen.

Abortions:

Dinosprostone: Dinoprostone is a synthetic PGE_2 preparation. It is administered vaginally. The drug enters the maternal circulation and is metabolized locally and in the lungs (95%). The half life is 2.5-5 minutes and the metabolites are excreted in the urine. Dosage for the abortifacient action is 20 mg dinoprostone vaginal suppository, repeat 3 to 5 hourly. The abortion takes around 17 hours to occur and may be incomplete, requiring other measures. For induction of labour, dinoprostone may be used as a gel (0.5 mg PGE_2) or as a controlled release formulation (10 mg PGE_2) that releases the drug at a rate of 0.3 mg/h over 12 hours. The softening of the cervix for induction of labour substantially shortens the time to onset of labour and the delivery time. The problems associated with these preparations are gastrointestinal side effects, incomplete abortions and severe cramps.

Misoprostol: Misoprostol is a synthetic PGE_1 analogue. It is available for oral and vaginal use. Since the vaginal route was associated with sepsis, so oral route is preferred. It is combined with an antiprogestin mifepristone for better efficacy.

Carboprost tromethamine: Carboprost tromethamine is a 15 methyl $PGF_{2\alpha}$. It is used to induce second trimester abortion and to control postpartum hemorrhage It is administered as a 250 µg intramuscular injection. Side effects include vomiting, diarrhoea and a rise in body temperature.

Facilitation of labour : PGE_2, $PGF_{2\alpha}$ and oxytocin have comparable induction to delivery intervals. However the adverse effects of nausea, vomiting, diarrhoea may be greater than with oxytocin. Fetal toxicity is uncommon. Oral PGE_2 is superior to oral oxytocin and equivalent to intravenous oxytocin. Oral $PGF_{2\alpha}$ has severe gastrointestinal toxicity.

Dysmenorrhoea: Primary dysmenorrhoea is due to increased endometrial synthesis of PGE_2 and $PGF_{2\alpha}$ during menstruation resulting in uterine contractions that lead to ischemic pain. Nonsteroidal antiinflammatory drugs relieve dysmenorrhoa in 80% of cases.

Males: PGE_1 analogue **alprostadil** is used as a second line treatment for erectile dysfunction. It is used in doses of 2.5-25 µg by intracavernosal injection or urethral suppository. Penile pain, prolonged erection and priapism are the side effects that may occur in less than 4% patients and can be minimized by titrating the dose carefully.

Renal system: Bartter's syndrome is an autosomal recessive trait associated with increased PG levels. There is hypokalemic metabolic allalosis. The patient has decreased sensitivity to angiotensin, hyperreninemia, hyperaldosteronism, excessive loss of potassium. After administration of COX inhibitors, sensitivity to angiotensin, plasma renin and aldosterone levels return to normal

Cardiovascular System: In pulmonary hypertension prostacyclin lowers peripheral, pulmonary and coronary resistance. It is used to treat primay and secondary pulmonary hypertension and porto pulmonary hypertension secondary to liver disease. Its synthetic analogues include

Epoprostenol: Epoprostenol is used for the treatment of primary pulmonary hypertension. It appears to improve symptoms, prolong survival, delay or prevent the need for lung transplant. It has to be administered as a continuous intravenous infusion

Treprostinil :Treprostinil has a longer half life but has to be administered as a continuous subcutaneous infusion.

Patent Ductus Arteriosus: The fetal ductus arteriosus is kept patent by PGE_2. At birth, there is decline in PGE_2 resulting in closure of patent ductus arteriosus. In cases of congenital heart disease, where the patency has to be maintained before corrective surgery PGE_1 analogue alprostadil is used. It has to be administered by continuous infusion. Side effects include apnoea, bradycardia, hypotension and hyperpyrexia. In delayed closure of the ductus arteriosus, COX inhibitions are often used to inhibit synthesis of PGE_2 and so close the ductus. In premature infants indomethacin is highly effective.

Blood: Low dose aspirin selectively inhibits platelet COX inhibiting synthesis of TXA_2. TXA_2 is a platelet aggregator and also activates other platelet agonists (ADP, thrombin, collagen). Low dose aspirin reduces the incidence of first myocardial infarction as well as secondary incidence of heart attack and stroke.

Respiratory system: Leukotreine receptor antagonists zafirlukast, montelukast are effective in asthma. A lipoxygenase inhibitor zileuton has also been used in asthma. Corticosteroids and cromolyn are also useful in asthma. Corticosteroids inhibit eicosanoid synthesis and cromolyn inhibit the release of eicosanoids and other mediators from mast cells.

Gastrointestinal System: PGE analogues protect against peptic ulcers produced by steroids or NSAIDs. Misoprostol is an oral synthetic analogue of PGE_1, used for prevention of NSAID induced peptic ulcer. It is administered at a dose of 200 μg. It is cytoprotective at low doses and inhibits gastric acid secretion at high doses. Adverse effects include abdominal discomfort and diarrhoea. Bone pains and hyperostosis have been observed in patients on long term PGE_1 therapy.

Immune Systems

Inflammation: NSAIDS and corticosteriods are both used to suppress inflammation in osteoarthritis, rheumatoid arthritis and other inflammatory conditions.

Cell mediated Organ Transplant Rejection: Organ transplanted rejection is a cell mediated immune response. Administration of PGE_2, PGI_2 and thromboxane inhbitors can reverse the rejection process. Corticosteroids inhibit both PLA_2 and COX-2 activity and are the first line drugs used for the treatment of acute rejection.

Glaucoma: $PGF_{2\alpha}$ analogues latanoprost, bimatoprost, travaprost, unoprostone are used as

topical preparations for glaucoma. Adverse effects include irreversible brown pigmentation of the iris and eyelashes, drying of the eyes and conjunctivitis.

Dietary Modification of Arachidonic Acid Metabolism: Arachidonic acid is derived from dietary linoleic and alpha linolenic acids. Thus use of food oils which contain linoleic acid is recommended (safflower, corn, sunflower oil). Also addition of oils containing omega 3 fatty acids (eicosapentanoic acid and docosahexaenoic acid), derived from cold water fish is also advocated. Both diets will change the phospholipid composition of cell membrane with resultant changes in prostanoid synthesis and function towards a more favorable cardiovascular functioning profile.

Platelet Activating Factor

Platelet activating factor (PAF) is a cell membrane derived polar lipid. PAF is 1-0-alkyl-2 acetyl-sn-glycero-3-phosphocholine. It is not stored in cells, but is synthesized in response to stimulation, like the eicosanoids. It is synthesized from 1-0-alkyl-2-acyl-glycerophospho-choline. This is a lipid found in high concentrations in the membranes of many cells (figure 6).

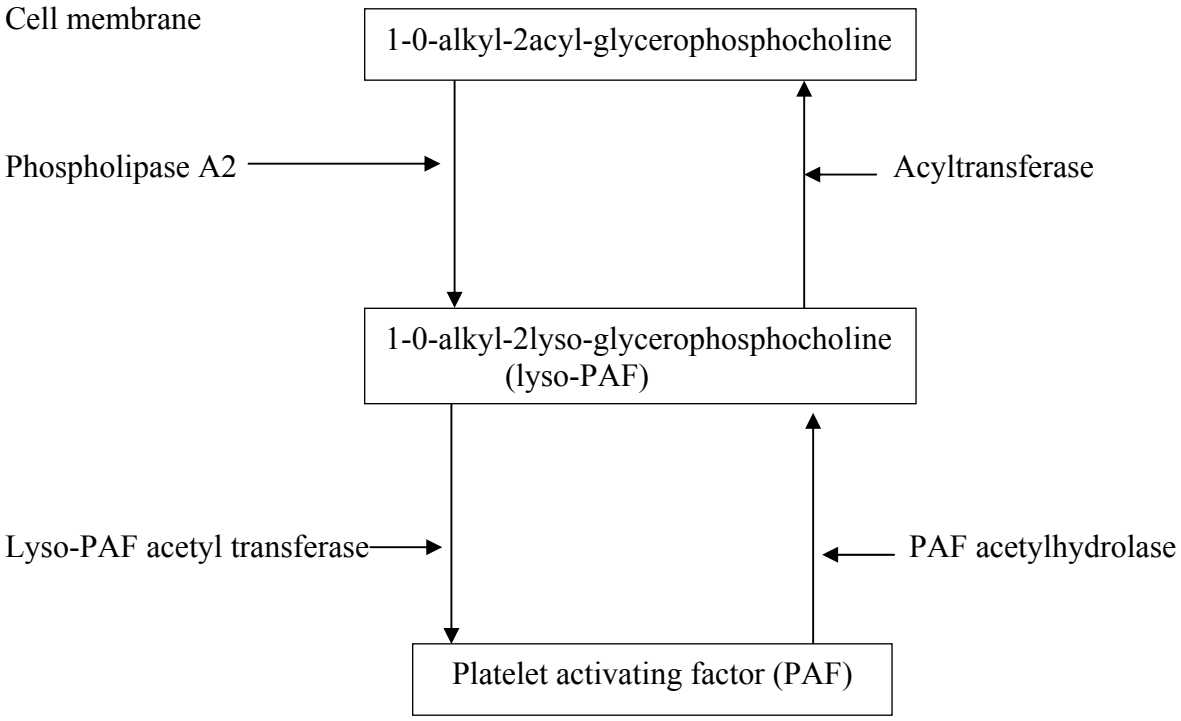


Figure 6: Platelet Activating Factor: Synthesis and Metabolism

The first step involves the action of PLA_2 resulting in the formation of 1-0-alkyl-2 lyso-glycero-phosphocholine (lyso PAF) and a free fatty acid. Eicosanoid and PAF biosynthesis are thus coupled.

The rate limiting step is performed by the enzyme acetyl coenzyme -A-lyso-PAF acetyl transferase. Both enzymes are calcium dependent enzymes.

PAF may be synthesized de novo by the action of enzyme lysoglycerophosphate acetyl coenzyme -A transferase on alkyl acetyl glycerol and phosphocholine. This path may be involved in synthesizing PAF for normal cellular functions.

PAF synthesis may be stimulated by antigen antibody reactions, chemotactic peptides, thrombin, collagen, and other autacoids. PAF is synthesized by platelets, neutrophils, monocytes, mast cells, eosinophils, renal mesangial and medullary cells and vascular endothelial cells.

PAF like molecules may be formed by oxidative fragmentation of membrane phospholipids (OxPLs) in presence of oxidative stress. They are different structurally from PAF, but bind to the same receptor and elicit the same responses. Their synthesis is unregulated and hence degradation is necessary to suppress toxicity of oxidative phospholipids (OxPLs).

Metabolism: PAF is acted upon by PAF acetyl hydrolase to form lyso PAF. Lyso PAF is then converted to 1-0-alkyl-2-acyl-glycerophosphocholine by an acyltransferase.

Mechanism of Action: Specific membrane bound receptors for PAF have been identified. They are G protein coupled receptors. PAF via Gq activates the PLC-1P3-Ca^{2+} pathway and phospholipases A_2 and D. They will result in mobilization of arachidonic acid from the cell membrane resulting in synthesis of PGs, TXA_2 and LTs. These will then function as PAF's extracellular mediators. PAF acts intracellularly also within the cell where it is synthesized. It may be expressed on the surface of the cell e.g. endothelium, where it may activate the PAF receptor or adjacent cells including, platelets, polymorphonuclear leucocytes and monocytes to promote adhesion.

Pharmacological Effects: PAF exhibits diverse action in the body. These are:
Cardiovascular system: PAF dilates most vascular beds, causing hypotension resulting from both direct and indirect actions. It may cause vasoconstriction depending on the concentration, vascular bed and involvement of platelets or leukocytes. PAF increases vascular permeability and edema. The increase in permeability is due to contraction of venular endothelial cells

Platelets: PAF is a potent stimulator of platelet aggregation directly. It does not require the presence of TXA_2 and other aggregating agents, although they are also released.

Leukocytes: PAF is chemotactic for eosinophils, neutrophils and monocytes. It promotes adhesion and migration of neutrophils. It causes polymorphonuclear leukocytes to aggregate, release LTs and lysosomal enzymes and generate superoxide. It also promotes aggregation of monocytes and degranulation of eosinophils. PAF causes leukocytopenia.

Smooth muscle: PAF contracts gastrointestinal, uterine and pulmonary smooth muscle. It contracts airway smooth muscle probably by releasing LTC4 or TxA2, increasing airway resistance. PAF also increases mucous secretion and permeability of pulmonary microvessels.

Stomach: PAF is a potent ulcerogen.

Kidney: PAF dilates renal afferent arterioles at low concentrations due to stimulation of nitric

oxide production by the endotheluim. At higher concentrations PAF constricts the vessels by production of COX products. PAF may decrease the glomerular filtration rate, urine volume and excretion of sodium.

Pathophysiological Roles of PAF: PAF is a mediator in a number of pathological events in the body. Derangement and dysregulation of PAF functioning has been associated with human diseases.

a) **Platelets** : PAF was thought to be an independent mediator of platelet aggregation in cycloxygenase inhibitor – resistant, thrombin induced aggregation. However, PAF antagonists failed to block thrombin induced aggregation.

b) **Inflammation and allergic Responses** : PAF has proinflammatory actions. It contributes to the pathophysiology of inflammatory disorders, including anaphylaxis, bronchial asthma, endotoxic shock, skin diseases etc. The role of PAF antagonists in these conditions has been disappointing. PAF antagonists have only partially reversed the pathological processes in bronchial asthma and anaphylactic shock. This is probably due to the complexity of the pathological conditions and involvement of multiple mediators.

c) **Reproduction and parturition** . A role for PAF in ovulation, implantation and parturition has been suggested. Embryos which produce PAF have a greater chance of surviving. PAF may be involved in progression of labour by directly contracting the uterus and releasing PGE_2. PAF antagonists delay labour in animals. Although a role for PAF in reproduction has been suggested, deficiency of PAF has also been associated with normal reproductivity. This suggests that PAF may not be essential for reproduction.

PAF Receptor Antagonists:

A number of natural and synthetic PAF receptor antagonists have been investigated. These include ginkolide B (plant product) and structural PAF analogues. Although the potential therapeutic role for PAF antagonists is tremendous as antiinflammatory antiallergens, anti asthmatic, in gastric ulceration, contraception, etc. none of the agents have been found to be clinically useful.

Suggested readings

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Lipid Derived Autacoids

The main phospholipid derived mediators are the eicosanoids (prostanoids and leukotrienes) and platelet derived activating factor.

The eicosanoid are derivatives of arachidonate that can be released from phospholipids by phospholipase action. The arachidonate can be metabolized by cycloxygenase to give rise to prostanoids or by 5 lipoxygenase to give rise to leukotrienes.

Platelet activating factor is derived by ILA_2 giving rise to lyso-PAF, which is acetylated to form PAF.

Prostanoids

PGI_2 mainly from vascular endothelium produces vasodilation and inhibition of platelet aggregation. TXA_2 predominantly from platelets produces platelet aggregation and vasoconstriction.

PGE_2 produces inflammatory responses, fever,

- contraction of bronchial and gastrointestinal smooth muscle,
- relaxation of bronchial, vascular and gastrointestinal smooth muscle,
- inhibition of gastric acid secretion, increased mucus production
- contraction of pregnant uterus,

$PGF_{2\alpha}$ acts on smooth muscle and corpus luteum resulting in uterine contraction

Main uses

- termination of pregnancy
- induction of labour
- postpartum hemorrhage
- prevention of peptic ulcer in patients NSAIDS

Leukotrienes

5 lipooxygenase acts on arachidonate to form 5 hydroperoxyeicosatetraenoic acid(5-HPETE which is converted to leukotriene A_4.($LTA_{4)}$. LTA_4 may convert into LTB_4, LTC_4 and LTD_4 and LTE_4.

Leukotrienes are involved in inflammation. LTB4 causes adherence, chemotaxis and activation of polymorphs and monocytes, stimulate proliferation and cytokine production from macrophages and lymphocytes.

- mediator of both early and late phases of asthma.
- cause contraction of bronchial muscle and of most blood vessels

Leukotriene antagonists are used in treatment of bronchial asthma.

Platelet activating factor

PAF is released indirectly from many activated inflammatory cells by phospholipase A2 activity. Actions include vasodilation, increased vascular permeability, chemotactic for leucocytes, activation and aggregation of platelets and spasmogenic for smooth muscles.

Is implicated in bronchial hyperresponsiveness and in delayed phase of asthma.

No therapeutic applications are there presently.