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Role of P_2Y_{12} and GP IIb/IIIa Receptor Antagonist as Antiplatelets- A Novel Approach

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ABSTRACT

Platelets help in providing the initial haemostatic plug at sites of peripheral vascular injury. They also participate in pathological thromboses that lead to myocardial infarction, stroke and peripheral vascular thromboses. Glycoproteins (GP) IIb-IIIa inhibitors help in preventing the aggregation of activated platelets. The agents are approved for clinical use. Due to its important function in mediating platelet aggregation GPIIb/IIIa has become a primary site for development of antiplatelet agents. Abciximab have shown to be highly effective in patients with ischemic heart disease. Abciximab prevents the aggregation of platelets by preventing or inhibiting the binding of fibrinogen, von Willebrand factor (vWF) to GPIIb/IIIa receptor sites of activated platelets. Activation of the glycoprotein IIb/IIIa receptor results in enhanced platelet degradation and thromboxane production, and platelet aggregation. Clopidogrel inhibits ADP induced platelet aggregation directly by prevention of adenosine diphosphate (ADP) binding to its receptor and resulting in subsequent ADP mediated activation of the glycoprotein GPIIb/IIIa complex. Clopidogrel along with aspirin has shown an incremental benefit of clopidogrel in patients with atherosclerotic heart disease. Clopidogrel is effectively used for the prevention of heart attacks and strokes in persons with cardiac disease and other blood circulation disease (peripheral vascular disease).

INTRODUCTION

Platelets (also called as thrombocytes) are the formed elements of blood. Platelets are small colourless, non-nucleated and moderately refractive bodies. Thus, the formed elements of blood are the fragments of cytoplasm. [1]

Platelets help in providing the initial haemostatic plug at sites of peripheral vascular injury. They also participate in pathological thromboses that lead to myocardial infraction, stroke and peripheral vascular thromboses. Potent inhibitory drugs of platelet function are called as ***antiplatelet drugs***. These drugs act by different mechanisms, and thus in combination, they show either additive or even synergistic effects. Their availability results in revolution of cardiovascular drugs. [2]

Platelet plays such a critical role in thromboembolic disease that it is no surprise that antiplatelets drugs are of great therapeutic value. Clinical trials of aspirin radically altered clinical practice, and more recently drugs that inhibit ADP and GPIIb/IIIa have also been found to be therapeutically active. Antagonist of the GPIIb/IIIa receptors have the theoretical attraction that they inhibit all Pathways of platelet adhesion (because these all converge on activation of GPIIb/IIIa receptors) a hybrid Murine-human monoclonal antibody Fab fragment directed against the GPIIb/IIIa receptor, which rejoice in the catchy little name of **abciximab**, is licensed for use in high-risk patients undergoing coronary angioplasty as an adjunct to heparin and aspirin. It reduces the risk of reterosis at the expense of an increased risk of bleeding. Immunogenicity limits its use to a single administration. [2]

PLATELETS

Size of platelets [1]

Diameter: 2.5 μ, *Volume*: 7.5 cuμ.

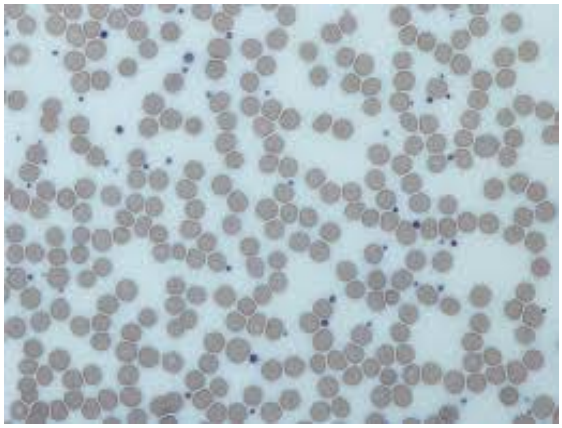

Figure No. 1: Microscopic structure of PLATELET[4]

Shape of platelets[1]

Normally, platelets are of several shapes, spherical or rod-shaped and they become oval or disk-shaped under inactivation. Sometimes, they have dumbbell, comma shape, cigar shape or any unusual shape. Inactivated platelets are without processes or filopodia and the activated platelets develop processes or filopodia (figure 2).

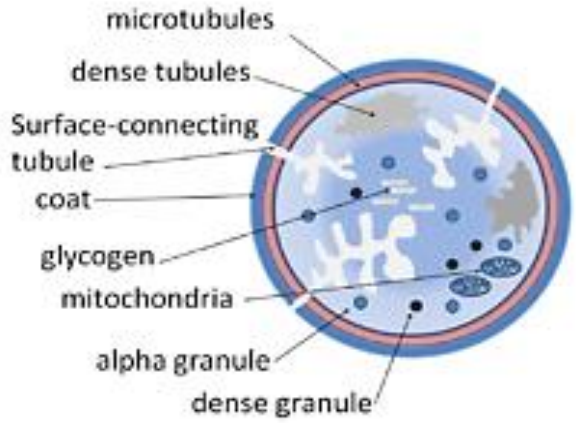

Figure No. 2 Cell organelles of platelet[16]

a. Proteins

i. Contractile proteins

Actin and myosin are the contractile proteins, which are responsible for contraction of platelets. A third contractile protein called thrombosthenin is also present. It is responsible for clot retraction.

ii. Von Willebrand factor

This is responsible for adherence of platelets and regulation of plasma level of factor VIII.

iii. Fibrin-stabilizing factor

It is a clotting factor.

iv. Platelet-derived growth factor (PDGF)

This factor is responsible for repair of damaged blood vessels and wound healing. It is a potent mitogen (chemical agent that promotes mitosis) for proliferation for smooth muscle fibers of blood vessels. It also accelerates proliferation of connective tissue.

v. Platelet-activating factor (PAF)

It causes aggregation of platelets during the injury of blood vessels, resulting in prevention of excess loss of blood.

vi. Vitronectin (serum-spreading factor)

Vitronectin promotes adhesion of platelets and spreading of tissue cells in culture.

vii. Thrombospondin

It inhibits angiogenesis (formation of new blood vessels from pre-existing vessels).

b. Enzymes: Adenosine triphosphatase (ATPase), Enzymes necessary for synthesis of prostaglandins.

c. Hormonal Substances: Adrenaline, 5-hydroxytryptamine (5-HT; serotonin), histamine.

d. Other Chemical Substances: Glycogen, substances like blood group antigens and inorganic substances such as calcium, copper, magnesium and iron.

e. Platelet Granules

Granules present in cytoplasm of platelets are of two types: Alpha granules and dense granules. Substances present in these granules are given in Table 1.

Table No. 1: Platelet granules [1]

Alpha granules	Dense granules
Clotting factors: fibrinogen, V and XIII	Nucleotides
Platelet-derived growth factor	Serotonin
Vascular endothelial growth	Phospholipids
Basic fibroblast growth factor	Calcium
Endostatin	Lysosomes
Thrombospondin	

NORMAL COUNT AND VARIATIONS [1]

Normal platelet count is 2,50,000/cu mm of blood. It ranges between 2 lakh and 4 lakh/cu mm of blood.

PHYSIOLOGICAL VARIATIONS [1]

1. Age

Platelets are less in infants (1.5 lakh to 2 lakh/cu mm) and reaches normal level at second to third month after birth.

2. Sex

There is no difference in the platelet count between males and females. In females, it is reduced during menstruation.

3. High Altitude

Platelet count increases in high altitude.

4. After Meals

After taking food, the platelet count increases.

PROPERTIES OF PLATELETS [1]

Platelets have three important properties (three 'A's):

1. Adhesiveness.

2. Aggregation.

3. Agglutination.

1. ADHESIVENESS

Adhesiveness is the property of sticking to a rough surface. During injury of blood vessel, endothelium is damaged and the subendothelial collagen is exposed. While coming in contact with collagen, platelets are activated and adhere to collagen. Adhesion of platelets involves interaction between von Willebrand factor secreted by damaged endothelium and a receptor protein called glycoprotein Ib situated on the surface of platelet membrane. Other factors which accelerate adhesiveness are collagen, thrombin, ADP, thromboxane A2, calcium ions, P-selectin and vitronectin.

2. AGGREGATION (GROUPING OF PLATELETS)

Aggregation is the grouping of platelets. Adhesion is followed by activation of a greater number of platelets by substances released from dense granules of platelets.

Activation of Platelets

During activation, the platelets change their shape with elongation of long filamentous pseudopodia which are called processes or filopodia.

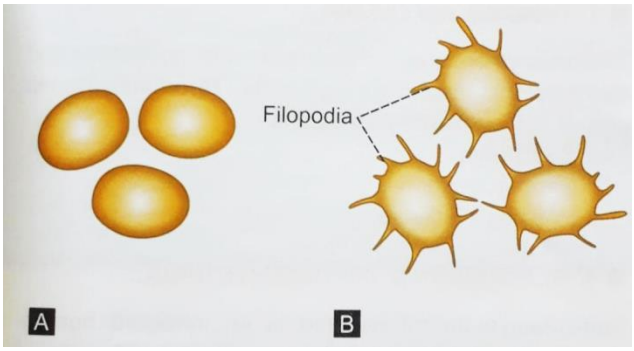

Figure No. 3 Activation of platelet

Filopodia help the platelets aggregate together. Activation and aggregation of platelets is accelerated by ADP, thromboxane A2 and platelet-activating factor (PTA) cytokine secreted by neutrophils and monocytes.

3. AGGLUTINATION

Agglutination is the clumping together of platelets. Aggregated platelets are agglutinated by the actions of some platelet agglutinins and platelet activating factor.

ACTIVATORS AND INHIBITORS OF PLATELETS [1]

ACTIVATORS OF PLATELETS

- Collagen.
- Von Willebrand factor.
- Thromboxane A2.
- Platelet-activating factor.
- Thrombin.
- ADP.
- Calcium ions.
- P-selectin: Cell adhesion molecule secreted from endothelial cells.
- Convulxin: Purified protein from snake venom.

INHIBITORS OF PLATELETS

- Nitric oxide.
- Clotting factors: II. IX, X, XI and XII.
- Prostacyclin.
- Nucleosidase which break down the ADP.

DEVELOPMENT OF PLATELETS [1]

Platelets are formed from bone marrow. Pluripotent stem cell gives rise to the colony-forming unit-megakaryocyte (CFU-M). This develops into megakaryocyte. Cytoplasm of megakaryocyte form pseudopodium. A portion of pseudopodium is detached to form platelet, which enters circulation.

Production of platelets is influenced by colony-stimulating factors and thrombopoietin. Colony-stimulating factors are secreted by monocytes and T lymphocytes. Thrombopoietin is a glycoprotein like erythropoietin. It is secreted by liver and kidneys.

LIFESPAN AND FATE OF PLATELETS [1]

Average lifespan of platelets is ***10 days***. It varies between 8 and 11 days. Platelets are destroyed by tissue macrophage system in spleen. So, splenomegaly (enlargement of spleen) decreases platelet count and splenectomy (removal of spleen) increases platelet count.

APPLIED PHYSIOLOGY PLATELET DISORDERS [1]

Platelet disorders occur because of pathological variation in platelet count and dysfunction of platelets. Platelet disorders are:

1. Thrombocytopenia.
2. Thrombocytosis.
3. Thrombocythemia.
4. Glanzmann’s thrombasthenia.

1. THROMBOCYTOPENIA

Decrease in platelet count is called thrombocytopenia. It leads to thrombocytopenic purpura. Thrombocytopenia occurs in the conditions like Acute infections, Acute leukemia, Aplastic and pernicious anemia, Chickenpox, Smallpox, Splenomegaly, Scarlet fever, Typhoid, Tuberculosis, Purpura, Gaucher's disease.

2. THROMBOCYTOSIS

Increase in platelet count is called thrombocytosis. Thrombocytosis occurs in the conditions: Allergic conditions, Asphyxia, Haemorrhage, Bone fractures, Surgical operations, Splenectomy, Rheumatic fever, Trauma (wound or injury or damage caused by external force).

3. THROMBOCYTHEMIA

Thrombocythemia is the condition with persistent arid abnormal increase in platelet count. Thrombocythemia occurs in the conditions: Carcinoma, Chronicieukemia, Hodgkin's disease.

4. GLANZMANN'S THROMBASTHENIA

Glanzmann's thrombasthenia is an inherited haemorrhagic disorder, caused by structural or functional abnormality of platelets. It leads to thrombasthenic purpura. However, the platelet count is normal. It is characterized usually by normal clotting time, normal or extended bleeding time but defective clot retraction.

PLATELET RECEPTORS [3][18]

Platelets receptors acts as the contacts between the platelet and their external world, which are used to determine the reactivity of platelets with the wide range of agonist and adhesive proteins. To a great extent, it is a surface receptor on platelets that, together with granules, determine the specific cellular identity of platelets.

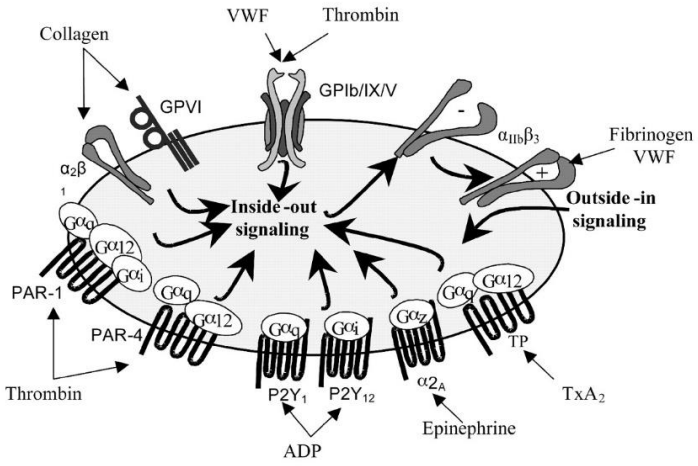

Figure No. 4: Major platelet receptors [18]

The main function of platelet is hemostasis. The major receptors present on the platelet have a direct role in this process, either in activating platelet or as adhesive receptors interacting with damage cell walls or with other platelets to contribute to thrombus formation. The variety receptors involved in this process, both positive and negative feedback loops, emphasizes their importance in platelet functioning and in the ways that platelets adapt their function to different situations.

I. Integrins

The integrins are major class of adhesive and signaling molecules present on most cell types. They consist of non-covalently associated heterodimers of and α and β subunits and are generally involved in linking aggressive molecules to the cellular cytoskeleton. Integrins usually exist in two affinities, low and high, that are altered by cytoplasmic signaling and phosphorylation of their cytoplasmic domains. Platelets have members of their family of integrins ($\beta_1, \beta_2, \beta_3$) and, in total, 6 different integrins: $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_L\beta_2$, $\alpha IIb\beta_3$ and $\alpha_v\beta_3$.

II. Leucine rich repeat family

GPIb-IX-V complex

The LRR is represented in platelets by the GPIb-IX-V complex with approximately 50,000 copies per platelet- the second most common platelet receptors. Its absence or deficiency leads to Bernard soulier syndrome the second most common bleeding disorder linked to platelet receptor.

The GP Ib-IX-V Complex is essential for complete adhesion under high shear.

III. Seven transmembrane receptors

The seven transmembrane receptor family is the major agonist receptor family in cells generally and is also very well represented on platelets. Members of this family are still being identified and characterized.

A. Thrombin receptors

B. ADP receptors

C. Prostaglandin family receptors

- Thromboxane receptor
- PGI_2 receptor
- PGD_2 receptor
- PGE_2 receptor

D. Lipid receptors

- Platelet activating factor receptor
- Lysophosphatidic acid receptor

E. Other seven transmembrane receptors

- V_{1a} vasopressin receptor
- A2a adenosine receptor
- β2 adrenergic receptors
- Serotonin receptor
- Dopamine receptor

IV. Immunoglobulin Superfamily

A. GPV1

B. FcγRIIA

C. FcεRI

D. Platelet and T-cell Antigen I

E. Junction Adhesion molecules (JAMs)

F. Intercellular Adhesion Molecule 2 (ICAM-2)

G. PECAM-1

H. CD47

I. Endothelial cell-selective adhesion molecule (ESAM)

J. TREM-like transcript-1 (TLT-1)

V. C-type Lectin receptor Family

A. P-selectin (CD62P0)

B. CD72

C. CD93

D. Other C-type lectin receptors

VI. Tetraspanins

Tetraspanins are a group of membrane proteins that contain four membrane-spanning domains (as the name indicates). They are thought to have important functions in signal transduction across the cell membrane, in complexes with other membrane receptors. The role of these receptors is poorly understood.

A. CD9

B. CD63

C. CD82

VII. Glycosyl Phosphatidylinositol (GPI)

Platelets have at least five glycoproteins that are linked by Glycosyl Phosphatidylinositol anchors. GPI-linked receptors have a poorly understood role associated with signal transduction. GPI-linked receptors identified in platelets include the classic CD55 and CD59, which are also present on a wide range of blood cells to protect them against complement when this is activated. These GPI-linked proteins are all affected by the clonal absence of GPI anchor in paroxysmal nocturnal hemoglobinuria.

VIII. Glycosaminoglycan-carrying receptors

Along with the GPI-linked glypican, there are some evidences of presence of platelets of other members of glycosaminoglycans-carrying receptor family, like syndecan and perlican.

IX. Tyrosine Kinase receptors

- Thrombopoietin receptor
- Leptin receptor
- Tie-1 (Tyrosine kinase with immunoglobulin and epidermal growth factor hamology-1) receptor
- Insulin receptor
- Platelet- derived growth Factors (PDGF) receptor.

FIBRINOLYSIS [1][19]

Fibrinogen is a soluble 340-kDa protein, circulates in whole blood at concentrations of 2–4 mg/mL. Fibrinogen consists of two sets of three different disulfide-linked polypeptide chains (Aα, Bβ, and γ). Thrombin's important site or target is fibrinogen, which is converted to fibrin monomers as thrombin removes N-terminal fibrinopeptides A and B. The resulting monomer constitutes of disulphide-linked trinodular protein whose N- and C-termini converge at the E- and D-nodules, respectively.

Lysis of clod inside the vessel is named fibrinolysis. It helps to get rid of the clot from lumen of the vessel. This process requires a substance called fibrinolysin.

Formation of Plasmin

Plasmin is made from inactivated glycoprotein called plasminogen. Plasminogen is converted into plasmin by tissue plasminogen activator (t-PA), lysosomal enzymes and thrombin. The t-PA and lysosomal enzymes are released from damaged tissues and damaged endothelium. Thrombin is derived from blood. The t-PA is prevented by a substance called t-PA inhibitor. It is also inhibited by factors V and VIII.

Activation of Plasminogen involves following sequence of events

1. During intravascular clotting, the endothelium of the blood vessel secretes thrombomodulin, which secreted by the endothelium of all the blood vessels, except the capillaries of brain.

2. Thrombomodulin forms a complex with thrombin and forms a thrombomodulin-thrombin complex.

3. Thrombomodulin-thrombin complex activates protein C.

4. Activated protein C inactivates factor V and Wu in the presence of a cofactor called protein S.

5. Protein C also inactivates the t-PA inhibitor.

6. Now, the t-PA becomes active.

7. Activated t-PA and lysosomal enzymes activate plasminogen to form plasmin. Plasminogen is also activated by thrombin and u-PA (Figure 5).

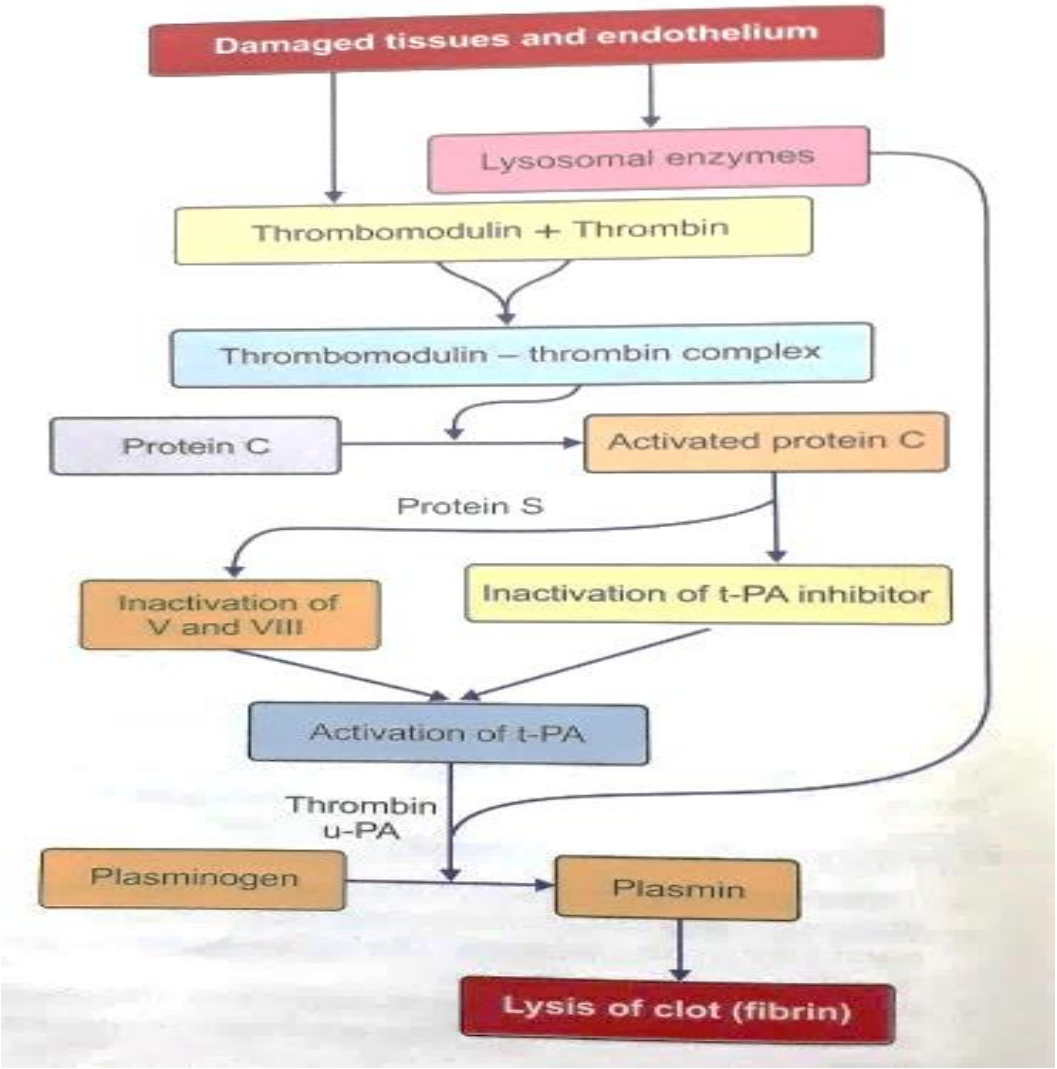

Figure No. 5: Pathway showing lysis of clot [1]

ANTICLOTTING MECHANISM IN THE BODY [1]

Under physiological conditions, intravascular clotting does not occur. It is because of two reasons:

A. Presence of clotting factors of blood in inactive state

B. Presence of some physical and chemical factors in the body

PLATELET FUNCTIONS [2]

- Healthy vascular endothelium prevents platelet adhesion.

- Platelets adhere to diseased or damaged areas and become activated, i.e. the change shape, exposing negatively charged phospholipids and glycoproteins (GPIIb/IIIa) receptors and synthesize and are released various mediators for example thromboxane A_2 and area which activate other platelets causing aggregation.

- Aggregation entails fibrinogen binding to GPIIb/IIIa receptors on adjacent platelets.

- Activated platelets constituent of focus for fibrin formation.

- Chemotactic factors and growth factors necessary for repair, but also implicated in atherogenesis, are released during platelet activation.

CLINICAL USES OF ANTIPLATELET DRUGS [2]

The main drug is aspirin other drugs with distinct action can have additive effect or be used in patients who are intolerant of aspirin. Uses of antiplatelet drugs related mainly to arterial thrombosis and include:

- Acute myocardial infarction

- High risk of myocardial infarction, including a history of myocardial infarction and joiner for intermittent claudication.

- Following coronary artery bypass grafting

- Unstable coronary syndromes (clopidogrel added to aspirin)

- Following coronary artery angioplasty and/or stenting (intravenous GPIIb/IIIa antagonist ex: abciximab are used in some patients in addition to aspirin)

- Transient cerebral ischemic heart thrombotic stroke, to prevent recurrence. (dipyridamole can be added to aspirin)

- Atrial fibrillation, if oral anticoagulation is contraindicated.

Other antiplatelet drugs (ex: epoprostenol) have specialized clinical applications in hemodialysis/ hemofiltration/ pulmonary hypertension.

Classification of Antiplatelet agents [4]

I. Irreversible cyclooxygenase inhibitors

Aspirin, Triflusal

II. Adenosine diphosphate (ADP) receptor inhibitors

Cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine

III. Phosphodiesterase inhibitors

Cilostazol

IV. Protease- activated receptor-1 (PAR-1) antagonists

Vorapaxar

V. Glycoprotein IIb/IIIa inhibitors (IV use only)

Abciximab, eptifibatide, tirofiban

VI. Adenosine reuptake inhibitors

Dipyridamole

VII.Thromboxane inhibitors

a. Thromboxane receptor antagonists

Terutroban

b. Thromboxane synthase inhibitors

$P2Y_{12}$ Receptor Antagonists [5][9]

- ADP plays an important role in the genesis of physiological platelet-rich haemostatic plugs as well as in the formation of pathological arterial thrombi.

- ADP released from platelet dense-granules and damaged cells binds to two platelet G-protein-coupled receptors, the $P2Y_1$ and $P2Y_{12}$ receptors.

- $P2Y_1$ is a Gq-coupled receptor that initiates ADP-induced aggregation of platelet by stimulating phospholipase C and phosphatidylinositol-signalling pathway.

- $P2Y_{12}$ is a type of Gi-coupled seven-transmembrane domain receptor, which helps inactivation of platelet by preventing the adenylate cyclase-mediated signalling pathway and decreasing intracellular cAMP levels. The gradual decrease in intracellular cAMP levels reduces the rate of phosphorylation of the vasodilator-stimulated phosphoprotein, thus inducing activation of the GPIIb/IIIa receptor and platelet aggregation.

- $P2Y_{12}$ receptor is a 342 amino acid Gi-coupled receptor dominantly expressed on platelets. $P2Y_{12}$ receptor is physiologically gets activated by ADP and inhibits adenyl cyclase (AC) to decrease cyclic AMP (cAMP) level, which results in platelet aggregation. It also activates PI3 kinase (PI3K) pathway leading to fibrinogen receptor activation, and protect platelets from apoptosis.

Mechanism of action of the $P2Y_{12}$ antagonists:[5][13]

➢ $P2Y_1$ and $P2Y_{12}$ are G-coupled receptors, which utilize ADP as an agonist.

➢ $P2Y_1$ is a Gq-coupled receptor, which initiates ADP-induced platelet aggregation through the stimulation of PLC and phosphatidylinositol-signalling pathway.

➢ $P2Y_{12}$ is a Gi-coupled 7-transmembrane domain receptor, which mediates platelet activation by inhibiting an AC-mediated signalling pathway and decreasing the cAMP intracellular levels. It also inhibits PI3K and induces Akt kinase activation. The decrease in intracellular levels of cAMP reduces the rate of phosphorylation of VASP (vasodilator-mediated phosphoprotein), thus inducing activation of the GPIIb/IIIa receptor and platelet aggregation.

➢ Active metabolites of the thienopyridine prodrugs (ticlopidine, clopidogrel and prasugrel) undergo covalent binding to the $P2Y_{12}$ receptor and are non-reversible, indirect platelet inhibitors.

➢ The newer drugs which directly act on $P2Y_{12}$ inhibitors (ticagrelor, cangrelor and elinogrel) leads to changes in the conformation of the $P2Y_{12}$ receptor, resulting in reversible, concentration-dependent inhibition of the receptor.

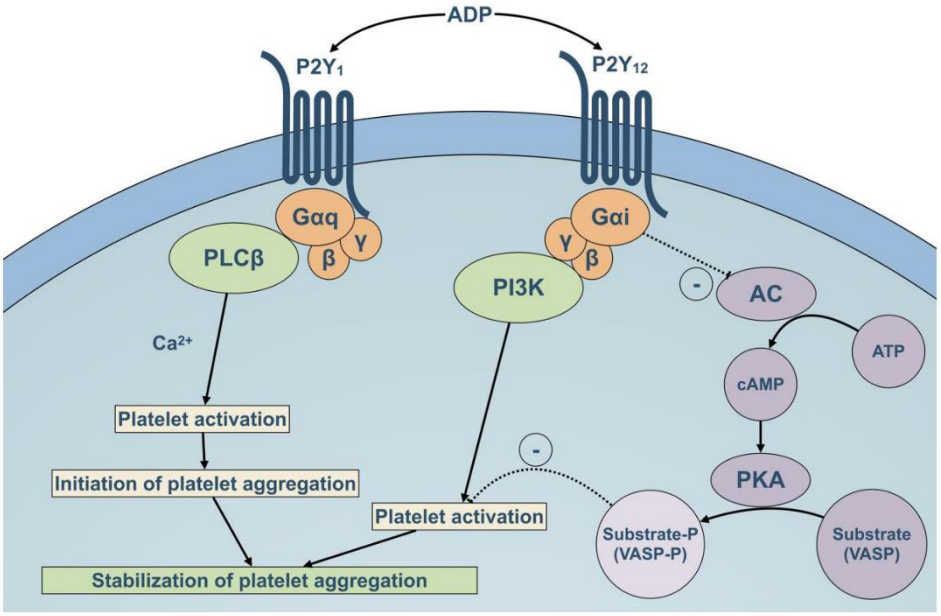

Figure No. 6: Pathway of $P2Y_{12}$ receptor through G-protein coupled receptor[11]

Patients with defective $P2Y_{12}$ receptor function [10][11]

Patients having a defective $P2Y_{12}$ receptor have a congenital bleeding disorder. A number of patients have been identified that shows decreased aggregation responses to ADP and low doses of other agonists such as collagen and thrombin. These patients show normal platelet shape change responses to ADP but have impaired abilities to inhibit adenylyl cyclase activity. While patients with defective $P2Y_{12}$ receptor function have dense granules that are normal in quantity and content, platelet release of granules is gradually decreased because of the potentiating effects of the $P2Y_{12}$ receptor on granule secretion.

CLOPIDOGREL [6][20]

Clopidogrel bisulphate (Plavix) acts as an inhibitor of ADP induced platelet aggregation which act by directly inhibiting the binding of ADP to its receptor and subsequently activation of the glycoprotein GPIIb/IIIa complex by ADP mediated pathway.

Mechanism of Action and Pharmacodynamic Properties [14]

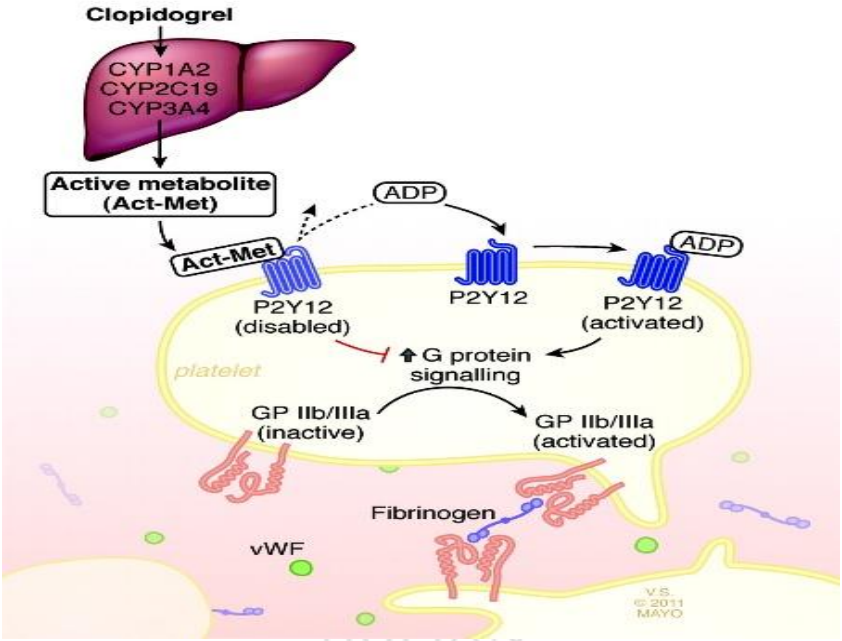

Figure No. 7: Mechanism of action of clopidogrel [17]

Clopidogrel is a prodrug, one of its metabolites acts as an inhibitor of platelet aggregation. A variety of medicines that inhibits platelet function are shown to decrease pathological events in people with cardiovascular atherosclerotic disease as seen in stroke or transient ischemic attacks, myocardial infarction, unstable angina or the necessity for vascular bypass or angioplasty. This indicates that platelets participate within the initiation and/or evolution of those events which inhibiting platelet function can reduce the event rate.

Act-Met permanently and non-reversibly disables the G protein−coupled platelet receptor known as $P2Y_{12}$. $P2Y_{12}$, undergoes activation by ADP, brings conformational change of the surface molecule GPIIb/IIIa. This change in conformation gradually increases the affinity of GPIIb/IIIa for the fibrinogen and VWF, hence allowing platelet aggregation. As such, activated clopidogrel-mediated disabling of this G protein−coupled receptor leads to diminished aggregation of platelets.[17]

Clopidogrel is metabolized by CYP450 enzymes to supply the active metabolite that inhibits aggregation of platelets. The active metabolite of clopidogrel selectively prevents the binding of ADP to its platelet $P2Y_{12}$ receptor and therefore the subsequently activating the glycoprotein GPII/IIIa complex by ADP mediated pathway, thereby inhibiting platelet aggregation. This process is irreversible.

- Platelets exposed to clopidogrel's active metabolite are affected for the rest of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists aside from ADP is additionally inhibited by blocking the amplification of platelet activation by released ADP.

- Platelet aggregation and bleeding time return to baseline values after treatment is discontinued, generally within 5 days.

Pharmacokinetics

Absorption: After single and repeated oral doses of 75 mg per day. Clopidogrel is rapidly absorbed. Main peak plasma levels of unchanged Clopidogrel (approximately 2.2-2.5 mg/mL after one 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%. Based on urinary excretion of clopidogrel metabolites**.**

Effect of Food: The effect of food on the bioavailability of the parent compound or active metabolite is currently not known.

***Metabolism*:** Clopidogrel is extensively metabolized by the liver. In vitro and in vivo, clopidogrel is metabolized consistent with two main metabolic pathways: one mediated by esterases and resulting in hydrolysis into its inactive acid derivative and one mediated by multiple cytochromes P450.

Elimination: After one, oral dose of 75 mg, clopidogrel features a half-life of roughly 6 hours. The elimination half-life of the inactive acid metabolite was 8 hours after single and repeated administration. In plasma and urine, the glucuronide of the acid derivative is additionally observed.

Indication and Uses:

Clopidogrel is preferred for the reduction of atherothrombotic events as follows:

• Recent MI:

Recent Stroke or Established Peripheral Arterial Disease For patients with a history of recent myocardial infarct (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to scale back the rate of a combined endpoint of latest ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

• Acute Coronary Syndrome:

For patients with non ST-segment elevation acute coronary syndrome (unstable angina/non Q-wave MI) including patients who are to be managed medically and people who are to be managed with percutaneous coronary intervention (with or without stem) or CABG, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

Contraindications:

The use of clopidogrel is contraindicated in the conditions as follows:

- Hypersensitivity to the drug product or any component of the product.
- Active pathological bleeding as seen in peptic ulcer or intracranial haemorrhage.

Adverse effects:

- The most frequent adverse drug reactions include haemorrhage and bleeding disorders including purpura, any rash, dyspepsia, abdominal pain and diarrhoea.
- Bleeding and clotting disorders including gastrointestinal haemorrhage, haemorrhagic ulcer and haemothorax.
- *Blood disorders:* agranulocytosis/ granulocytopenia, aplastic anaemia. neutropenia and thrombocytopenia.
- *GIT disorders*: Duodenal, gastric or peptic ulcer, gastritis.
- *Skin disorders*: Any rash and bullous eruption.

GP IIb/IIIa Receptor Antagonist [7] [15]

Glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$) serves as the receptor on platelets that binds plasma-borne adhesive proteins, such as fibrinogen and von Willebrand factor (vWF), to allow platelet aggregation. Aggregation of platelets is mediated by this pathway, regardless of the agonist that stimulates platelets and irrespective of the stimulus-response–coupling pathway that is used to activate GP IIb/IIIa to aggregate platelets. Agents which block this final common pathway by obstructing the binding of adhesive proteins to GP IIb-IIIa, termed GP IIb/IIIa antagonists, are currently considered the most powerful specific inhibitors of platelet participation in acute thrombosis. However, the haemostatic function of platelets is also dependent on this pathway. Thus, this novel form of antiplatelet therapy comes with potential safety risks, yet the first fruits of the benefits of this therapeutic approach have begun to emerge.

GP IIb/IIIa receptors bind fibrinogen molecules, which form bridges between adjacent platelets which facilitate platelet aggregation. Inhibitors of GP IIb/IIIa receptors also bind to these receptors, inhibits the binding of fibrinogen and thus preventing platelet aggregation. Although the principal mechanism for platelet aggregation is the binding of fibrinogen to GP IIb/IIIa receptors, other adhesive GPs including fibronectin, von Willebrand factor (vWF) and vitronectin also binds to these receptors.[12]

Various antagonists of GP IIb/IIIa are currently receiving considerable attention from the pharmaceutical industry and clinical cardiologists, and they are being studied in a variety of clinical settings. The first of these agents, the monoclonal antibody abciximab, has been approved for use in percutaneous coronary intervention (PCI). More recently, 2 parenteral antagonists have also been approved: tirofiban, a nonpeptide, for treatment of acute coronary syndromes and eptifibatide, a peptide, for use in PCI as well as acute coronary syndromes.

Table No. 2: Classification of glycoprotein IIb/IIIa Antagonists [7]

S. No.	Type	Name	Route
1	Monoclonal antibodies	Abciximab	Parenteral
2	Peptides	Eptifibatide Tirofiban	Parenteral Parenteral
3	Small molecules	Lamifiban Fradafiban Xemilofiban Orbofiban	Parenteral Parenteral Oral Oral

ABXICIMAB [8][20]

Abciximab, Fab fragment of the chimeric human monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and thus prevents the aggregation of platelets. The rapid onset and offset of GP IIb/IIIa antagonist action to inhibit extensively platelet aggregation differentiates them from oral agents.

Mechanism of Action

Abciximab acts by binds to the GPIIb/IIIa receptor (a member of the integrin family of adhesion receptors) of activated platelet and therefore major platelet surface receptor involved in platelet aggregation. Abciximab mainly inhibits aggregation of platelets by preventing the binding of fibrinogen, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets. The mechanism of action is assumed to involve stearic hindrance and/or conformational effects to stop access of huge molecules to the receptor instead of direct interaction with the RGD (arginine glycine-aspartic acid) binding site of GPIIb/IIIa.

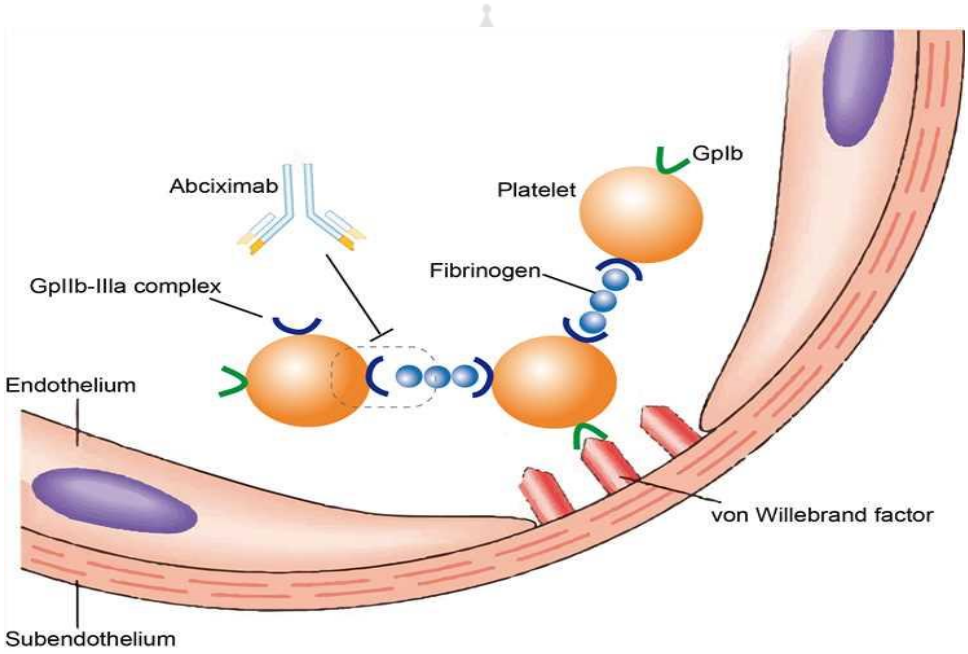

Figure No. 8: Mechanism of action of abciximab

Pharmacokinetics

Following intravenous bolus administration, free plasma concentrations of Abciximab decrease rapidly with an initial half-life of less than 10 minutes and a second phase half-life of about half an hour, probably related to rapid binding to the platelet GPIIb/IIIa receptors.

Platelet function generally recovers over the course of 2 days, although Abciximab remains within the circulation for more than 15 days in a platelet bound slate. Intravenous administration of a 0.25 mg/kg bolus dose of abciximab followed by continuous Infusion of 10 microg/min produces nearly constant free plasma concentration throughout the infusion. At the termination of the infusion period, free plasma concentrations fall rapidly for about six hours then decline at a slower rate.

Indications and Usage:

Abciximab is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.

Abciximab is meant to be used with aspirin and heparin.

Contraindications:

Because Abciximab may increase the risk of bleeding, Abciximab is contraindicated in the following Clinical situations:

- Active internal hemorrhage.
- Gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance.
- Cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit.
- Bleeding diathesis.
- Administration of oral anticoagulants within seven days unless prothrombin time is ≤1.2 times control.
- Thrombocytopenia (< 100,000 cells/μL).
- Intracranial neoplasm, arteriovenous malformation or aneurysm.
- Severe uncontrolled hypertension.

- Presumed or documented history of vasculitis.

- Use of intravenous dextran before percutaneous coronary intervention. or intent to use it during an intervention.

Adverse effects

Cardiovascular system: Bleeding, intracranial hemorrhage and stroke, thrombocytopenia.

GI system: diarrhea, gastroesophageal reflux.

Nervous system: anxiety, dizziness.

CONCLUSION

Antiplatelet drugs have the major role in heart disease, problems with blood circulation, abnormal heartbeat and congenital heart defect. Antiplatelet drugs are effective for prevention of platelet-rich arterial thrombi that is formed under high-shear conditions. Antiplatelet agents are also successful for the prevention of fibrin-rich thrombi that form under low-shear conditions, such as VTE and left atrial appendage thrombi that form in patients with atrial fibrillation, but for these indications, antiplatelet drugs are less effective than anticoagulants. The efficacy of antiplatelet drugs for thrombosis prevention is explained by their ability to block well-characterized pathways involved in platelet activation and aggregation. It is these actions that also lead to the major side effect of antiplatelet therapy, which is bleeding. Clopidogrel is safe and well tolerated. The clopidogrel v/s Aspirin in patients at risk of ischemic events trial has found clopidogrel recipients to have a usually lower annual risk of primary ischemic events than aspirin recipients. Abciximab extensively used in interventional cardiology for the treatment of unstable angina and as an adjunct therapy following percutaneous coronary intervention. Abciximab is available intravenously only.

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