Our body employs many mechanisms in order to maintain homeostasis. One particular term that is worth our attention when it comes to tackling homeostasis is hemostasis or the body’s tendency to prevent the contents of our intravascular compartment (blood) to leak into different compartments within the body and into the external environment. This term also refers to the body’s maintenance of the smooth flow of blood within the blood vessels. Hemostasis consists of intricate interdependent mechanisms. These have been the focus of many pharmacological studies that aim to address certain blood disorders. Read everything about it here.
Generally, hemostasis is composed of 4 main processes that eventually lead to the halting of the leakage of blood from the blood vessels.

1. **Vascular constriction** (from spasms due to damage)
2. **Platelet plug formation**
3. **Blood clotting**
4. **Fibrous restructuring** of the blood clot

Under normal circumstances, the endothelium of the blood vessels is an anticoagulant in nature. However, a break in its integrity triggers its tendency to become procoagulant, leading to hemostatic mechanisms. Any break in the surface of the endothelium exposes collagen and von Willebrand factor which are substances that promote platelet adherence to the area.

Once platelets are aggregated in the site of injury, their products during initial activation such as thromboxane A\(_2\) (TXA\(_2\)), adenosine diphosphate (ADP) and serotonin (5-HT) are released. These substances are responsible for the vasoconstriction and further platelet recruitment and activation. Receptors on the platelets’ surface, particularly the \(\alpha_{IIb}\beta_{IIIa}\) integrin (IIb/IIIa) receptors also change in conformation during activation, making them more receptive to additional platelets and fibrinogen.

The formed clot or thrombi can take on either 2 forms. **White thrombi** are generally made up of platelets and are commonly seen in blood vessels with high flow velocities such as the arteries. On the other hand, **red thrombi** consist of more fibrin and trapped red blood cells than platelets and are commonly found in low-pressure vessels such as the veins. These are usually the cause of deep vein thromboses.
After the initial blood clot is formed, further conversions are set off. First off, the conversion of prothrombin to thrombin in the presence of activated platelets, prothrombin activator and calcium ions on the injured site happens. Thrombin, in turn, cleaves fibrinogen to form fibrin.

Fibrinogen and fibrin are actually what make blood coagulable. Fibrinogen is produced by the liver. Its absence in other body fluids such as the lymph and interstitial fluid confers their inherent uncoagulable states. The activated form, fibrin, serves in the formation of a meshwork that reinforces the formed blood clot.

The newly reinforced blood clot is now able to trap in more platelets and red blood cells. After a few minutes from the formation, the blood clot would then contract, thanks to some factors released by the activated platelets. This extracts a factor-free fluid from the clot called serum. This also pulls the edges of the clot that are apposed to the vessel wall, thereby contracting the breakage on the site.

The clotting cascade

Once a platelet plug is formed, the same substances that are produced from the platelets continue to act and set off the clotting cascade, a series of reactions that lead to the coagulation of blood.

It all starts off with the formation of thrombin with the help of the substance that limits the whole clotting cascade, the prothrombin activator. This is produced in two different but interconnected ways that eventually lead to the activation of prothrombin. These pathways are basically a series of reactions converting different zymogen factors into potent clotting factors.
Extrinsic pathway

Damaged endothelium and tissues release tissue factor, which is then later used along with factor VII and calcium ions to activate factor X. The now activated factor X (factor Xa) combines with phospholipids coming from the tissue factor and platelets, and with factor V to form prothrombin activator complex which is responsible for the cleavage of prothrombin to thrombin in the presence of calcium ions.

Intrinsic pathway

The exposure of blood to collagen (or glass in vitro) triggers the activation of factor XII to factor XIIa. This also causes the platelets to express phospholipids that contain platelet factor 3 (pf3). Factor XIIa along with high-molecular-weight kininogen and the enzyme prekallikrein activates factor XI. Factor Xla activates factor IX. In the presence of factor VIIIa, and phospholipids and factor III coming from the platelets, factor IXa cleaves factor X. Factor Xa binds with factor V and phospholipids to form the same prothrombin activator complex produced in the extrinsic pathway.

Fibrinolysis

Once the injury in the blood vessels is healed, there would not be any need for the presence of a blood clot. This is where fibrinolysis comes in handy. This is set off by cleaving the zymogen plasminogen into a potent clot remodeling and degrading agent plasmin with the help of tissue plasminogen activator or t-PA. This mechanism is inherently inhibited under normal circumstances in the presence of plasminogen activator inhibitor or that is released by the endothelium.
Conditions that Affect Coagulation

Excessive bleeding conditions

Excessive bleeding is essentially caused by the lack of any of the clotting factors and substances involved in hemostasis. Conditions under this are categorized into three:

1. **Vitamin K deficiency**: Liver disease, in neonates with absent vitamin K producing intestinal flora, fat malabsorption
2. **Hemophilias**: Classic hemophilia or hemophilia A (factor VIII deficiency), Christmas disease or hemophilia B (factor IX deficiency)
3. **Thrombocytopenia**

Hypercoagulable conditions

As mentioned before, a problematic thrombus could form if coagulation is not regulated. It causes more trouble when it lodges to remote areas in the form of an **embolus**. There are two known causes for thrombus formation to happen:

1. **Roughened endothelium**: Arteriosclerosis, infection or trauma
2. **Stasis of blood**: Immobility, varicosities

Pharmacology: Anticlotting agents

![Diagram of anticlotting agents]

**Antiplatelets**
Antiplatelet drugs are targeted to manipulate the substances that are found outside the platelet and interact with its membrane receptors, those that are found within the platelet but interact with its membrane receptors and those that are produced and remain inside the platelet.

- **Adhesion**: GPIIb/IIIa (called αIIbβ3 in Europe) allow “adherence” directly to collagen
- **Aggregation**: GPIIb/IIIa (called αIIbβ3 in Europe) cross-links to other platelets as well as binds to vWF
- **Release**: Thromboxane A2 and ADP is released when platelets bind to damaged tissue

**Aspirin**

As mentioned a while ago, TXA₂ is produced from platelets and is helpful in causing platelet aggregation by changing the structure of the platelets. Its inhibition by aspirin is made possible by the irreversible acetylation of cyclooxygenase, an enzyme needed by the platelets and tissues to produce TXA2. Effects of aspirin are eliminated once a new set of platelets are produced in the body. This usually takes 3–7 days. This drug is known to reduce the occurrence of myocardial ischemia, stroke, and peripheral arterial ischemia.

**Glycoprotein IIb/IIIa inhibitors**

*Abciximab, Eptifibatide, and Tirofiban* are drugs that inhibit the clumping of platelets by acting on the IIb/IIIa receptors on the surface of platelets. This, in turn, inhibits the binding of these receptors to fibrinogen, fibronectin, and von Willebrand factor, all of
which facilitate platelet adhesion and aggregation. This is used to treat acute coronary syndromes and is given to patients after angioplasty to prevent restenosis.

## ADP inhibitors

Since ADP is needed for platelet aggregation as well, one way to inhibit aggregation is to keep this substance unbound to platelets. **Clopidogrel, Prasugrel,** and **Ticlopidine** achieve this by irreversibly binding to ADP receptors on the platelets after their conversion in the liver. **Ticagrelor,** a relatively new drug does not require hepatic conversion in order to be inactive. Unlike the previously mentioned ADP inhibitors, it works by reversibly inactivating the IIb/IIIa receptors. ADP inhibitors are given to prevent transient ischemic attacks, stroke, and restenosis of stents.

## PDE/Adenosine uptake inhibitors

Cyclic guanosine monophosphate or cGMP and adenosine are naturally occurring platelet inhibitors. Of course, an increase in their amounts in the bloodstream would result in a delay in clotting. This is possible in the presence of Dipyridamole and Cilostazol which blocks the action of phosphodiesterase, an enzyme that metabolizes cGMP leading to their decreased amount. These drugs also inhibit the uptake of adenosine, keeping them available to the platelets. They are given in combination with other drugs as maintenance for heart valve replacement and stroke prevention. Cilostazol, in particular, is given for intermittent claudication.

### Antiplatelets: Uses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Reduce subsequent MI, stroke, peripheral arterial ischemia</td>
</tr>
<tr>
<td>Eptifibatide, tirofiban</td>
<td>Prevent restenosis after angioplasty, used in ACS</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Prevent TIA’s, strokes; reduce restenosis of stents</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Adjunct to warfarin in patients with heart valve replacement</td>
</tr>
<tr>
<td></td>
<td>Adjunct to aspirin in patients for secondary prevention of stroke</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Treat intermittent claudication</td>
</tr>
</tbody>
</table>

### Antiplatelets: Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Bleeding (0.3 %)</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Bleeding (0.5 %), severe neutropenia (1 %), TTP (rare)</td>
</tr>
<tr>
<td>Eptifibatide, tirofiban</td>
<td>Bleeding, thrombocytopenia (chronic use)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Bleeding (&lt; 1 %)</td>
</tr>
</tbody>
</table>
Pharmacology: **Anticoagulants**

**Heparins**

Under normal circumstances, antithrombin, an endogenous anticoagulant, inhibits the coagulation by forming complexes with clotting factors IIa, IXa, and Xa. However, in the presence of Heparin, this reaction is sped up by a thousand-fold. This is due to the exposure of more active sites of antithrombin after binding with Heparin. Working as a cofactor, Heparin is released from the complex unchanged, ready to bind with more antithrombin. Unfractionated Heparins are neutralized by protamine and are known to cause Heparin-induced thrombocytopenia and thrombosis (HITT), and osteoporosis. For this reason, newer low molecular weight Heparins (enoxaparin, dalteparin, and tinzaparin) are developed.

**Direct thrombin inhibitors**

*Bivalirudin, Argatroban, and Dabigatran* bind to the active site of thrombin, thereby inhibiting its action. These drugs are favorable choices for patients who have had HITT.

**Warfarin**

This and other coumarin derivatives inhibit coagulation by keeping prothrombin, and clotting factors VII, IX and X inactive. This is done by prohibiting vitamin K epoxide reductase and the vitamin-K dependent carboxylation of the glutamate residues in the said substrates for coagulation. These drugs usually have an 8- 12-hour delay in onset of action. However, their effects depend on the rate of replacement of the inactive substrates. This may take up to 60 hours.

**Direct factor Xa inhibitors**

*Rivaroxaban, Apixaban, and Edoxaban* act on the point where the extrinsic and intrinsic pathways converge. These drugs are used for stroke prevention in non-valvular atrial fibrillation, deep vein thrombophlebitis prevention in post-op hip and knee surgery patients and soon for aspirin replacement.
Pharmacology: Thrombolytics

Streptokinase, Urokinase, Alteplase, Retepiease, and Tenecteplase lyse thrombi by facilitating the rapid formation of plasmin from plasminogen. These drugs generally have a systemic effect, lysing all thrombi that may come in their way. Because of this mechanism, patients receiving thrombolytics are at high risk for intracranial hemorrhage and bleeding. The use of these drugs requires meticulous evaluation. Before percutaneous coronary interventions were used for myocardial infarction, thrombolytics were the first-line management for cardiac perfusion problems.

Pharmacology: Procoagulants

Vitamin K

Vitamin K is a fat-soluble substance in green leafy vegetables that assist in the post-ribosomal activation of prothrombin and factors VII, IX, and X. This vitamin may also be synthesized in the intestines by normal flora available in parenteral and oral forms. Vitamin K is given to reverse the effects of Warfarin and to address vitamin K deficiency in certain cases.

Replacement factors

In cases where there is a deficiency in the clotting factors, such as in hemophilia, the more logical treatment would be the use of replacement factors. This may be in the form of plasma-derived factor concentrates that may have been heat- or detergent-treated to prevent transmission of blood-borne diseases such as hepatitis and HIV infection. Recombinant and lyophilized replacement factors are also available. Mixtures of clotting factors and monoclonal antibodies (idarucizumab) are already introduced in the latest treatment plans.

Vasopressin agonists

Desmopressin acetate, an anti-diuretic hormone analog can work as a procoagulant by increasing factor VIII activity. This can be used as a prophylaxis during minor surgeries or tooth extractions. It can also work in combination with factor replacement for hemophilia A.

Antiplasmin agents

Aminocaproic acid and tranexamic acid exert their anthrombolytic effect by keeping the active form of plasminogen, plasmin from forming. These drugs also increase the formation of von Willebrand factor and factor VIII. Antiplasmin agents are used as an adjunct to hemophilia therapy and as treatment and prophylaxis for post-op bleeding.

Review Questions

The correct answers can be found below the references.

1. Basing from the formation of serum during clot formation and stabilization, how would you compare it from plasma?

   A. Unlike plasma, the serum does not contain any clotting factors and other
substrates for coagulation.
B. Serum and plasma are essentially the same in composition.
C. The serum is relatively more coagulable especially if exposed to collagen in vivo or wet glass in vitro.
D. The serum is the fluid contained within the clot while plasma composes the liquid compartment of blood.

2. What is the primary reason why Heparin is given along with Warfarin during anticoagulant therapy?

   A. Both drugs work synergistically in achieving anticoagulation.
   B. Benefits of Heparin are achieved while waiting for Warfarin to work after a few days.
   C. The use of Heparin in conjunction with Warfarin decreases the incidence of Heparin-induced thrombocytopenia and thrombosis.
   D. Heparin automatically assumes the anticoagulant role once the effects of Warfarin wane.

References


Correct answers: 1A, 2B

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