Chemical Mediators of Inflammation

*Chemical mediators* are substances that are responsible for many of the inflammatory events. According to their origin, they are either

1. **Plasma-derived** (e.g. complements & kinins): these are present in plasma in precursor forms and need to be activated to function.
2. **Cell-derived**: either
   a. **ready-made** within intracellular granules (e.g., histamine in mast cell granules) or
   b. **synthesized on need** (e.g., prostaglandins, cytokines) in response to a stimulus. The major cellular sources are platelets, neutrophils, monocytes/macrophages, and mast cells.

Most mediators perform their job by binding to specific receptors on target cells. Most mediators have the potential to cause harmful effects; that is why their biological actions are short-lived or they are inactivated or degraded rapidly by other substances. One mediator can stimulate the release of other mediators. The secondary mediators may be have identical or similar action to the initial mediators but may have opposing activities.

**General effects of chemical mediators include:**

1. **Vasodilatation**: Histamine, Prostaglandin's (PGE2), Nitric oxide
2. **Increased Vascular Permeability**: Histamine, Complement components (C3a, C5a), Bradykinin, Leukotrienes C4, D4, E4, Platelet activating factor
3. **Chemotaxis, leukocytes activation**: C5a, leukotrienes B4, bacterial products
   - chemokines (IL-8)
4. **Fever**: IL-21, IL-6, TNFα, prostaglandins
5. **Pain**: prostaglandins, bradykinin
6. **Tissue damage**: neutrophils & macrophage lysosomal enzymes, oxygen metabolites, nitric oxide

The more important mediators of acute inflammation are

**A-PLASMA FACTORS:**

1. **Products of the complement system.**
   A cascade system of plasma proteins that can be activated by:
• Antigen- Antibody complexes along the classical pathway.
• Bacterial endotoxins, complicated polysaccharides and aggregated globulins along the alternate pathway.

Complement components with inflammatory activity include:
   a- \textbf{C3a}, which increases vascular permeability.
   b- \textbf{C5a}, which increases vascular permeability and is chemotactic to most leukocytes.
   c- \textbf{C3b} and \textbf{C3bi}, which are opsonins, recognizing receptors on neutrophils, monocytes and eosinophils, thus, important for phagocytosis.
   d- \textbf{C5b6789}, the membrane attack complex that lyses cells and stimulates leukotrine synthesis and production of reactive oxygen metabolites by leukocytes.

2- \textbf{The Kinin system.}
Surface activation of Hageman factor produces clotting factor XIIa, which converts plasma prekallikrein into kallikrein. \textbf{Kallikrein} has chemotactic activity, causes neutrophil aggregation, and cleaves high molecular weight kininogen in plasma to produce Bradykinin. \textbf{Bradykinin} is a potent permeability factor, can cause vasodilatation, stimulates contraction of extra-vascular smooth muscle, and when injected into skin causes pain.

3- \textbf{Products of the clotting and fibrinolytic systems.}
The clotting system is also activated by Hageman factor, culminates in the conversion of fibrinogen into fibrin by the action of thrombin. Activation of the fibrinolytic system results in the formation of plasmin, an active proteolytic enzyme, which can activate the complement system, and splits fibrin into degradation products that can increase vascular permeability and are chemotactic.

\textbf{B- TISSUE FACTORS.}
\textbf{1-Vasoactive amines.}
Histamine and serotonin are found in mast cells, basophils and platelets can cause vasodilatation and increased vascular permeability.

\textbf{2- Arachidonic acid metabolites.}
The inflammatory prostaglandins (produced by the cycloxygenase pathway) and leukotrienes (produced by the lipooxygenase pathway) include:
   • \textbf{PGI2 (prostacyclin)} and \textbf{PGE2}, which cause vasodilatation.
   • \textbf{ThromboxaneA2} which cause vasoconstriction.
- **Leukotrienes C4, D4 and E4**, which are produced by mast cells and cause increased vascular permeability and vasoconstriction.
- **Leukotriene B4**, which is produced by neutrophils, and is a potent chemotactic factor to other neutrophils and eosinophils.

**Suppressors of cyclooxygenase activity (aspirin, nonsteroidal anti-inflammatory drugs, and COX-2 inhibitors [coxib]) reduce inflammation in vivo**

3- **Platelet activating factor (PAF)**
Produced by mast cells and other leukocytes induce platelet aggregation and release reaction, bronchoconstriction, vasodilatation, increased vascular permeability, increased leukocyte adhesion, and leukocyte chemotaxis.

4- **Cytokines.**
These are polypeptide factors produced by activated macrophages, lymphocytes and other cell types.

*Interlukin-1 (IL-1)* and *Tumor necrosis factor (TNF)* have these shared effects:
  a- Endothelial activation
  b- They induce systemic acute phase responses including fever, neutrophilia and haemodynamic effects.
  c- They induce fibroblastic proliferation, collagen formation and collagenase synthesis.

*Interlukin-8* is a chemokine induced in macrophages and endothelial cells by other cytokines like IL-1 and TNF. It is a powerful chemoattractant of neutrophils.

5- **Nitric oxide.**
Activated macrophages and endothelial cells produce nitric oxide. It causes vasodilatation, inhibits platelet aggregation and adhesion, and can act as a free radical becoming cytotoxic to certain microbes, tumor cells and other tissue cells. It has been implicated in a variety of inflammatory diseases including septic shock.

6- **Lysosomal constituents of leukocytes.**
- Neutrophils contain two types of granules:
  a- Specific: containing lactoferrin, lysozyme, alkaline phosphatase and collagenase.
  b- Azurophilic: containing myeloperoxidase, cationic proteins, acid hydrolases and neutral proteases.

Monocyte granules contain acid hydrolases, collagenase, elastase and plasminogen activator.
**Cationic proteins** increase vascular permeability and cause chemotaxis. **Neutral proteases** degrade extracellular matrices, and activate the complement system.

7. **OXYGEN-DERIVED FREE RADICALS**

Oxygen-derived free radicals may be released extracellularly from leukocytes after exposure to microbes, chemokines, and immune complexes.

Their physiologic functions:

A-is to destroy phagocytosed microbes.

B-Extracellular release of low levels of these potent mediators can amplify the inflammatory response.