Mediators of inflammation

Types of chemical mediators:

1. Cell Derived mediators:
   - A. Preformed mediator in secretory granules:
     Histamine, Serotonin
   - B. Newly synthesized:
     Prostaglandins, Leukotrines, Platelet Activating Factor, ROS, NO
     Cytokines, Neuropeptides
2. Plasma protein derived mediators:
   - A. Complement system
   - B. Kinin system
   - C. Factor XII (Hageman)

Histamine:

Function: Arteriolar dilatation, increased vascular permeability, endothelial activation
Source: Mast cells, Basophils, Platelets
Stimuli: Physical injury, IgE binding to Fc, C3a and C5a, Neuropeptides
Certain Leukocytes (e.g. IL-1, IL-8), Leukocyte-derived histamine-releasing protien

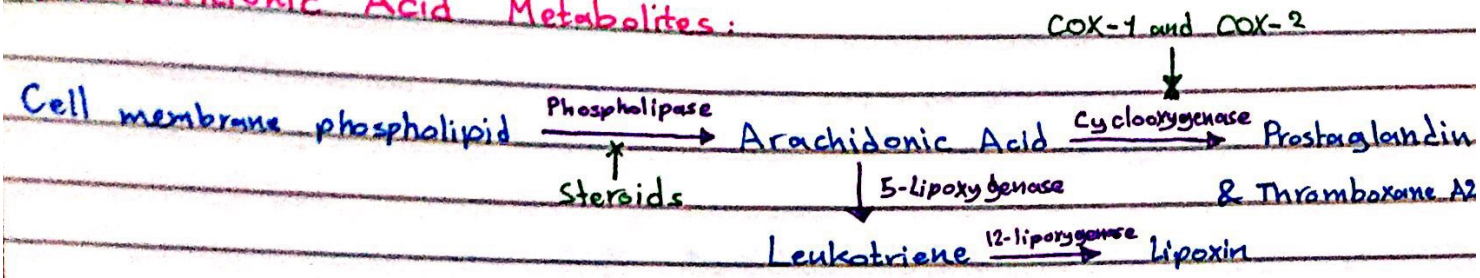
Serotonine:

Source	: Function
Platelet	: Vasoconstriction during clotting
Neurons	: Neurotransmitter
Enterochromaffin	: Regulates intestinal motility

Platelet Activation Factor (PAF)

Function: Bronchoconstriction, Vasodilatation, Increase vascular permeability, Stimulation of platelets, (leukocyte adhesion, chemotaxis, degranulation, oxidative burst)
Induce most of the reactions of inflammation: Leukocyte adhesion, Chemotaxis Degranulation, intracellular killing, stimulates synthesis of other mediator
Source: Neutrophils, Monocytes, Basophils, Endothelial cells

Arachidonic Acid Metabolites:



* Thromboxane A2 : Vasoconstriction, promotes platelets aggregation
* Lipoxin A_4, B_4 : Inhibition of inflammation
* Leukotrines : (Produced by 5-lipoxygenase)
  - C_4, D_4, E_4 : Vasoconstriction, Increase vascular permeability, Bronchospasm
  - B_4 : Chemotaxis, leukocyte adhesion (and activation)
* Prostaglandins : (Produced by cyclooxygenase)
  - PGE_1 : Vasodilatation
  - PGI_2 : Vasodilatation, Inhibits platelets aggregation, Increase vascular permeability
  - PGD_2, PGE_2 : Vasodilatation, increase vascular permeability
  - PGE_2 : also produce Pain and Fever
  - PGC_4, PGD_4, PGE_4 : smoot muscles contraction

Cytokines :

* Chemokines : Leukocyte attraction (chemotaxis) and activation
* Interleukins : TNF, IL-1 : Fever, endothelium activation

TNF, IL-1, IL-6 :

Local : Endothelial activation (increase expressing of E-selectin)

Systemic : Fever, Hypotention (shock), Metabolic abnormalities (e.g. Insulin resistance)

Reactive oxygen species (ROS)

Function : Destruction of phagocytosed microbes and necrotic cell

Source : Neutrophils and activated macrophages

Nitric Oxide :

Function : Endothelial cells → Vasodilatation
Macrophages → Cytotoxic metabolite

Suppresses acute inflammation :
A. PAF antagonist
Reduction of leukocyte recruitment

Lysosomal enzymes of Leukocytes:

Acid Proteases: active only within phagolysosomes

Neutral proteases: active in extracellular matrix causing their destruction

Neuropeptides: Ex. substance P

Function: Transmit pain signals, Regulate vessel tone, Modulate vascular permeability

Source: Nerve Fibers

Plasma protein derived mediators

Complements:

C3a, C5a: (Anaphylatoxins) 1. mast cell activation → vasodilatation
2. leukocyte chemotaxis and activation (Neutrophils)

C3b: Opsonization

C5b-9: Membrane attack complex (MAC)

Kinin:

Bradykinin: increased vascular permeability, Vasodilatation, smooth muscle cont. Pain

Kallikrein: chemotactic activity, Potent activator of Hageman factor

Hageman factor (XII factor):

Pathway
- Activated upon exposure to subendothelial or tissue collagen / Contact activated platelet
- Activates: Complement system, kinin system, Coagulation and fibrinolytic system

Cardinal Signs

A. Redness (rubor) and warmth (calor) → Vasodilatation → key mediators are histamine, prostaglandins, and bradykinin

B. Swelling (tumor) → Exudation post capillary venules → key mediators are histamine and tissue damage

C. Pain (dolor) → Sensitization of nerve endings → Bradykinin and PGE_2

D. Fever → TNF and IL → Hypothalamus → Increased PGE_2

Role of mediators in Different Reactions of Inflammation

Vasodilatation (Redness and warmth):

Key mediators: Histamine, Bradykinin, Prostaglandins

Other mediators: PAF, Nitric Oxide

Increased vascular permeability (Swelling):

Key mediators: Histamine, Tissue damage

Other mediators: Serotonin, Bradykinin, Leukotrienes (C_4, D_4, E_4), PAF, Substance P

Chemotaxis, leukocyte recruitment and activation

TNF, IL-1, Chemokines, $C3a$, $C5a$, Leukotriene B_4, Bacterial products

Fever:

TNF, IL-1 → Hypothalamus → PGE_2

Pain:

Bradykinin, PGE_2

Tissue damage:

ROS, NO, lysosomal enzymes of leukocytes