

Other Mediators of Inflammation

Platelet-activating factor · Coagulation products · Kinins · Neuropeptides

Inflammatory mediators: mechanisms and clinicopathologic interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning outcomes

- Classify platelet-activating factor, coagulation products, kinins, and neuropeptides by origin.
- Trace their documented effects on vascular responses, platelets, pain, and inflammatory regulation.
- Distinguish established mediator actions from tentative causal associations.

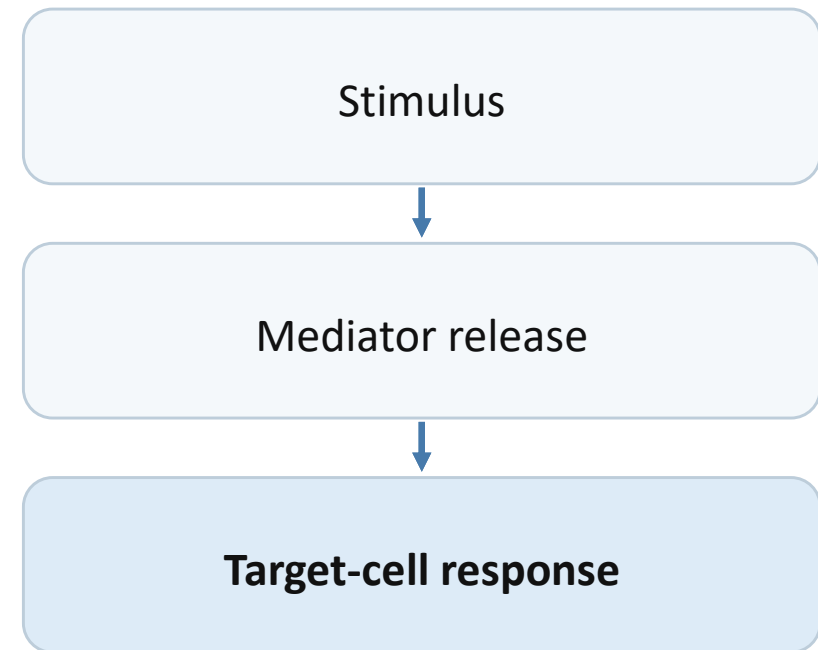
Origins

Mechanisms

Evidence

Inflammatory mediators initiate and regulate responses

- Inflammatory mediators are substances that initiate or control inflammation.
- Different mediators evoke distinct, partly overlapping components of the response.
- The biologic response depends on mediator production, targets, and termination.



Four additional mediator systems

- Platelet-activating factor (PAF): Phospholipid-derived mediator.
- Coagulation products: Thrombin, protease-activated receptors, and possible fibrinopeptide effects.
- Kinins: Vasoactive peptides formed from plasma proteins.
- Neuropeptides: Neural and leukocyte-associated regulatory peptides.

PAF

Coagulation
products

Kinins

Neuropeptides

Cellular and plasma-derived mediators differ

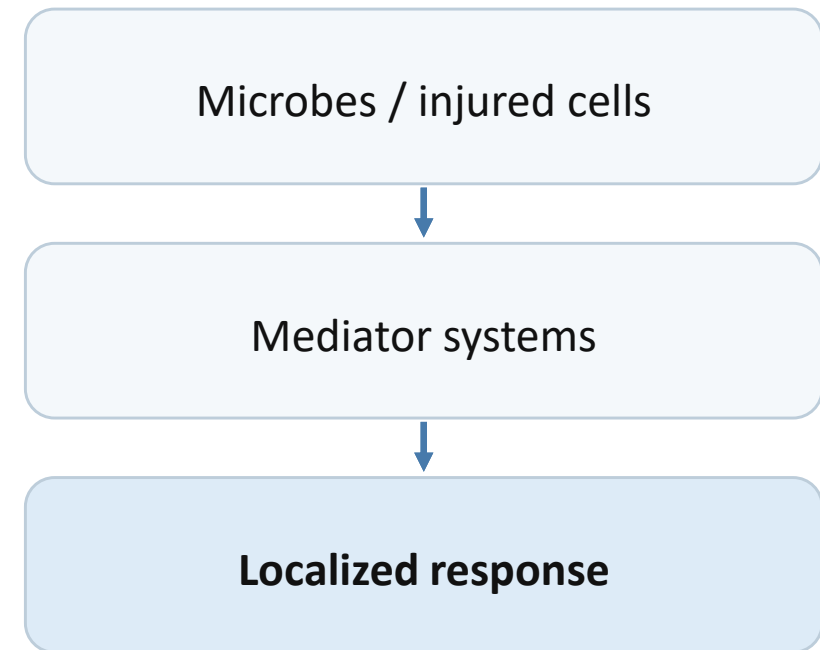
- Cells may rapidly release stored products or synthesize mediators following stimulation.
- Plasma protein pathways often require proteolytic activation of inactive precursors.
- PAF and neuropeptides have cellular sources; Kinins derive from circulating substrates.

Cellular mediators

Plasma-derived
mediators

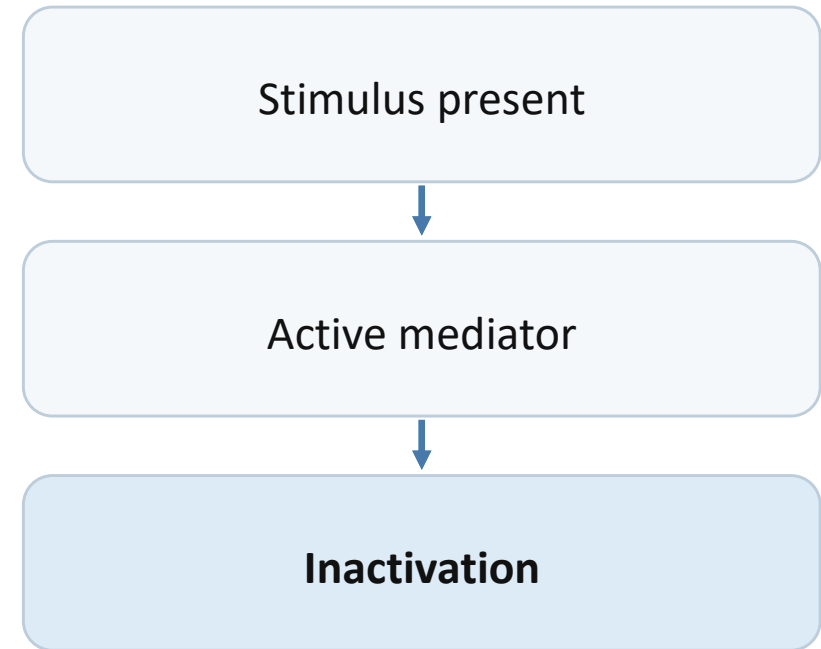
Tissue injury triggers mediator generation

- Microbial products and substances released from injured or necrotic cells can initiate mediator responses.
- Production is normally concentrated where initiating stimuli are present.
- The same tissue injury may activate inflammatory and coagulation pathways.



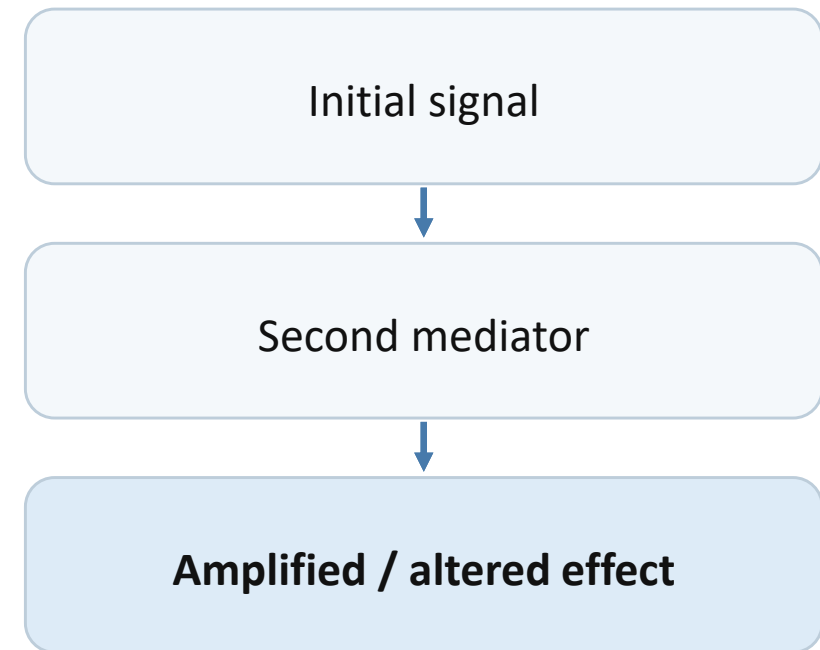
Mediator activity is deliberately transient

- Most mediators have short half-lives or are rapidly degraded, scavenged, or inhibited.
- Short-lived activity helps prevent persistence after removal of an offending stimulus.
- Bradykinin is a clear example because kininase rapidly inactivates it.



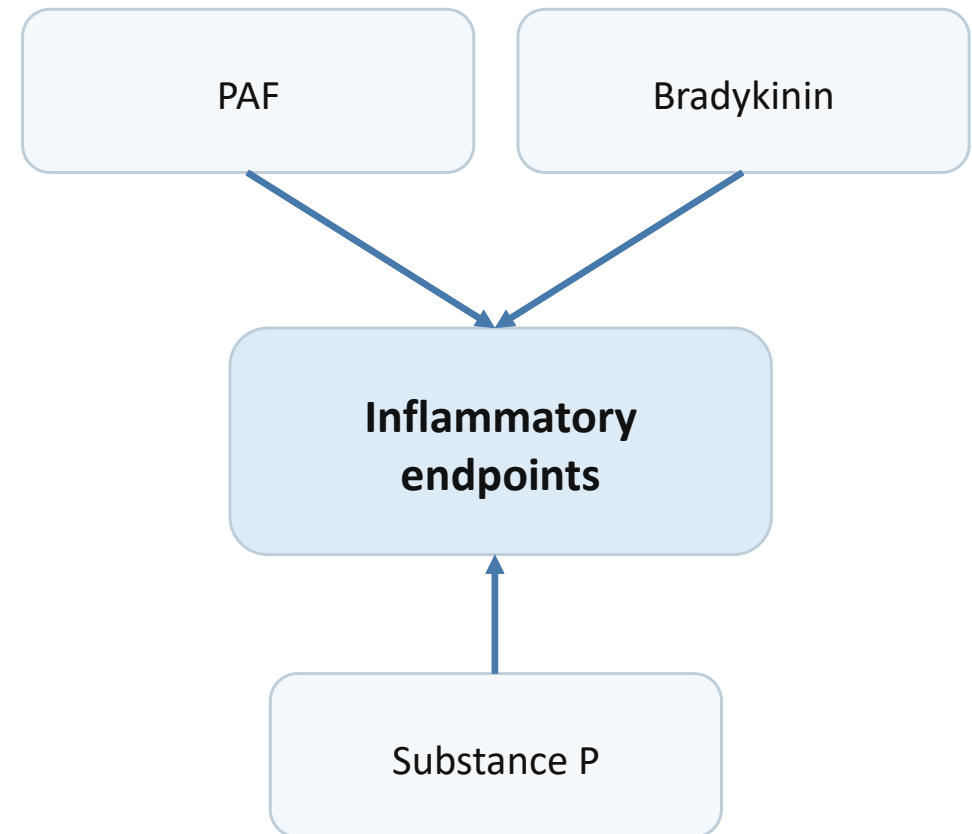
One mediator can induce secondary mediators

- A mediator can stimulate cells to release additional inflammatory signals.
- Secondary mediators may amplify, modify, or oppose the original effect.
- The source describes complement-driven histamine release and TNF-driven endothelial mediator production.



Redundancy stabilizes inflammatory responses

- Several mediators can converge on the same physiologic endpoint.
- Vascular leakage and pain each have more than one mediator.
- That redundancy makes the protective response robust.



Mechanistic orientation: Source to effect

- Identify the origin of each mediator before attributing a function.
- Distinguish directly described functions from hypothesized pathway effects.
- Use the physiologic endpoint—edema, pain, airway response, or immunoregulation—to interpret each pathway.

Origin

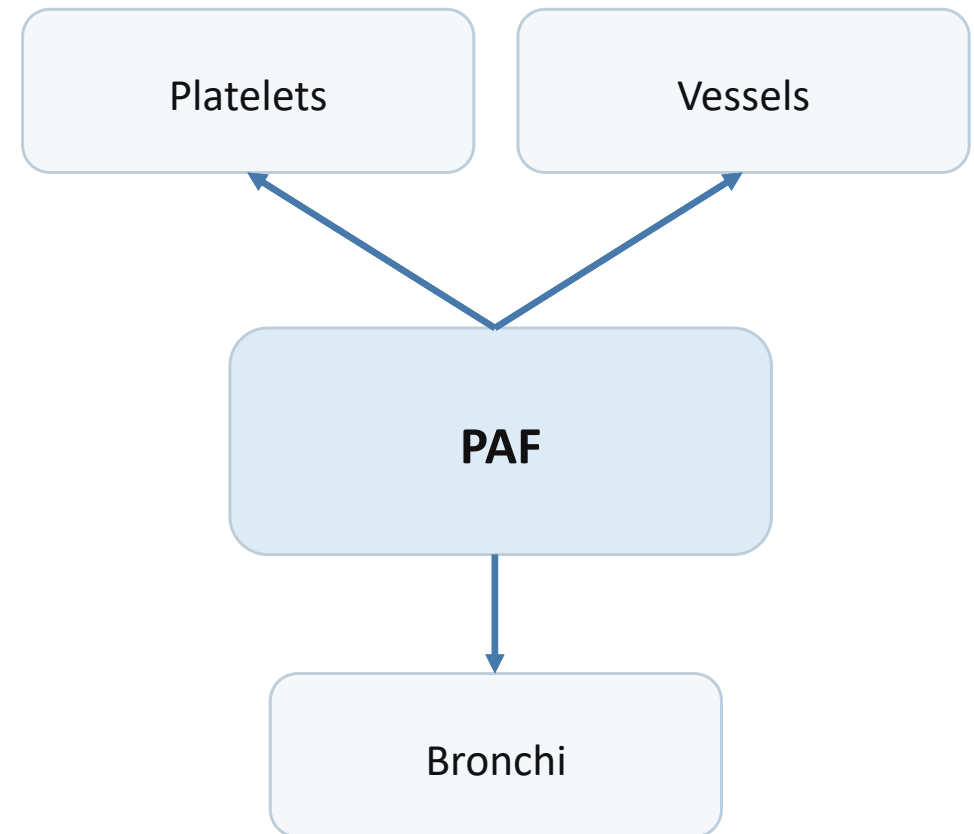
Activation

Effector target

Outcome

PAF is a phospholipid-derived mediator

- Its original identification depended on platelet aggregation.
- Subsequent work showed multiple inflammatory effects beyond platelets.
- Its activities include effects on vascular tone, permeability, and airways.



PAF is synthesized by several cell populations

- Platelets, basophils, and mast cells can elaborate PAF.
- Neutrophils and macrophages are also sources.
- Endothelial cells contribute to the same mediator network.

Platelets

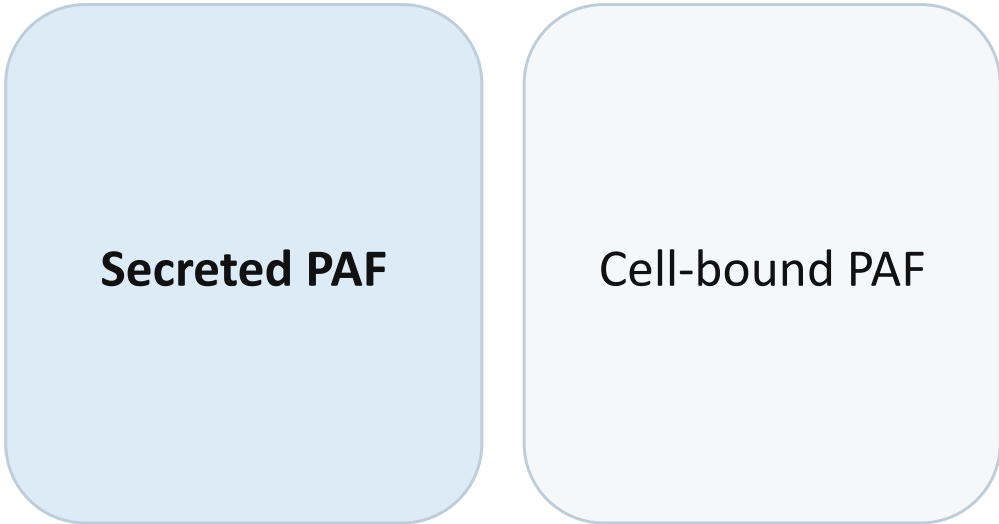
Basophils / mast
cells

Neutrophils /
macrophages

Endothelial cells

PAF can be secreted or remain cell-bound

- Both secreted and cell-bound PAF.
- This distinction broadens the ways PAF may participate in inflammatory signaling.
- The excerpt does not assign specific effects exclusively to either form.

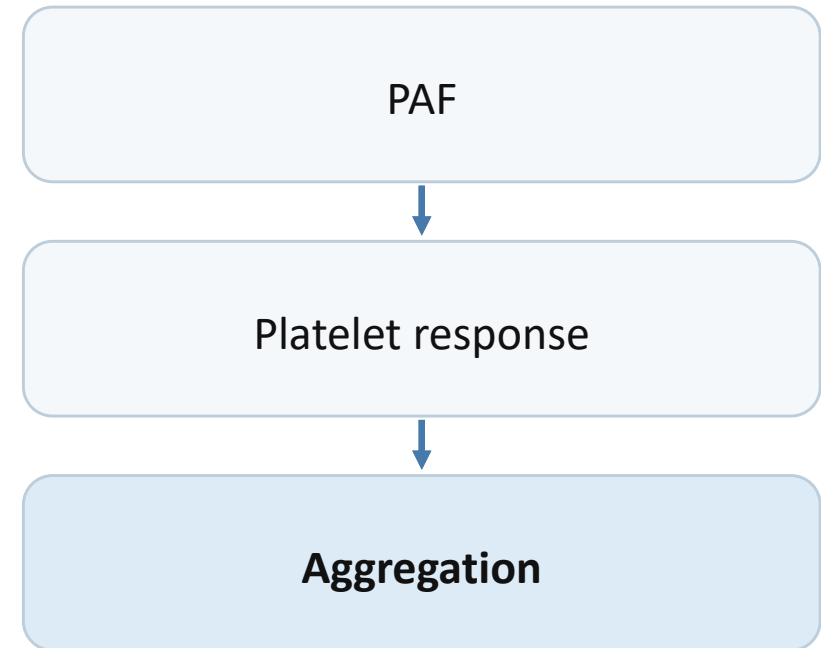


Secreted PAF

Cell-bound PAF

Platelet aggregation is the historical PAF effect

- PAF was discovered as a factor inducing platelet aggregation.
- This platelet effect is only one component of its reported biologic activity.
- Its name should not obscure its non-platelet inflammatory actions.



PAF can cause vasoconstriction

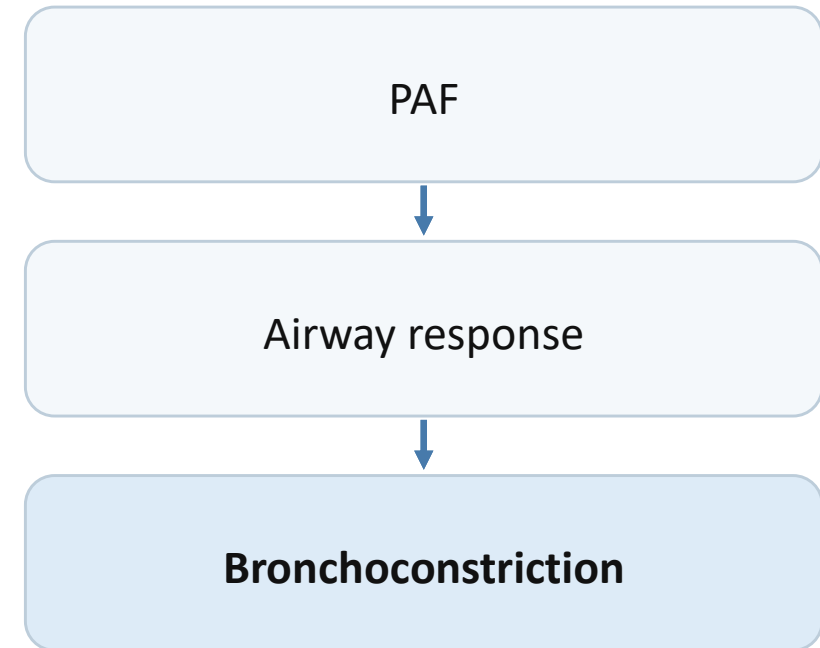
- Vasoconstriction among the actions of PAF.
- This finding must be read alongside the low-concentration vasodilator effect.
- PAF should not be memorized as having a single fixed effect on vascular tone.

Vasoconstriction

Low-dose
vasodilation

PAF can cause bronchoconstriction

- Bronchoconstriction is an explicitly described action of PAF.
- It extends mediator biology to airway smooth-muscle responses.
- The source does not quantify the magnitude or assign a particular disease-specific role.



Low concentrations of PAF induce vasodilation

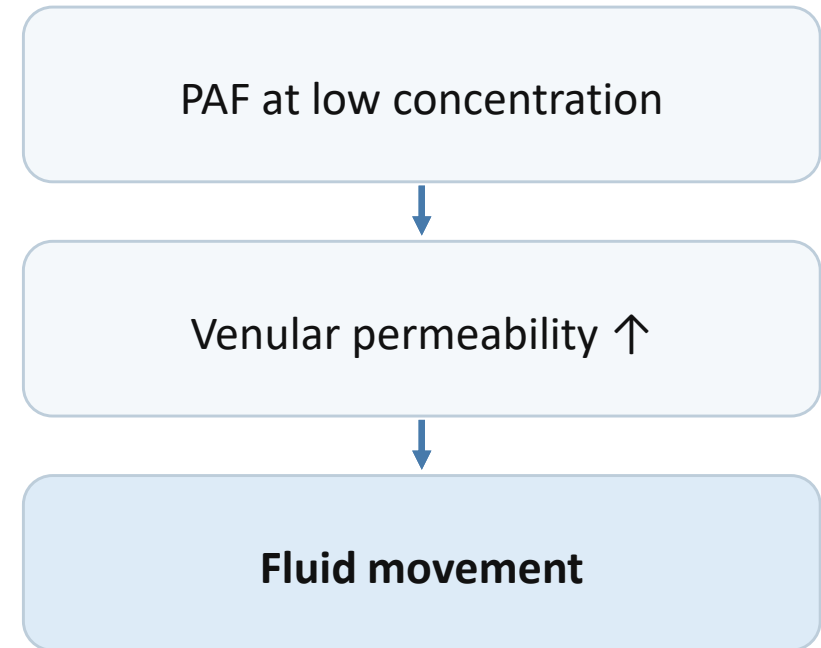
- At low concentrations, PAF produces vasodilation.
- This is a concentration-qualified effect, not a universal statement for all exposure levels.
- Qualitative arrows should not be mistaken for a measured dose-response curve.

Low concentration

Vasodilation

PAF can increase venular permeability

- Low concentrations of PAF increase venular permeability.
- Increased permeability facilitates the movement of fluid out of small vessels.
- Vascular leakage is shared with several other inflammatory mediators.



PAF actions depend on context

- Both constrictor actions and low-concentration vasodilation.
- Concentration matters when summarizing a mediator's vascular effect.
- No numerical threshold for these contrasting responses is given.

**Platelet
aggregation**

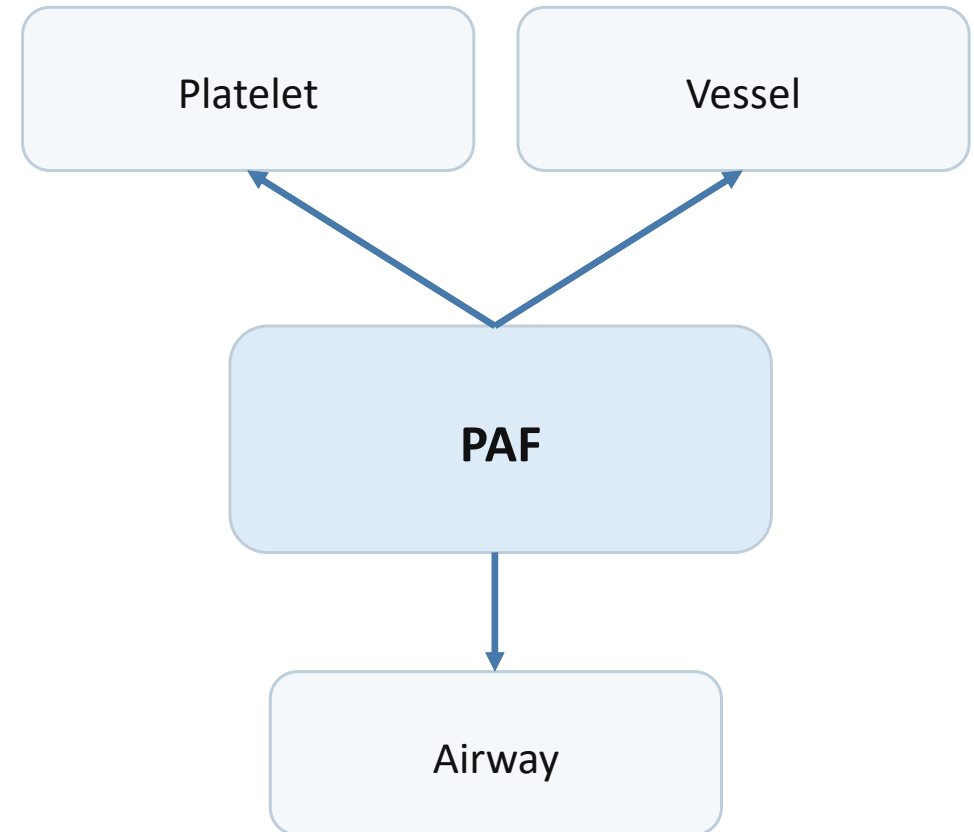
Vascular tone

Airway tone

Venular
permeability

PAF connects multiple inflammatory compartments

- Platelets: Aggregation.
- Blood vessels: Effects on tone and venular permeability.
- Airways: Bronchoconstriction.



PAF antagonists have not proved clinically useful

- PAF has several striking experimentally characterized effects.
- Nevertheless, PAF antagonists have not been useful in the inflammatory diseases tested.
- Molecular activity alone does not guarantee clinical benefit from blocking a target.

**Biologic effects
established**

Clinical benefit not
demonstrated

Application: Identify the PAF-related pattern

- A conceptual mediator produces platelet aggregation and bronchoconstriction.
- At low concentration it also increases venular permeability.
- The combination is compatible with the properties assigned to PAF.

Clinical reasoning • hypothetical example

Platelet aggregation

Bronchoconstriction

Permeability ↑

Injury can recruit coagulation and inflammation

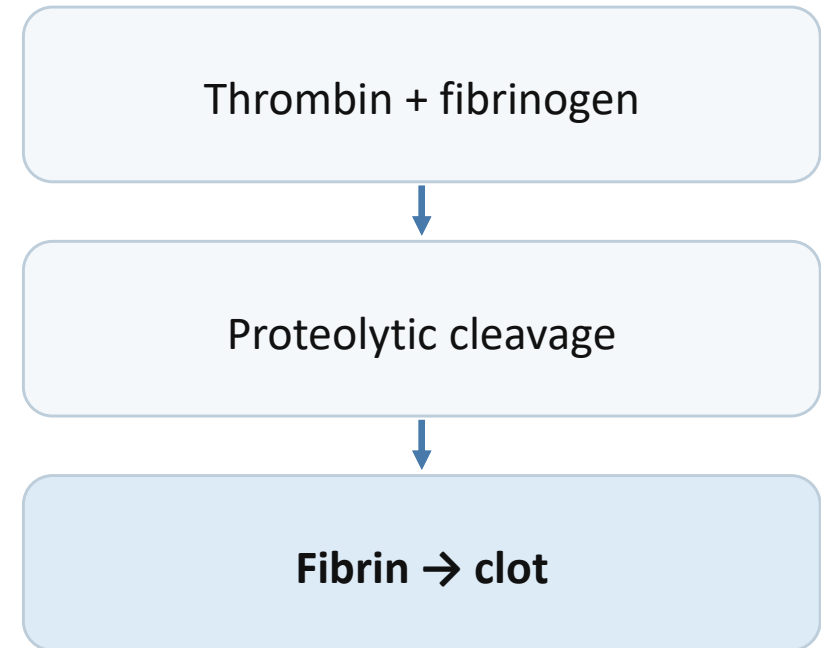
- Many injuries simultaneously produce clotting and inflammation.
- Co-occurrence is not itself evidence that coagulation products drive inflammation.
- This distinction is central to the textbook's discussion.

Coagulation

Inflammation

Thrombin cleaves fibrinogen to form fibrin

- Thrombin is the protease that acts on fibrinogen.
- Fibrin forms the structural basis of the clot.
- The described enzymatic step is established independently of proposed inflammatory effects.



Fibrin and fibrinopeptides are not synonymous

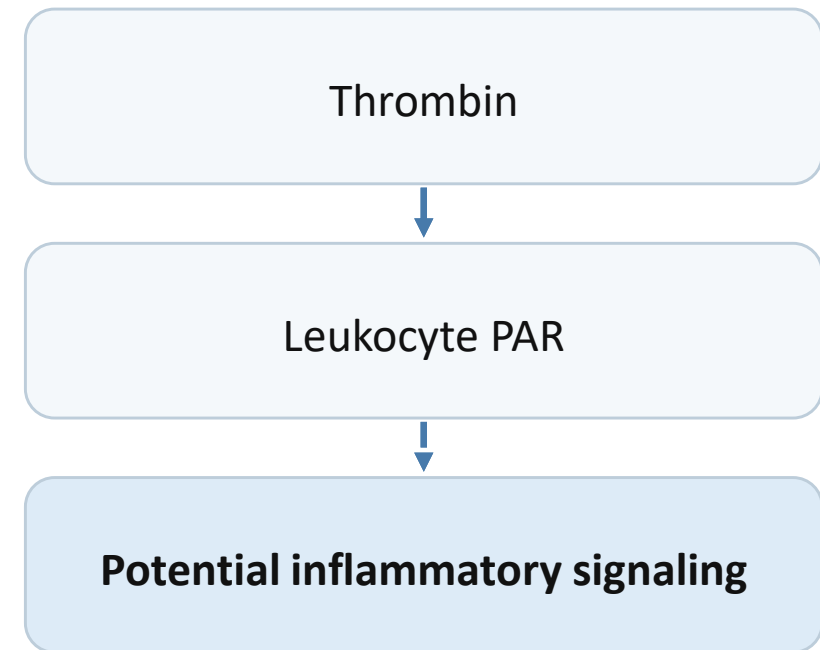
- Fibrin is the clot-forming product of fibrinogen cleavage.
- Fibrinopeptides are cleavage products proposed to influence inflammation.
- Distinguish the established clotting function from the less certain inflammatory activity.

**Fibrin: Clot
formation**

Fibrinopeptides:
Possible inflammation

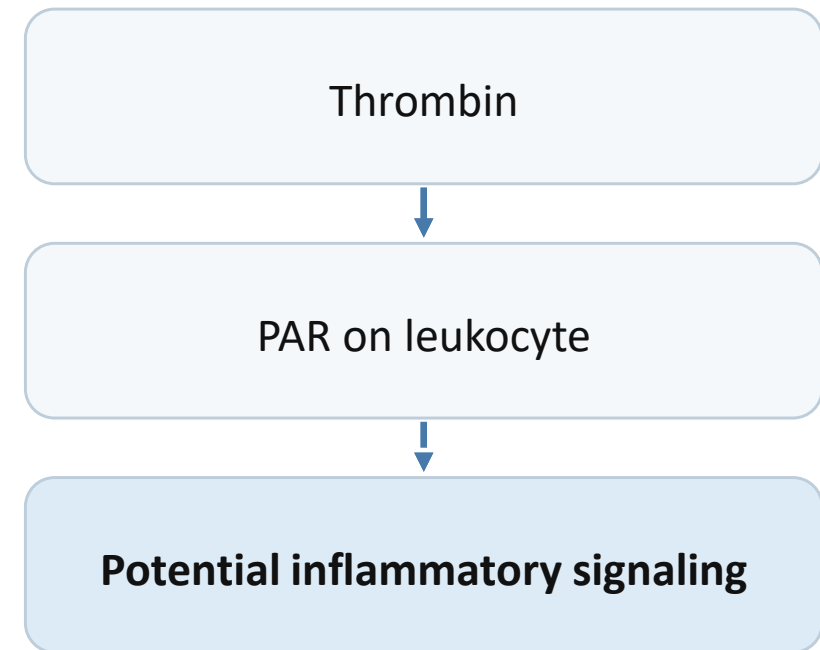
Protease-activated receptors link enzymes to cells

- Protease-activated receptors (PARs) are present on leukocytes.
- Thrombin can activate these receptors.
- This offers a possible molecular connection between coagulation proteases and inflammatory cells.



Leukocytes express thrombin-responsive PARs

- PAR expression makes leukocytes potential targets of coagulation proteases.
- The presence of a receptor and activation by thrombin support mechanistic plausibility.
- The net contribution to inflammation in vivo remains insufficiently established in the source.



Platelet activation is likely the major PAR function

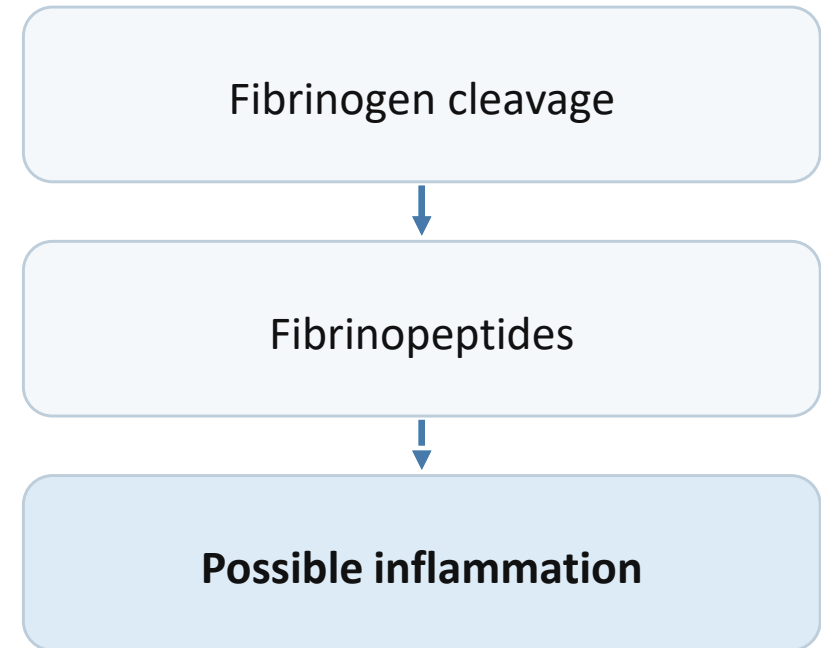
- PARs probably play their major role in platelet activation during clotting.
- This role should be distinguished from PAR expression on leukocytes.
- A receptor may be shared across cell types without identical physiologic importance.

**Platelet PAR:
Likely dominant**

Leukocyte PAR:
Possible link

Fibrinopeptides may stimulate inflammation

- Some evidence supports inflammatory activity of fibrin cleavage products.
- This is described as suggestive rather than conclusively established.
- Avoid presenting the association as a universally accepted causal pathway.



Coagulation-related causality remains unresolved

- Tissue injury is a common cause of both clotting and inflammation.
- It is not established whether coagulation products themselves stimulate inflammation in some settings.
- The mechanistic diagram therefore separates known reactions from proposed effects.

Injury → clotting

Established

Injury → inflammation

Compare
evidence

Products → inflammation ?

Interpret the strength of coagulation evidence

Statement	Status	Interpretation
Thrombin → fibrin	Established	Clotting reaction
Thrombin → leukocyte PAR	Established	Receptor activation
Products → inflammation	Unresolved	No firm causal conclusion

Do not infer inflammation from a clot alone

- The same damaged tissue can activate coagulation and inflammation in parallel.
- Detecting a clot does not identify the dominant inflammatory mediator.
- Mechanistic reasoning requires a causal chain, not just simultaneous observations.

Clinical reasoning • hypothetical example

Shared injury

Two parallel outcomes

Causality unproven

Application: Classify coagulation claims

- Claim A: Thrombin produces fibrin from fibrinogen.
- Claim B: Thrombin activates PARs expressed on leukocytes.
- Claim C: Coagulation products are necessarily the cause of inflammation after every injury.

Clinical reasoning • hypothetical example

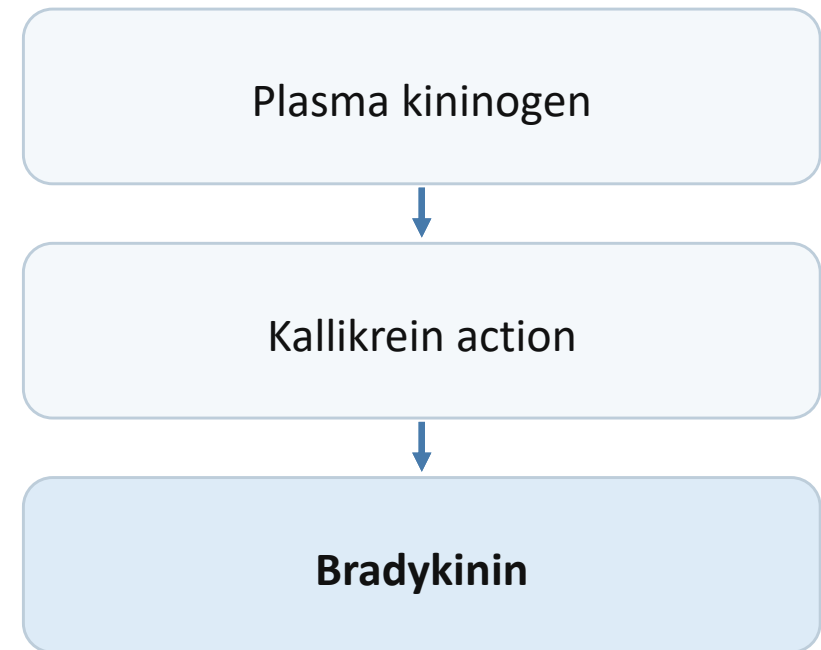
A: Established

B: Established

C: Unsupported

Kinins are plasma-derived vasoactive peptides

- Kinins arise from plasma proteins called kininogens.
- Proteolytic enzymes called kallikreins generate active kinin peptides.
- Bradykinin is the principal example emphasized by Robbins.



Kininogens supply inactive precursors

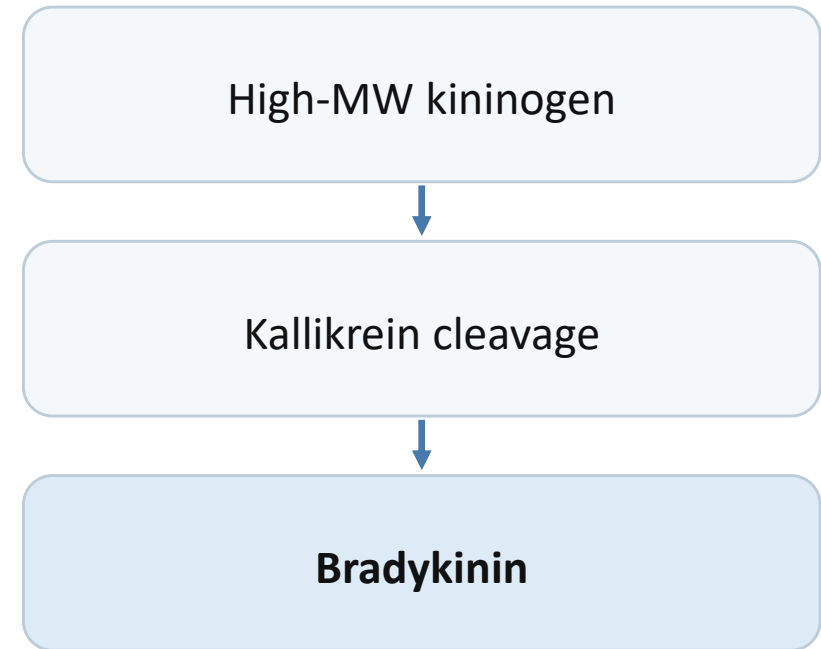
- The source identifies high-molecular-weight kininogen as a plasma glycoprotein precursor.
- Precursor cleavage is the key activation step.
- This contrasts with release of an already active granule-stored mediator.

**Inactive plasma
precursor**

Proteolytically
generated peptide

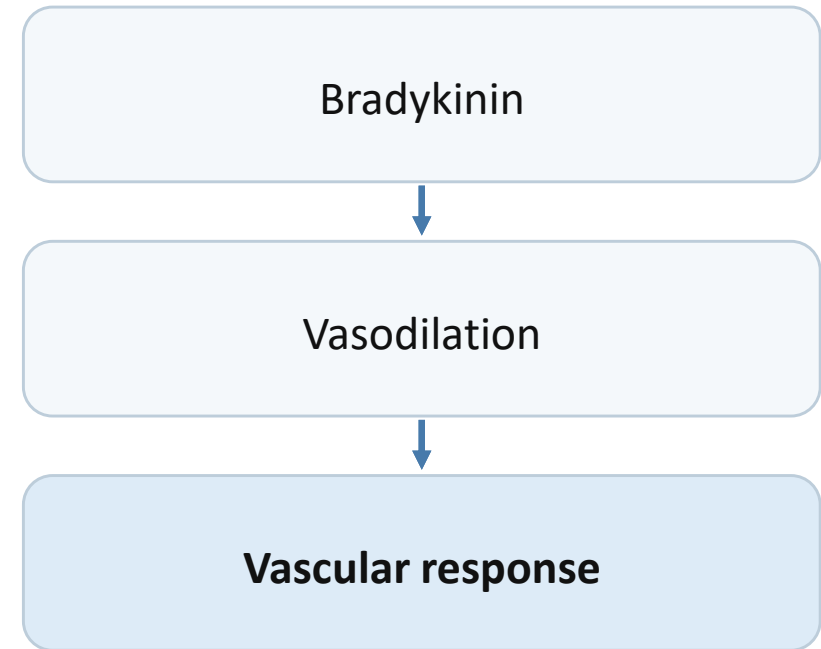
Kallikrein generates bradykinin

- Kallikrein cleaves high-molecular-weight kininogen.
- The cleavage reaction produces bradykinin.
- This is a direct example of inflammation-related proteolytic mediator generation.



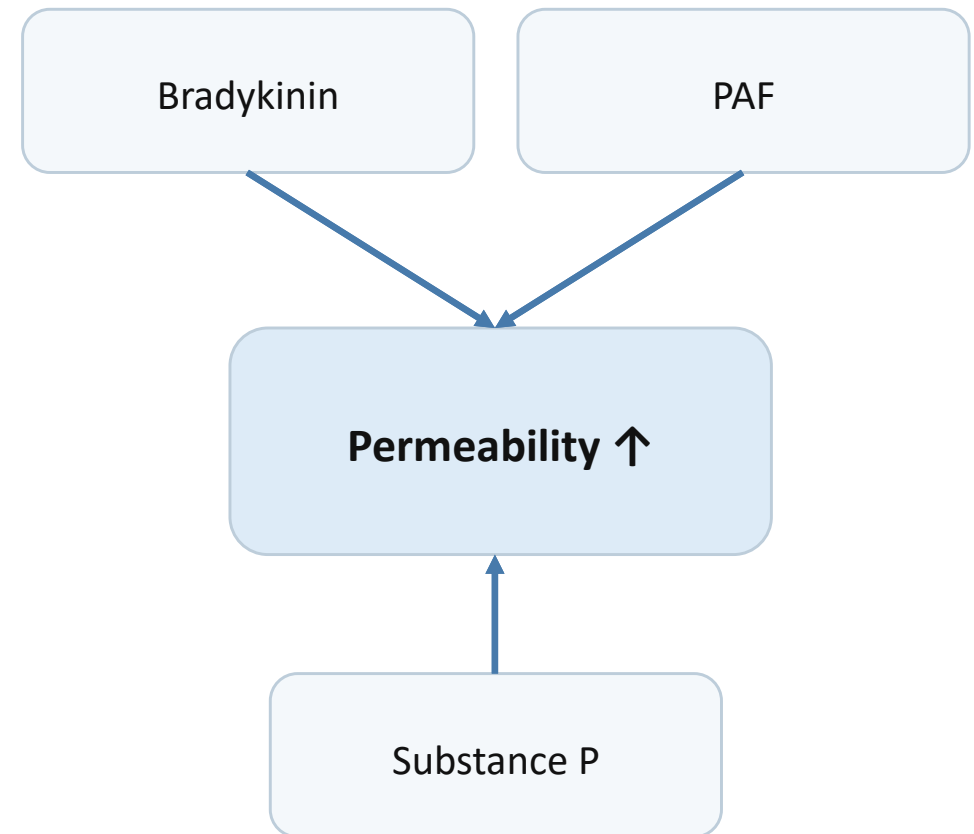
Bradykinin dilates blood vessels

- Vasodilation is among the textbook-described actions of bradykinin.
- Increased local blood flow is one way mediator activity contributes to vascular reactions.
- Bradykinin therefore overlaps functionally with histamine.



Bradykinin increases vascular permeability

- Bradykinin directly increases vascular permeability.
- This action provides a mechanistic contribution to inflammatory fluid leakage.
- The endpoint is shared by histamine, PAF, and substance P.



Bradykinin contracts smooth muscle

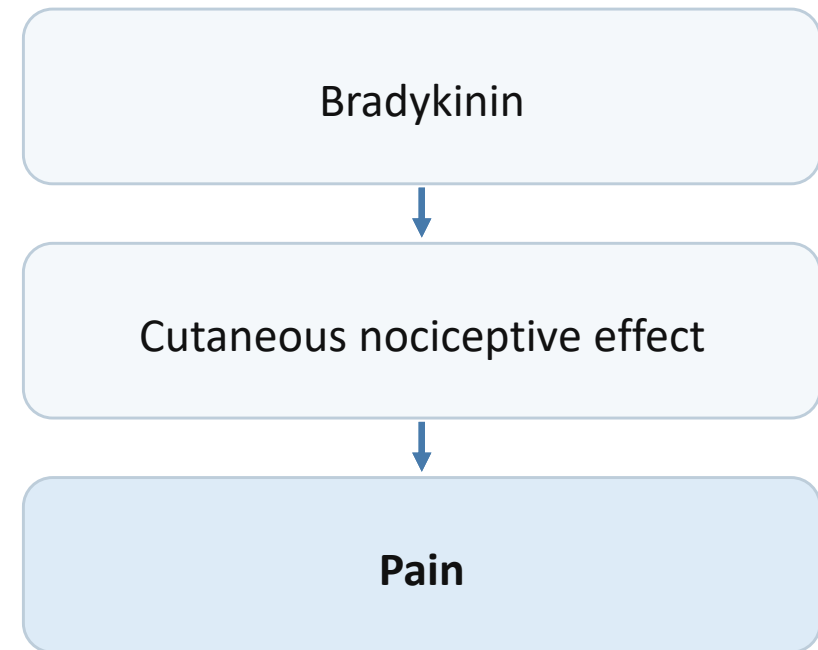
- Smooth-muscle contraction is listed among bradykinin actions.
- Do not confuse smooth-muscle contraction with the vascular dilation also caused by the same mediator.
- Biologic actions vary with tissue and physiologic context.

Vasodilation

Smooth-muscle
contraction

Bradykinin mediates pain

- Bradykinin produces pain when injected into the skin.
- The textbook's summary also lists it among principal pain mediators.
- Pain can be mediated chemically even without direct proof of infection.



Bradykinin resembles histamine functionally

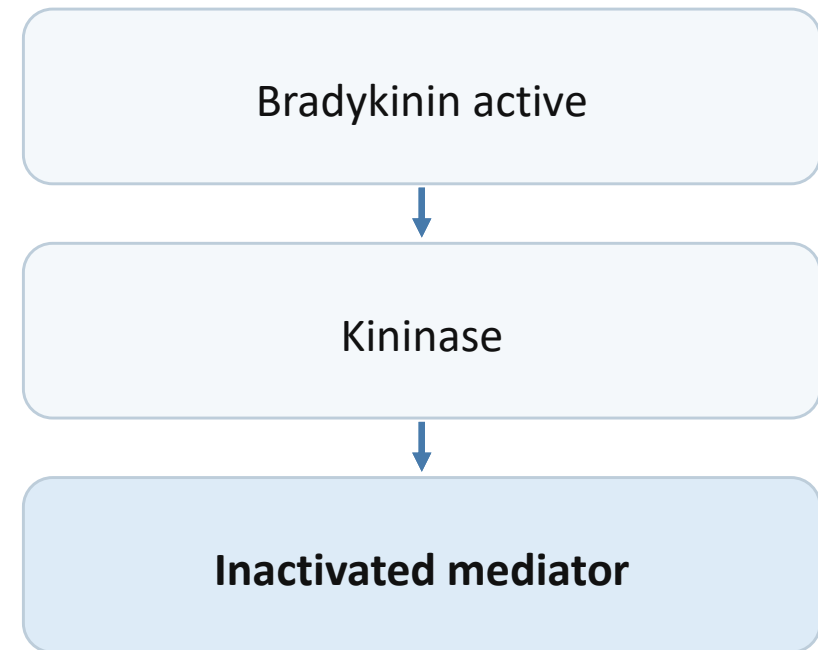
- Both mediators contribute to vascular dilation and increased permeability.
- The textbook explicitly calls bradykinin's effects similar to histamine.
- Similarity of effects does not imply identical biochemical origin.

Bradykinin:
Plasma peptide

Histamine:
Vasoactive amine

Kininase rapidly ends bradykinin action

- Bradykinin is short-lived because kininase rapidly inactivates it.
- Enzymatic clearance provides a concrete mechanism for mediator control.
- This reflects the general principle that inflammatory mediators do not persist indefinitely.



Bradykinin may participate in anaphylaxis

- Robbins implicates bradykinin in some allergic reactions, including anaphylaxis.
- The wording does not establish that bradykinin is the sole or dominant mediator.
- Multiple mediators can contribute to a single clinical reaction.

**Associated with
allergic reaction**

Not a single-mediator
explanation

Application: Edema accompanied by pain

- A hypothetical injury produces localized edema and pain.
- One plausible mediator with both actions is bradykinin.
- The finding alone cannot uniquely identify bradykinin because mediator effects overlap.

Clinical reasoning • hypothetical example

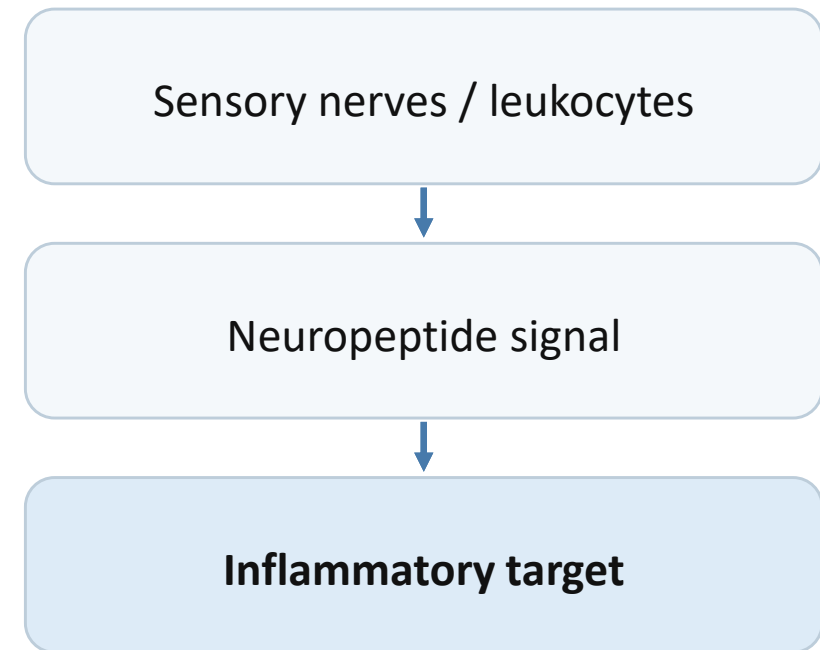
Vascular leakage

Pain

Bradykinin compatible

Neuropeptides link nervous and immune systems

- Neuropeptides are small regulatory peptides secreted by sensory nerves and leukocytes.
- They may participate in initiation and regulation of inflammatory reactions.
- Their effects establish a route for neural–immune communication.



Substance P and neurokinin A are examples

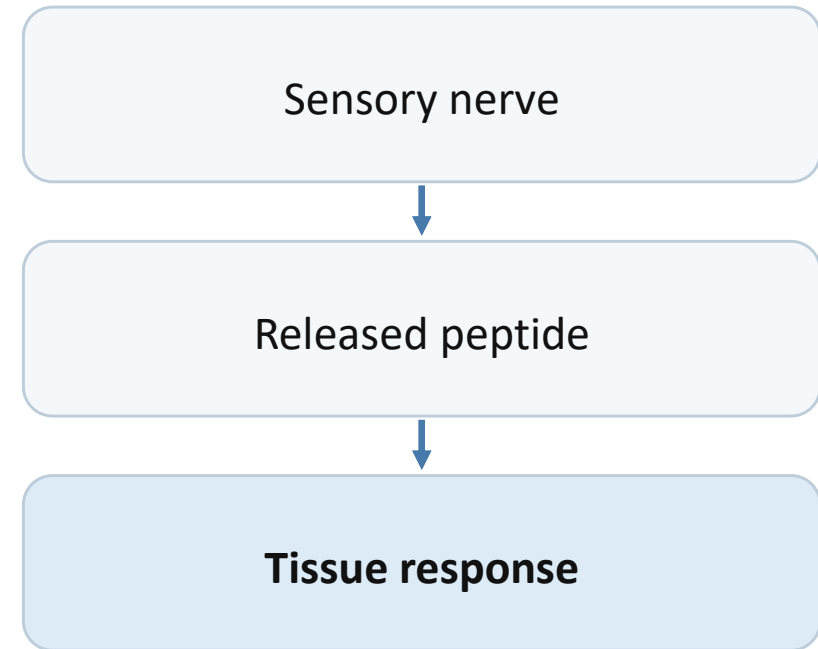
- Substance P and neurokinin A as neuropeptides.
- They are produced in central and peripheral nervous systems.
- Substance P has explicitly described functions in pain and vascular permeability.

Substance P

Neurokinin A

Sensory nerves are a neuropeptide source

- Nerve endings can secrete peptides involved in local inflammation.
- This creates an interface between tissue sensation and vascular reactions.
- The source also recognizes leukocyte-derived neuropeptides.



Leukocytes also supply neuropeptides

- Leukocytes are among the cells capable of secreting neuropeptides.
- Immune and neural compartments thus share mediators rather than functioning in isolation.
- The source does not provide quantitative contributions from each source.

Neural origin

Leukocyte origin

Substance P-containing fibers occur in lung and gut

- Substance P-containing nerves are especially prominent in the lungs and gastrointestinal tract.
- These sites illustrate the anatomic proximity of neural signaling and barrier tissues.
- Presence of such fibers should not be treated as a disease-specific diagnostic finding.

Lung

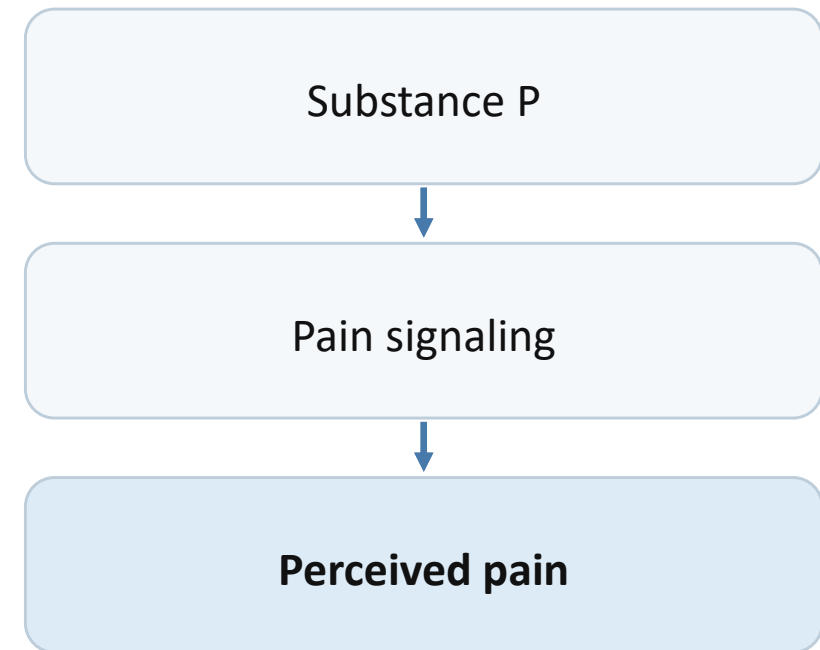
Gastrointestinal
tract

Nerve fibers

Local tissue
response

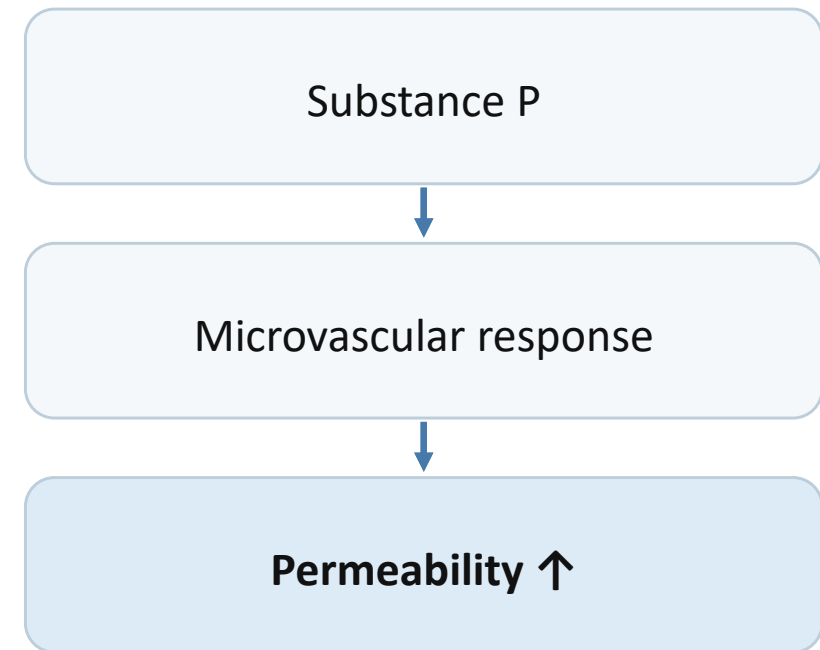
Substance P participates in pain transmission

- Transmission of pain signals is an inflammatory-relevant action of substance P.
- Robbins also lists substance P in its mediator table for pain.
- Neuropeptide activity connects sensory signaling to tissue responses.



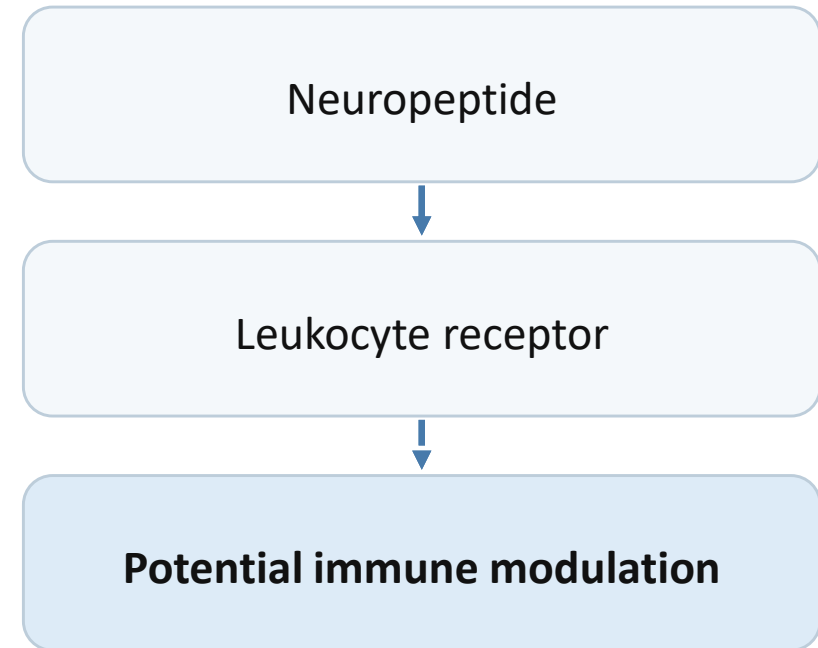
Substance P can increase vascular permeability

- Substance P also increases vascular permeability.
- Neurogenic mediators therefore contribute to a vascular endpoint shared with plasma-derived kinins.
- The source does not assign a universal quantitative contribution to tissue edema.



Leukocytes bear receptors for neuropeptides

- Leukocytes express receptors for numerous neuropeptides.
- Nerve-derived signals can therefore be received by immune-effector cells.
- This supports neural regulation of inflammation without identifying a single universal response.



Neural and immune cells share peptide signals

- Neuropeptides may originate from either nerves or leukocytes.
- Leukocyte receptors provide an additional route for neural mediators to act.
- These features motivate a network, rather than a one-cell-one-mediator, model.

Sensory neuron

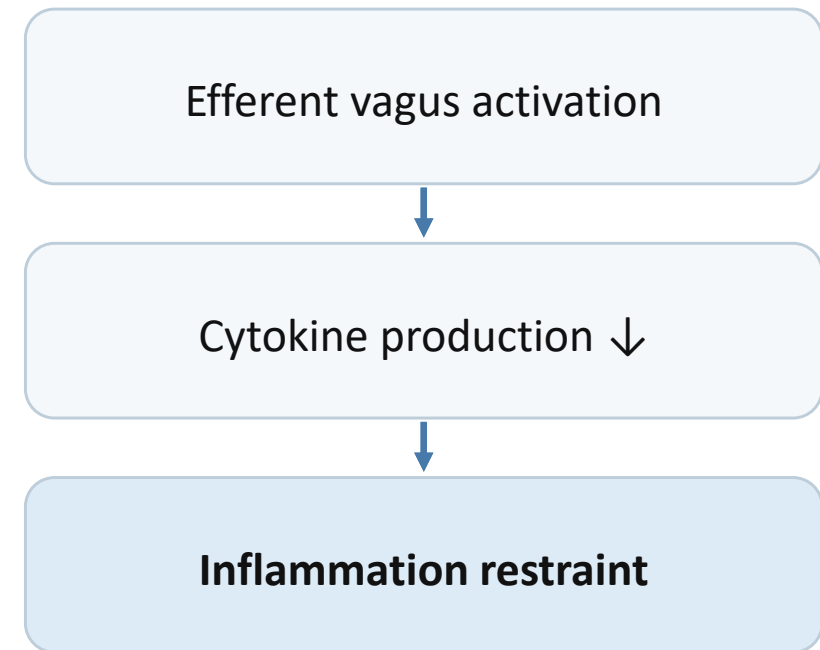
Neuropeptide

Leukocyte

Tissue

Efferent vagal activity can suppress inflammation

- Activation of the efferent vagus nerve inhibits production of proinflammatory cytokines.
- TNF is the explicit example given.
- This is a regulatory mechanism rather than another pathway of edema or pain.



TNF suppression demonstrates a neural brake

- TNF participates in leukocyte recruitment and endothelial activation.
- The excerpt describes vagal activity inhibiting TNF production.
- Thus neural signaling can oppose as well as promote inflammatory responses.

**Substance P:
Permeability / pain**

Vagal activity: TNF
suppression

Vagus stimulation has been tested in rheumatoid arthritis

- The vagal antiinflammatory observation prompted clinical trials in rheumatoid arthritis.
- The excerpt mentions trials but provides no outcomes or efficacy estimates.
- Clinical testing should not be conflated with established treatment efficacy.

Mechanistic observation

Established

Clinical trial motivation

Compare
evidence

Outcome not specified

Neural mediators can have opposing directions

- Substance P may increase vascular permeability and contribute to pain.
- Efferent vagal activation can inhibit proinflammatory TNF production.
- The effect of neural signals depends on the pathway being activated.

**Proinflammatory
activity**

Antiinflammatory
activity

Application: Interpret a neural antiinflammatory claim

- An intervention activates efferent vagal pathways in an experimental model.
- A reduction in TNF production is consistent with the mechanism described.
- The observation alone does not establish clinical efficacy for rheumatoid arthritis.

Clinical reasoning • hypothetical example

Vagal activation

TNF production ↓

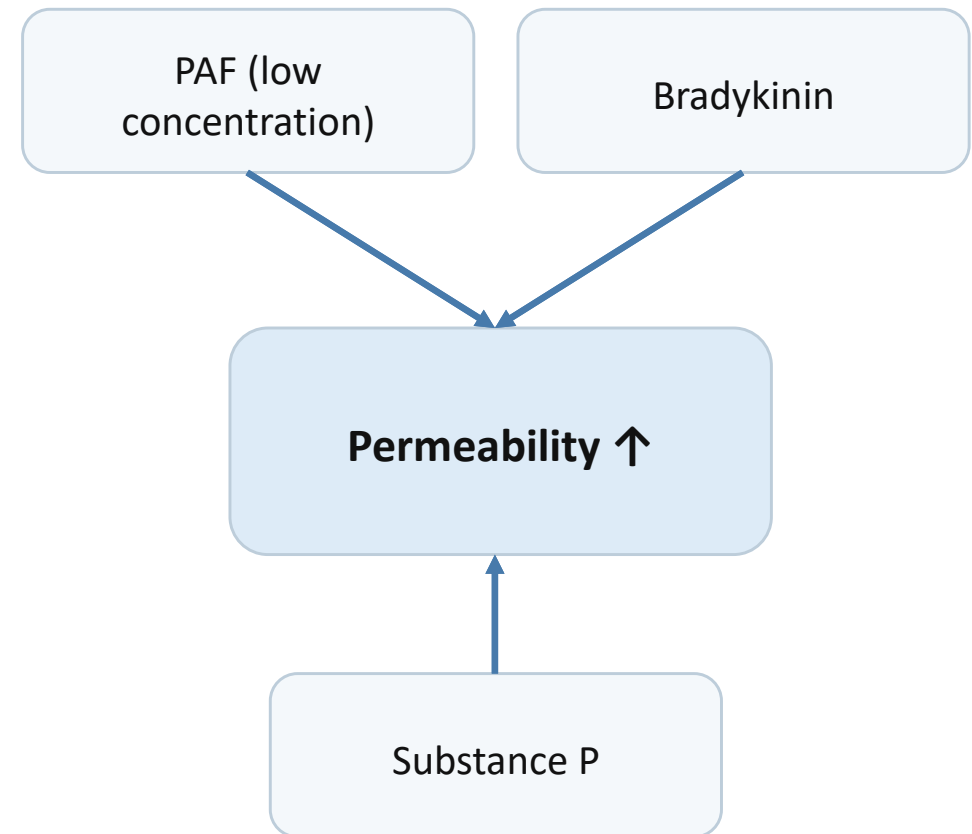
Efficacy still separate

Integrating mediator origin and principal effects

Mediator	Origin	Selected actions
PAF	Multiple cell types	Aggregation; vascular/airway actions
Coagulation products	Coagulation cascade	Clot; possible inflammatory link
Bradykinin	Kininogen cleavage	Dilation; leakage; pain
Neuropeptides	Nerves / leukocytes	Pain; leakage; TNF modulation

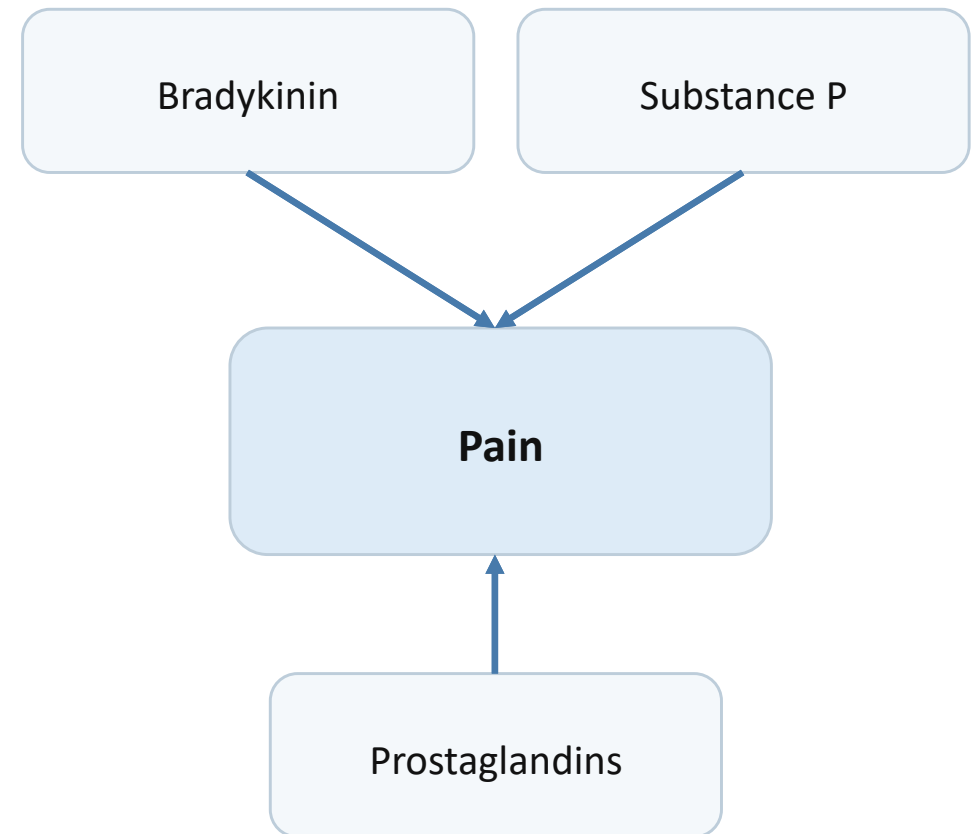
Multiple mediators increase permeability

- PAF at low concentrations increases venular permeability.
- Bradykinin and substance P also increase vascular permeability.
- Shared endpoints are not proof that the mediators act through identical biochemical pathways.



Pain has chemically distinct mediators

- Bradykinin is pain-producing and is generated by proteolysis.
- Substance P contributes to neural pain transmission.
- Robbins' summary also identifies prostaglandins as major pain mediators.



A mediator may have several target effects

- PAF acts on platelets, vascular tone, permeability, and airways.
- Bradykinin affects vascular responses, smooth muscle, and pain.
- Multiple physiologic effects make single-output definitions incomplete.

One mediator

Multiple
physiologic
outputs

Not all proposed links are equally established

- PAF, bradykinin, and substance P have stated biologic effects.
- Coagulation-product causation of inflammation remains uncertain in the source.
- Vagus stimulation trials are mentioned without demonstrated therapeutic outcomes.

Documented action

Established

Mechanistic proposal

Compare
evidence

Clinical efficacy not supplied

Clinicopathologic reasoning: Edema and pain

- Edema indicates increased fluid movement, not a unique mediator identity.
- Pain may involve bradykinin, substance P, or prostaglandins.
- Link observed findings to possible mechanisms while respecting overlap and uncertainty.

Clinical reasoning • hypothetical example

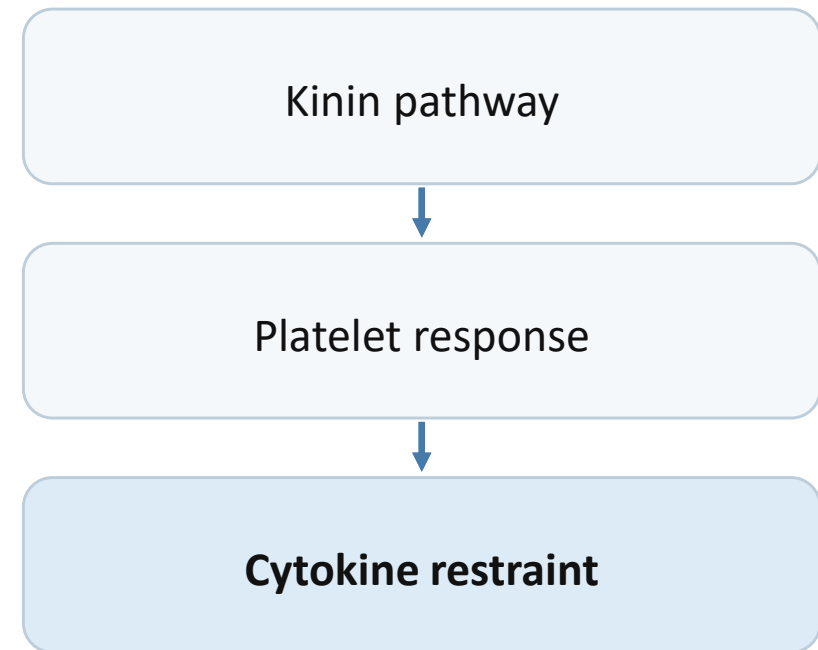
Observed edema

Observed pain

Multiple compatible mediators

Knowledge check: Match mediators to claims

- Which mediator is produced by kallikrein cleavage of kininogen?
- Which mediator is derived from phospholipids and induces platelet aggregation?
- Which neural pathway is described as inhibiting TNF production?



Knowledge check: Mechanistic answers

- Kallikrein cleavage of high-molecular-weight kininogen generates bradykinin.
- Platelet-activating factor (PAF) can induce platelet aggregation.
- Activation of the efferent vagus nerve inhibits TNF production.

Bradykinin

PAF

Efferent vagus

Distinct
mechanisms

Integrated principles

- Mediator origin predicts the route of production but not one exclusive effect.
- Vascular leakage and pain are shared outputs of several chemically distinct mediators.
- Distinguish documented actions, plausible pathways, and clinically proven target benefits.

Origin

Biologic effect

Evidence strength

Clinical relevance

Primary reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Section: Other Mediators of Inflammation; parent sections on mediator principles and cytokines.
- Related contextual material: mediator principles, cytokines, and the summary of inflammatory mediator actions.