

# Veterinary Bioscience: Cells to Systems

VETS30029 / VETS90121



## Autacoids: diverse regulators and therapeutic targets

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Part 1 of 2

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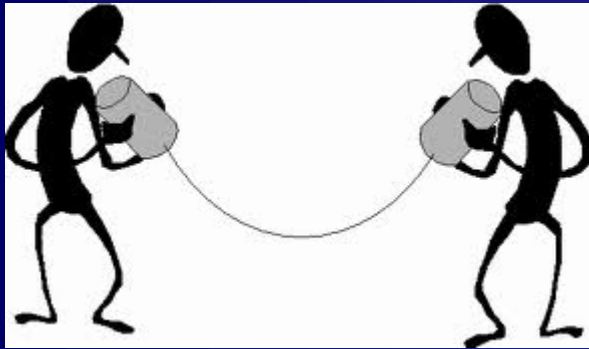
# What Will We Be Looking at Today?

- Autacoids
- Classification of autacoids
- Focus on **histamine** as an example- synthesis, storage, release, receptors, effects and therapeutics **PART 1**
- The scope of **peptides/proteins** as autacoids and chemical signalling molecules
  - Focus on **bradykinin** as an example
- **Eicosanoids**- important drug targets (steroidal and non-steroidal anti-inflammatory drugs) **PART 2**

# Cell-Cell Communication

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Nerve mediated



Message targeted

Local mediator  
(autacoid)



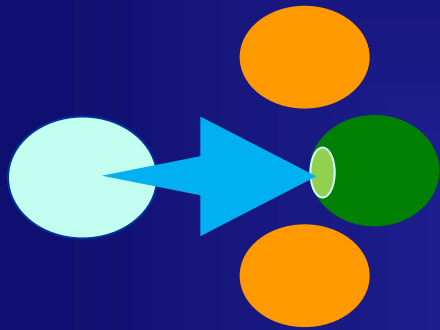
Restricted actions

Hormone

Broad actions- impact  
on any cell 'listening'  
(has receptor)

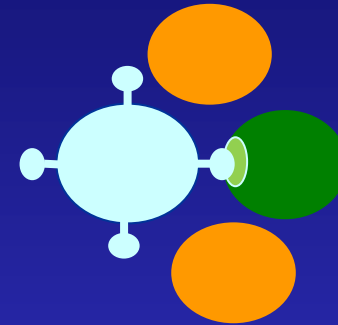
# Chemical signalling between cells

1. Release of molecules



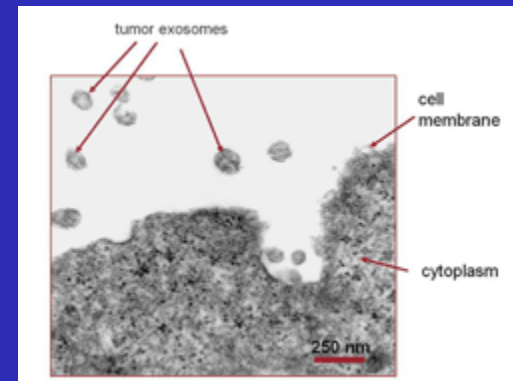
Neurotransmitters (wired networks)  
Hormones (broadcast)  
Local mediators (shouting)

2. Membrane bound molecules

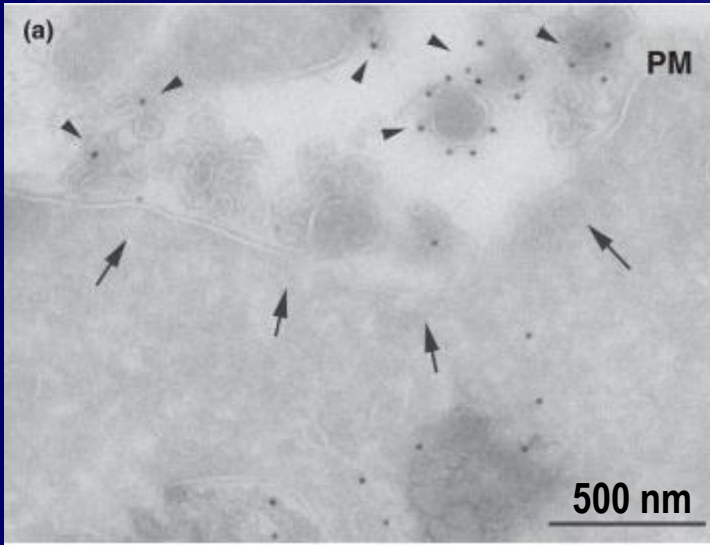


Immune system  
(Cellular neighbours)

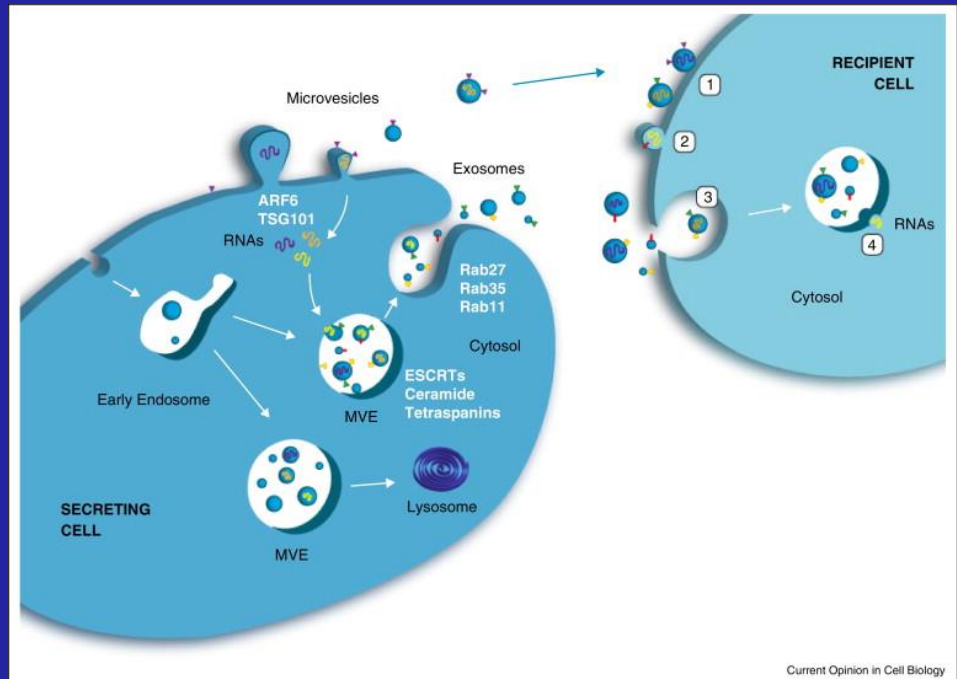
## Exosomes?



# Exosomes/Extracellular vesicles



Communicators  
Diagnostic biomarkers?  
Therapeutics?



Extracellular vesicles shuffling intercellular messages: for good or for bad. Lo Cicero A, Stahl PD, Raposo G. Curr Opin Cell Biol. 2015;35:69-77

# Autacoids

- Diverse group of (patho)physiological mediators.
- Often considered as defense mediators - formation and release associated with **infection and inflammation**.
- Are important therapeutic targets.
- **Modulatory Functions**
  - Smooth muscle tone/length
  - Glandular secretion
  - Permeability (vascular & airway)
  - Sensory nerves (pain & itch)

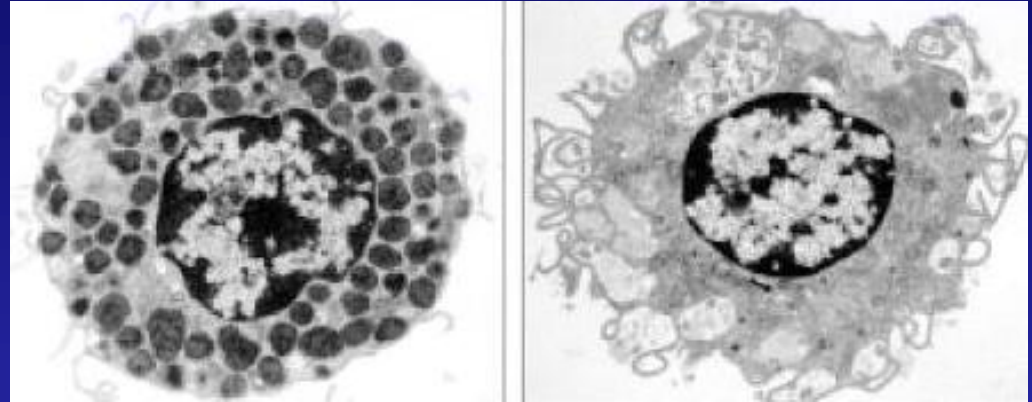
# Autacoids

- Autacoid- 'Self Remedy'
- Multiple interacting mediators that include:
  - Histamine
  - Bradykinin
  - Eicosanoids
    - Prostaglandins
    - Leukotrienes
- Why do they usually only act locally?
  - Often quite labile or are rapidly broken down close to their site of release.



# Histamine

- Largely stored in and released from:
  - **Mast cells** (tissues-particularly mucosal surfaces/skin)
  - **Basophils** (blood)
- Enterochromaffin-like cells (GIT) – regulate stomach acid secretion
- (Also peripheral and central **histaminergic neurones.**)

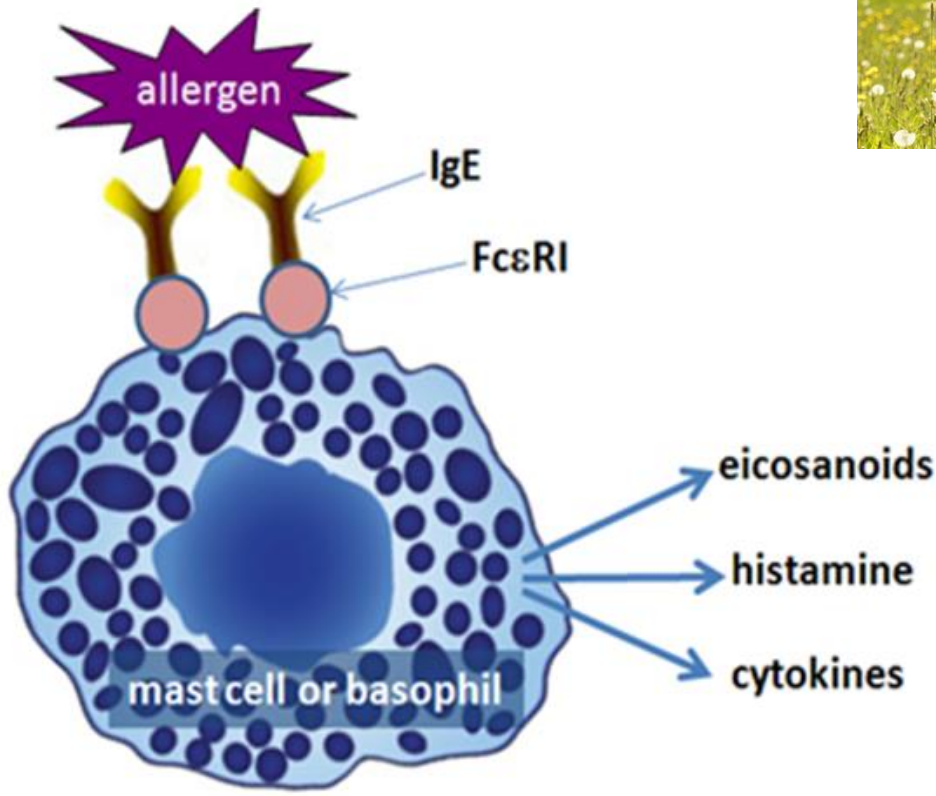


Janeway et al; Immunobiology 5<sup>th</sup> edition; Fig. 9.35



The Age.com.au

# Mast Cells and Histamine



[www.mendsstreetpharmacy.com.au](http://www.mendsstreetpharmacy.com.au)



[www.imperial.ac.uk](http://www.imperial.ac.uk)



[www.heraldsun.com.au](http://www.heraldsun.com.au)

# Histamine

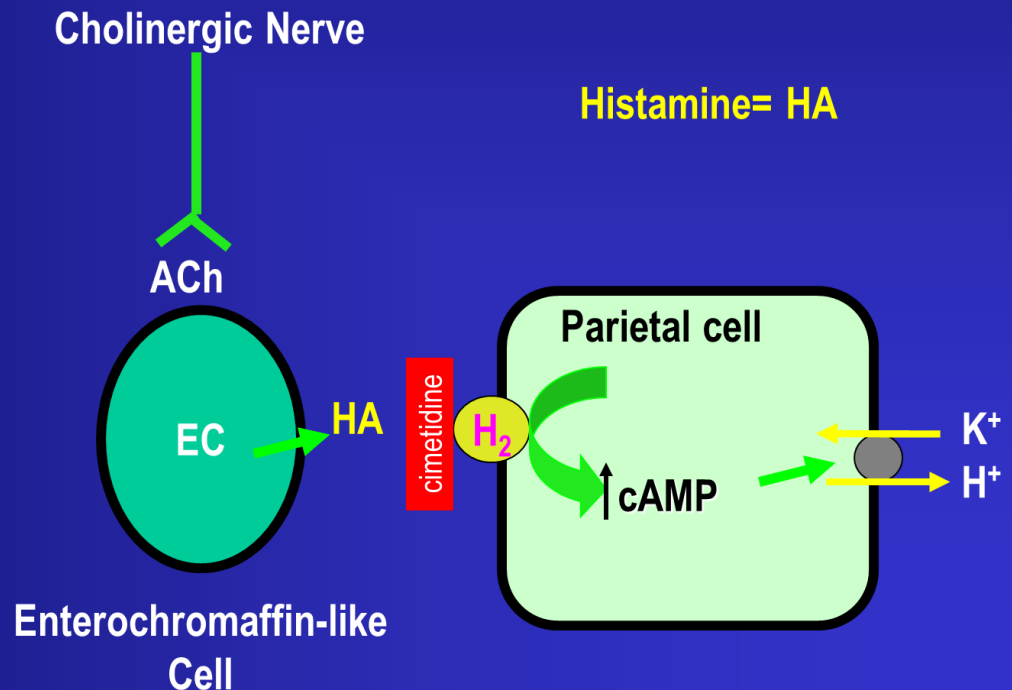
- Mediates its activities through interacting with 4 distinct receptors-  $H_1$ ,  $H_2$ ,  $H_3$  &  $H_4$
- All are **GPCRs**.
- **Therapies**
  - $H_1$ R antagonism- allergic disease (mainly)
  - $H_2$ R antagonism- peptic ulcer disease (and related conditions)
  - $H_3$ R antagonism- narcolepsy
  - $H_4$ R antagonism- none approved yet (pruritus?)

# H<sub>1</sub> Receptor Antagonists- 'Antihistamines'

- **Competitive, reversible antagonists of H<sub>1</sub> receptors**
- Useful in treating:
  - Hayfever (allergic rhinitis)
  - Atopic dermatitis (adjunct to glucocorticoids)
  - Urticaria
  - Anaphylaxis & angiodema (adjunct to adrenaline)
  - Bites & stings

# H<sub>2</sub> Receptor Antagonists

- Were revolutionary in the treatment of peptic ulcers
  - “Blockbuster drugs”
  - Cimetidine/Ranitidine
- Improved understanding of the condition have led to alternative methods of treating peptic ulcers



# The Song of the European Histamine Research Society

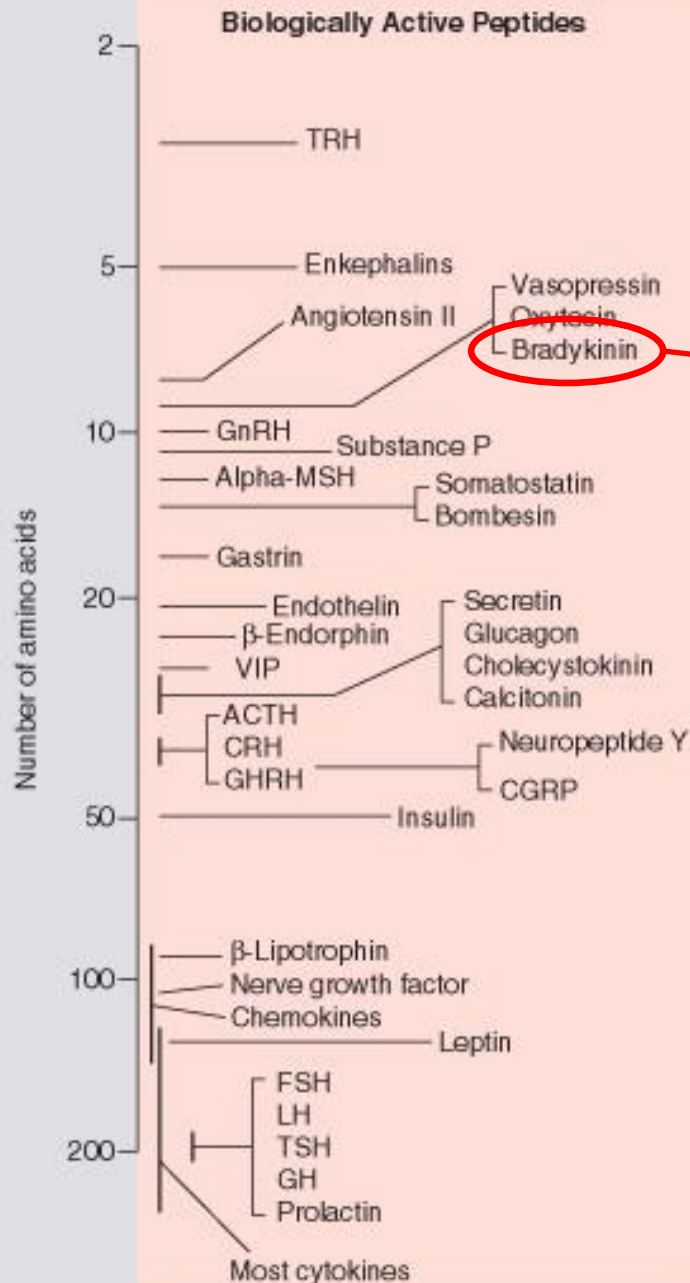
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## Chorus

For it's mine, for it's mine,  
Decarboxylated Histidine,  
We've extracted you and weighed you,  
By the living gut assayed you,  
But we've yet to find your function - Histamine!

<http://www.ehrs.org.uk/wp-content/uploads/2016/11/Histamine-Anthem-updated-2016.pdf>

# Regulatory Peptides/Proteins



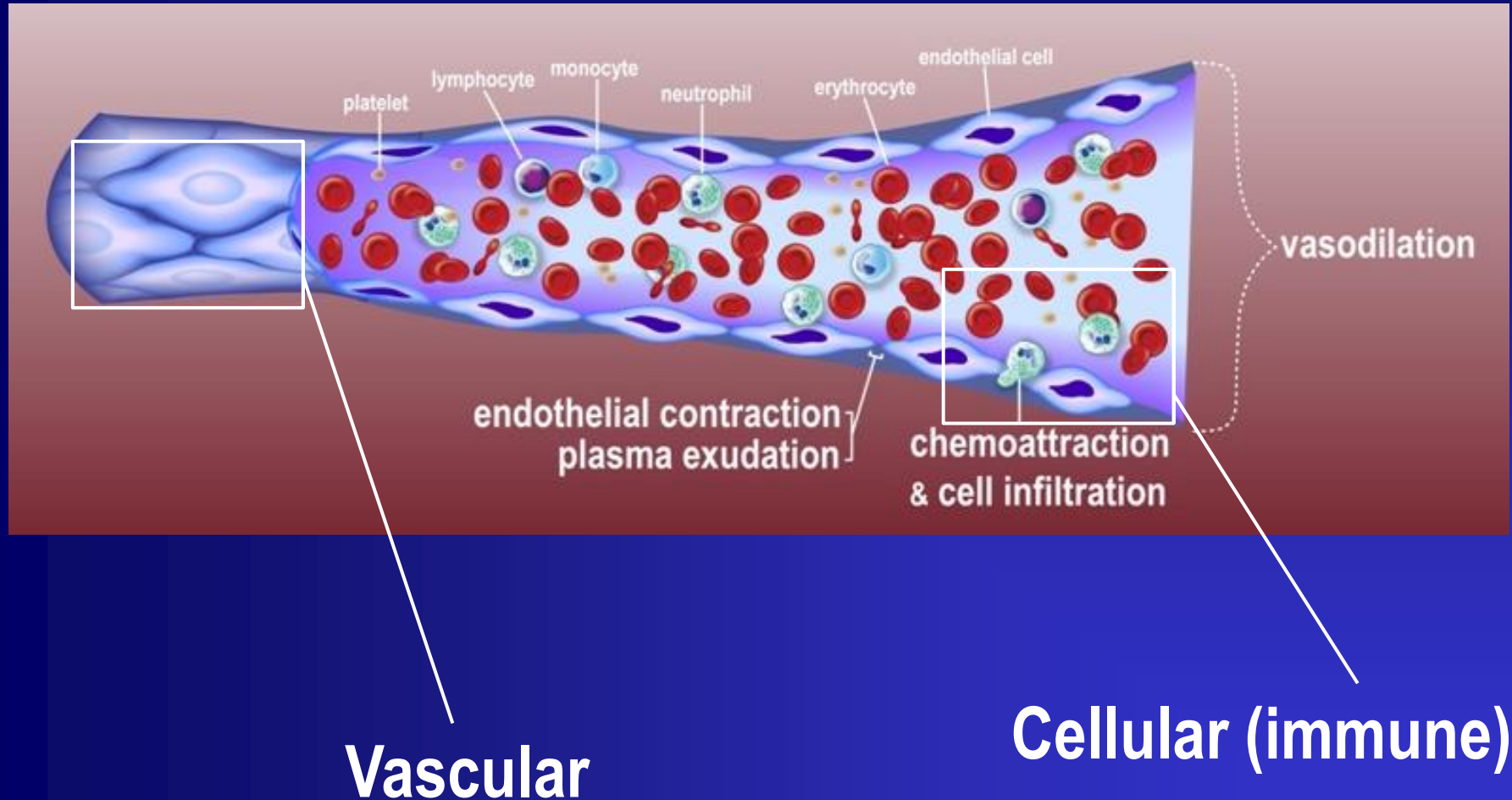
“Slow movement”

Can range in size from just a few amino acids to many hundred residues

Rang et al; Fig. 13.1



# Inflammation- Two Major Components



Stewart AG and Mackay GA. (2008). The Pharmacotherapy of Inflammation. *Encyclopedia of Life Support Systems* (EOLSS), Developed under the Auspices of the UNESCO, EOLSS Publishers, Oxford ,UK, [<http://www.eolss.net>].



# Regulatory Peptides- Autacoids

- **Bradykinin (BK)**- Local peptide mediator in pain and inflammation.
- **Generated after plasma exudation during inflammation.**

**Prekallikrein**  
(inactive plasma protein)



Activated 'Hageman' factor  
(Factor XII)  
(becomes active outside blood)

**Bradykinin**

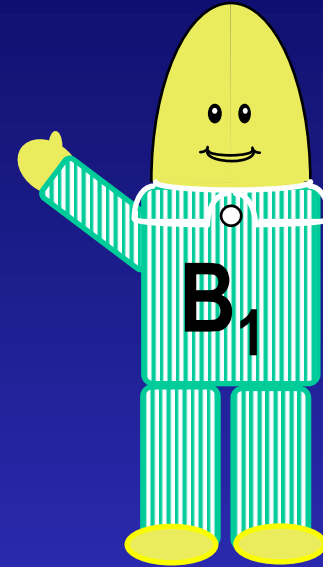
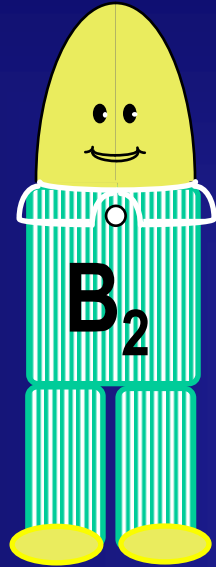
High-molecular weight kininogen  
(inactive plasma protein)

# Bradykinin - Actions

- **Vascular**
  - Dilate arterioles & venules (released PGs / NO)
  - Increased vascular permeability
- **Neural**
  - Stimulate sensory nerve endings - pain

# Bradykinin Receptors

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Both GPCRs

Clinical use: Limited at present

Selective B<sub>2</sub> receptor antagonist **icatibant** (*useful: hereditary angioedema*)

# Learning Outcomes

- **After studying Part 1 of this topic you should be able to:**
  - Understand the importance of locally released regulatory mediators and give examples of agents that belong to this category.
  - Describe the synthesis, storage and biological effects of **histamine** (including receptors).
  - Describe the clinical uses of histamine receptor antagonists.
  - Understand the varied nature of peptides/proteins as chemical signals in the body.
  - Describe the synthesis and effects of **bradykinin**.

# Suggested Readings

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## ➤ Rang & Dale's Pharmacology

9<sup>th</sup> edition, 2020, Elsevier, Churchill Livingstone

**Chapter 18, 19, 27, 34**

<https://www.clinicalkey-com-au.ezp.lib.unimelb.edu.au/#!/browse/book/3-s2.0-C2016004202X>

## **Veterinary Pharmacology and Therapeutics,**

by Riviere JE and Papich MG (eds) 9<sup>th</sup> edition, 2009, Wiley-Blackwell

**Chapters 16-19**

## **Handbook of Veterinary Pharmacology**

Hsu WH (2008). 1<sup>st</sup> edition. Blackwell.

**Chapter 3**

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## Autacoids: diverse regulators and therapeutic targets

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Part 2 of 2

# A Cure For 'Agues'

Photo Henriette Kress



**Willow**

Photo Henriette Kress



**Spiraea**



# Active Constituent?

- **Salicylate**
- Synthetic salicylates made- acetylsalicylic acid (aspirin)
- Found to have **anti-pyretic** (fever), **analgesic** and **anti-inflammatory** actions.
- Introduced late 19<sup>th</sup> century- big seller!
- **How was this drug producing its effects?**

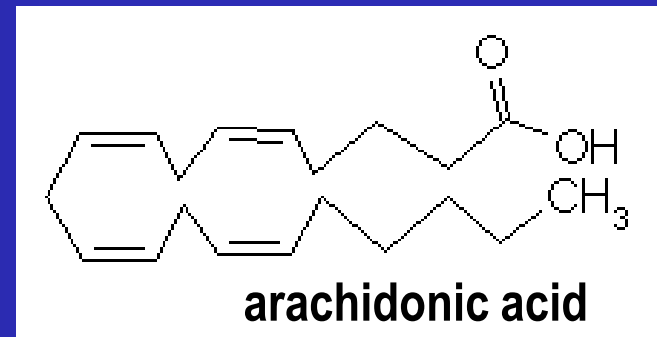
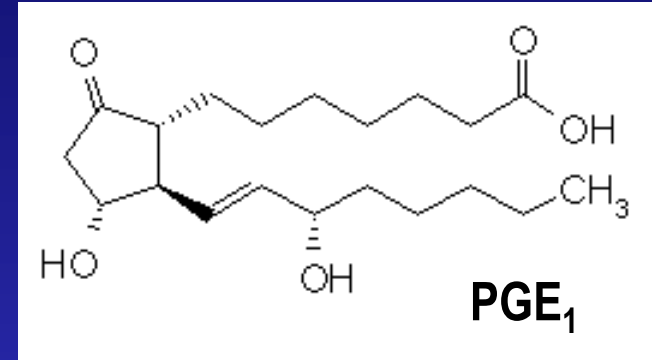


# Bioactive Component in Semen

- Contraction (or relaxation) of the uterus observed during artificial insemination.
- *In vitro/vivo* studies- contraction of smooth muscle and reduction of blood pressure demonstrated when semen/reproductive gland extracts administered.
- Active components thought to be from prostate gland- termed **Prostaglandins**.

# What Next?

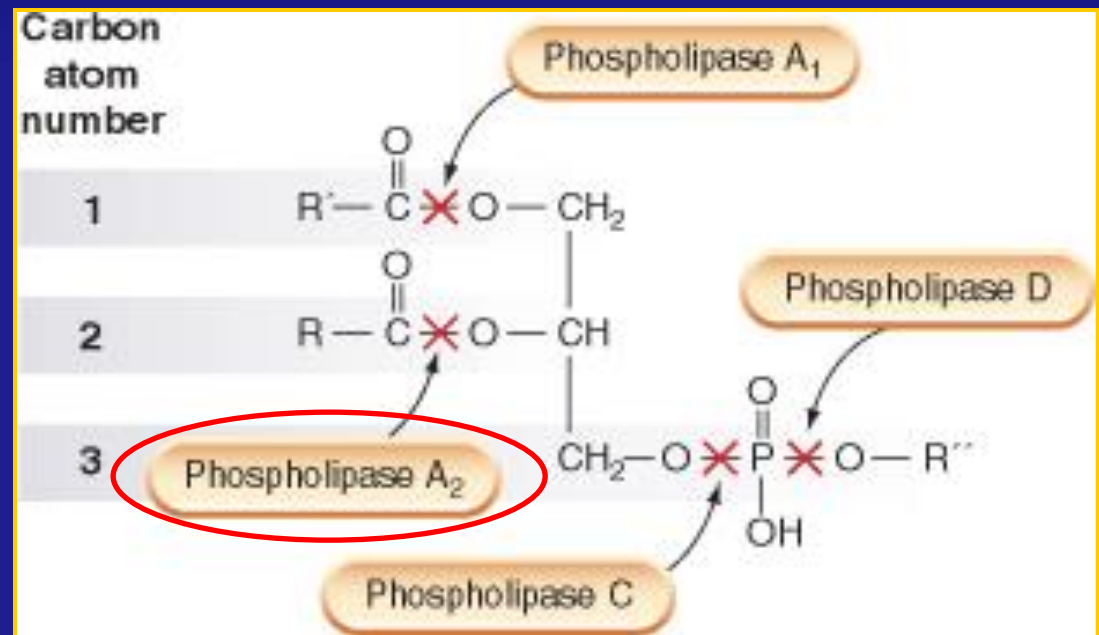
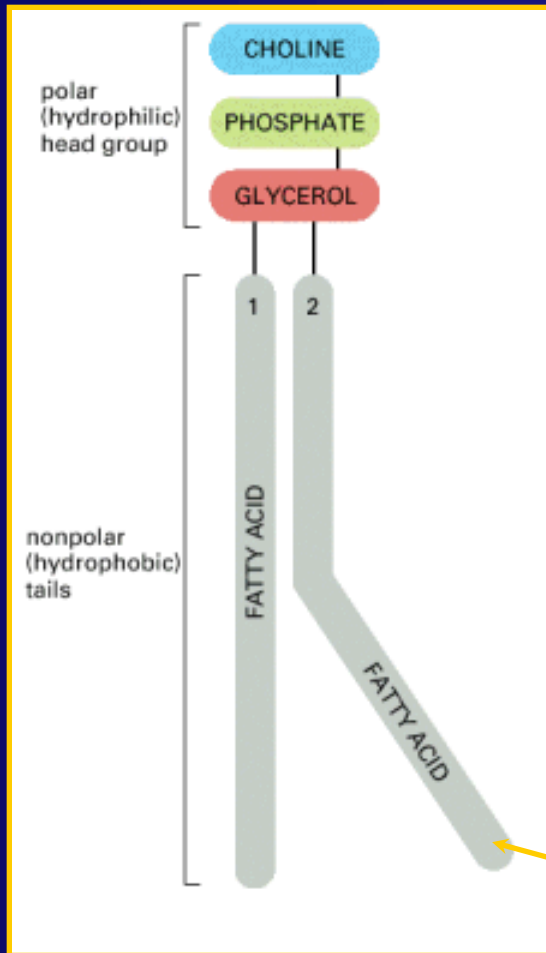
- Isolation and characterisation of bioactive component in semen.
- 20 carbon containing compounds- **eicosanoids**
- Structural similarity to essential fatty acids- **arachidonic acid**



# What Next?

- Enzymatic pathways to eicosanoid generation uncovered.
  - Many different prostaglandins and other bioactive products derived from arachidonic acid revealed.
    - Prostaglandins
    - Thromboxanes
    - Leukotrienes
- } **Prostanoids**
- Prostaglandins produced by most cells- broad regulatory activities
  - Eicosanoids not stored by cells- produced on demand (synthesised *de novo*)

# Phospholipids and Release of Arachidonic Acid by PLA<sub>2</sub>



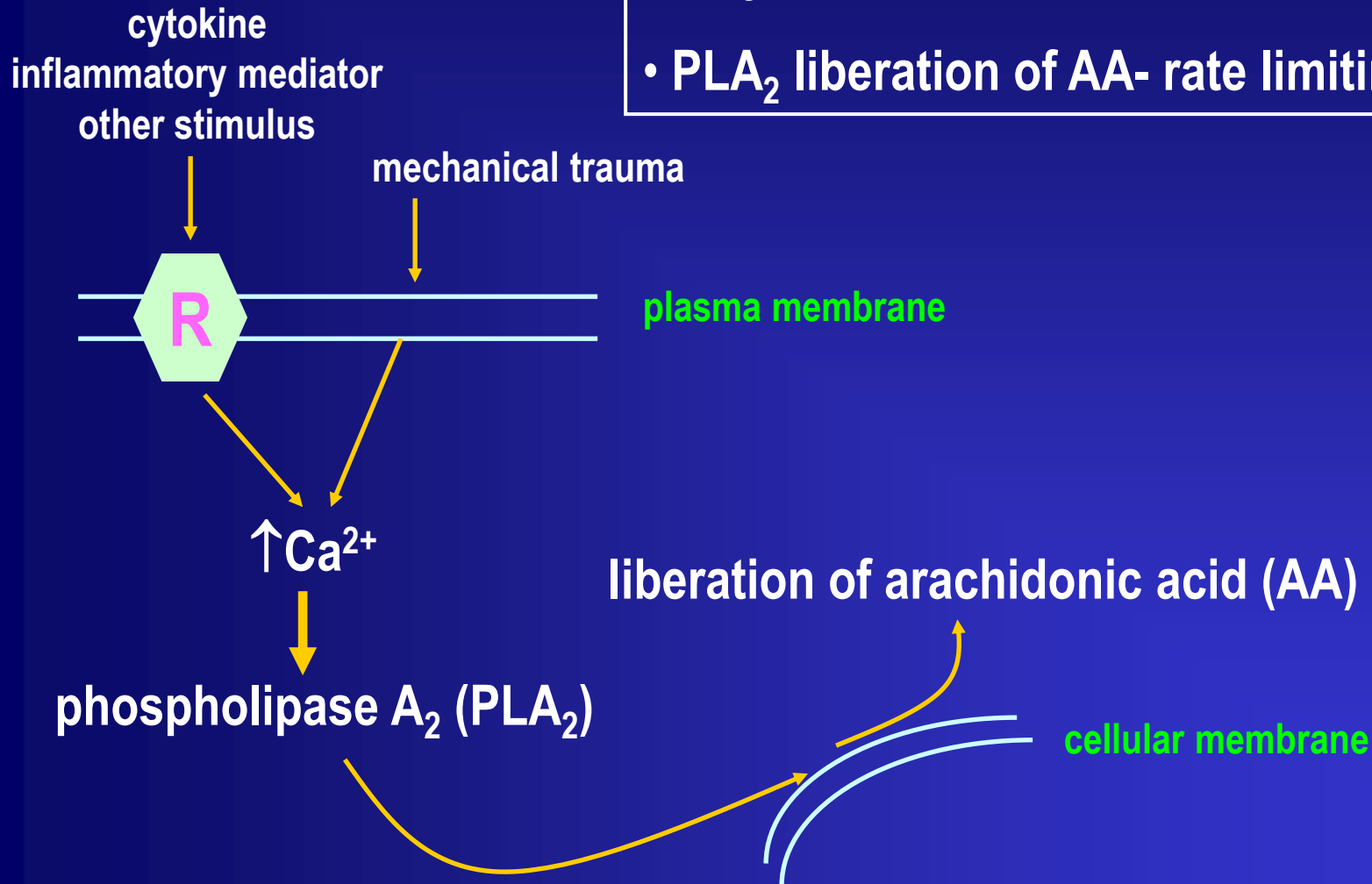
Rang: Fig. 13.6

*arachidonic acid*

Alberts: Fig. 10-2

# Generation of Eicosanoids

- Very low levels of free AA in resting cells
- PLA<sub>2</sub> liberation of AA- rate limiting step



**Phospholipids**

**PLA<sub>2</sub>**

**Arachidonic Acid**

**Cyclooxygenase  
COX**

**Lipoxygenase  
LOX**

**Prostanoids**

**Leukotrienes**

- **Prostaglandins**
- **Thromboxanes**

# Arachidonic Acid

**Cyclooxygenase  
COX**

Most cells

**PGG<sub>2</sub>**

**PGH<sub>2</sub>**

Cell specific  
synthase enzymes

**PGI<sub>2</sub>**

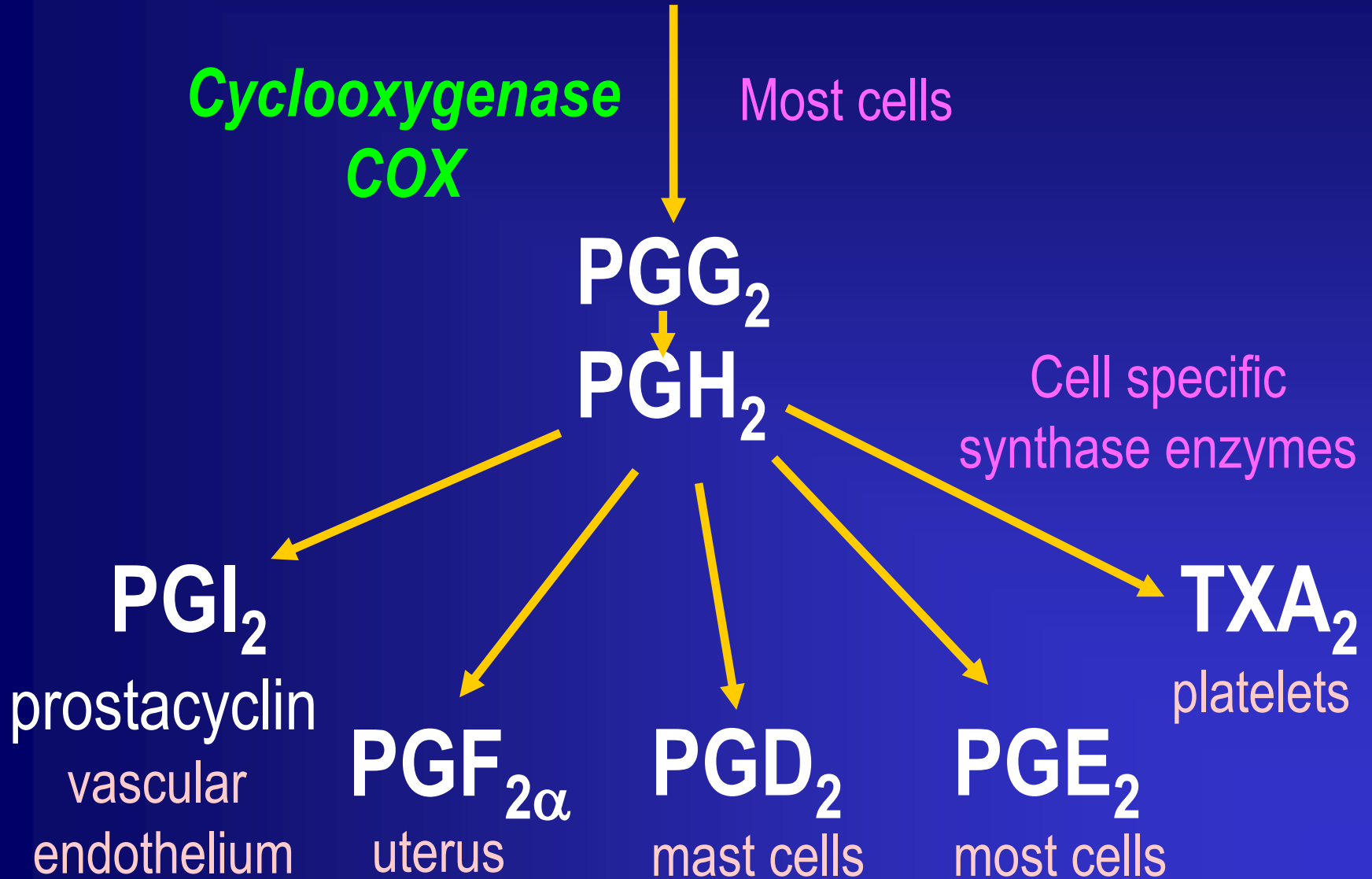
prostacyclin  
vascular  
endothelium

**PGF<sub>2α</sub>**  
uterus

**PGD<sub>2</sub>**  
mast cells

**PGE<sub>2</sub>**  
most cells

**TXA<sub>2</sub>**  
platelets



# Arachidonic Acid

**5-Lipoxygenase**

Mainly inflammatory cells

**LTC<sub>4</sub>**



**LTD<sub>4</sub>**



**LTE<sub>4</sub>**

**LTB<sub>4</sub>**

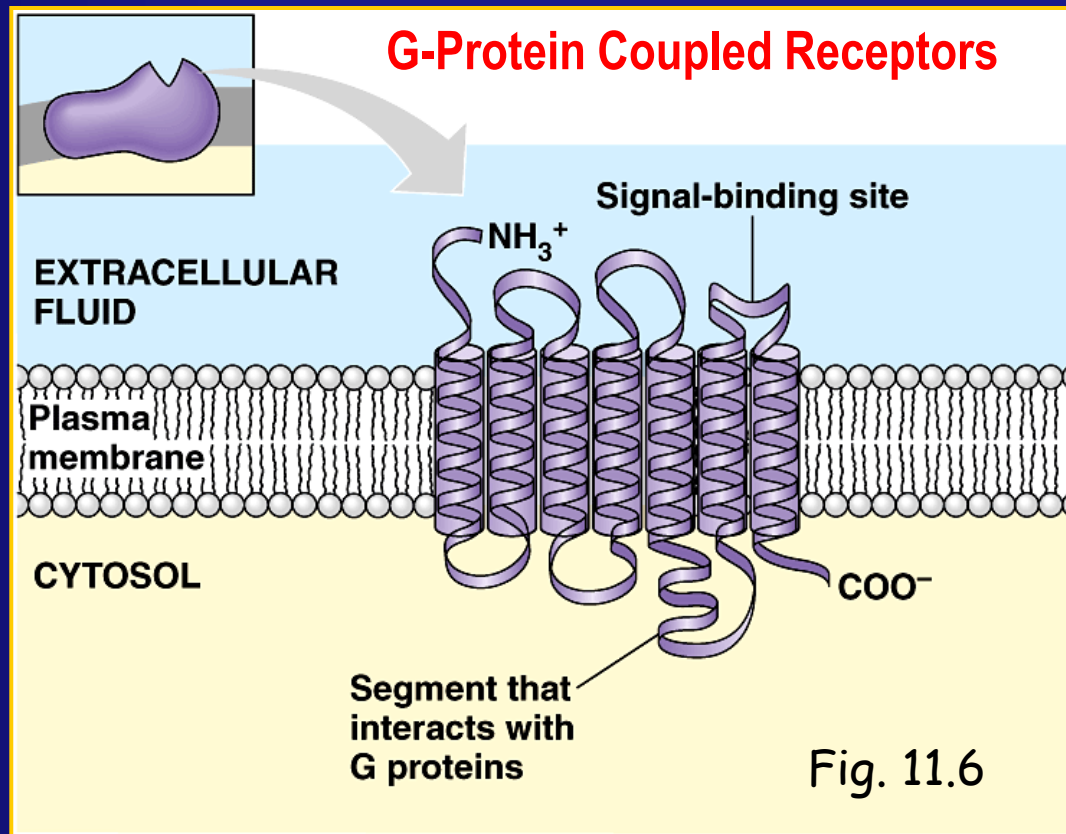
Cysteinyl-  
leukotrienes

• First identified in activated leukocytes



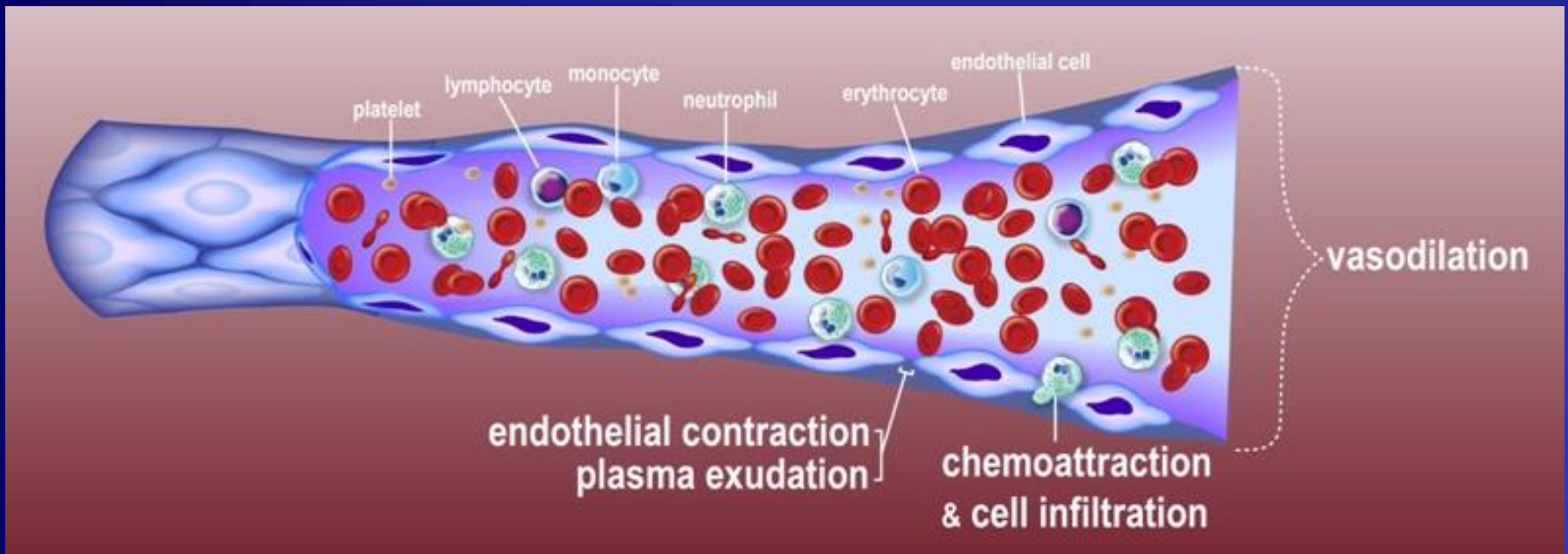
# How do eicosanoids produce their effects?

- Act via selective receptors- all G-protein coupled receptors (GPCRs)
- Subsequent generation of second messenger molecules



# PGs- Inflammation

**Reddening- vasodilatation at initiating site**  
**Wheal- increase in vascular permeability**

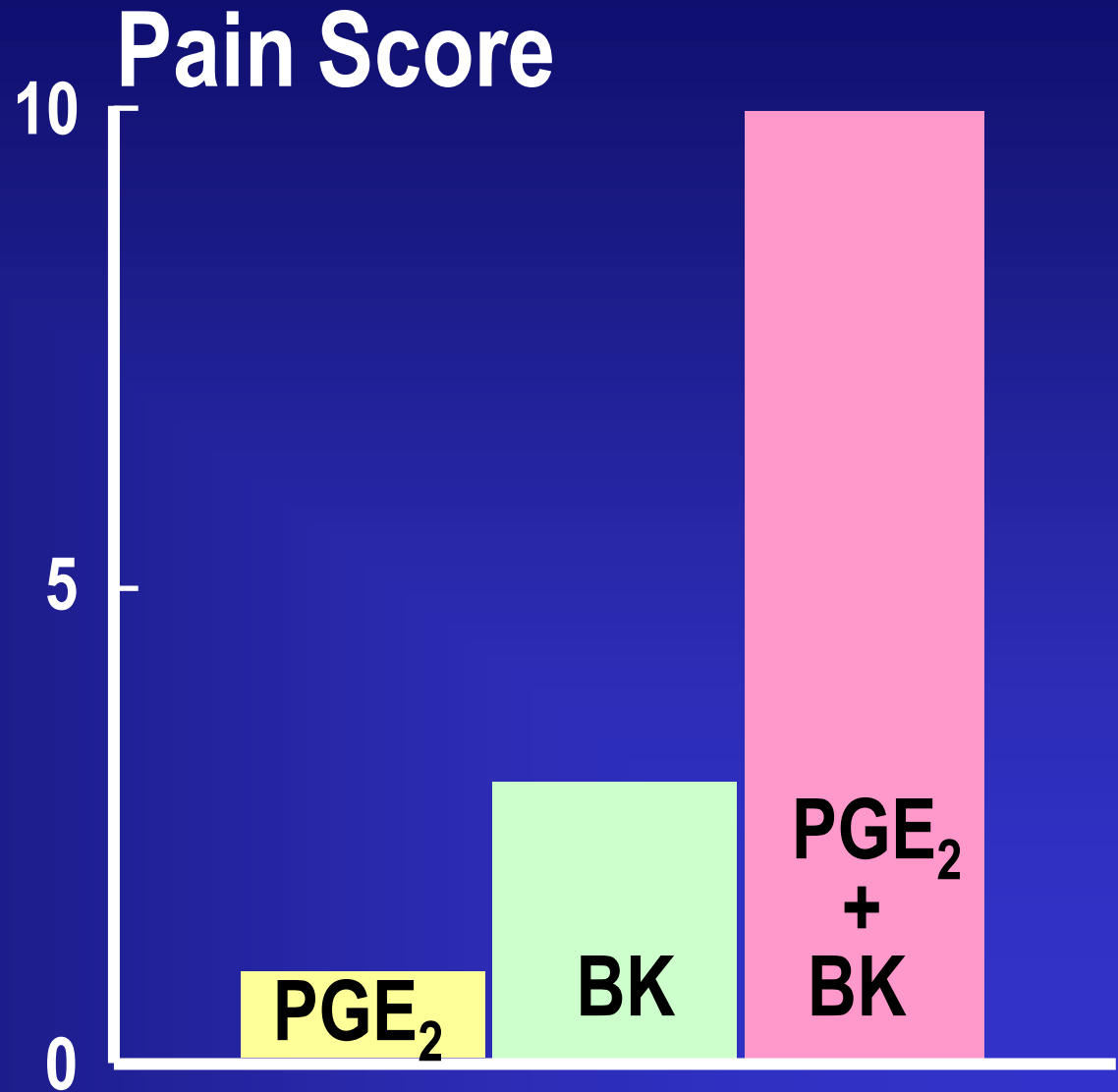


Stewart AG and Mackay GA. (2008). The Pharmacotherapy of Inflammation. *Encyclopedia of Life Support Systems* (EOLSS), Developed under the Auspices of the UNESCO, EOLSS Publishers, Oxford ,UK, [<http://www.eolss.net>].

# Pain

- $\text{PGE}_2$  and  $\text{PGI}_2$  are **hyperalgesic** *i.e.* increase sensitivity of receptors to painful stimuli

BK=bradykinin



# Fever

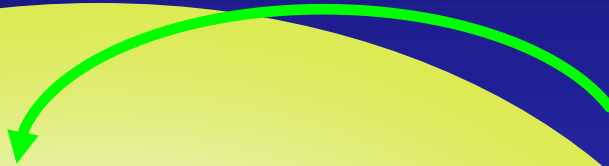
Inflammation



Neutrophil  
Activation



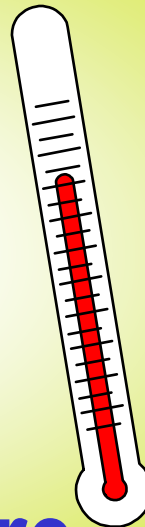
Cytokines



PGE<sub>2</sub>



Raise  
temperature



Hypothalamus

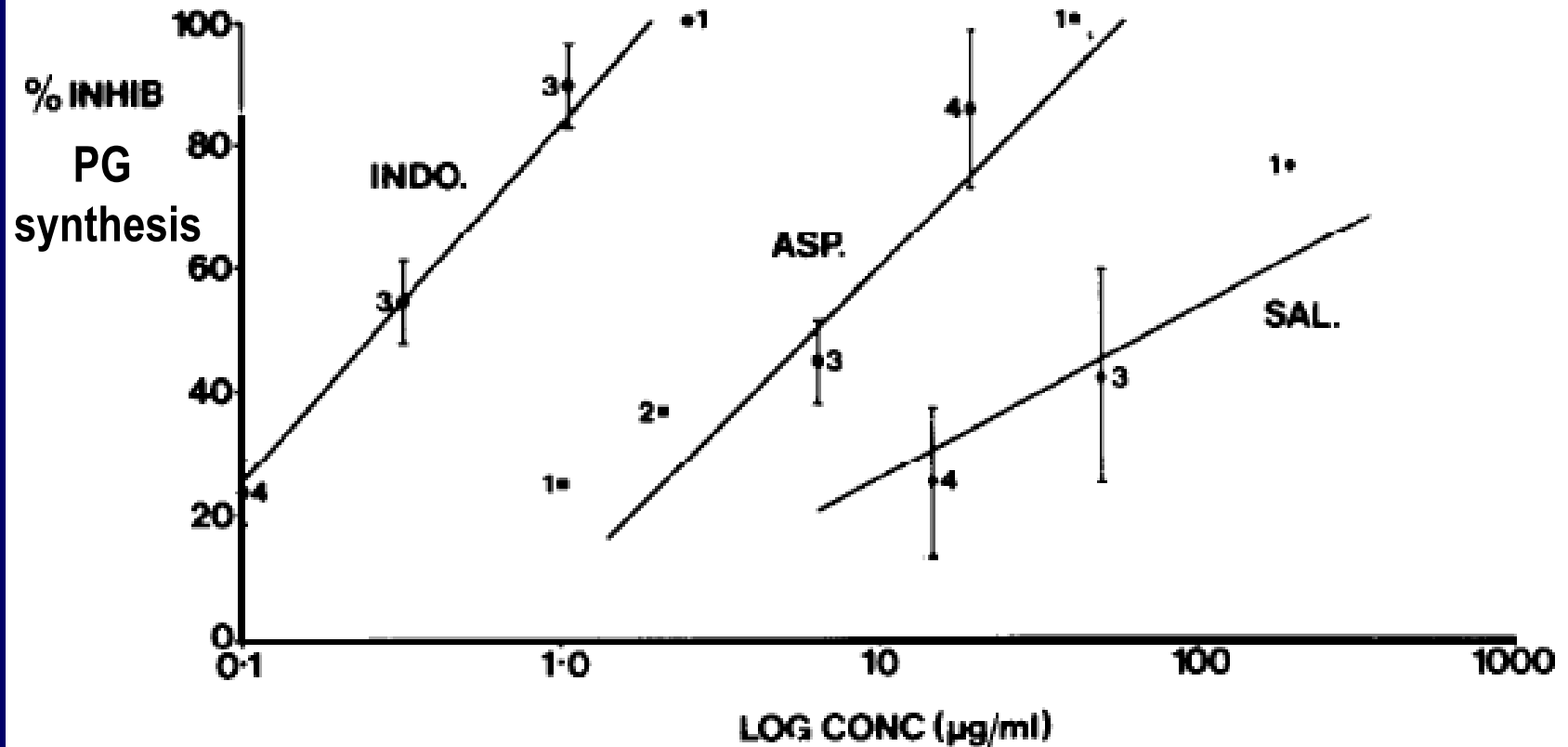
# Actions of eicosanoids

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- Fever
- Pain
- Inflammation

•Could it be.....

# Deciphering the mechanism of action of aspirin and related drugs



*Vane; Nobel Lecture; 1982*

# Phospholipids

NSAIDs

PLA<sub>2</sub>

## Arachidonic Acid

Cyclooxygenase  
COX

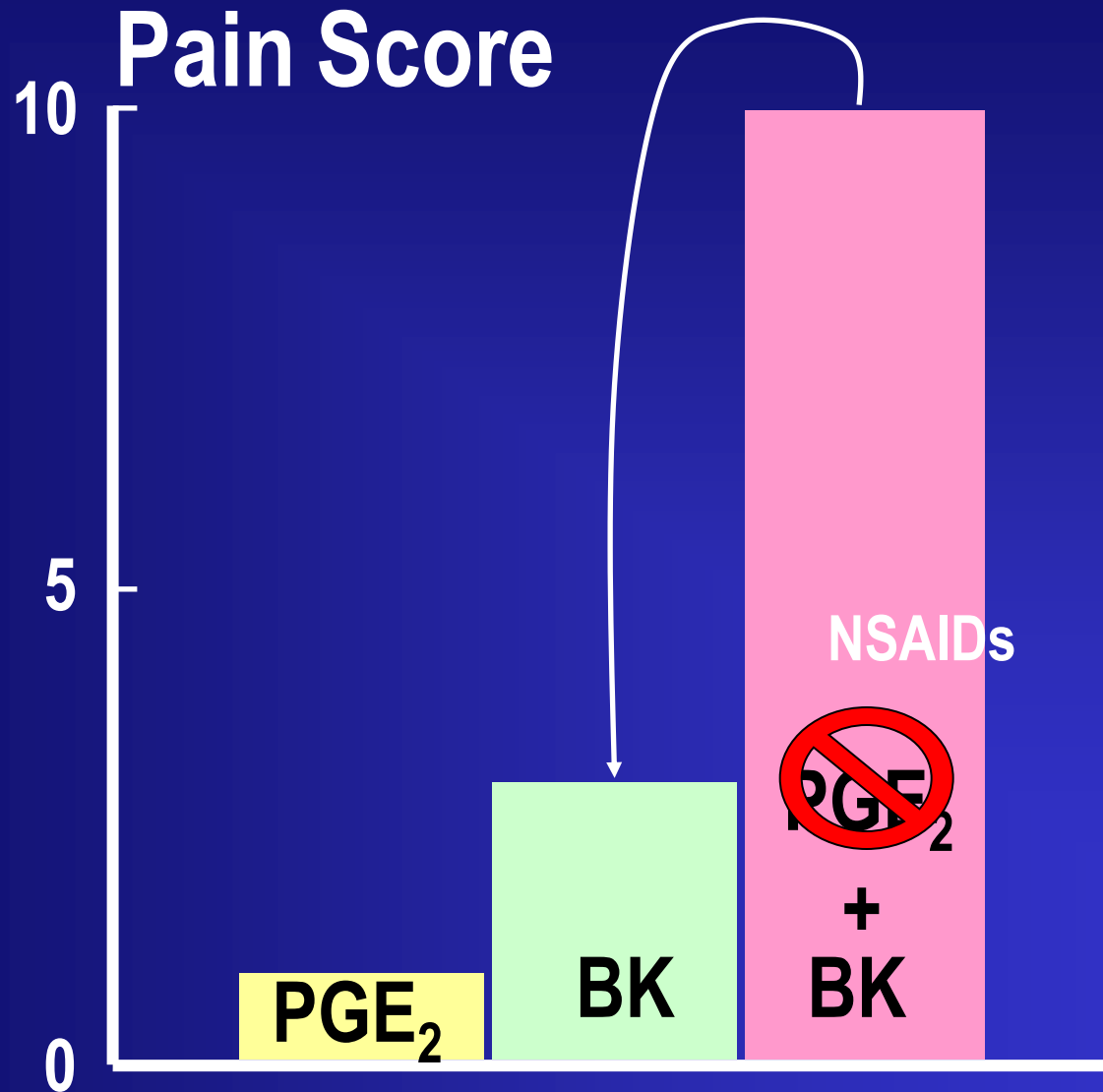
Lipoxygenase  
LOX

## Prostanoids

## Leukotrienes

- Prostaglandins
- Thromboxanes

# Prostanoids often have synergistic actions with other mediators





# Glucocorticoids

- Bind to receptors inside the cell to modify gene transcription.

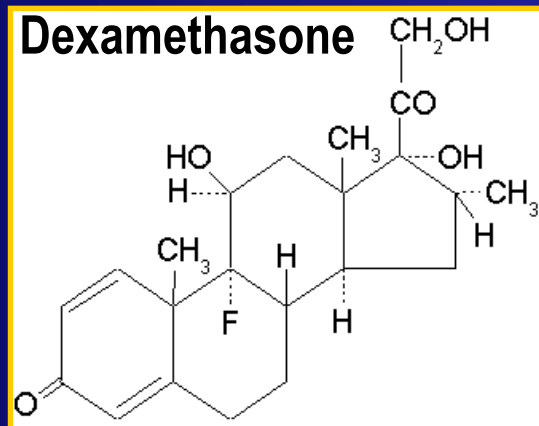
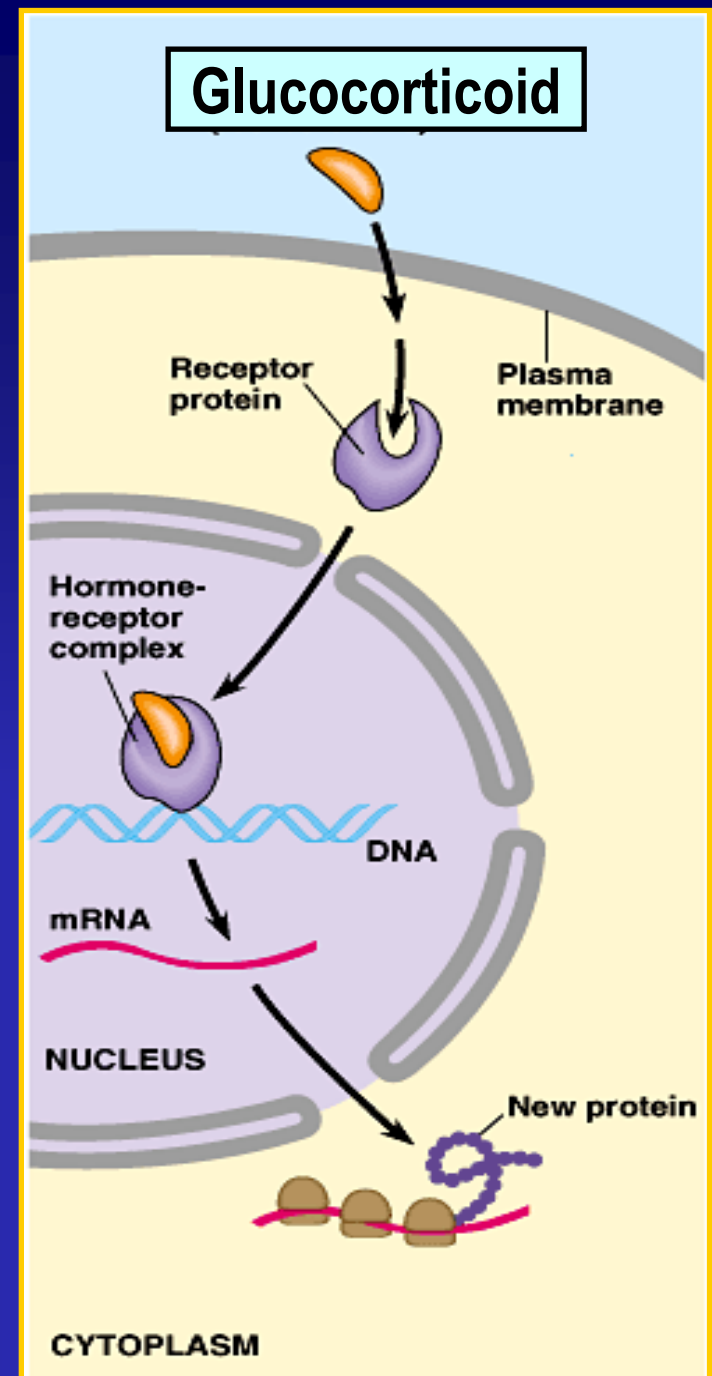


Figure 11.10, (Campbell & Reece, 2002)



# Glucocorticoids

- **Potent anti-inflammatory agents**
- Inhibition of the eicosanoid synthesis pathway (at several levels)
  - Inhibits COX/PLA<sub>2</sub> induction
  - Generate an inhibitor of PLA<sub>2</sub> activity
- **But also a lot more !!!**
- Broad inhibition of the generation of cytokines
- Inhibition of adhesion molecule expression etc

# Learning Outcomes

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- **After studying Part 2 of this topic you should be able to:**
  - Describe how **eicosanoids** are generated with particular emphasis upon the key roles played by the enzymes PLA<sub>2</sub>, cyclooxygenase and lipoxygenase.
  - Give examples (where appropriate) of key prostanoids produced by particular cell types and their actions.
  - Relate the synthesis and actions of the prostanoids to the therapeutic utility of the non-steroidal anti-inflammatory drugs (NSAIDs) and the glucocorticoids (noting the extensive additional actions of the latter drug class) .

# Suggested Readings

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## ➤ Rang & Dale's Pharmacology

9<sup>th</sup> edition, 2020, Elsevier, Churchill Livingstone

**Chapter 18, 19, 27, 34**

<https://www.clinicalkey-com-au.ezp.lib.unimelb.edu.au/#!/browse/book/3-s2.0-C2016004202X>

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**Chapter 3**