PC
Pharmacology Concepts
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Autacoids Pharmacology

Website

Videos

Pharmacology 2 | U2

"AUTACOIDS"

"AUTA" = Self, "AKOS" – Healing or Remedy

Autacoids are the endogenous biomolecules that are produce on demand, and act directly in tissues where they produce.

Also known as Local Hormone - acts locally at site of synthesis & release.

Major Response → ① Inflammatory Response
② Immunological response
③ Neurotransmission in CNS

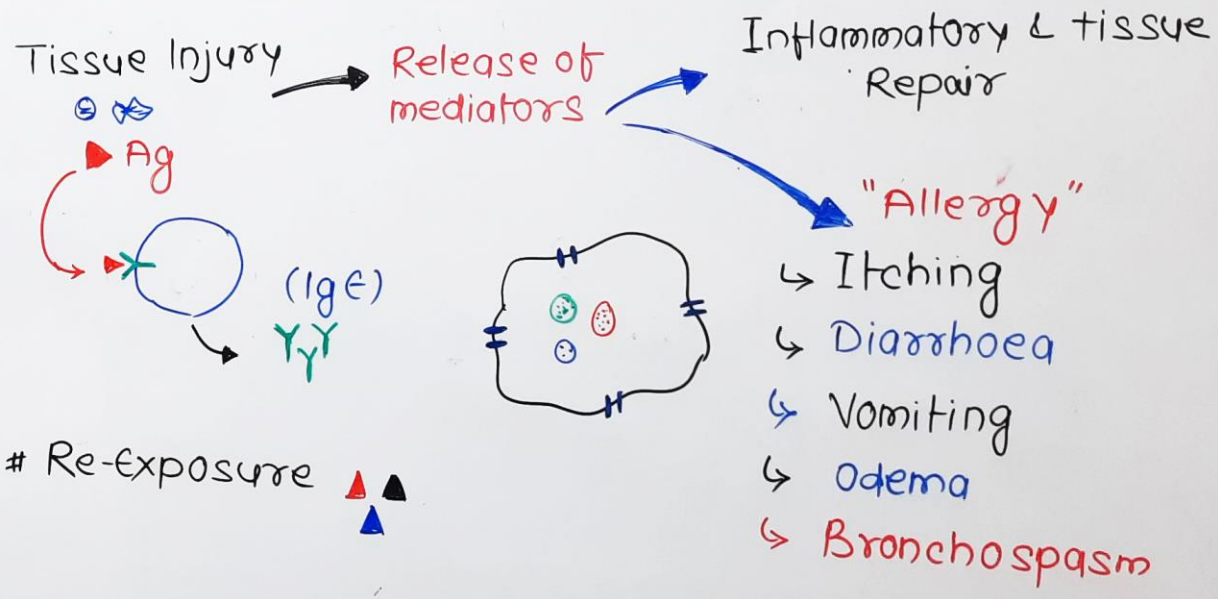
They have also veriety of physiological action

CLASSIFICATION –

1. Amines – Histamine, Serotonin (5-HT)
2. Lipids → Eicosanoids (Prostaglandins, Thromboxane, Leukotriens), Platelet Activating Factor
3. Peptides – Plasma kinins (Bradykinin, Kallidin) Angiotensins
4. Others – Cytokines (IL, TNF), Nitric oxide, Gastrin, Sometostatin, cholestokinines, Vasoactive intestinal peptides.

INFLAMMATORY & IMMUNE RESPONSE

Inflammation – Self healing & repair process of living tissue
L Sign → Rubor (Redness), Tumor (Swelling), Calor (Heat), Dolour (Pain), Funtio laesa (Inability to function)



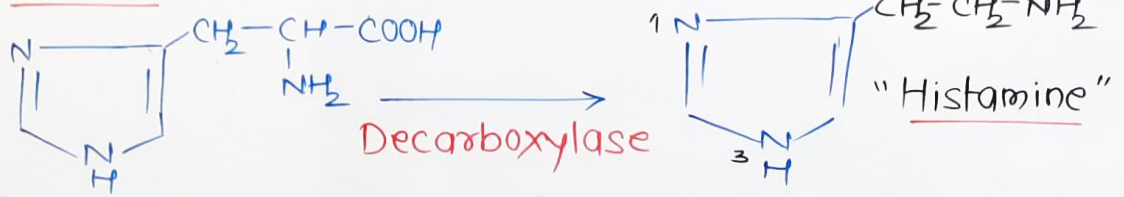
Re-Exposure

"HISTAMINE"

Histamine (Tissue Amine) is an amine derivative "AUTACOIDS" Found in animals, human, & plants (Stinging nettle)

First isolated by "Barger & Dale" in 1911 from Ergot and in 20th century "Dale" studied its "Allergic & Hypersensitivity reaction"

BioSynthesis :→



2-(1H-Imidazol-5-yl) Ethyl amine

METABOLISM

- Diamine Oxidase → * Imidazole Acetic Ac
- N-Me. Transferase → *N-methyl histamine

STORAGE : # in storage granules of mast cells of skin, GI mucosa, Liver, Lungs & Placenta (*Slow Turnover Cells)

in non-mast cells (*fast turnover) → neurons, epidermis, vascular Endothelial Cells

RECEPTORS → H_1 (G_qPCR), H_2 (G_sPCR), H_3 & H_4 (G_iPCR)

Classified in to H_1 & H_2R by "Asch & Schild" in 1966

Sir James Black (1972), → Burimamide (H_2R blocker)

1983, H_3R (Autoreceptor) - located in Brain

Bitahistine (Hist. analogue) - Control Vertigo in "Meniere disease" due to vasodilatory effect in internal Ear

IAg–Ab → IP_3 → Ca^{2+} → Hist(+) & Acidic Protein, Hist(-) – Heperin → Na^+/Ca^{+2} → Histamine → Allergy

Cell injury – Inflammatn

PHARMACOLOGICAL ACTION

1. H_1R Mediated :→

a) Smooth Muscles (Intestine, Uterus, Bronchi) → Contraction

b) Blood Vessels → # Small – Dilation (NO-dependent)
Large – Constriction (IP_3/Ca^{2+})

*ID inj – Triple Response
1) Flush (Red Spot) – Capillary dilation
2) Wheal – Secretn of Fluid from capillary
3) Flare – Redness on Surrounding area due to arteriole dilation

c) Afferent nerve ending & Ganglia – Stimulation

d) Adrenal medulla – release of CAs (NA, DA)

e) Brain – Neurotransmitter

2. H_2R Mediated Action

a) GI Glands → ↑ Acid Secretion

b) Heart → (+) Chrono & (+) Inotropic effects

c) Smooth mus. (BV, uterus) – dilation

d) Brain → Neurotransmission

3. H_3R Mediated Action – Auto-Receptor

a) Brain – ↓ Histaminergic transmission – Sedation

b) Lungs, Skin, GI mucosa – ↓ Histamine release

c) Intestine – ↓ Ach release

d) BV – ↓ NA release – dilatn

ANTI-HISTAMINICS

→ H_1R- Antagonist

CLASSIFICATION of Anti-Histaminics

I. 1st Generation / Sedative

Highly Sedative - Diphenhydramine*, Diphenhydrinate, Promethazine*, Doxylamine*, Hydroxyzine

Moderate :- Phenaramine*, Cinnarzine*, Cyprohiptadine, Pyrilamine

Mild - Chlorphenaramine, Cyclizine, Betahistine

II. 2nd Gen. / Non Sedative

*Terfinadine, *Astimazole, L-Cetirizine

*Foxafenadine, Rupatidine (PAF Antagonist)

PHARMACOLOGICAL Action

I) 1st Gen ⇒ 1. Anti-Allergic*

→ ↓ TypeI / Immidiate Hypersensetive

→ used in - Asthma, Urticaria, Itching, Anaphylactic Reactn, Angiodema

2. CNS = Sedation*

3. Anti Ach action = Centrally ⇒ Extrapyrimidal Side effect

* EPS = Parkinson like - Tremmor, Akinasia, ↓ motor co-ordination

Anti-Emetic - ↓ motion sickness*

Peripheral - GI upsate

4. Local Anaesthetic - Phenaramine - mem. stabilizer

5. Smooth mys - Relax

ADR - Sedatn, EPS, Fatigue

use* - Anti-emetic, Antiallergic

Cinnarzine, Betahistine - Anti-Vertigo

Cyproheptadine - ↓ SHT → ↑ Hunger

II 2nd Gen :- No Sedatn & No-Anticholinergic Action

use - Anti-allergic, Cold & Cough, Pre anaesthetic, Anti-Vertigo

* Terfenadine → Foxafenadine.

↳ Torsades De point (Arrhythmia)

↳ block rectifying K^+ channel

SEROTONIN (5-HT) PHARMACOLOGY

Serotonin was identified in 1948, originated from platelets & found in blood serum as a potent "Vasoconstrictors"

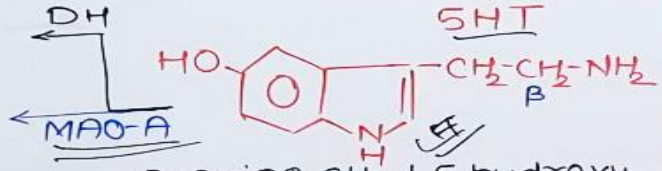
Location - ↳ GI mucosa - 90%, Enterochromaffin cell → enteramine / 5HT
"Vasoconstriction" ← enteramine / 5HT
↳ Rest are found in platelets & Brain
↳ In brain → Inhibitory Neurotransmitter

Synthesis & Metabolism - GI & Brain

Tryptophan —hydroxylase→ 5-Hydroxy tryptophane —decarboxylase→ 5HT

5-hydroxy tryptophol

5-hydroxy indole Acetic acid (5HIAA) ← MAO-A ← DH



β-amino ethyl 5 hydroxy Indole

5HT Receptor :- $5HT_1$ to $5HT_7$

↳ Gaddum & Picarelli, (1957) classified 5HT R, into Musculotropic (D Type) & Neurotropic (M type) based on their blockade by Dibenzyline and Morphine
↳ Later classified into various categories

$5HT_1$ (1A, 1B, 1D) → GiPCR → CNS(−), Behavioral, BV
$5HT_2$ (2A, 2B, 2C) - GqPCR → CNS(+), Smooth mus. platelet
$5HT_3$ → LGIC (Na^+ channel) - CNS(+), Emesis
$5HT_4$ → GsPCR → CNS(+), Prokinesis

PHARMACOLOGY

A. CVS - Heart - $5HT_2$ → (+) Inotropic & (+) chronotropic
➤ Intact Animal (Heart) - Bradycardia due to activat° of chemoreflex (Bezold Jarisch Reflex) through actn on vagal → Bradycardia Hypotension and aphoea.

Artery - Large (constrictn), Small (dilation, EDRF) - $5HT_2$
* BP (Triphasic) - (I) sharp ↓ in BP (due to coronary chemoreflex
(II) Rise in BP - due to vasoconstriction & ↑ CO
(III) Prolonged fall in BP - due to arteriolar dilation

B) Smooth muscles ($5HT_2$) → Stimulatory & constriction
↳ GIT, Bronchi, uterus

C) Glands → ↓ Gastric Secretn & ↑ mucus production - Protective

D) Respiration → Stimulation & Hyperventilation

E) Platelet - $5HT_{2A}$ - Weak Aggregator

F) CNS - act as neurotransmitter, Behavioral effects

PHYSIOLOGICAL ROLE ⇒ Neurotransmission, Precurssor of melatonin, Neurohormonal control, Vomitting, Migraine, Raynaund's phenamenon, etc

PHARMACOTHERAPY of 5HT MODULATORS

① Sumatriptan - $5HT_{1D}$ Agonis → ↓ Migrain
② Methyl serigide - $5HT_{1A/C}$ Antag. — ↓ Migrain
③ Ondansetron - $5HT_3$ Antagonist - Antiemetic
④ Buspirone - $5HT_{1A}$ Agonist → Antianxiety
⑤ Cisapride - $5HT_4$ Agonist - Prokinetic / ↓ emesis
⑥ Ketanserin - $5HT_{2A}$ Antagonist - used in Hypertension & Raynauds phenamena
⑦ Fluvoxetin - SSRI - Antidepressant

Eicosanoids And Platelet Activating Factors

Eicosanoids:- are the lipid derivative, which are generated from phospholipids or Polyunsaturated fatty acids (PUFAs) & produce inflammatory Response

DAG → PL-C

PL-A_2 → Corticosteroids

"Arachidonic acid"

COX I/II (→ NSAIDs) → PG-G_2 → PG-F_2 Cyclic Endoperoxids

- PGI_2 (Prostacycline) → Vasodilatn (Gs)
- PGs Synthase
  - $PG-E_2$ (Gq) → Vasodilatn (EDRF), Inflammation, Ulcer protective
  - $PG-F_{2\alpha}$ (Gq) → Bronchoconstrictn
  - $PG-D_2$ (Gs) → Vasodilation & ↓ Platelet Aggregation
- TXA Synthase → $TX-A_2$ (Thromboxane) → Thrombocytic & Vasoconstriction (Gq)

5-LOX (→ Zelutin) → LT-A_4 (Leucotriens)

- LT-B_4 (Neutrophilic) → Chemotaxis
- Cysteinyl or Eosinophilic LTs: $LTC_4 \rightarrow LTD_4 \rightarrow LTE_4$ → LTF_4 (+) → LTR (GqPCR)
  - (→ Montelukast, Zefirlucast)
  - ↳ Bronchoconstriction
  - ↳ ↑ Vas. permiability

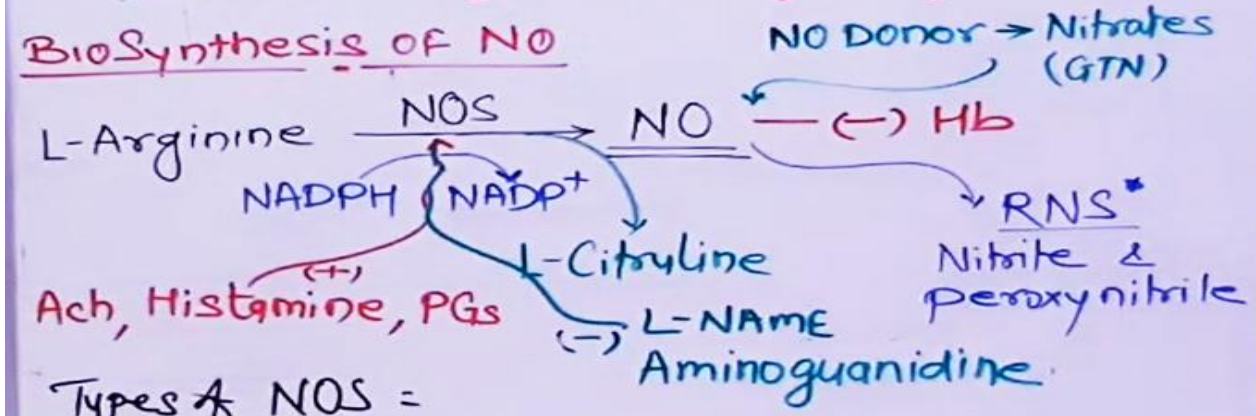
Lyso-glyceryl phosphoryl chain → (→ Ginkgolide-B, Laxipafent) → PAF [GqPCR]

- ↳ Vasodilation (EDRF)
- ↳ ↑ Cap. permiability
- ↳ Bronchoconstriction

NITRIC OXIDE (NO)

→ Discovered in 1979 as a potent Vasodilator
→ It is a Autacoids, And in the body it acts as a-
  ↳ Paracrine Vasodilator
  ↳ Neurotransmitter in CNS
  ↳ Appoptosis
  ↳ 2nd messanger in NO-Signalling pathway

BioSynthesis of NO



Types of NOS =

① NOS-I / n-NOS → Neuronal cells of CNS & PNS
  ↳ Activated by Ca^{+2} - dependent Signalling

② NOS-II / i-NOS = Inducible NOS
  → +nt on most Nucleated cells & Macrophages
  → Activated by Inflammatory mole. (Ck, IL)
  → Inflammatory & Oxidative stress

③ NOS-III / eNOS - Endothelial NOS
  → +nt Vas. endothelial cell
  → Ca^{+2} - dependent Activation

P'COLOGICAL ROLE -

CNS - Neurotransmitter
→ + long term Learning & memory

+n NOS → NO ⇝ (+) GC/cGMP → ↑ Glutamate → + NMDA R
Ca^{+2}-Cam
∓ Learning/memory ←

CVS: → Potent Vasodilator = ↓↓ BP

NO ⇝ + GC (Intracellular enz) → ↑ cGMP (+) → MLCP → Vaso-Relaxation

→ Helps to Gas exchange b/w Haemoglobin & Cell

Smooth mus - Relaxant effect-

Immune System -

Inflammation (+) WBC/macrophages (+2) → iNOS → NO → ↓ Bac. Infection

Nitroso/Oxidative Stress

Inflammatn → iNOS → ↑↑ NO ⇝ RNS* (Free Radical)

"Oxidative Damages of Cell. Proteins, Lipids, & Nucleic Acid"

VASOACTIVE PEPTIDES

↳ Peptides which directly affect the vasculature tonicity

Vesoconstrictors	Vasodilators
# Angiotensin-II	# Bradykinin & Kallidin
# Vasopressin (AVP, ADH)	# Natriuretic peptide (ANP & BNP)
# Endothelins (ET)	# Vasoactive intestinal peptide (VIP)
# Neuropeptide-Y (NPY)	# Substance-P
# Urotensin	# Calcitonin gene related peptide (CGRP)
	# Adrenomedullin

"VASOCONSTRICTORS"

Ang-II → (+) AT_1R → GqPCR → Vasoconstriction
Peripheral Edema
CVS Remodeling
(+) Sympathetic outflow

Endothelins → ET_1, ET_2 & ET_3 (21 AA)
↳ ET_A — Vasoconstriction

Vasopressin → (+) V_1R (GqPCR) — Constriction

Neuropeptide-Y (36 AA) → Co-transmitter with NA, DA, 5HT, GABA
↳ Y_1, Y_2, Y_5R ↳ Y_1R (GqPCR) → Vasoconstriction

Urotensin II (11 AA) → UTR → Constriction

"VASODILATORS"

Kinins → B_2R → ↑NO → Vasodilation

Natriuretic peptide (ANP, BNP, CNP) → NP-R (GC-En2 linked Receptor) → cGMP — Vasodilation

VIP (28 AA) → Co-transmitter with Ach
↳ $VPAC_1$ & $VPAC_2R$ → GsPCR → Vasodilation

Sub-P → NK_1, NK_2, NK_3R - GqPCR - NO ↑

CGRP → Calcitonin Receptor like Receptor (CLR) GsPCR

Adrenomedullin — NO-mediated Vasodilation

Clink the icon → Video Lectures Website/Notes

Renin Angiotensin Aldosteron System (RAAS/RAS)

RAAS - Regulates BP, Electrolyte & Fluid homeostasis, And Inflammatory & Oxd. Stress

↓ Renal Blood Perfusion / (+) Symp. System

Angiotensinogen [Liver]

Pro-Renin → Renin (+)

Aliskiren (−)

Angiotensin I (1-10) — ACE-2 → Ang (1-9)

ACE Inhibitor (−) | ACE ← (Endothelial cell)
Chymase
Cathepsin A

Kininogen → Bradykinin → B1/B2 R
Bradykinin — ACE
→ Vasodilation
→ CK release
→ Res. mucous Sec.

Ang (1-9) — ACE → Ang (1-7)

Aminopeptidase A

Ang-III ← Ang-II (1-8) — ACE-2 → Ang (1-7)

Ang-III — Aminopeptidase N → Ang-IV → (+) AT4 R

Ang-II (1-8) → (+) GqPCR → AT1R
ARB (−) AT1R
Ang-II (1-8) → AT2R

(+) GqPCR (P) RR

Vasodilation
Neuronal Develop.

→ Vasoconstriction
→ (+) Inflammath
→ (+) Oxd. Stress
→ Hypertrophy
→ Apoptosis

BV → Vasoconstriction
→ Hyperplasia / Fibrosis
→ Inflammatn & Ox. Stress
Heart → Hypertrophy
CNS → + Symp. Outflow
Kidney - Aldosteron Release
Na+/water Retaintion
P. Edema

AT2R → Vasodilation
(−) Fibrosis
(−) Cell Proliferation

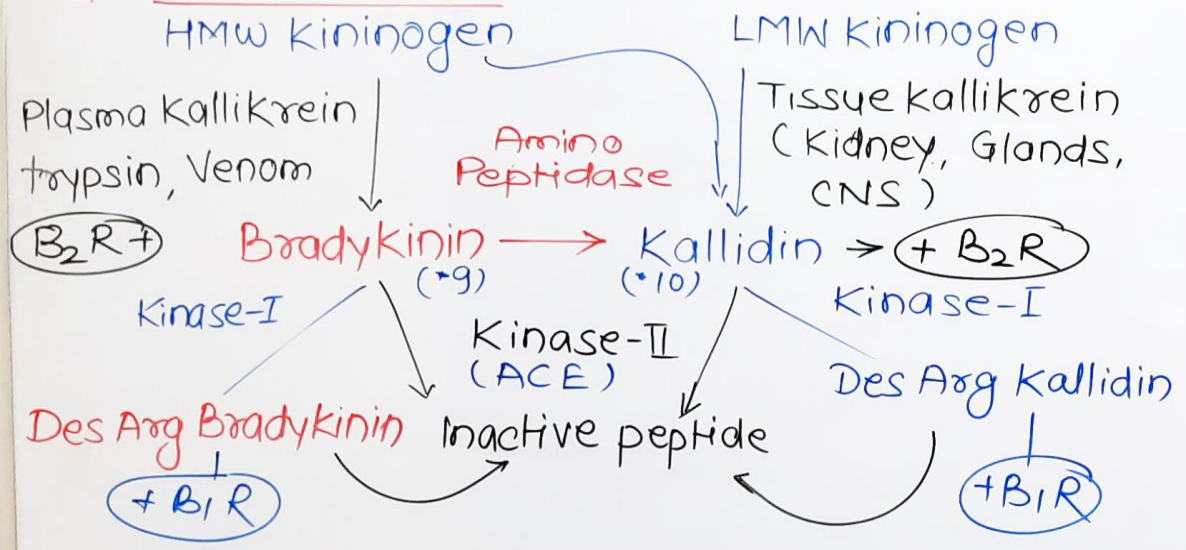
Ang (1-7) (+) → Mass R

→ Vasodilation
→ (−) Angiogenesis
→ (−) Fibrosis/Cell Proliferatn
→ (−) Inflamm. & Oxd. stress

BRADYKININ AND KALLIDIN

↳ Vasodilatory plasma kinin (Polypeptide), which are discovered in about 1950s.
↳ Kinins are generated by proteolytic reactn triggered by tissue injury, inflammation, allergy, etc

Syntesis & Metabolism



Biological Action ⇒

A) Blood Vessels = More potent Vasodilatory (Arterioles) action than Ach & Histamine through NO-mediated action. In other hand, Large arteries & veins are constricted through direct (G_qPCR) action.
↳ ID injection caused wheel & flare (Similar to hist.)
↳ ↑ vascular permiability, "Reflux action on heart)

(B) Smooth muscle - Contraction of intestine, uterus, and broncho-airway, but not prominent.

C) Neurones - Stimulate nociceptive afferent neuron → Acute pain, burning sensatn. inj to brain cause release of CAs

D) Kidney - ↑ Renal blood flow & excretn of Na^+/water

Pathophysiological Role ⇒

↳ Inflammatory Response - + B_1R (Macrophage) - IL, TNFα
↳ Nociception (Mediation of pain)
↳ Functional hyperemia (In gland during secretion)
↳ Hereditary Angioedema - ↑ Level
↳ Renin-Angiotensin-System

= Antagonist - Icatibant

↳ Decapeptide B_2R antagonist resistant to kinin degrading Enzyme.
↳ Used in Hereditary Angioedema to reduce swelling and other symptoms.

SUBSTANCE-P

↳ A intestinal smooth muscle constrictor detected in several tissues by Von Euler and Gaddum in 1931 & named Substance-P.

↳ Made up of 11 amino acid neuropeptide distributed widely in brain, spinal cord, peripheral sensory nerve, enteric nervous system, blood vessels & Skin.

↳ Neurokinin-A & Neurokinin-B (decapeptide) → (Tachykinin) → Constrictor

Synthesis : Preprotachykinin → Sub-P, NKA, NKB

Inflammation & pain ← Sub-P

NKA, NKB → neuromodulators

Biological Action →

Tachykinin → (+) NK_1, NK_2, & NK_3 Receptor (GqPCR)

* Substance-P → ++ NK_1R

↳ Smooth muscle contraction
↳ Glandular secretion
↳ NO Release
↳ Cell proliferation
↳ production of afferent impulse
↳ Vasodilation through action of Nitric oxide (NO)

Biological Role –

↳ Arteriodilator (↓ BP) & ↑ Vascular permiability
↳ veins & other smooth muscle – constriction
↳ kidney → Natriuretic & Diuretic effects

Brain → involved in mood, behaviour, anxeity, stress, depression, reinforcement, nociception, etc.

↳ CTZ – NK_1R & $5HT_3$ ⇒ Vomittin in response to noxious stimuli

↳ Sub-P – involves in pain perception & inflammatory response.

↳ Sub-P → + Cytokines → Inflammath, Cell proliferath, growth, angiogenesis → Tumors

Substance-P Antagonist

* Aprepitan (Fosaprepitant) → adjuvant antiemetic for cancer chemotherapy
* May useful in anxiety, depression, stress condition, Inflammatory bowel disease, arthritis, cancer, etc.