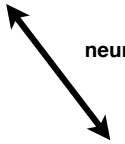
Autacoids

neurotransmitters



neuromodulators

inflammatory mediators

autacoids

- 5 hydroxytryptamine
- adenosine
- peptides
- histamine
- eicosanoids
- plus many others

5HT

- gut lining
- platelets
- CNS

5HT

- synthesis, storage, release & uptake very similar to NA
- affected by same drugs
- co-transmission
  - somatostatin
  - substance P
  - vasoactive intestinal peptide

5HT effects

- increased gut motility
- vasoconstriction / dilatation
- smooth muscle contraction
- platelet aggregation
- excitation of nociceptors

5HT CNS effects

- may be involved in
  - sleep
  - appetite
  - mood / anxiety
  - vomiting
  - pain perception
  - stereotypy

5HT receptors

- 15 subtypes at present
  - 5HT3 ligand gated ion channel
  - rest G protein coupled
- all over the body
- mediate a huge range of effects

5HT receptors

- 1A - CNS - (autoreceptor) sleep, appetite, anxiety
- 1B - CNS - (autoreceptor) behavioural effects
- 1D - CNS, blood vessels - vasoconstriction
- 2A - platelets - aggregation, smooth muscle - contraction
- 2B - stomach - contraction
- 2C - choroid plexus - CSF secretion
- 3 - P/CNS - vomiting, anxiety
- 4 - gut - motility
- 5A&B - CNS - unknown function
- 6 - CNS - unknown function
- 7 - hypothalamus, intestine - unknown function
- other receptors in slimy things

5HT drugs

- 5HT1 - ergot (antagonist)
- 5HT1A - buspirone (partial agonist)
- 5HT1D - sumatriptan (agonist)
- 5HT2 - LSD (agonist)
- 5HT3 - ondansetron (antagonist)
- 5HT4 - metaclopramide, cisapride (agonist)
- uptake 1 - fluoxetine (blocker)

purines

- adenosine
- adenosine triphosphate

adenosine receptors

- A1 - inhibits adenyl cyclase
- A2 - stimulates adenyl cyclase

drugs

- A1 agonists
  - adenosine
- A1 antagonists
  - caffeine
  - theophylline

peptides

- very widely distributed
- most come from nervous system / endocrine glands
- most act as co-transmitters / neuromodulators

peptides

- 3 - 200 amino acids
- small peptides
  - G protein coupled receptors
- large peptides
  - tyrosine kinase linked receptors
- active peptides cleaved from proteins

peptides as drugs

- not often used
  - poorly absorbed
  - rapidly broken down
  - do not cross blood brain barrier
  - expensive
- metabolic enzyme inhibitors

peptides

- opioids
  - β endorphin, endomorphins
  - enkephalin
  - dynorphin
  - nociceptin

peptides

- tachykinins
  - substance P (NK1 receptor)
  - neurokinin A (NK2 receptor)
  - neurokinin B (NK3 receptor)

tachykinin effects

- smooth muscle contraction
- increased capillary permeability
- burning pain / hyperagesia
- pruritus
- exocrine gland secretion

drugs

- capsaicin
  - depletes substance P
- many experimental NK1 antagonists
  - spantide

inflammatory mediators

- histamine
- eicosanoids
- platelet activating factor
- bradykinin
- cytokines

inflammation

- swelling
- pain
- redness
- heat
- loss of function

histamine

- released from mast cells
- lungs, skin, gut, CNS
- species differences in response
  - mice very resistant
  - guinea pigs very susceptible
  - dogs act more like guinea pigs

histamine receptors

- H1 - skin, smooth muscle
  - antagonists commonly used
- H2 - gastric parietal cells
  - antagonists block acid production
- H3 - presynaptic on neurones (inhibition)
- H4??

H1 antagonists

- (acepromazine)
- promethazine
- chlorpheniramine
- mepyramine
- newer human drugs
  - terfenadine
  - astemizole
  - cetirizine

H2 antagonists

- cimetidine
- ranitidine
- etc, etc

non-specific antagonist

- tripelennamine

eicosanoids

- prostaglandins
- thromboxanes
- leukotrienes
- lipoxins

eicosanoids

- derived from arachidonic acid
- main mediators of inflammation?

prostaglandin uses

- luteolysis in cattle
- induction of parturition
- prevent gastric ulcers
- block platelet aggregation

eicosanoid blockers

- steroids
- nonsteroidal anti-inflammatory drugs
- experimental drugs
  - prostaglandin receptor antagonists
  - 5 lipoxygenase inhibitors

platelet activating factor

- important inflammatory mediator
- synthesis blocked by steroids
- experimental receptor antagonists
- PAF antagonists in many plants

bradykinin

- vasodilatation
- slow contraction of smooth muscle
- pain
- increased fluid secretion
  - airways and gut

bradykinin

- broken down by angiotensin converting enzyme
- involved in diarrhoea???
- experimental receptor antagonists

cytokines

- large (c200 amino acid) peptides
- regulate inflammatory / immune reactions

cytokines

- interleukin 1 (IL1)
- IL2 - 10
- tumour necrosis factor a & b
- interferons
- growth factors
- etc, etc, etc

anti-cytokine drugs

- all have lots of other effects!!
  - steroids
  - cyclosporin
  - tacrolimus

problems

- infection
- inflammation
- pain

autacoids

- autacoids are a large and important group of neuromodulators / inlammatory mediators
- rarely act alone - potentiate or inhibit other transmitters
- most drugs which alter smooth muscle function or inflammation interact with autacoids
- important as CNS neuromodulators