Vasoactive Peptides

- Peptides used by most tissues for cell-to-cell communication
- Found in ANS, CNS
- Usually released with NTs
- Many peptides exert effects on smooth muscle, including vascular
  - Vasoconstrictors
  - Vasodilators
Vasoconstrictor Peptides

- Angiotensin II
- Vasopressin
- Neuropeptide Y
- Urotensin
- Endothelin
Vasodilator Peptides

- Bradykinin/kinins
- Natriuretic peptides
- Vasoactive intestinal peptide (VIP)
- Neurotensin
- Substance P
- CGRP (migraines)
- Adrenomedullin
Renin-Angiotensin System

• Angiotensinogen converted to Angiotensin I (Ang I) by enzyme renin
• Renin synthesized from preprohormone prorenin
• Ang I converted to Angiotensin II (ANG II) by angiotensin converting enzyme (ACE)
• Ang II converted to Angiotensin III by amino peptidase enzyme
Renin-Angiotensin System

1. Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-R
   Angiotensinogen

2. Prorenin

3. Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu
   Angiotensin I

4. CONV. ENZYME

5. Asp-Arg-Val-Tyr-Ile-His-Pro-Phe
   Angiotensin II

6. AMINOPEPTIDASE

7. Arg-Val-Tyr-Ile-His-Pro-Phe
   Angiotensin III

8. Angiotensinases

9. Peptide fragments
Renin-Angiotensin System

• Kidney responsible for long-term control of BP
  – Controls blood volume
• Renin-angiotensin system hormonal system that regulates
  – BP
  – Fluid balance/homeostasis
• When blood volume low, baroceptors in kidney detect drop in BP
  – Stimulate production, release of renin in kidneys
Angiotensin

• Renin stimulates production of angiotensin
• Ang II causes arteries in kidney to constrict
  – Increases glomerular filtration
  – Increases BP
• Ang II also stimulates secretion of aldosterone from adrenal
  – Causes kidneys to increase reabsorption of sodium and water into blood
  – Also increases BP
Renin Secretion

- Synthesized in kidneys: released in response to
  - Decreased stretch in renal vascular stretch receptor
  - Decreased rate of delivery of Cl\(^-\) or Na\(^+\) to distal tubule
  - Increased renal nerve activity: epinephrine, norepinephrine
  - Increasing levels of cAMP, cGMP, intracellular Ca\(^{++}\)
- Ang II inhibits renin secretion
- Therapeutic drugs can alter release of renin
Control of Renin Secretion
Angiotensinogen

• Synthesized in, released from **liver**
• Production increased by
  – Corticosteroids
  – Estrogens
  – Thyroid hormones
  – Angiotensin II
• All of the above are associated with hypertension
• Decrease production of angiotensinogen to reduce hypertension??
ACE

- Dipeptidyl carboxypeptidase
- Converts Ang I to Ang II
- Also inactivates bradykinin
- Cleaves enkephalins, substance P
  - Physiologic significance unclear
- ACE widely distributed throughout body
Ang II

• **Blood pressure**
  – Vasoconstrictor; contracts vascular smooth muscle
  – Interacts with ANS: stimulates release of epinephrine, norepinephrine

• **Adrenal cortex/kidney**
  – Simulates aldosterone synthesis, release
    • Can stimulate glucocorticoid synthesis
  – Inhibits release of renin
    • Causes renal vasoconstriction
    • Increases tubular Na$^+$ reabsorption
Ang II

- CNS
  - Can thirst/drinking
  - Increases secretion of ACTH, vasopressin
- Cell growth
  - Mitogenic: stimulates cell division, mitosis
  - May cause hypertrophy in cardiac cells
- Binds GPCRs
  - AT₁, AT₂
- Rapidly metabolized by angiotensinase
Angiotensin System
**Kinins**

- Formed by enzymatic activity of **kallikreins** (kininogenases) on protein substrates called **kininogens**
- Three kinins in mammals
  - Bradykinin
    - Released by plasma kallikrein
  - Kallidin (lysylbradykinin)
    - Released by tissue kallikrein
  - Methionyllysylbradykinin
    - Released by pepsin/pepsin-like enzymes
Kallikrein-Kinin System

Angiotensinogen

RENIN
- renal
- local

Kininogen

KALLIKREIN

Angiotensin I (1-10)

ACE
- lung
- local

Bradykinin

NO ↑
Prostacyclin ↑
EDHF ↑

Hydrolysis products

Chymase
Carboxypeptidase
Cathepsin G

ANGIOTENSIN II (1-8)

⇒ Biological effects

NEPs

AMINOPEPTIDASES

Angiotensin III (2-8)

Angiotensin IV (3-8)

Angiotensin-(1-7)
Kinins

- Kallikreins can convert prorenin to renin
  - Physiologic significance unclear
- Kininogens precursors to kinins
  - Found in plasma, lymph, interstitial fluid
  - Two forms found in plasma
    - High molecular weight
    - Low molecular weight
  - LMW kininogen accounts for about 80%
    - Crosses capillary wall, enters tissue
Effects of Kinins

- Kinins are potent vasodilators
  - Heart, liver, kidney, intestines, skeletal muscle
- Vasodilator effects direct or indirect
  - Direct: inhibitory effects on vascular (arteriolar) smooth muscle
  - Indirect: stimulate release of NO or vasodilator prostaglandins
- Induce rapid, brief drop in BP when administered IV
Effects of Kinins

• **Inflammation**
  – Kinins rapidly generated after tissue injury
  – Bradykinin produces redness, heat, swelling, pain

• **Glands**
  – Kinins and kallikreins found in many exocrine, endocrine glands
  – Function not well characterized
  – Marked effects on smooth muscle
  – Role in activation of prohormones?
Kinin Actions

• Bind GPCRs
  – $B_1$ and $B_2$ (bradykinin)

• Most actions of kinins mediated by $B_2$ receptor
  – Widely distributed
  – $B_1$ role limited to inflammatory response?

• Rapidly metabolized by non-specific kininases
  – Kininase I
  – Kininase II is identical to ACE
Drugs Affecting Kinin System

- Few currently available clinically
- Receptor antagonists hold promise for
  - Inflammation
  - Nociceptive pain
- Icatibant
  - $B_2$ receptor antagonist used to treat bradykinin-induced angioedema: swelling of dermis and mucosa in airways, GI tract, extremities, genitalia
- Kallikrein inhibitors
  - Aprotinin, ecallantide
Vasopressin

- Important role in regulation of BP
  - Long term: acts in kidneys to increase water reabsorption
  - Short term: potent vasoconstrictor
- Binds 3 different GPCRs
  - $V_{1A}$, $V_{1B}$ and $V_{2}$
  - $V_{1A}$ controls vasoconstrictor effects
- **Terlipressin**: $V_{1A}$ agonist, vasopressin analog
  - Used to treat vasodilatory shock states
  - Also used for hypotension
Vasopressin Antagonists

- **Relcovaptan**
  - $V_{1A}$ antagonist
  - Clinical trials for Raynaud’s Disease (vasospastic disorder), tocolysis (suppresses contractions, labor)

- **Tolvaptan**
  - $V_2$ antagonist
  - Used to treat hyponatremia (low blood sodium)

- **Conivaptan**
  - $V_1, V_2$ antagonist
  - Hyponatremia
Natriuretic Peptides

• Family of peptides with natriuretic (excretion of $\text{Na}^+$ thru urine), vasodilator, other properties
  – Atrial natriuretic peptide (ANP)
  – Brain natriuretic peptide (BNP)
  – C-type natriuretic peptide (CNP)

• Three receptors
  – $\text{NPR}_1$, $\text{NPR}_2$, $\text{NPR}_3$ re
  – Single transmembrane spanning region: stimulate production of cGMP
Natriuretic Peptides

• No therapeutic drugs targeting synthesis or receptors

• ANP, BNP metabolized by neutral peptidase (NEP)

• Omapatrilat
  – Inhibits NEP (also inhibits ACE)
  – Promotes natriuresis, vasodilation
  – Used to treat hypertension, congestive heart failure
  – Not FDA approved due to angioedema
  – Others in development
Endothelins

• Proteins produced by endothelial cells
  – Constrict blood vessels, raise BP
  – Cardiovascular, lungs, kidney (decrease water, Na\(^+\) excretion)

• Endothelin 1-3 (ET-1, ET-2, ET-3)

• Three GPCRs
  – ET\(_A\), ET\(_B1\), ET\(_B2\)

• Overproduction of endothelins
  – Hypertension, cardiac hypertrophy, atherosclerosis, myocardial infarction, coronary artery disease
Endothelin Antagonists

• Bosentan
  – Competitive antagonist at $\text{ET}_A$, $\text{ET}_B$ receptors
  – Used for pulmonary artery hypertension (PAH)

• Ambrisentan
  – Antagonist at $\text{ET}_A$ receptor (PAH)

• Sitaxetan
  – Antagonist at $\text{ET}_A$ receptor (PAH)
  – Withdrawn due to liver toxicity

• Actively investigated for cardiovascular disorders
**VIP**

• Small peptide of glucagon-secretin family
• Widely distributed throughout body
  – CNS, PNS
• Potent vasodilators
  – Particularly in cardiovascular system
• Activate 2 GPCRs
  – VPAC1, VPAC2
• Several drugs currently in development
  – Analogs/agonists and receptor antagonists
Substance P

• Many effects
  – Vasodilation, inflammation, pain

• Binds neurokinin receptors (NK$_1$-NK$_3$)
  – Substance P high affinity for NK$_1$
  – NK$_1$ found in CRT, vomiting center

• Several NK$_1$ antagonists used as antiemetics
  – Aprepitant
  – Fosaprepitant
  – Vestipitant (under development)
  – Casopitant (under development)
Neurotensin

- Functions as
  - Neurotransmitter/neuromodulator in CNS
  - Local hormone in periphery (vasodilator)
- In CNS modulates
  - DA, glutamate neurotransmission
- Binds GPCRs: NTR$_1$ – NTR$_3$
- Agonists, antagonists in development
  - CNS disorders (schizophrenia, Parkinson’s, alcoholism/drug abuse
  - Cardiovascular disorders
**NPY**

- Small peptide (36 aa); one of most abundant in CNS, PNS
  - Frequently localized in noradrenergic neurons
- Vasoconstrictor; CNS, cardiovascular, renal
- Four GPCRs
- Receptor antagonists investigated for
  - Hypertension, cardiovascular disorders
  - Appetite suppression/anti-obesity
  - Depression, anxiety, pain
  - Alcoholism
Urotensin

- 11 aa amino acid peptide
- One of most potent known vasoconstrictors
- Found in brain, spinal cord, kidneys, plasma
  - Heart, lungs, liver
- Binds GPCR; UT
- Antagonists being developed
  - Urantide, palosuran
  - Renal disease
  - Cardiovascular disorders