Biol212 Biochemistry of Disease

Cardiovascular Disorders: Hypertension
Hypertension (high blood pressure).

- 25% of the population of industrialized societies are hypertensive.

- A major risk factor for stroke, myocardial infarction, heart failure and end-stage renal disease.

- Genetic and environmental factors play significant roles and abnormal expression of multiple genes is likely to underlie most hypertensive phenotypes.

- More than 50 different genes have been implicated in the regulation of blood pressure.

- A common feature of the control of blood pressure by these gene products is regulation of sodium and water excretion/retention by the kidney.
Variation of chart provided by WHO/ISH
The renin/angiotensin/aldosterone system.

- This pathway is the main mediator of vasoconstriction, sodium retention, the sensation of thirst and increased water intake.

- Renin is released from juxta-glomerular (JG) cells in the kidney in response to a decrease in blood volume.

- Secretion of renin is also controlled by the autonomic nervous system. Noradrenaline released from sympathetic neurones acts on JG cell β-adrenergic receptors to stimulate exocytosis of the renin secretory vesicles.

- Renin is derived, by proteolytic cleavage, from an inactive precursor prorenin. Renal kallikrein carries out this proteolytic cleavage.
Renal juxtaglomerular apparatus.
Angiotensinogen (452 amino acids, MW ~ 61,000) is a glycoprotein synthesized by the liver. It is a member of the serpin (serine protease inhibitor) family, although it does not appear to function as such.

The first 10 amino acids are cleaved from angiotensinogen, by renin, to produce the angiotensin I decapeptide. This appears to be the rate-controlling step of the pathway.

Subsequent cleavage by angiotensin converting enzyme (ACE), present in a variety of vascular beds, generates the active octopeptide, angiotensin II (ang II).
ACE inhibitors (e.g. captopril, above) have been used as anti-hypertensive agents for many years.
Ang II receptors

- There are at least 2 types of receptor for ang II, but the control of blood pressure appears to be mediated by the AT1 receptor.

- Disruption of the mouse AT1 receptor gene leads to a significant reduction in blood pressure.

- As a treatment for hypertension, blocking the receptor (e.g. with losartan) may prove to be more specific, with fewer side effects, than using ACE inhibitors which may also affect bradykinin (a vascular smooth muscle relaxant) metabolism.

Losartan, a non-peptide antagonist of the angiotensin II receptor.
The AT1 receptor belongs to the seven-transmembrane-domain superfamily of G-protein coupled receptors.

It is coupled to a number of signalling pathways via Gq and rapidly activates phospholipase C and PK-C. Subsequently, phospholipase D, phospholipase A2 and MAP kinase pathways are also activated.
Aldosterone

Ag II controls aldosterone secretion by the zona glomerulosa of the adrenal gland.
- Aldosterone stimulates sodium reabsorption by the distal tubules and, to a lesser degree, the cortical collecting ducts of the kidney.

- Sodium reabsorption increases the osmolarity of the blood and is accompanied by passive absorption of water which restores plasma volume (and blood pressure).
Epithelial sodium channels (ENaCs)

- ENaCs in the distal tubule are regulated by aldosterone.

- The ENaC channel is a heterotetramer ($\alpha_2\beta\gamma$).

- Each polypeptide consists of 250-aminoacid transmembrane domains joined by an extracellular loop, with intracellular amino- and carboxyl-terminal domains.

- The extracellular loop is the site for amiloride binding (blocking the channel) and the carboxyl region is a 'hot spot' for mutations causing altered channel function in humans—and hypertension.
Sodium-Proton Exchangers (NHEs)

- Increased activity of NHE1 and NHE3 is associated with hypertension.

- NHE1 is ubiquitous in mammals and regulates cell volume and pH.

- NHE3 is found primarily in renal proximal tubules and intestinal epithelia where it promotes transcellular sodium absorption.

- The NHEs are also inhibited by amiloride.
Vasodilation/Natriuresis

Natriuretic peptides (e.g. atrial natriuretic peptide, ANP).

- ANP is a 28 amino acid peptide derived from a 126 amino acid precursor (pro-ANP) in the heart from where it is released into the blood stream.
- It signals through receptors that possess guanylyl cyclase activity.

- Infusions of ANP, over-expression of ANP in transgenic mice, or inhibition of degradation all lower blood pressure. Additionally, disruption of the ANP gene leads to salt-sensitive hypertension.

- ANP inhibits aldosterone secretion and the release of renin.

- It causes relaxation of blood vessels - possibly by antagonizing the vasoconstrictor actions of ang II.

- All these actions effectively reduce the retention of sodium and water and therefore decrease blood volume. ANP may also suppress fluid and salt intake - leading to a decrease in peripheral blood pressure.

- The renin/angiotensin/aldosterone and the ANP/GC/cGMP signalling pathways are antagonists of each other and provide a critical balance of blood pressure regulation.
Nitric oxide

- NO mediates the effects of various hormones on the smooth muscle vasculature.

- The NO synthase expressed in endothelial cells plays a major role in blood pressure regulation.

- This enzyme is activated by elevations in intracellular $\text{Ca}^{2+}$ acting through calmodulin.

- The effects of NO on smooth muscle are mediated by a *soluble* form of guanylyl cyclase.

- Mice lacking the endothelial cell NO synthase gene show a chronic elevation in blood pressure in support of data obtained with NO synthase inhibitors.
Summary

- More than 50 different genes have been implicated in the regulation of blood pressure.

- A common feature of the control of blood pressure by these gene products is regulation of sodium and water excretion/retention by the kidney.

- The renin/angiotensin/aldosterone pathway is the principal mediator of vasoconstriction, sodium retention, the sensation of thirst and increased water intake.

- As a treatment for hypertension, blocking the angiotensin receptor may prove to be more specific, with fewer side effects, than using ACE inhibitors which may also affect bradykinin metabolism.

- Aldosterone stimulates sodium reabsorption by the distal tubules. This is accompanied by passive absorption of water which restores plasma volume (and blood pressure).

- Epithelial sodium channels are regulated by aldosterone; altered regulation could contribute to some forms of hypertension.