BSc Pharmacology and Translational Medicine

Module: Principles of Pharmacodynamics and Pharmacokinetics
Tutorial: Pharmacology in Action: Drug MOAs in Hypertension
Date: Tuesday27th October 2011

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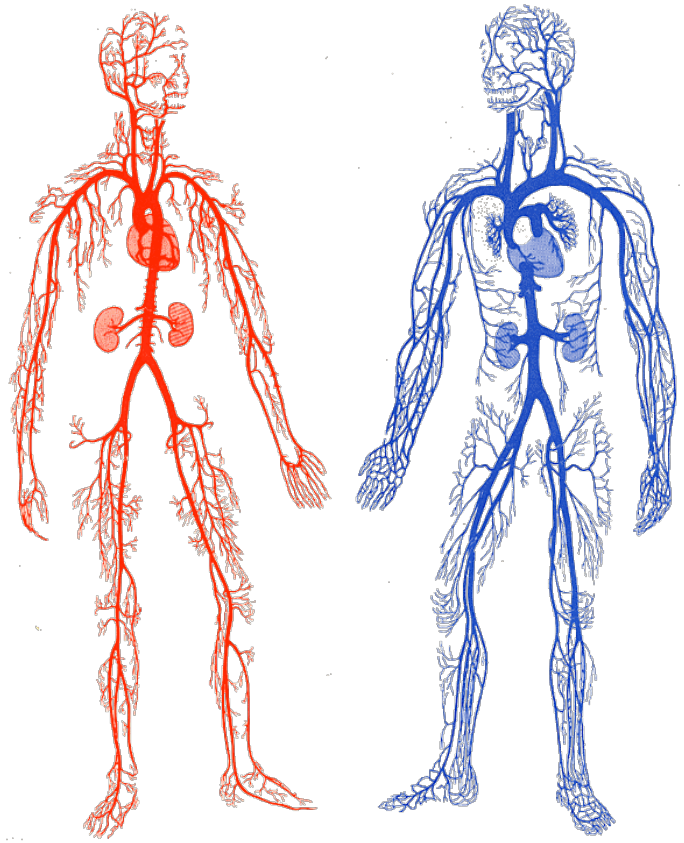
Lecture Outline

Tutorial Outline

- Introduction
  - Systemic hypertension
  - Autonomic nervous system
  - Renin-angiotensin-aldosterone system
  - β-blockers

- Task
  - Answer questions (~20 mins)
  - Group discussion / review of antihypertensive drugs



Introduction

- Systemic blood pressure (BP) is determined by
  - Cardiac output (CO)
  - Total peripheral resistance (TPR)

BP = CO x TPR

	Systolic	Diastolic
Normal	90-119	60-79
Prehypertensive	120-139	81-89
Stage I	140-159	90-99
Stage II	>160	>100

mm Hg

- Represents the pressure of the circulating blood on the vessel walls
- Described using the systolic and diastolic pressures
- Reported in units of mm Hg
- E.g. 139/86 mm Hg
- Hypertension is classed as a BP of >140/90 mm Hg

Introduction

- The target of treatment of hypertensive individuals is to reduce BP to 140/90 mm Hg or below

- Over the longer term, maintenance of BP to the 'normal' range reduces morbidity and mortality related to a number of diseases with hypertension as a risk factor:
  - Cardiovascular disease e.g. atherosclerosis
  - Stroke
  - Nephropathy
  - Retinopathy

- Causes of systemic hypertension:
  - Unknown in the majority (95%) of hypertensive individuals (idiopathic)
    - Primary / essential hypertension
  - Underlying disease
    - Secondary hypertension

Introduction

Hypertension – Risk Factors

- Age
- Ethnicity
- Gender
- Obesity
- Lifestyle
  - Smoking
  - Salt intake
  - Alcohol intake

Introduction

Blood Pressure Regulation

- There are three main systems that regulate and maintain blood pressure
  - Autonomic nervous system
  - Renin-angiotensin-aldosterone system
  - Locally-mediated vascular effects

Autonomic Nervous System

Blood Pressure Regulation

Autonomic Nervous System

- The autonomic nervous system provides rapid changes in blood pressure as required. The nervous control for these processes are:
  - Mediated by baroreceptors (pressure sensors)
  - Found in aorta and carotid artery

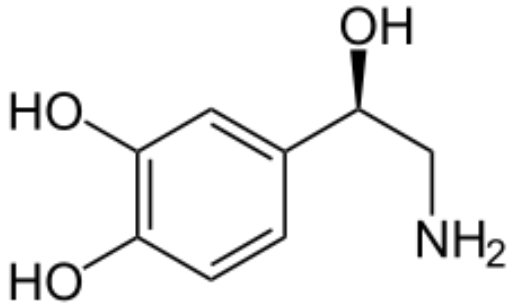
- Stimulation of baroreceptors causes appropriate changes in nervous stimulation of the sympathetic and parasympathetic nervous systems.
- Increase in pressure
  - Increased neuronal firing in the (NTS and RVLM) of the brain CNS
  - Inhibition of the sympathetic nervous system output (i.e. reduced 'fight-or-flight')
    - Results in decrease in blood pressure
- Decrease in pressure
  - Decreased neuronal firing in the (NTS and RVLM) of the brain CNS
  - Increase of the sympathetic nervous system output (i.e. increased 'fight-or-flight')
    - Results in increase in blood pressure

- The NTS and RVLM are stimulated to increase neronal firing (and therefore decrease sympathetic output) by α_2-adrenoceptor agonists and imidazoline receptor agonists

Blood Pressure Regulation

Autonomic Nervous System

- The autonomic nervous system regulates blood pressure using several mechanisms. Nervous impulses in the sympathetic nervous system release of noradrenalin from postganglionic neuron synapses…
  - …*in the heart*
    - Stimulates postsynaptic β_1-adrenoceptors
    - Increases myocardial contractility
    - Increases heart rate
  - …*in arterial resistance vessels*
    - Stimulates α_1-adrenoceptors
    - Results in vasoconstriction
  - *… in venous capacitance vessels*
    - Stimulates α_1-adrenoceptors
    - Results in vasoconstriction



Noradrenalin

- *Note*: Stimulation of the parasympathetic nervous system also serves to regulate blood pressure
  - Stimulation of vagus nerve
  - Increases muscarinic cholinergic release in heart
  - Decreases myocardial contractility
  - Decreases heart rate

Blood Pressure Regulation

Adrenoceptors

- The effects sympathetic nervous system are (almost all) mediated at the postganglionic nerve terminals by signal transmission using noradrenaline
  - Noradrenergic

- Nerve impulses cause depolarisation of the membrane
  - Allows influx of Ca^{2+}
  - Stimulates rapid release of noradrenalin

- Receptors for noradrenalin (also adrenalin and isoproterenol – used to determine agonist potency) effect the action of the sympathetic nervous system
  - G-protein-coupled receptors
  - Classed (originally) according to their agonist potency
    - α_1 NA>A>ISO
    - α_2 A>NA>ISO
    - β_1 ISO>NA>A
    - β_2 ISO>A>NA (NA = noradrenalin, A = adrenalin, ISO = isoproterenol)

Blood Pressure Regulation

Adrenoceptors

- In general:
  - α_1 and β_2 act on smooth muscle (vasoconstriction)
  - β_1 found mainly in the heart (heart rate / contractility)

- The selectivity of drugs for the agonism/antagonism of these receptors varies considerably

Tissue \ Receptor	α_1	α_2	β_1	β_2
Smooth Muscle Blood Vessels	Constrict	Constrict/dilate	-	Dilate
Heart Rate	-	-	Increase	Increase (minor)
Heart Contractile Strength	-	-	Increase	Increase (minor)
Adrenergic Nerve terminals	-	Decrease NA release	-	-

Adapted from: Rang *et al.* Pharmacology

Renin-Angiotensin-Aldosterone System

Blood Pressure Regulation

Renin-Angiotensin-Aldosterone System

- The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure over longer periods than the autonomic nervous system

- The juxtaglomerular apparatus in the kidney are sensitive to blood pressure. Reduction in blood pressure cause the production and secretion of **renin** from the kidney.
  - Enzyme (angiotensinogenase)
  - Catalyses the production angiotensin I from angiotensinogen (produced in the liver)

- Angiotensin I is cleaved by angiotensin converting enzyme (ACE) (produced by the kidney and pulmponary cells) to produce angiotensin II

- Angiotensin II is the mediator for a number of concerted processes that result in increased blood pressure

Note: The juxtaglomerular apparatus is highly innervated and will also respond to sympathetic nervous stimulation.

Blood Pressure Regulation

Renin-Angiotensin-Aldosterone System

- Angiotensin II acts on several tissue types, primarily through two receptor types:
  - The most important is: AT_1R
    - Results in vasoconstriction (venous system)
    - Stimulates aldosterone secretion (adrenal gland)
    - Increases presynaptic noradrenaline release

- Additionall, angiotensin II will stimulate production of aldosterone in the adrenal cortex (adrenal gland).

- Cells in the distal tubules of the kidney have aldosterone receptors that mediate the expression of sodium channels that allow reabsorption of Na^+ (and associated H_2O)

- Thus, normally, elevated aldosterone will lead to an increase in blood pressure.

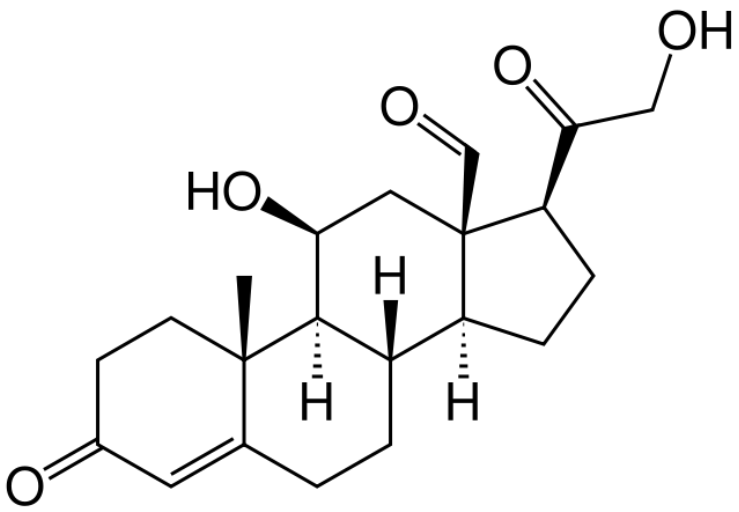
Blood Pressure Regulation

Aldosterone

- Produced by adrenal cortex in response to angiotensin II
  - AT_1R

- Activates receptors in distal tubule epiethelial cells in the kidney
  - Upregulates production of
    - Basolateral Na^+/K^+ pumps
    - Apical Na^+ channels
  - Results in increased Na^+ and water reabsorption

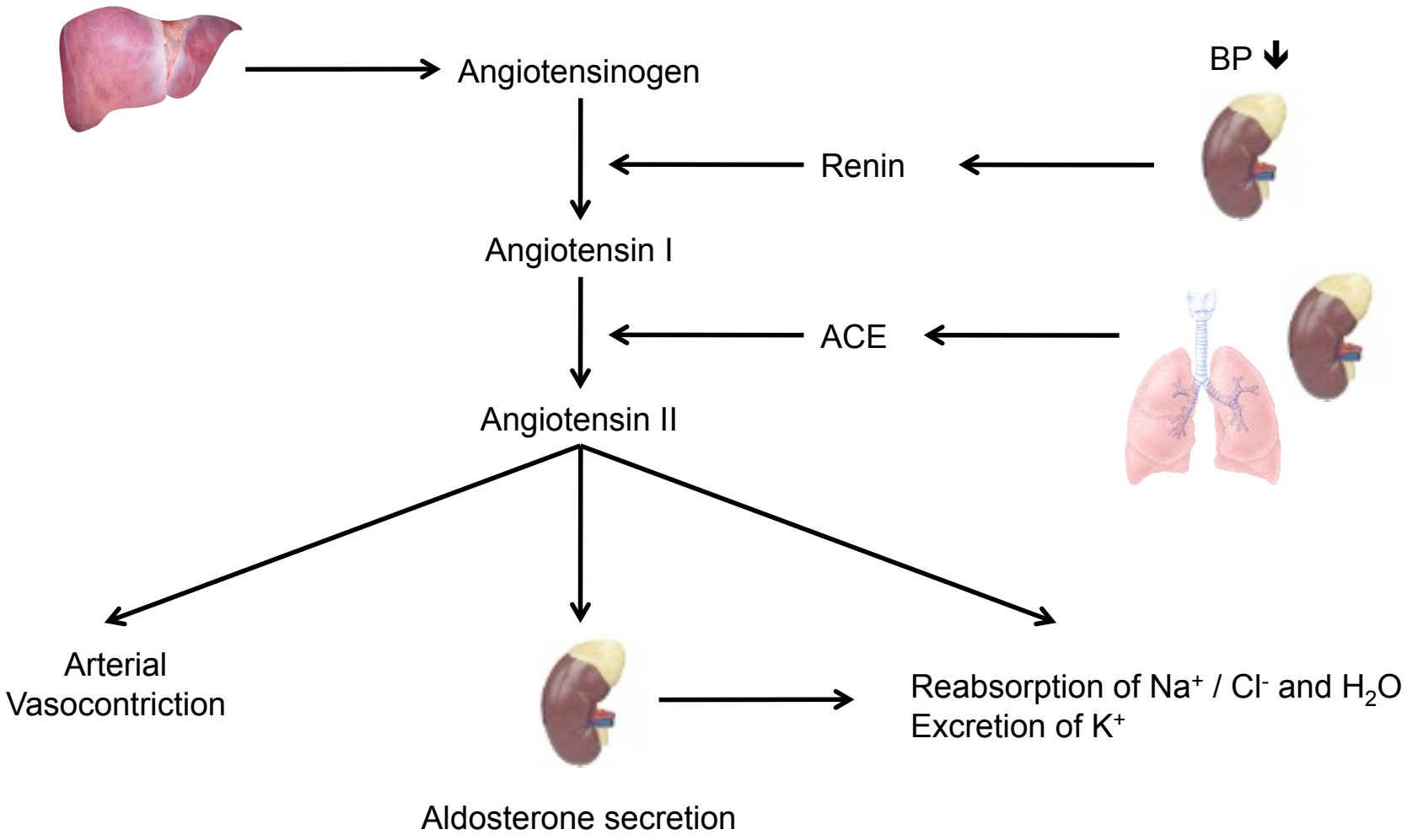
- Increased water reabsorption
  - Increased blood volume
  - Increased systemic blood pressure



Aldosterone

Blood Pressure Regulation

Renin-Angiotensin-Aldosterone System



Task

Task

Questions

For each of the drug in the table, state whether they would be useful as antihypertensive agents. If so, explain where they would act, and by what mechanism.

Drug	Action
Prazosin	α_1-antagonist
Atenolol	β_1-antagonist
Clonidine	imidazoline receptor agonist / α_2-agonist
Labelatol	β_1-antagonist / α_1-antagonist
Pindolol	β_1-antagonist / β_2-agonist
Furosemide	$Na^+/K^+/2Cl^-$ transporter inhibitor
Bendroflumethiazide	Na^+/Cl^- transporter inhibitor
Spirolactone	Aldosterone receptor antagonist
Captopril	ACE inhibitor
Losartan	AT_1R inhibitor