Central control of blood pressure. What is wrong in patients with essential hypertension?

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SK Teaching Website: http://www.bris.ac.uk/Depts/Physiology/Staff/Pysk/Teaching/
%age of Men & Women with hypertension in England

Men: 34%
Women: 30%

Data Source: www.heartstats.org
Financial Burden of Hypertension

For 2005:
The cost of cardiovascular diseases (including high blood pressure) in the USA alone is estimated to be $393.5 billion.
Are We Good at Treating High Blood Pressure?

% with Un-controlled hypertension

78% 67%

Data Source: www.heartstats.org
Evidence for higher sympathetic tone?

WHAT IS SYMPATHETIC N.S. and how brain controls it?
Autonomic - ???

Can you change your heart rate?
Can you change the diameter of the pupil in your eye?

ANS operates without our conscious command
ANS anatomy

**sympathetic**

**PARASYMP**

Modified from Gannong’s textbook
What do these two systems do?

**SYMPATHETIC**

“Fight or Flight”

**PARASYMPATHTETIC**

“Rest and digest”

WE ONLY DO SYMPATHETIC in class. Please have a look at parasympathetic system effects at your own time later.
Fight or Flight
Effects related to cardio-vascular system. For other effects see handouts.

Heart:
1. Increase in heart rate
2. Increased force of contraction
   → more blood pumped, more oxygen delivered to the tissues
Blood vessels

Arterioles: re-distribution of blood in favour of the "critical organs"

- Strong constriction
  - Skin
  - Abdominal viscera
  - Kidneys

- Relaxation or weak constriction
  - Heart
  - Brain
  - Lungs
  - Skeletal muscles

Veins: in many areas veins also constrict, thus more blood returns to the heart for faster re-circulation.
1. Cardiac output increase

2. Increased resistance to blood flow (constriction of arteries)

3. Increased return of venous blood

Systemic blood pressure increases:
Parasympathetic system: dominates at rest and during sleep. 
“Night is the realm of vagus” (the main parasympathetic nerve) 
“Rest and digest”.
Important effects of parasympathetic system on the heart:

1. Decrease in heart rate
2. Decrease in force of contraction

As less oxygen is required by peripheral tissues the heart may also “have a rest”
Reflex fall in heart rate triggered by afferent baroreceptors.

An increase in blood pressure →
- a) decrease in heart rate
- b) dilation of blood vessels

Blood Pressure Decrease
Brainstem autonomic centres

Brain in informed about the blood pressure by peripheral baroreceptors

Afferents of the ANS

Data from Dr. H. Waki
These sensory nerve endings get excited by stretch: the higher blood pressure the stronger the signal.
Effector organ – heart or blood vessel

Information processing by the brain

Afferents of the ANS

Parasympathetic - INCREASE

Sympathetic - DECREASE

Adrenaline

Effector organ - heart or blood vessel
Is there an abnormality within the central link in hypertension?
Can you identify these structures on your diagram?
Is there something wrong going on here in hypertension???
End of lecture 1
Lecture 2.
New insights into the central control of blood pressure

OR: USING VIRAL VECTORS TO STUDY HYPERTENSION

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The Brainstem

- RVLM
- NTS
- CVLM
- NA
- DMN
- Medulla oblongata
- Cerebellum
- Spinal cord
- Parasympathetic
  - Heart slows
- Sympathetic
  - Vasoconstriction
  - Increase HR
- Baroreceptors

Parasympathetic
  - Heart slows

Sympathetic
  - Vasoconstriction
  - Increase HR
A hypothesis:
1. In hypertension transmission of baroreceptor information is inhibited at the level of NTS.
2. This effect may be due to the actions of nitric oxide.
Some facts about nitric oxide:
1. A gas produced by (mainly) two enzymes, neuronal nitric oxide synthase and endothelial nitric oxide synthase (eNOS)
2. Acts on various neurones and can activate inhibitory synapses in NTS (therefore can inhibit baroreflex pathway)

Q. How can we test this hypothesis?
A. Use a genetic tool to inhibit NO production in NTS and measure cardiovascular parameters in a freely moving animal.
Our tools: replication-deficient viral vectors

VIRUSES AS VECTORS

To make a virus act as vector we need to delete part of its genome to:
1) Make it unable to replicate and therefore to cause a disease
2) Clear room to accommodate the expression cassette, i.e. delete a part of the viral genome
3) Learn how to proliferate the vectors and how to purify them to high titres
4) Establish efficient transfection protocols
Viral vectors
- high efficiency of gene delivery in vivo
- high levels of transgene expression
- stability of expression

Vectors derived from
1) Adenovirus (common cold virus)
2) Lenti/Retrovirus (relatives of HIV)
And several others...
Adenoviral (Ad) vectors
- non-enveloped double stranded DNA virus associated with mild human infections

36 kb genome

Early 'E' genes

Later transcription

Late 'L' genes

penton bases
fibre projections
Entry of adenoviruses into the cells
Radiotelemetry: Measuring cardiovascular parameters in conscious freely moving rats

Transmitter

Ambient Pressure Reference

Calibrated Pressure Output Adapter

Receiver

Automated analysis System
How to block eNOS?

Inhibition of “endothelial” NOS by expression of its dominant negative truncation mutant (Lee et al. 1995). The expression was driven by a non-selective HCMV promoter.
The outcome:
Expression of eNOS dominant negative decreases blood pressure in SHR
Conclusion:
In this experiment viral gene transfer has been used to prove a role for the eNOS (endothelial nitric oxide synthase) in pathological hypertension.
Other uses of viral technology:

In experimental medicine

1. To increase concentration of a protein under study in a cell and study its function (over-expression)

2. To make the cell produce a protein with functions which are not yet understood. Then - see what happens

3. To make the cell produce indicator proteins (for example, fluorescent). These may be used to monitor various variables within the living cells
Other uses of viral technology:

In clinical medicine -
Gene therapy - to deliver therapeutic genes

Examples:
Genes which protect heart from damage caused by ischemia (during heart attacks)

Genes which improve survival of vascular grafts used for transplantation

Genes which produce proteins which can lower blood pressure
WHAT IS WRONG WITH THE SYMPATHETIC N.S. IN HYPERTENSION?