LOCAL CONTROL OF TISSUE BLOOD FLOW

- Local control of tissue responds to tissue needs:
  - Oxygen
  - Other nutrient , such as glucose, amino acids, and fatty acids
  - Removal of CO2
  - Removal of hydrogen ions
  - Maintenance of proper concentrations of other ions in the tissues
  - Transport of various hormones
- In general, the greater the metabolism in an organ, the greater its blood flow
  - However, there is a large capacity to up-regulate flow (as in blood flow to muscles during exercise
  - By controlling blood flow on a need and tissue specific basis, the tissues never suffer from nutritional deficiency and yet the workload on the heart is kept at a minimum

MECHANISMS OF BLOOD FLOW CONTROL:

ACUTE CONTROL:

- Achieved by rapid changes in local vasodilation or vasocontriction of the arterioles, metarterioles and precapillary sphincters
- OXYGEN:
  - If tissue oxygen decreases, the blood flow through the tissues increases markedly
  - There are two basic theories for the regulation of local blood flow
    - **VASODILATOR THEORY:**
      - The greater the rate of metabolism, the greater the rate of production of a VASODILATOR substance, which is believed to diffuse back through the tissues and cause dilation
      - Implicated substrates include **adenosine**, CO2, ADP, histamine, potassium and hydrogen ions
        - **Adenosine observed to cause local vasodilation in the heart**
        - Decreased O2 ->ATP degradation -> adenosine release ->vasodilation
      - Most of the above substances are released in relation to oxygen deficiency
      - DRAWBACKS:
        - It has been difficult to prove that sufficient quantities of any single vasodilator substance are

indeed formed in the tissues to cause all the measured increase in blood flow

- **OXYGEN LACK THEORY:**
  - Aka nutrient lack theory
  - **Oxygen and other nutrients are required to maintain vascular muscle contraction**
  - **Therefore, in their absence, blood vessels relax and dilate**
    - **Decreased O2 in exercise leads to dilation**
  - Other situations of O2 lack include:
    - High altitude
    - Pneumonia
    - CO poisoning
    - Cyanide poisoning
- Pre-capillary sphincters are normally completely open or closed
  - Number open and duration of open time proportional to the metabolic needs of the tissues for oxygen

2 theories by which ⇑tissue metabolic demand → ⇑tissue blood flow:

- **Vasodilator theory: product of metabolism (e.g. adenosine) → vasodilation**
- **Oxygen lack theory: oxygen needed to maintain vascular smooth muscle tone**

- POSSIBLE ROLE OF OTHER NUTRIENTS:
  - Under special conditions, lack of glucose causes local tissue vasodilation (same can be shown for amino acids, fatty acids)
  - **Beriberi (B-group vitamin deficiency -> thiamine, niacin, and riboflavin):**
    - **Peripheral vascular blood flow increases twofold to threefold**
    - All of these vitamins are required for oxidative phosphorylation for generating ATP, thereby leading to diminished smooth muscle contractile ability and local vasodilation

- SPECIAL EXAMPLES:

  - **Reactive hyperaemia:**
    - When blood supply is blocked and then unblocked, blood flow normally increases 4-7 fold->reactive hyperaemia
    - Repays oxygen deficit

  - **Active hyperaemia:**
    - Exercising muscle leads to increased blood flow

- Increased local metabolism causes the cells to devour the tissue fluid nutrients extremely rapidly and also to release large quantities of vasodilator substances (e.g. adenosine).

Reactive hyperaemia: obstruction of blood flow
Active hyperaemia: ⇑metabolic demand

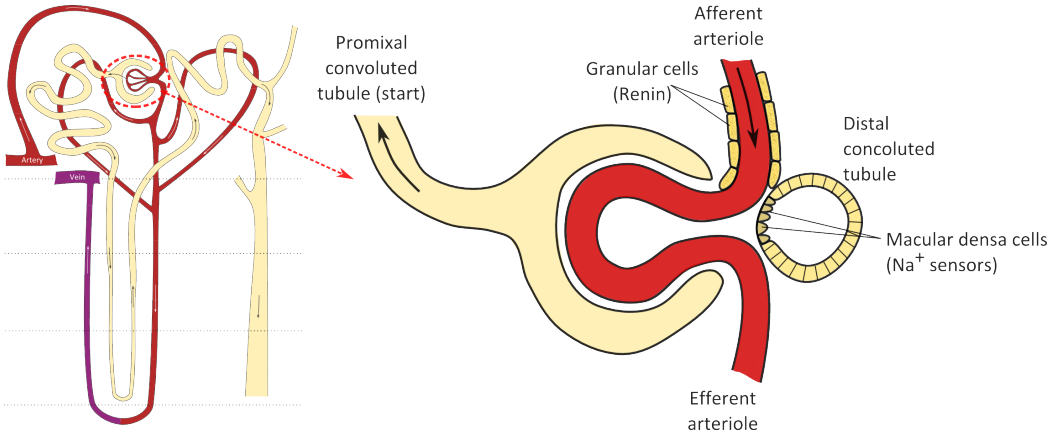
AUTOREGULATION OF BLOOD FLOW IN RESPONSE TO B.P. CHANGES

- Acute increase in arterial pressure causes an immediate rise in blood flow, which returns to near normal levels within minutes
  - If arterial pressure increases from 70-175mmHg, the blood flow increases only 30%, even though arterial pressure increases 150%
- Flow = pressure / TPR
- ⇓ Pressure → vasodilation (⇓TPR) → ⇑ flow
- ⇑ Pressure → vasoconstriction → ⇓flow

- TWO EXPLANATIONS FOR THIS OBSERVATION:
  - **METABOLIC THEORY:**
    - Excess flow provides too much oxygen and too many other nutrients to the tissues, causing the blood vessels to constrict
  - **MYOGENIC THEORY:**
    - Based on the observation that sudden stretch of small blood vessels causes the smooth muscle of the vessel wall to contract
    - Doubtful that this is an important mechanism as a strong myogenic contraction everywhere in the body would lead to death:
      - Increase pressure, increase in contraction ->increased TPR->increased pressure->increased contraction and so on

SPECIAL MECHANISMS FOR ACUTE BLOOD FLOW CONTROL

- **KIDNEYS**:
  - Blood flow control is vested mainly in a mechanism called **tubuloglomerular feedback**
  - Composition of the fluid in the EDT detected by the **macula densa**
    - This is located where this tubule abuts against the afferent and efferent arterioles at the **JUXTAGLOMERULAR APPARATUS**
  - When too much fluid filters, a feedback signal from the macula densa causes constriction of both the afferent and efferent arterioles, thereby reducing renal blood flow and glomerular filtration



- **BRAIN:**
  - Concentrations of **CO2** and **hydrogen ions** play very prominent roles
  - An increase in either will dilate the cerebral vessels and allows rapid washout of the excess of either
  - **⇑CO2 / acid → vasodilation**

DILATING UPSTREAM VESSELS:

- Local mechanisms described thus far dilate only the very small microvessels
- However, when blood flow through the microvascular portion of the circulation increases, this entrains secondarily another mechanism that does dilate the larger arteries as well
- Endothelial vessels lining the arterioles and small arteries synthesise several substances that effect degree of contraction of blood vessels
- EDRF (**nitric oxide**) is most important
  - **Half life 6 seconds**
  - **Shear stress** from increased flow contorts the endothelial cells in the direction of flow and results in greatly increased EDRF release, causing local vessel to dilate

LONG-TERM REGULATION:

- If a tissue becomes chronically overactive and therefore requires chronically increased quantities of oxygen and other nutrients, the blood vessels usually increase within a few weeks almost to match the needs of the tissue
- MECHANISM:
  - Principally to **change the degree of vascularity of the tissues**
  - Occurs rapidly in new-growth tissues (cancerous or scar tissue)
- **Angiogenic factors:**
  - **Vascular endothelial growth factor (VEGF)**
  - **Fibroblast growth factor**

    - **Angiogenin**
- Essentially all promote new vessel growth in the same manner
- First step is dissolution of the basement membrane
- Then rapid reproduction of new endothelial cells directed toward the source of the angiogenic factor, eventually creating new vessel
- Some steroid hormones have exactly the opposite effect, decreasing blood vessel production

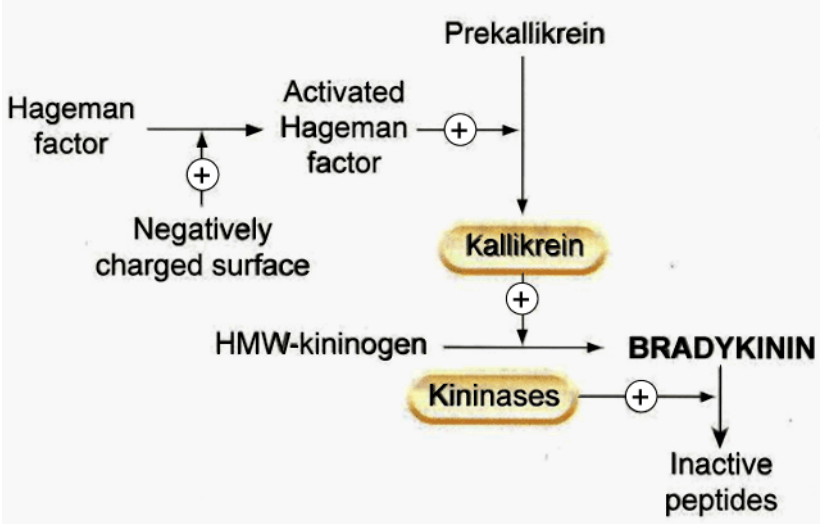
- Vascularity is determined by **maximum** blood flow need, not by average need
    - During exercise, blood flow increases to 6-8 times resting flow, but only for brief periods a day
    - Nevertheless, enough VEGF can be formed by the muscles to increase the vascularity to the required amount
    - These extra vessels normally remain vasoconstricted until required
- Similar concepts apply during formation of collateral circulation

HUMORAL REGULATION OF THE CIRCULATION:

- VASOCONSTRICTOR AGENTS:
    - **Noradrenaline and adrenaline:**
        - **Noradrenaline is an especially powerful vasoconstrictor hormone (α1) – Gq → ⇑Ca → contraction vasc SM**
        - Adrenaline less so, and in coronary vessels, is a vasodilator
        - Sympathetic nerve endings release noradrenaline when activated
        - SNS activation also cause secretion of both from the adrenal medullae into the blood
    - **Angiotensin:**
        - One of the most powerful vasoconstrictor substances known
        - Powerfully constricts arterioles
        - Normally acts on ALL arterioles to increase TPR and thus increase blood pressure
    - **ADH (vasopressin):**
        - Even slightly more powerful than angiotensin
        - Released from hypothalamus and secreted from posterior pituitary
        - Plays little role in vascular control
        - Released in large amounts during haemorrhage, increasing pressure by as much as 60mmHg
        - Major role is in increasing water reabsorption into the blood
    - **Endothelin**:
        - A powerful vasoconstrictor in damaged blood vessels

        - Usual stimulus for release is **damage to the endothelium** and prevents excessive loss (especially through small (<5mm) vessels

- VASODILATOR AGENTS:
    - **Bradykinin**:
        - Kinins are split away by proteolytic enzymes from alpha-2 globulins
        - Important pre-enzyme is **kallikrein**, activated by maceration of the blood, inflammation etc
        - **Kallikrien is activated by factor 12**
        - Kallikrein acts on globulins, to release kallidin ->converted to bradykinin by tissues
        - Causes both powerful arteriolar dilatation and increased capillary permeability
        - Short half life (degraded by carboxypeptidases)
        - Kininogen → Bradykinin, enzyme is Kallikrein



    - **Histamine**:
        - Released in essentially every tissue of the body when the tissue becomes damaged or inflamed, or is subject to an allergic reaction

- EFFECTS OF IONS AND OTHER CHEMICAL FACTORS:
    - **Calcium->vasoconstriction**
    - **Potassium->vasodilation**
    - **Magnesium->powerful vasodilation from generalised smooth muscle inhibition (e.g. used in asthma)**
    - Acetate and citrate ->vasodilation
    - Hydrogen ions cause dilation of the arterioles

- CO_2 ->vasodilation in most tissues, more marked in the brain