CEREBRAL BLOOD FLOW AND METABOLISM

Part 8
INNERRATION

vasoactive substances released by the endothel

PARENCHYMA

tissue metabolites
local effects

vasoactive hormones
blood-born mediators
biomechanical stimuli

LUMEN
The control of cerebral blood flow

~750 ml/min, ~15% of resting cardiac output, due to the profound autoregulatory capacity, it is largely independent of perfusion pressure between 60-160 mmHg, relatively stable value.

Controlling factors:
- Cerebrovascular endothelium
- Cerebrovascular smooth muscle
- Perivascular nerves
- Brain parenchyma
- Changes in blood chemistry:
  1. hypercapnia,
  2. hypoxia,
  3. hipoglycemia elicit arteriolar vasodilation and increase global cerebral blood flow.

The distribution of perfusion among brain regions is variable.
The cerebral resistance vessels

Innervation:

- sympathetic efferent,
- parasympathetic efferent,
- trigeminal sensory

Denervation does not increase blood flow, basal tone is dominant

Fig. 1 Whole-mount preparation of rat cerebral artery demonstrating a ground plexus of neuropeptide Y-immunoreactive nerve fibers surrounding the blood vessel.
Middle cerebral artery (MCA)

(a–d) serves here as an example of characteristics common for both MCA and basilar artery (BA) displaying immunolabelling positive for TH (originally green) (a) and p75 receptor (originally red) (b).

Note that the nerve fibres positive for either of the antigens show similar plexiform network/pattern, which is also seen (originally yellow) in a merged image of both labellings (c).

(d) In a control specimen no immunolabelling is seen when antibodies for TH and p75 receptor were replaced by the non-immune normal serum.
Representative immunohistochemical findings

Immunoreactivity (IR) for nNOS is seen in nerve fibers innervating the basilar (A) and anterior cerebral artery (B) but not in the basilar (C) or anterior cerebral artery (D) in the absence of primary antibody. Bar = 100 μm.

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The cerebral resistance vessels

**Innervation:**
- sympathetic efferent,
- parasympathetic efferent,
- trigeminal sensory mainly

Denervation does not increase blood flow, basal tone is dominant
Circle of Willis

3D CT Angiography
MCA is the largest branch that comes off the ICA. It has deep branches that supply part of the internal capsule and basal ganglia (putamen, caudate nucleus and globus pallidus). It passes out to the lateral surface of the cerebral hemisphere where it supplies blood to the cortical areas of the temporal, frontal and parietal lobes.
Functional contraction

Interaction of:

**Myogenic** (intrinsic) tone:
- Independent of any other influence
- Reference tone for vascular resistance control

**Neurogenic** (extrinsic) tone:
- Neurotransmitter, hormones, metabolic products
- Important decrease of ABP 50mmHg if denervated
- Coordinated rapid redistribution of blood to functionally important area to specific activities

function with cardio-receptors
stand up without hypotension or syncope after awakening
Regulation of venous capacity

70% of blood in veins and venules

- Relatively flaccid and larger diameter than arteries

Smooth muscles in the wall

- Alter volume by sympathetic venoconstriction

Critical in the regulation of venous return and cardiac output (by Starling's law)
Neuroeffector Junction

Postganglionic autonomic nerve

Primary plexus $\rightarrow$ terminal effector plexus $\rightarrow$

neuromuscular contact (100nm cleft)

- Only small fraction of cells in vascular muscle are neuronally innervated

- Other cells: Electrically and mechanically coupled
Sympathetic Components

Controle whole body hemodynamics and local vascular tone in many areas.

Vasoconstriction roughly proportional to neural activity.

Vasodilatation of vessels to skeletal muscles

- Human and some species
- Transient and confident to arterioles

Different fiber groups for blood flow control

- To skeletal muscle / to skin / to abdominal organs
Parasympathetic components

By cranial and sacral nerves: Vasodilatation

- Arterioles in brain, heart and erectile tissue, glands
- Not contribute vascular tone control significantly

Transmitters coexist

1. Acetylcholine

   no major role in brain, constriction rather than dilation

2. Vasoactive intestinal peptide (VIP)

   contribute to vasodilation of head and pelvis

3. Nitric oxide (NO)

   plays major role in cerebral blood vessels dilation
Sympathetic neurotransmitters

Norepinephrine
- Produce (fast phase of) vasoconstriction
- By activating $\alpha$-adrenoreceptors on vascular wall
- Stored in granular vehicles
- Removed from junction by uptake 80% back to terminal, 20% capillaries

Neuropeptide Y (NPY), galanin
- Colocalized with norepinephrine
- Vasoconstrictor potency of NPY~25×NE
- Slow phase of vasoconstriction
Neural control of Veins

High capacity regions
- Splanchnic bed and Cutaneous bed

Richly innervated
- α-adrenergic sympathetic nerves only
- Particularly large veins

Vasoconstriction of vein
- Regulate ventricular filling pressure
- Compensate mild hemorrhage
- Upright posture
- Heat stress
Entire SNS activate en masse to produce uniform outflow (1915)

- Significant regional variation in responsiveness of arterioles

**Factor for differential vasomotor control**

- Density of adrenergic innervations
- Sensitivity of vascular smooth muscles
- Heterogeneity of adrenergic receptors: $\alpha, \beta$
- Different neuronal uptake of NE
- Structure and vascular size difference of tissues
- Regional variation of myogenic tone

**Differential Vasomotor Control**
Blood flow and metabolism

Blood flow is closely linked to rate of metabolism

- In active vascular beds skeletal muscles, cerebral, coronary

Metabolic activity ($↑$) $→$ autoregulatory vasodilatation of blood vessels

- Override sympathetic neural control

Circulating hormones

- Impede or promote neurogenic vasoconstriction

- Another factor for regional difference
Cerebral perfusion

1. Cardiovascular regulatory mechanism
   - Perfusion autoregulation: constant blood flow under BP changes

2. Autonomic innervations of cerebral vessels
   - Vasoneural coupling: respond to metabolic needs

3. CO2/ O2-driven changes
   - To respond arterial blood gas changes
Neural innervation

For brain vessel caliber alteration to w/o change to BP, metabolic need, arterial blood gases

Intrinsic neural system

- Arising within brain‡  brain tissues‡  parenchymal vessels

Extrinsic neural system

- Arising within brain‡  pass out of brain‡  innervation to cerebral vessels

- Autonomic Nervous System
Sensory nerves

- Trigeminal nerves appear to become important only under special circumstances, such as hypertension and seizures, when their stimulation can effect a substantial increase in CBF.
- Despite the abundance of these nerve fibers, CBF appears to be primarily regulated by local metabolism with only minor modulation by extrinsic nerves.
- It is unclear how these peripheral neurons may contribute to the moment-by-moment governance of the cerebral circulation during normal activity.
### Extrinsic Neural Influence

<table>
<thead>
<tr>
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<th>Effects on CBF</th>
<th>Transmitter</th>
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<tbody>
<tr>
<td>Sympathetic</td>
<td>-</td>
<td>Noradrenaline, NPY</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>+</td>
<td>Acetylcholine, VIP, NO</td>
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</table>
| Tigeminal
(5\textsuperscript{th} cranial nerve)
Antidromic & orthodromic | +              | Substance P, CGRP      |
Sympathetic Nervous System

- Dense in forebrain (blood supply by carotid) than hindbrain (by vertebrobasilar)
- Transmitters: NE with NPY
- Vasoconstriction
- Permissive role to cerebral autoregulation
  - Extend upper limit of autoregulation
  - NPY: constrict in more prolonged time course
Cerebral Autoregulation (Autoregulatory Shift)

Cerebral Blood Flow

Mean Arterial Pressure (mmHg)

0 200

Normal

Chronic Hypertension
Acute Sympathetic Stimulation
Parasympathetic Nervous System

Neural vaodilator influence

- But no effect on autoregulation on local metabolic change on hypoxic hypercapnic vasodilatation
- Vasodilation during physiologic threat (ischemia impaired ordinary metabolic driving)

Transmit through facial nerve (n. VII)

Transmitters

- Ach NO VIP
Cerebral Circulation

- Gets about 15% of total resting CO
- Held constant (750ml/min) over varying conditions
  - Because loss of consciousness occurs after few seconds of interrupted flow
- Is not normally influenced by sympathetic activity
Regulation of Cerebral Circulation

- Is regulated almost exclusively by intrinsic mechanisms
  - When BP increases, cerebral arterioles constrict; when BP decreases, arterioles dilate (=**myogenic regulation**)
  - Arterioles dilate & constrict in response to changes in CO₂ levels
  - Arterioles are very sensitive to increases in local neural activity (=**metabolic regulation**)
  - Areas of brain with high metabolic activity receive most blood
Alterations in $P_{a\,CO_2}$ result in marked vasodilation.

Exponential relationship between $P_{a\,CO_2}$ and CBF within a $P_{a\,CO_2}$ range of 25 to 60 mmHg, with a CBF change of approximately 4%.

Flow changes induced by alterations in $P_{a\,CO_2}$ occur within 2 min and reach a new plateau within 12 min. (This regulatory mechanism has been shown to be a function of changes in the perivascular pH in the vicinity of the vascular smooth muscle cells, rather than a direct effect of CO2 per se.)

In addition to the direct effects of hydrogen ions on the vascular smooth muscle, local changes in pH can modulate the vasomotor responses to other agents that affect vessel calibre, such as norepinephrine.
Arterial pCO2-perfusion relationship

Prolonged alterations in Pa$_{\text{CO2}}$ result in chronic adaptation, and after approximately 36 h the blood flow changes tend to return to prealteration levels.

At Pa$_{\text{CO2}}$ levels of 70 mmHg, maximal vasodilation has occurred and CBF does not increase as Pa$_{\text{CO2}}$ increases further. Similarly, Pa$_{\text{CO2}}$ levels less than 20 mmHg cause no further decrease in CBF. These low Pa$_{\text{CO2}}$ levels should be avoided in the clinical setting, since the ensuing blood flow reductions can lead to tissue ischemia.
Hypoxia also elicits cerebral vasodilation—it is difficult to investigate because drop in BP.
Effects of hypoxia on cerebral blood flow and cerebral vascular resistance
Cerebral blood flow and cerebral vascular resistance ± s.e.m.
Summary of cerebral blood flow regulation

**METABOLIC**
- Neuronal activity
- CBF

**CHEMICAL**
- CO₂
- (alkalosis) (acidosis)
- Brain ECF pCO₂

**AUTOREGULATION**
- Perfusion pressure
- CBF
- (low) (high)

**EXTRINSIC NEUROGENIC**
- Sympathetic stimulation
- CBF
Some feedback loops by which various stimuli cause changes in cerebral blood flow