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. hypoglycemia 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 mainly

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.

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† terminal effector plexus‡

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
Sym pathetic 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~$25 \times$NE
- Slow phase of vasoconstriction
Neural control of Veins

High capacity regions
- Splanchnic bed and Cutaneous bed

Richly innervated
- $\alpha$-adrenergic sympathetic nerves only
- Particularly large veins

Vasoconstriction of vein
- Regulate ventricular filling pressure
- Compensate mild hemorrhage
- Upright posture
- Heat stress
Differential Vasomotor Control

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
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 without 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>
<th></th>
<th>Effects on CBF</th>
<th>Transmitter</th>
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<tbody>
<tr>
<td>Sympathetic</td>
<td>-</td>
<td>Noradrenaline</td>
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<tr>
<td></td>
<td></td>
<td>NPY</td>
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<tr>
<td>Parasympathetic</td>
<td>+</td>
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<td>Tigeminal</td>
<td>+</td>
<td>Substance P</td>
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<tr>
<td>(5&lt;sup&gt;th&lt;/sup&gt; cranial nerve)</td>
<td></td>
<td>CGRP</td>
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<td>Antidromic &amp; orthodromic</td>
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</tbody>
</table>
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)

- 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.
Metabolic regulation-\(\text{CO}_2\)

- Alterations in \(\text{Pa}_{\text{co}_2}\) result in marked vasodilation.
- Exponential relationship between \(\text{Pa}_{\text{co}_2}\), and CBF within a \(\text{Pa}_{\text{co}_2}\) range of 25 to 60 mmHg, with a CBF change of approximately 4%.
- Flow changes induced by alterations in \(\text{Pa}_{\text{co}_2}\) 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.
Prolonged alterations in $\text{Pa}_{\text{CO}_2}$ result in chronic adaptation, and after approximately 36 h the blood flow changes tend to return to prealteration levels. At $\text{Pa}_{\text{CO}_2}$ levels of 70 mmHg, maximal vasodilation has occurred and CBF does not increase as $\text{Pa}_{\text{CO}_2}$ increases further. Similarly, $\text{Pa}_{\text{CO}_2}$ levels less than 20 mmHg cause no further decrease in CBF. These low $\text{Pa}_{\text{CO}_2}$ 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**

CBF vs. Neuronal activity

**CHEMICAL**

CBF vs. brain ECF pCO2

**AUTOREGULATION**

CBF vs. Perfusion pressure

**EXTRINSIC NEUROGENIC**

CBF vs. sympathetic stimulation

- (alkalosis)
- (acidosis)
Some feedback loops by which various stimuli cause changes in cerebral blood flow
Cortical spreading depression (CSD)
Cortical spreading depression is a wave of hyperactivity followed by a wave of inhibition, usually in the visual cortex.\[1\]

The term is used by neuroscientists to represent at least one of the following cortical processes:

- The spreading of a self-propagating wave of cellular depolarization in the cerebral cortex.
- The spreading of a wave of ischemia passing through an area of cortex.
- The spreading of a wave of vasoconstriction following vasodilation of contiguous cortical arterioles.\[2\]
Definition of CSD

- Propagating electrical inactivation (2-5 mm/min, wavefront-like pattern)
- Elicited by: trauma, ischemia, K+, electrical stimulation
- Combined with blood flow changes (neurovascular coupling)
Typical features of CSD

- Slow propagation: 2-5 mm/min
- Spreading in all directions
- Refracter period
- Suppression of other, simultaneous activity
Evoking stimuli

- Electric stimulation
- Mechanical stimulation
- High concentration KCl solution
- Ischemia
- NMDA (N-methyl-D-aspartate)
  - Under experimental condition
  - Spontaneous, (patho)physiological elicitation (?)
Evoking stimuli

Hypotheses:
- High extracellular K$^+$ concentration - $[K^+]_e$
- High extracellular glutamate concentration

Depolarization:
- Neurons and glia involved
Evoking stimuli- ischemia

$O_2$ and glucose deprivation (ischemic stroke)

ATP synthesis $\downarrow$

$\text{Na}^+/$$\text{K}^+$ pump $\downarrow \rightarrow$ spontaneous depolarisation

neurotransmitter release (glutamate)
Pathophysiological relevance

- Migraine (aura phase)
- Traumatic brain injury
- Stroke (ischemic and haemorrhagic)
The original discovery

Aristides Leão
Ph.D. student at Harvard Medical School in the 1940s

Field of study: epilepsy
Anesthetized rabbits
Exposed cerebral cortex
Electrically provoked seizure discharges
ECoG recording
SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX*

ARISTIDES A. P. LEÃO
Department of Physiology, Harvard Medical School, Boston, Massachusetts

(Received for publication August 14, 1944)

This study originated in an attempt to secure more data for the understanding of the cortical electrogram which occurs in "experimental epilepsy," and of the conditions in which it is brought forth by electrical stimulation. Early in the development of the study an interesting response, elicited by electrical stimulation, was noticed in the cortex of rabbits. The distinctive feature of this response was a marked, enduring reduction of the "spontaneous" electrical activity of the cortex. We have endeavored to define experimentally some of the characteristics of this response.
The original illustration of CSD (after electrical stimulation)

Leão AAP (1944) Journal of Neurophysiology
Exp. code: imag55, SD1
Suppression of other activity

Leão AAP (1944) Journal of Neurophysiology
Mechanisms of CSD propagation

- Non-synaptic
- Synchronous depolarization of neighbouring cells

Hypotheses:

- $[K^+]_e$: diffusion in the interstitium
- Gap junctions:
  - Communication between neurons
  - Communication between astrocytes – Ca$^{2+}$ waves
Hemodynamic changes

Hyperaemia

Baseline flow

Transient hypoperfusion

Long lasting hypoperfusion
Simultaneous imaging of CSD and the CBF response

Exp. code: VSL07 CSD1

Migraine
Pathophysiological relevance – migraine

Karl Spencer Lashley

Visual aura:
bright flashing lights, visual blindness
Wave of intense excitation of the visual cortex
followed by complete inhibition of activity;
Rate of propagation: 3 mm/ min

Pathophysiological relevance – migraine

Link between migraine aura and CSD:

- Rate of propagation is similar
- Similar electrical discharges and inhibition
  → P.M. Milner (1958): possible connection between migraine aura and CSD

Proof: difficult to collect:

- Experimental animals (in which CSD detection is possible) cannot report visual aura
- Patients: non-invasive methods not available at the time
Pathophysiological relevance – migraine

Early 1980’s: cerebral blood flow imaging in patients

→ The indirect imaging of migraine aura-related CSD is feasible:

• Early vasodilation coincides with the suppression of activity
• Sustained hypoperfusion – spreading oligemia
Migraine aura - summary

- Dark pink area: reduced CBF (20-30% for 2-6h)
- Light pink stripe: neuronal depolarization
- Arrows: direction of propagation

Lauritzen (1994) Brain
superior salivatory nucleus (SSN; a5)
Stroke
Pathophysiologic significance

- Stroke
- Subarachnoid hemorrhage
- Traumatic brain injury
Stroke: animal studies

Middle cerebral artery occlusion (MCAO)

CSD as it appears after MCAO

Exp. code: MCAO10
The relevance of CSD for stroke

Are CSD and infarct size related?
Experimental setup #1

Experiment:

- MCAO → ischemia
- Removal of the brain, TTC staining

Estimation of infarct size,
Correlation analysis between infarct size and number of CSD events
Experimental data #1

Gemma et al., Frontiers in neuroscience, Brain Aging

TTC

The relevance of CSD for stroke

Is there a causal relationship between infarct size and CSD occurrence?
Experiment:

- MCAO $\rightarrow$ ischemia
- CSD elicitation in the ischemic region
- Removal of the brain, TTC staining

Assessment of causality between CSD elicitation and infarct size
Experimental data #2

Back et al (1996) JCBFM
The relevance of CSD for stroke

What are the mechanisms, through which CSD increases infarct size?
Experimental setup #3

Experiment:

- MCAO $\rightarrow$ ischemia
- Recording of cerebral blood flow

Examination of the hemodynamic response to CSD
Experimental data #3

Human studies

Human studies

Human studies

Dreier et al., (2009) Brain