Cerebral artery pharmacology (1)
Basics

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Question

If you HAD to choose between getting either a heart attack or a stroke: what will you choose?

Why?
Exams...
Objectives

• Define strokes and subtypes
• Explain pathogenesis of strokes
• Discuss signaling mechanisms for strokes
• Be able to compare stroke subtypes
• Describe cerebral blood flow
• List risk factors and symptoms
Worldwide Statistics

• **WHO**: 15 million people suffer stroke worldwide each year. Of these, ~6 million die and another 5 million are permanently disabled. 4 million new cases worldwide / year

• Lifetime risk of stroke is 8-10%. More than 30% of stroke survivors have severe disabilities and ~50 million healthy life-years will be lost because of stroke by 2015.

• High blood pressure contributes to more than 12.7 million strokes worldwide.

• Europe averages approximately 650,000 stroke deaths each year.

• In developed countries, the incidence of stroke is declining, largely due to efforts to lower blood pressure and reduce smoking. However, the overall rate of stroke remains high due to the aging of the population.
Canadian Statistics

- In 2000, stroke accounted for 7% of all deaths – 15,409 Canadians.
- Every seven minutes, a Canadian dies of heart disease or stroke.
- Stroke was the second largest contributor to hospital care costs among cardiovascular diseases (2000-2001).
- Eighty percent of Canadians have at least one of the risk factors for heart and/or cerebrovascular disease: daily smoking, physical inactivity, being overweight, self-reported high blood pressure, or diabetes.
- Between 1969 and 1999, death rates for cerebrovascular disease decreased by 62%.
Interesting facts

- Causes of death: i) heart ii) cancer iii) stroke
- Black men 1.5x higher, black women 2.3 x higher
- Male : female ratio: 1.35:1
- Someone in USA dies every 3.3 minutes from stroke
- Four out of five families will be somehow affected by stroke over the course of a lifetime.
- 15 percent die shortly after the stroke.
- About 25 percent of stroke victims will have another within five years.
- The risk of stroke is two-and-a-half times higher in people with diabetes (diabetes and obesity epidemic is underway).
- **Highest:** Japan, Portugal, China, Korea. **Lowest:** UK, Germany, New Zealand.
- Incidence doubles every decade after the age of 45:
  - 104 per 100,000 when 45-54 years old
  - 1113 per 100,000 when 75-84 years old
  - ~70% in people aged >65
Famous people who had a stroke

- Richard Nixon (US President)
- Oscar Schindler (Humanitarian)
- Catherine the Great (Empress of Russia)
- Gene Kelley (actor/dancer)
- Frederico Fellini (director)
- Winston Churchill (British PM)
- Zsa Zsa Gabor (actress)
- Felix Mendelssohn (musician)
- Ron Carey (actor)
- Willie Stargell (baseball)
- Arthur Hailey (writer)
- Israeli Prime Minister Ariel Sharon
- Tom Parker (Elvis manager)
- Mae West (actress)
Stroke: definitions

- Stroke is a rapidly developing cerebrovascular event triggered by a thrombus or embolism in an cerebral vessel and resulting in clinical symptoms of neurological impairment due to the interruption of blood flow to the brain.
Two types of stroke

- Ischemic-80-85%
- Thrombotic-mainly due to atherosclerosis
- Lacunar—thrombosis of small, deeply penetrating arteries causing a small lake or cavity (chronic hypertension)—necrotic tissue reabsorbed
- Embolic-clot travels from source outside the brain (commonly heart: AF, valvular disease etc)
Hemorrhagic Strokes

- **Intracerebral hemorrhages (ICH)** is spontaneous bleeding into the brain (hemorrhagic strokes). ICH constitutes 15% of all strokes in the USA and Europe and 20–30% in Asian populations. Advancing age and hypertension are the most important risk factors for ICH. Degeneration and rupture of small arteries or arterioles because of sustained hypertension is the most common cause of ICH, accounting for more than 60% of cases.
Intracerebral Hemorrhage

- Occurs when diseased blood vessel bursts, causing blood leakage in brain
- Increases pressure within brain…leads to unconsciousness / death
- Commonly in basal ganglia, cerebellum, brainstem, cortex
- Cause: hypertension (most common), trauma, infection, tumors
Aneurysms

- Occurs when a blood vessel just outside the brain ruptures
- Area of skull surrounding brain (subarachnoid space) fills with blood
- Sudden, intense headache, neck pain, rapid loss of consciousness
- Causes: abnormal artery structures (aneurysms)
Vasospasm
## Spasmogens in SAH (1)

<table>
<thead>
<tr>
<th>Spasmogen Type</th>
<th>Agents</th>
<th>FOR</th>
<th>AGAINST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic factors</td>
<td>Adrenergic, cholinergic, peptigeric</td>
<td>Innervation, NE uptake altered by Hb</td>
<td>Innervation does not correlate with SAH; no effect of sympathectomy;</td>
</tr>
<tr>
<td>Biogenic amines</td>
<td>Histamine, NE</td>
<td>Vasoconstrictors, metabolites in CSF,</td>
<td>Constral arteries insensitive to NE; no effect of PBZ; NE constrictions same after SAH</td>
</tr>
<tr>
<td>5-HT</td>
<td>Injection of 5-HT into subarachnoid causes vasospasm; increased 5-HT nerve activity increased after SAH</td>
<td>Constrictions transient; vasospasm insensitive to 5-HT inhibitors; CSF levels of 5-HT unchanged after SAH; responses to 5-HT same in SAH</td>
<td></td>
</tr>
<tr>
<td>Eicosanoids</td>
<td>Prostaglandins</td>
<td>PG’s constrict; levels increased in SAH (PGI₂ decreased)</td>
<td>No effect of PG synthesis inhibitors</td>
</tr>
<tr>
<td>Thromboxanes</td>
<td>TX’s constrict</td>
<td>TXA₂ same in SAH (BV’s)</td>
<td>No effect of PG synthesis inhibitors</td>
</tr>
<tr>
<td>Leukotienes</td>
<td>LT’s constrict</td>
<td>LT’s same in SAH (CSF)</td>
<td>No effect of PG synthesis inhibitors</td>
</tr>
<tr>
<td>Endothelin</td>
<td>ET-1,big ET-1, ECE increased; mRNA for ETₐ and ETₐ increased; Et binding increased</td>
<td>No change in CSF ET; ET levels do not correlate with vasospasm; ET-1 antibodies have no effect on vasospasm</td>
<td></td>
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</tbody>
</table>
### Spasmogens in SAH (2)

<table>
<thead>
<tr>
<th>Spasmogen Type</th>
<th>Agents</th>
<th>FOR</th>
<th>AGAINST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and CSF</td>
<td>Incubation with</td>
<td></td>
<td>Constrictions transient</td>
</tr>
<tr>
<td></td>
<td>i) blood-CSF or</td>
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<td></td>
<td>ii) RBCs or</td>
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<td></td>
<td>iii) platelets</td>
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<td></td>
<td>iv) hemolysate</td>
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<td></td>
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<tr>
<td></td>
<td>causes vasospasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Oxy-Hb</td>
<td>Severe, chronic vasospasm; inhibits NO production; releases PGs and ET; produces free radicals; damages perivascular nerves</td>
<td>Pure oxy-HB does not cause severe vasospasm (monkey); Hb contains many fractions (endotoxins, lipids and proteins);</td>
</tr>
<tr>
<td>NO</td>
<td>Increased after injury; innervation by NO-nerves; reduced by oxy-Hb; iNOS upregulated</td>
<td>NO is a vasodilator</td>
<td></td>
</tr>
<tr>
<td>Free radicals</td>
<td>Lipid peroxides elevated; cause vasoconstriction; gene transfer of SOD is beneficial; free radical scavengers reduce oxy-Hb effects</td>
<td>SOD and catalase do not inhibit oxy-HB vasospasm; lipid peroxidation seems to be result rather then cause of vasospasm</td>
<td></td>
</tr>
</tbody>
</table>

- Taken from *Trends in Cardiovascular Medicine* 15: 24-34, 2005
Figure 1. Approximate time frames of selected cellular events in the ischemic brain that may be relevant to therapeutic time windows of neuroprotective strategies. Key: EAA, excitatory amino acids; IEGs, immediate early genes; ROS, reactive oxygen species; PMN, polymorphonuclear leukocytes. From: Therapeutic Time Window - Stroke Nov 2000 pg 26
Vasospasm

- Aneurysm rupture: blood travels from arterial lumen (1), through ruptured aneurysm (2) into the subarachnoid space. A vasoactive thrombus forms (3). Formation of oxyhemoglobin triggers a cascade of events in the vascular endothelium (4), smooth muscle (5), and adventitia (6), leading to vasospasm and ischemia. *Oxyhemoglobin generates free radicals*

- (Yellow) adventitial neurons; (green) fibroblasts.
Ischemic Strokes

- Most strokes (85%) are ischemic; that is, they result from an occlusion of a major cerebral artery by a thrombus or embolism. This results in loss of blood flow and a major decrease in the supply of oxygen and nutrients to the affected region. The remaining strokes are hemorrhagic, where a blood vessel bursts either in the brain or on its surface.

- China: higher proportion of patients suffering a cerebral hemorrhage
Ischemic stroke is a sudden loss of function due to loss of blood supply to an area of the brain that controls that function. It is usually caused by partial or complete blockage of an artery that supplies the brain e.g. atherosclerosis in the carotid artery of the neck reduces blood flow to the brain or a rupture in the plaque can cause a blood clot to form. This clot *(thrombus)* may break loose *(embolus)* and travel to an artery in the brain where it becomes lodged and totally blocks blood flow, causing permanent damage. Bleeding of an artery in the brain can also cause a stroke. Stroke can cause loss of function (use of an arm, leg or drooping of the face).
Ischemic Stroke

- Occurs when artery is blocked
- Most common problem: narrowing of arteries of brain / neck (atherosclerosis)
- Formation of blood clots (thrombosis)—dislodge and become trapped in arteries close to brain (embolis)
Ischemia

- Ischemia is defined as a reduction in blood flow that is sufficient enough to alter normal cellular function: *even brief ischemic periods to neurons events that can cause cell death (Grey matter more susceptible than white matter)*
- Cerebral blood flow (CBF) is approximately 50–60 ml/100 g brain tissue/min. In ischemia, the cerebral autoregulation causes local vasodilatation to increase extraction of O₂ oxygen and glucose. A reduction of CBF of less than 10 ml/100 g/min results in irreversible neuronal injury.
- Brain ischemia leads to “excitotoxicity”: activation of destructive vasoactive enzymes from endothelium, leucocytes, platelets and other neuronal cells. Glutamate, is cleared from the extracellular space by an energy dependent process. Glutamate causes the opening of calcium channels [28,29]. Intracellular calcium activates a series of destructive enzymes, such as proteases, lipases and endonucleases that enable the release of cytokines and other mediators, resulting in the loss of cellular integrity
Comparison of Stroke Types

**Ischemic**
- Rarely leads to death in first hour
- Patient may be drowsy but unlikely to be unconscious
- Deterioration in first 24-48 hours

**Hemorrhagic**
- Can be fatal at onset
- Patient more likely to be semi-conscious or unconscious
- Patient more ill and deteriorates rapidly
Hemorrhagic Stroke

- Hemorrhage/blood leaks into brain tissue

Ischemic Stroke

- Clot stops blood supply to an area of the brain
The acute neurochemical changes after ischemic stroke. Abbreviations: ER, endoplasmatic reticulum; NO, nitric oxide; ROS, reactive oxygen species; VSCC, voltage...
Ischemia: initial events
Ischemia: later events (reperfusion)
Ischemia: cellular pathways

Diagram showing the relationship between ischemia, reperfusion, inflammation, and cytokines, with pathways involving glutamate, calcium, mitochondrial dysfunction, phospholipase, PKC, Bad, akt, cytochrome C, caspases, cell death (necrosis), cell death (apoptosis), hemorrhagic transformation, BBB breakdown, and edema.
Ischemic penumbra

- **Ischemic penumbra**: ‘ischemic tissue that is potentially destined for infarction but not yet irreversibly injured and is the target of acute stroke therapies’. Metabolically suppressed but destruction is not yet inevitable.

- The crucial time period during which this volume of brain tissue is at risk is referred to as the ‘**window of opportunity**’ because the neurological deficits created by ischemia can be partly or completely reversed by reperfusing the ischemic yet viable brain tissue within a crucial time period.

- **‘Time is brain’**: importance of rapid treatment because ~ 1.9 million neurons are dying / minute after stroke
Ischemic penumbra
Types of strokes (3)

- Three main mechanisms causing ischemic strokes are: thrombosis, embolism and global ischemia (hypotensive) stroke:
- **Thrombosis**: Atherosclerosis is the most common pathological feature of vascular obstruction resulting in thrombotic stroke. Vessel occlusion accounts for approximately 85% of all strokes.
- **Embolism**: Embolic stroke can result from embolization of an artery in the central circulation. Most emboli lodge in the MCA (80% of the blood carried by the large neck arteries flow through the MCA). The two most common sources of emboli are: the left ventricular emboli and large arterial emboli (e.g. ‘artery to artery’) that result from detachment of a thrombus from the internal carotid artery at the site of an ulcerated plaque.
- **Hypotensive**: caused by hemodynamic changes especially in regions with marginal blood supply resulting from vessel stenosis or decrease in arterial blood pressure. Global ischemia causes the greatest damage to areas between the territories of the major cerebral and cerebellar arteries known as the ‘boundary zone’ or ‘watershed area’.
Strokes

- Caused by blocked or bleeding arteries
- Blocked arteries: ischemic strokes
- Ruptured arteries: hemorrhagic strokes
Cerebral Blood Supply

- Middle cerebral artery
- Vertebral artery
- Common carotid artery
- Arch of aorta
Cerebral Circulation Review

• Brain derives its arterial supply from carotid and vertebral arteries
• Carotid and vertebral arteries begin extracranially
• Internal carotid arteries and branches supply anterior 2/3 of cerebral hemispheres
• Vertebral and basilar arteries supply posterior and medial regions of hemispheres, brainstem, cerebellum and cervical spinal cord
Circle of Willis

- Sits at the base of the brain
- Joins the anterior and posterior circulation
- Important route of secondary or collateral circulation
- Most common site for congenital aneurysm
“Brain Attack”

- One third of people with ruptured aneurysms die before they get to the hospital.
- One third die after they get to the hospital.
- One third survive after they get to the hospital......40% have life changing neurological problems.
Risk factors

- Hypertension
- Heart Disease
- Diabetes
- Previous stroke
- Tobacco smoking
- High dose estrogen therapy
- Cocaine/Crack use
- Blood abnormalities
- Excessive Alcohol use
Symptoms

• Sudden, unexplained and intense headache
• Dizziness, loss of balance or coordination, especially when combined with another symptom
• Blurred or decreased vision in one or both eyes
• Difficulty speaking or understanding simple statements
• Weakness, numbness or paralysis of the face, arm or leg, especially on one side of the body
Signs of a stroke
(1 in 6 people at risk)

- **S** — Speech or problems with language
- **T** — Tingling or numbness in your body
- **R** — Remember or any problems with memory
- **O** — Off balance or any problems with coordination
- **K** — Killer headache
- **E** — Eyes or any problem with vision
If you experience any of these symptoms, call 9-1-1 or your local emergency number immediately.

- **Weakness** - Sudden loss of strength or sudden numbness in the face, arm or leg, even if temporary.

- **Trouble speaking** - Sudden difficulty speaking or understanding or sudden confusion, even if temporary.

- **Vision problems** - Sudden trouble with vision, even if temporary.

- **Headache** - Sudden severe and unusual headache.

- **Dizziness** - Sudden loss of balance, especially with any of the above signs.