HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

HST.583: Functional Magnetic Resonance Imaging: Data Acquisition and Analysis, Fall 2008
Harvard-MIT Division of Health Sciences and Technology
Course Director: Dr. Randy Gollub.

HST.583 Block 3: Imaging Brain Physiology with functional MRI

Divya S. Bolar
MD/PhD Candidate
Harvard Medical School
MIT Dept. of Electrical Eng.
Division of HST

Before we begin:

What is functional MRI?

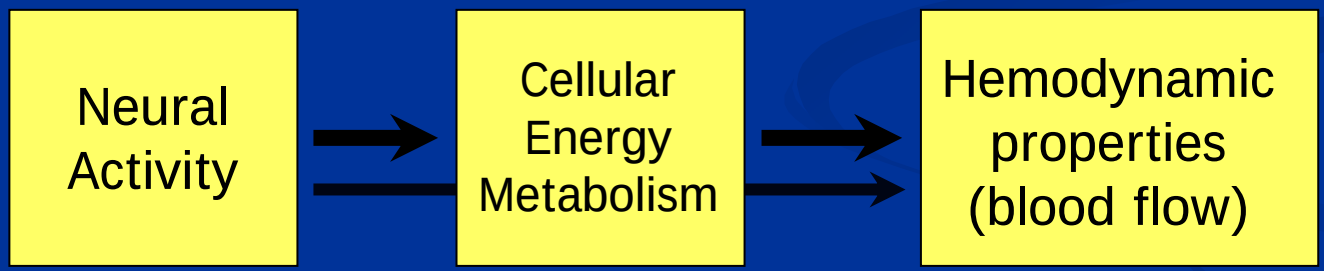
- Broad sense: fMRI refers to any MR technique that goes beyond anatomy to measure aspects of local physiology.
- **Specific sense: fMRI refers to MR techniques that measure changes in brain function over time.**
- "Brain function" results from information processing activity of ensembles of neurons throughout the brain
- *Primary goal of fMRI is to detect signal changes corresponding to neuronal activity.*

Buxton RB. Introduction to Functional Magnetic Resonance Imaging, 2002.
Huettel S, Song AW, McCarthy G. Funcitonal Magnetic Resonance Imaging, 2004.

How do we measure neuronal activity with MRI?

- Currently not possible to directly measure neural activity (i.e. electrochemical activity) with MRI
- Can visualize downstream correlates of neural activity:

Simplified flowchart



- The following lectures will discuss the nature of these different aspects of neurophysiology, and to what extent MRI can be used to image them

Overview of Imaging Physiology Block

- Lecture 1: Brain at baseline: neural activity, energy metabolism, and cerebral blood flow
- Lecture 2: “Activated” brain: changes in brain physiology in response to external stimuli, and Introduction to BOLD fMRI
- Lecture 3: BOLD fMRI in-depth
- Lecture 4: Beyond BOLD: state-of-the art fMRI techniques to directly image physiological parameters

Lecture 1:
Brain at baseline: neural activity, energy metabolism, and cerebral blood flow

Baseline Brain Activity

- *What do we mean by "brain at baseline"?*
  - Refers to the *intrinsic* functional activity of the brain, as opposed to activity *evoked* through stimulation
- Brain is *never* in zero-activity state; "resting" and "active" distinctions are actually misnomers
- Intrinsic functional activity far greater (60 – 80% of brain's energy budget) than evoked activity to external stimuli (0.5 to 1%)
- Next few slides will detail intrinsic processes that are occurring in the brain *all the time.*

Overview

- Brain “activity” can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion
- This is a very sophisticated system that is far from understood; we will present a simplified view.

Overview

- Brain “activity” can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion

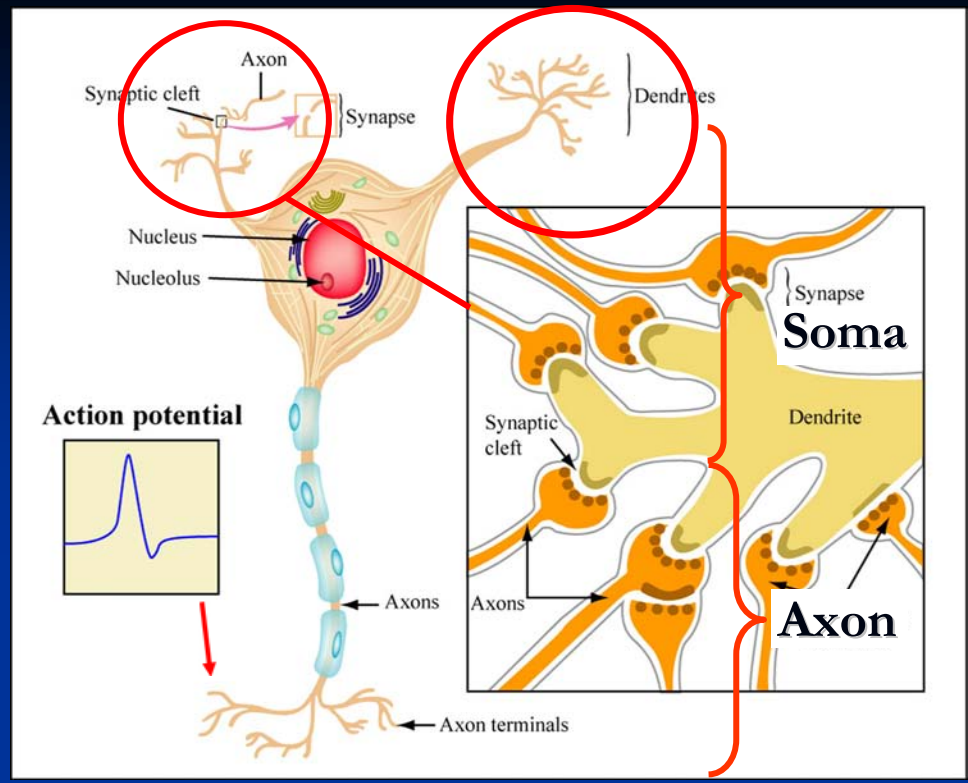
Neural Activity

- Let's begin with the smallest unit of functional activity in the brain: the neuron*
- Human brain has ~100 billion neurons
- Neural activity typically originates from ensembles of interconnected neurons communicating via electrical impulses
  - ***Integrative Processes***
  - ***Signaling Processes***

* *New research suggests that glial cells are more than just support cells; i.e. they have significant functional importance. Note that glial cells outnumber neurons by at* least *10:1*

Neuronal Anatomy

- **Dendrite**: receiving end of neuron, receives and ***integrates*** input signals from other neurons
- **Soma**: provides metabolic and structural support for the neuron
- **Axon**: transmitting end of the neuron; ***signals*** elicited via *action potentials* to one or more neurons
- **Synapse**: Specialized junction between dendrite and axon through which information is transferred



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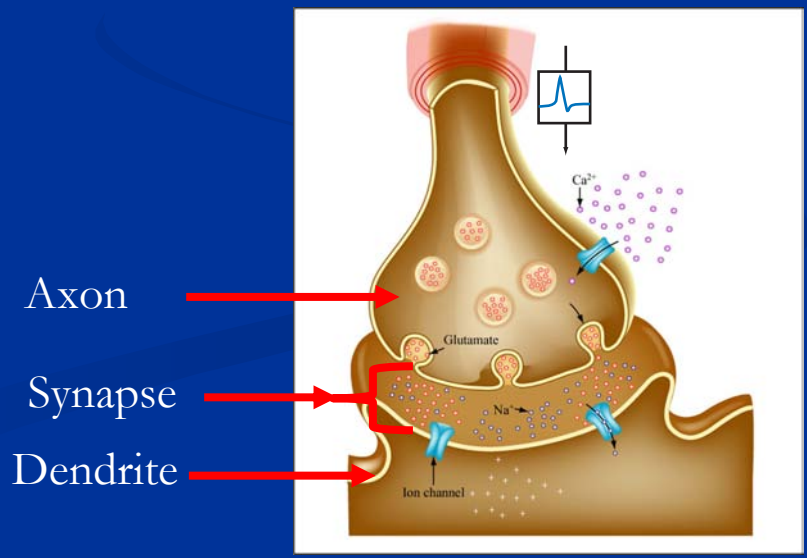

Immunofluorescence images

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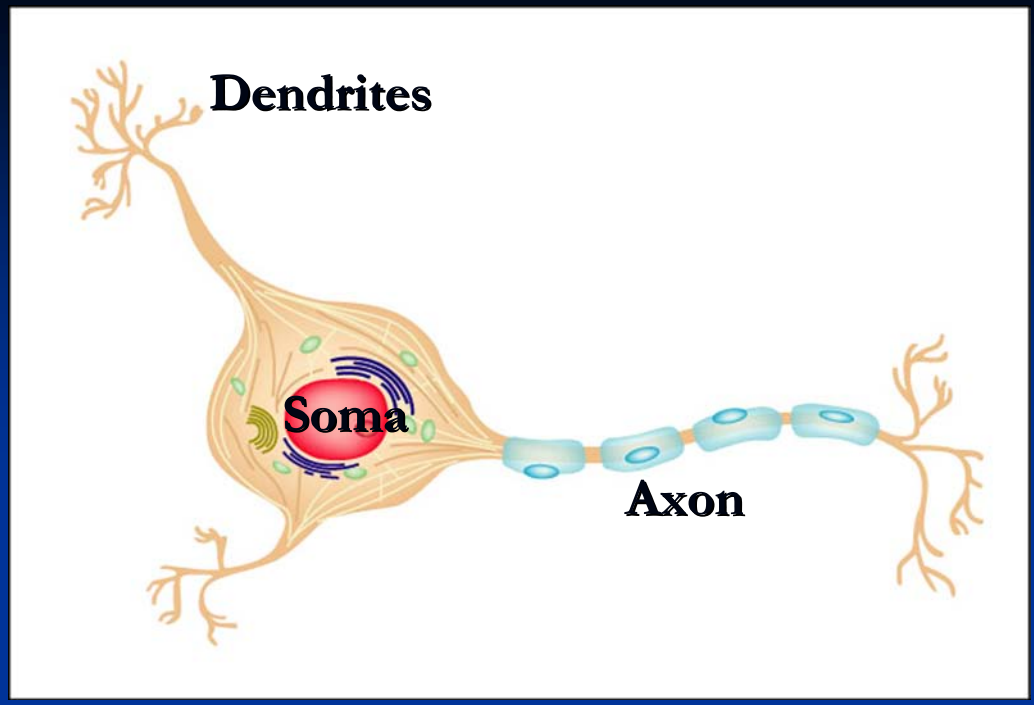
Figure 1-22A (Muldigl and De Camilli, Yale) in Nolte, John. *The Human Brain*. 5th ed. Philadelphia, PA: Elsevier, 2002. ISBN: 9780323013208.

Image removed due to copyright restrictions.
Cover of *Nature* by McPherson et al.
Vol 379 No 6563 (25 January 1996).

Signal Conduction



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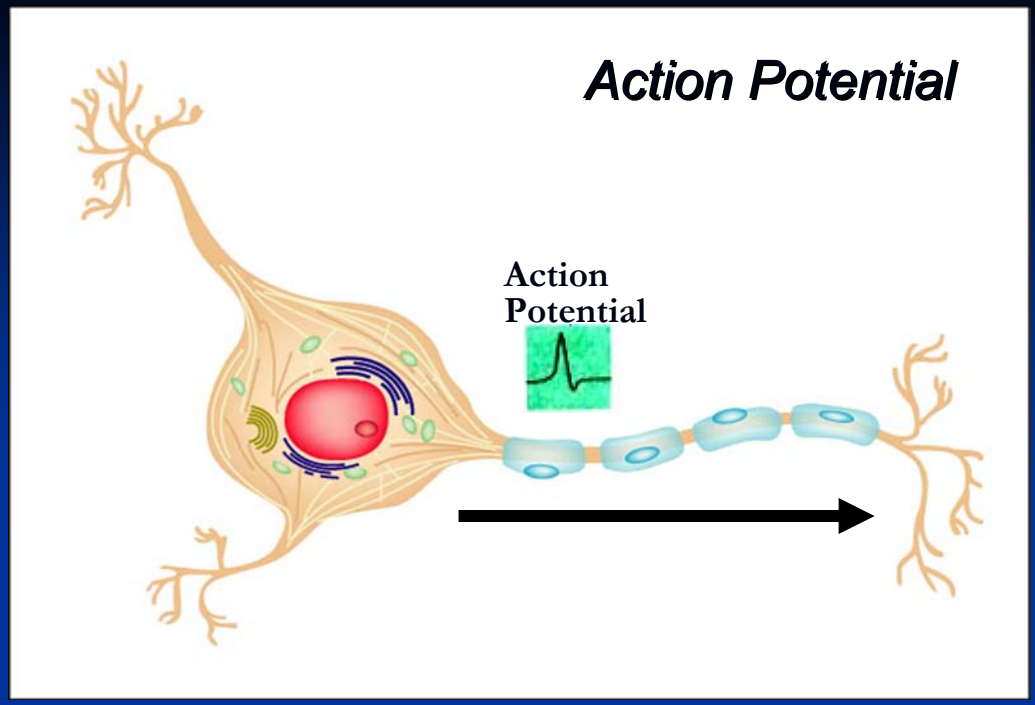

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Signal Conduction

- Signal conduction begins at base of axon with the *Action Potential*
- *Action Potential* is a wave of electrical activity that sweeps down axon

Signal Conduction

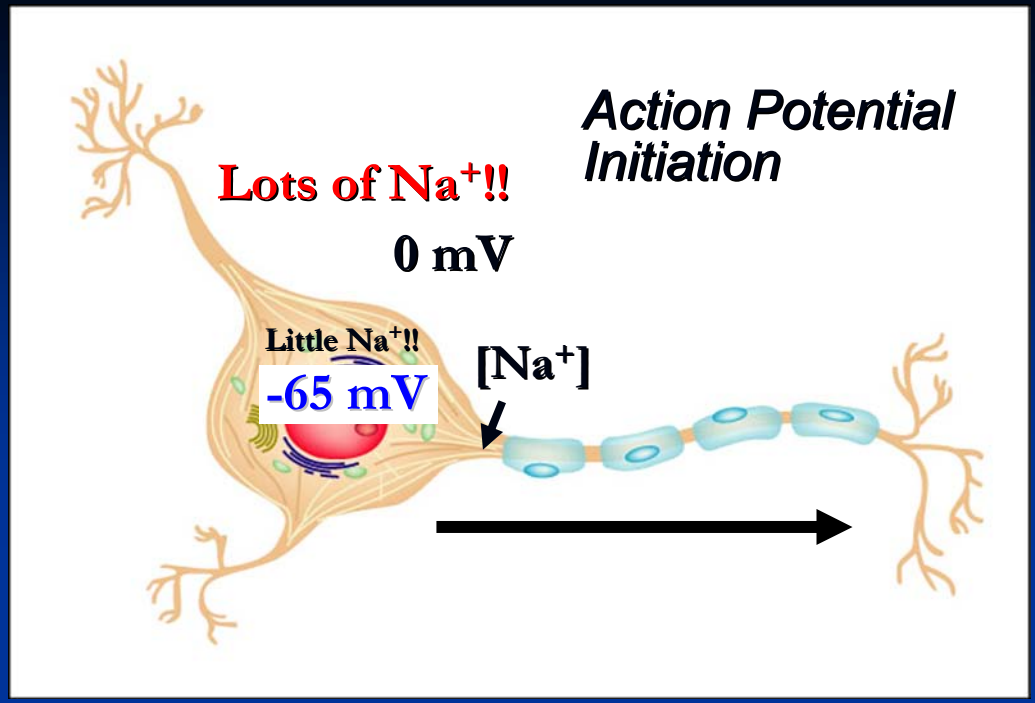
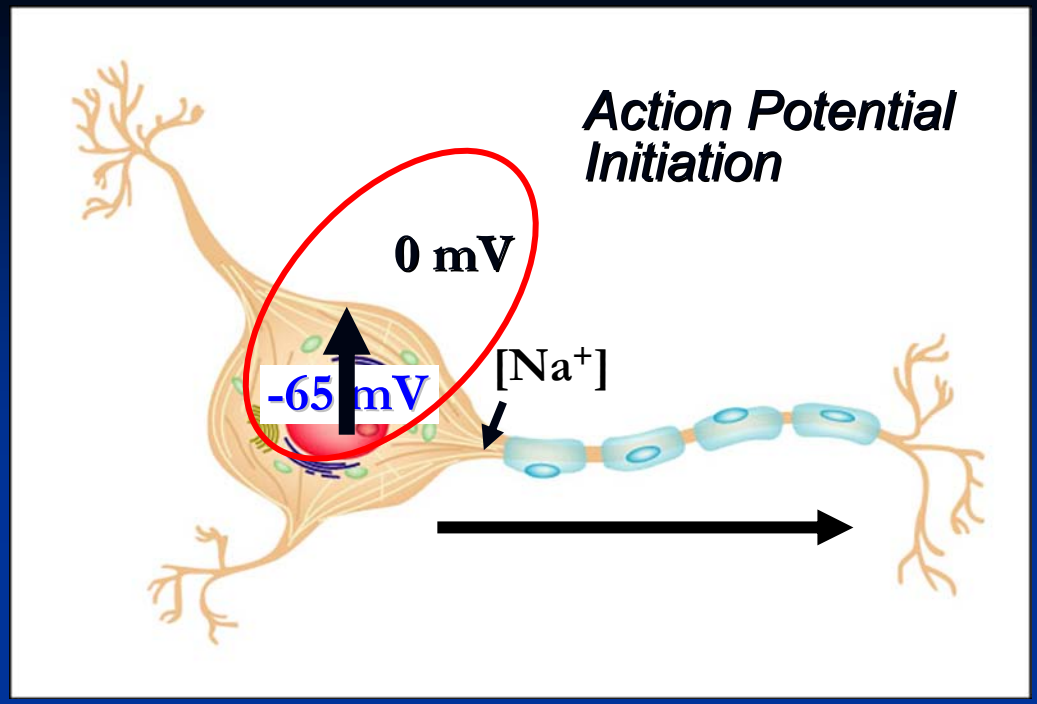


Figure by MIT OpenCourseWare.

- *AP* initiates when Na^+ channels open in axon base and allow Na^+ ions to flow in
- *Electrochemical gradient* drives Na^+ inflow:
  1. High concentration of Na^+ outside of neuron, low [Na^+] inside
  2. Outside of neuron more electrically positive than inside
- Flow of positively charged Na+ into cell is energetically favorable process (does not require energy)



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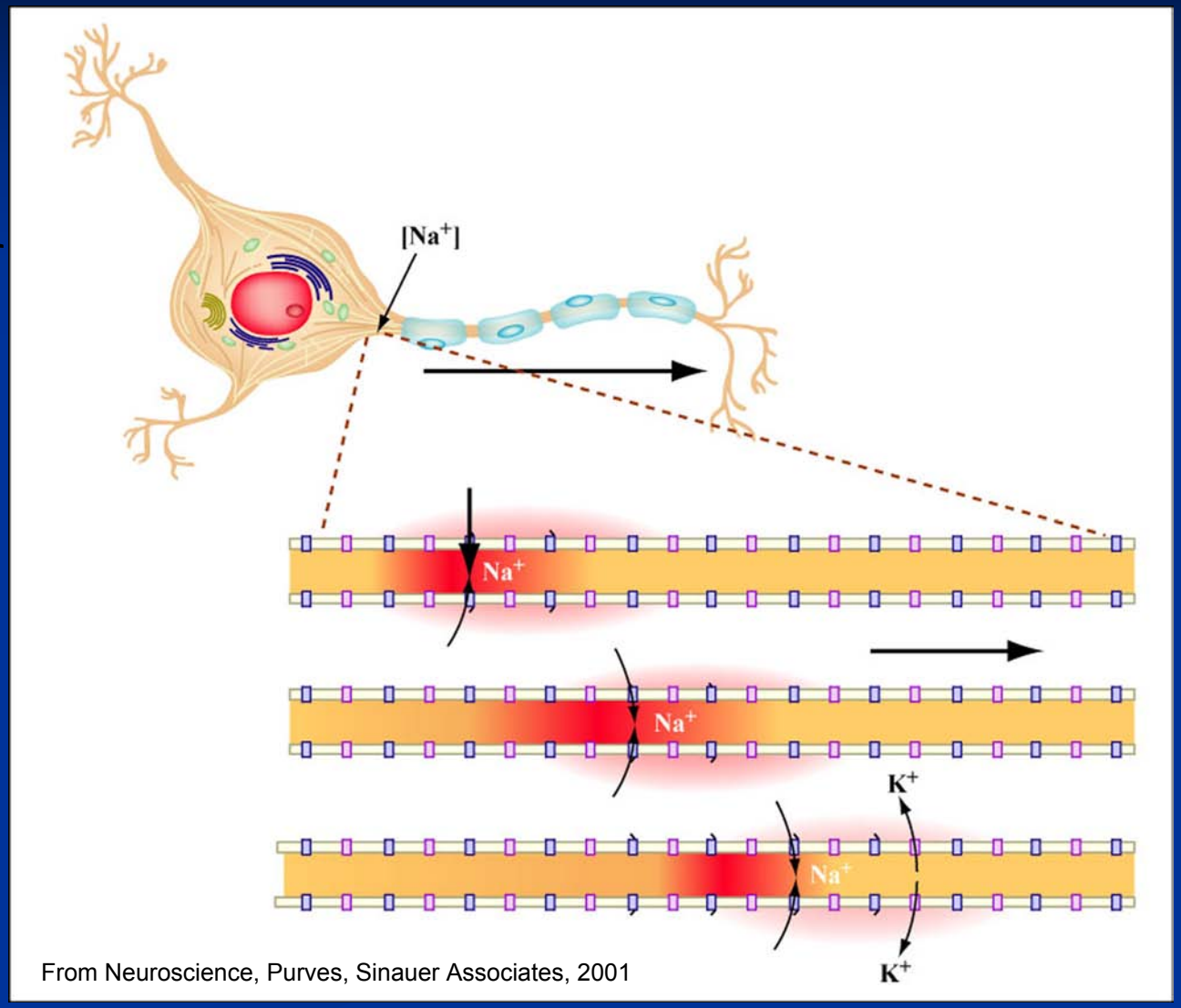
Signal Conduction

- AP onset causes a *depolarization:*
- Decrease of the potential difference between the outside and inside of neuron
- Occurs since inside becomes *less negative* with Na^+ inflow

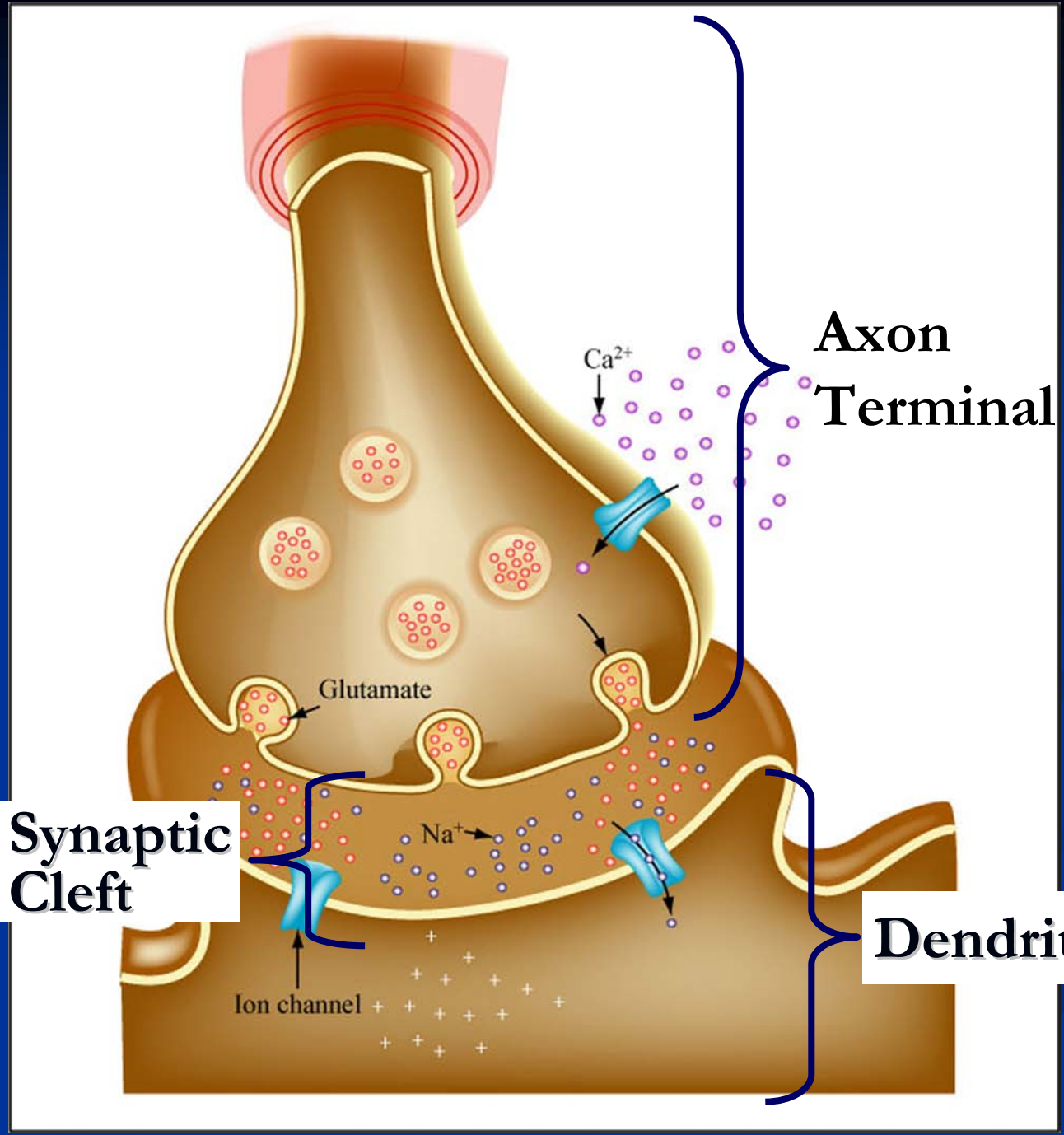
Signal Conduction

AP self-propagates and travels towards axon terminal



From Neuroscience, Purves, Sinauer Associates, 2001

Figure by MIT OpenCourseWare.



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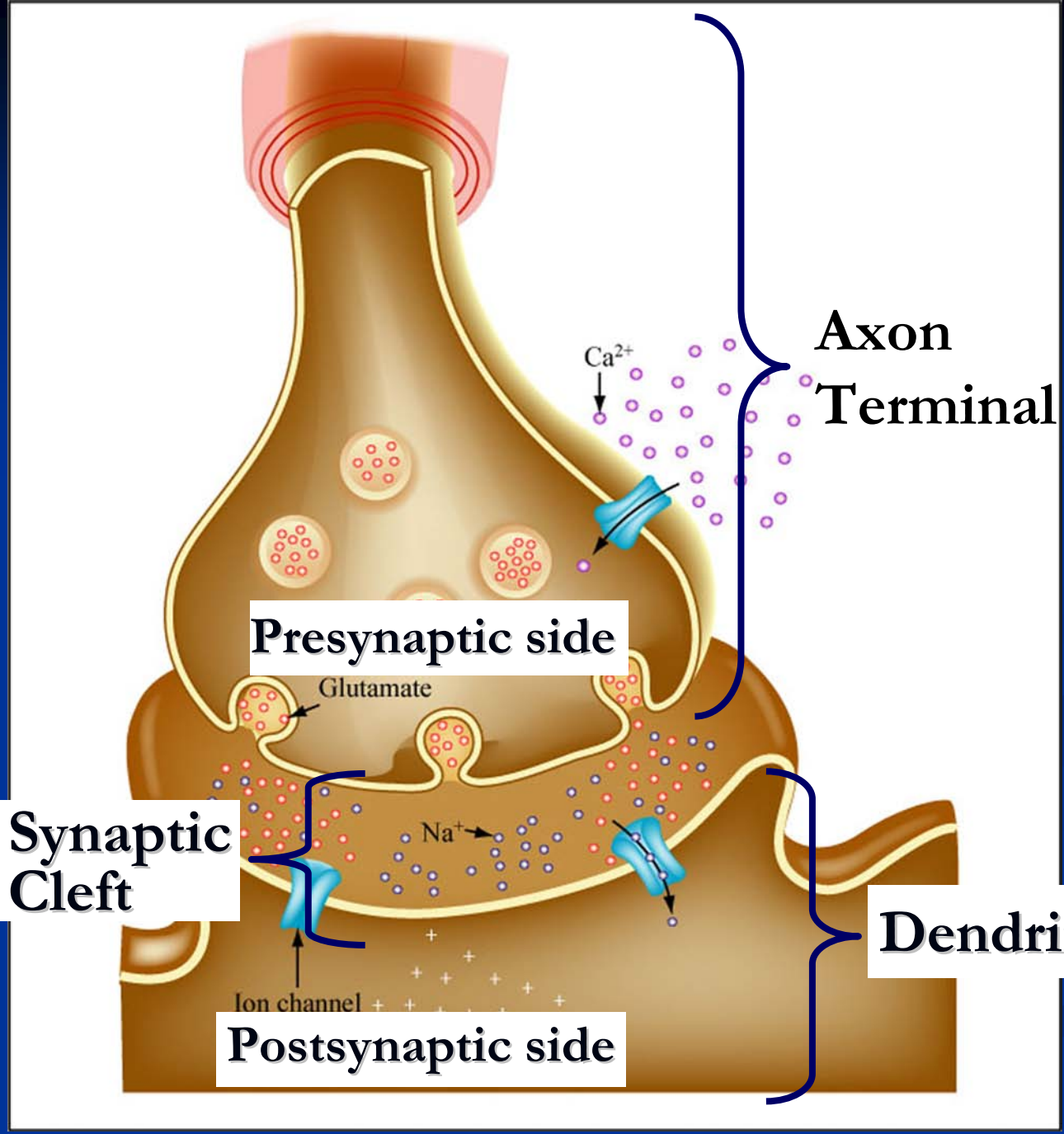
Adapted from *fMRI*, Huettel, Song, McCarthy, Sinauer Associates, 2004.



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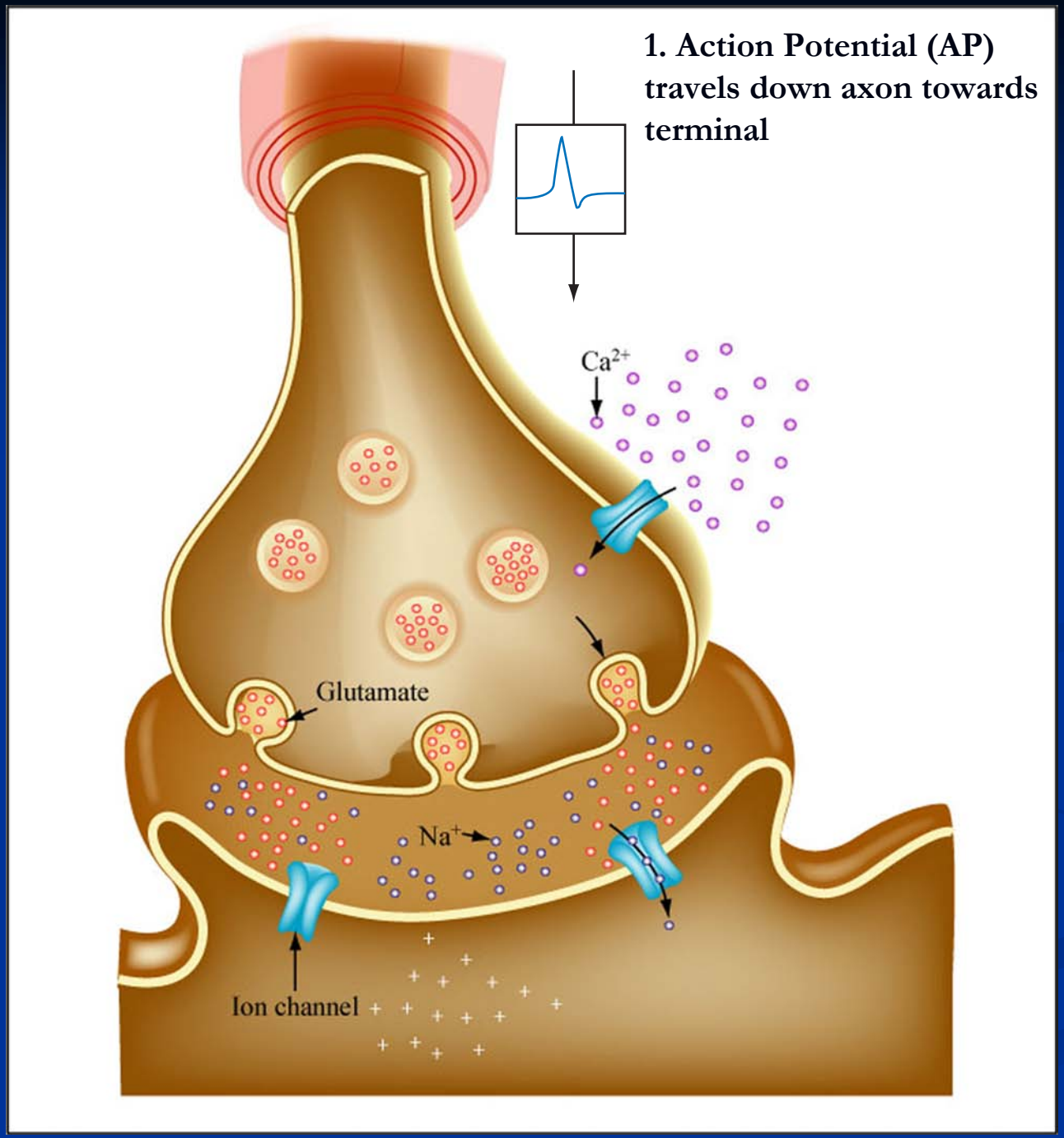
Adapted from *fMRI*, Huettel, Song, McCarthy, Sinauer Associates, 2004.



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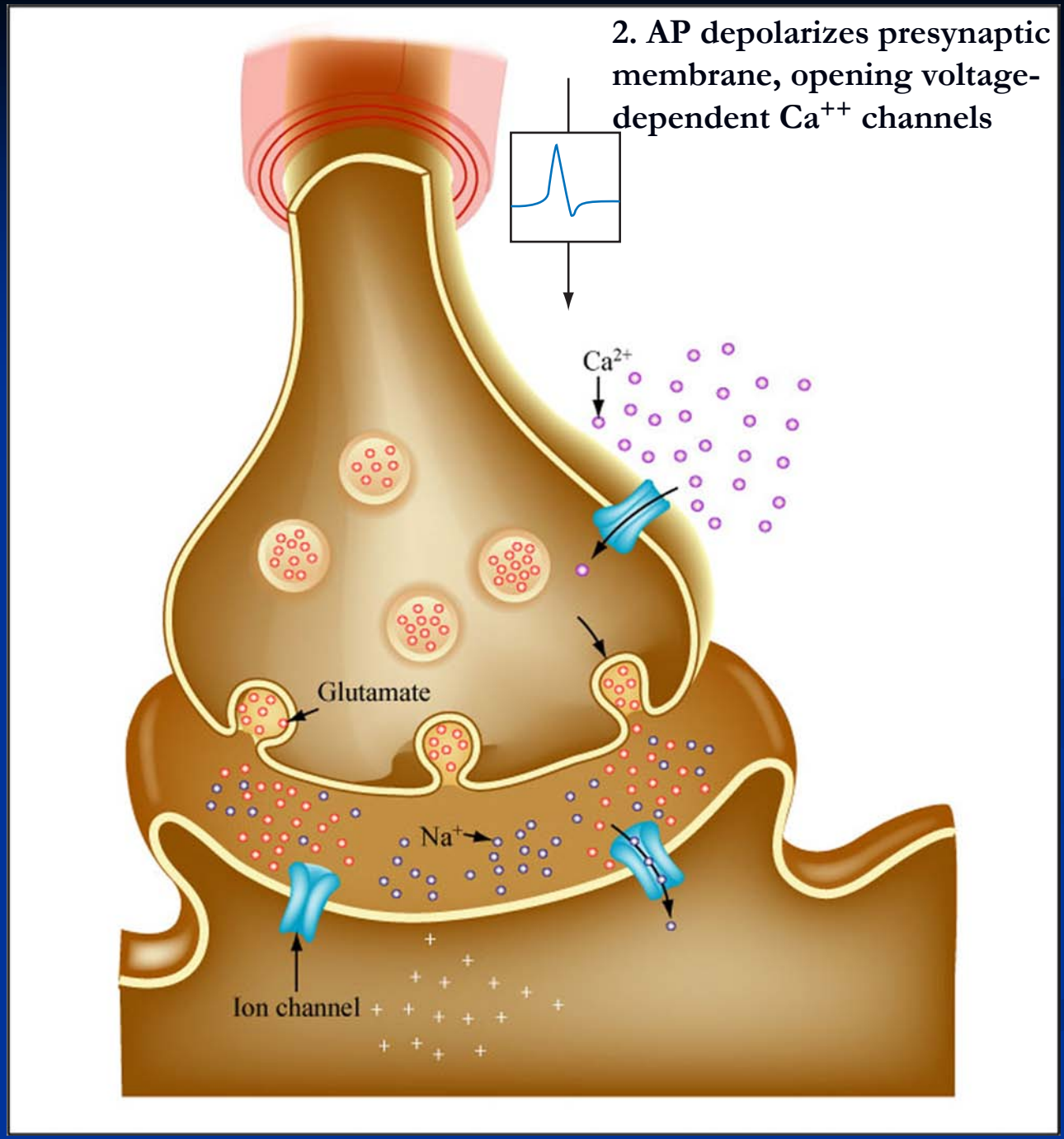
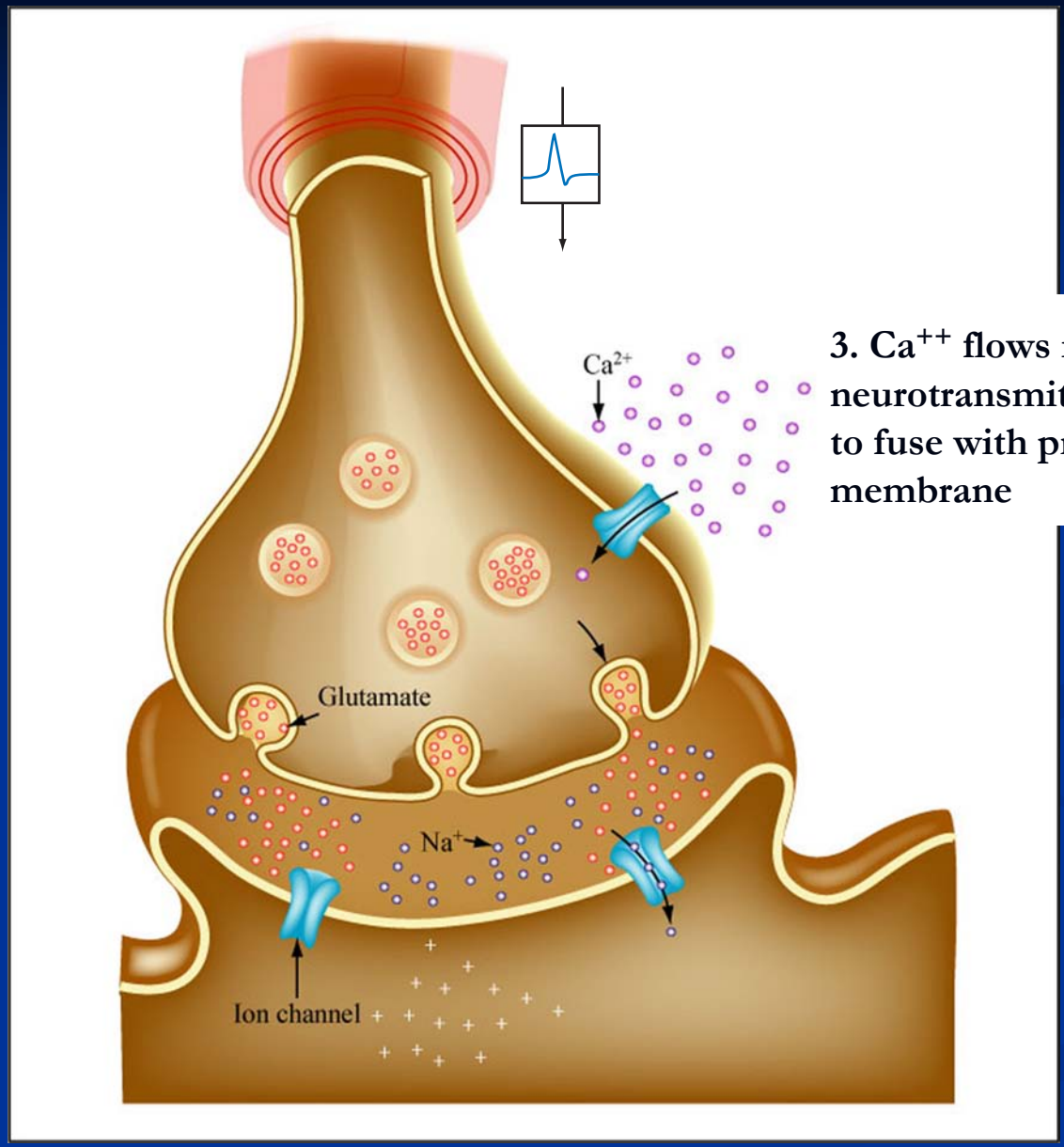


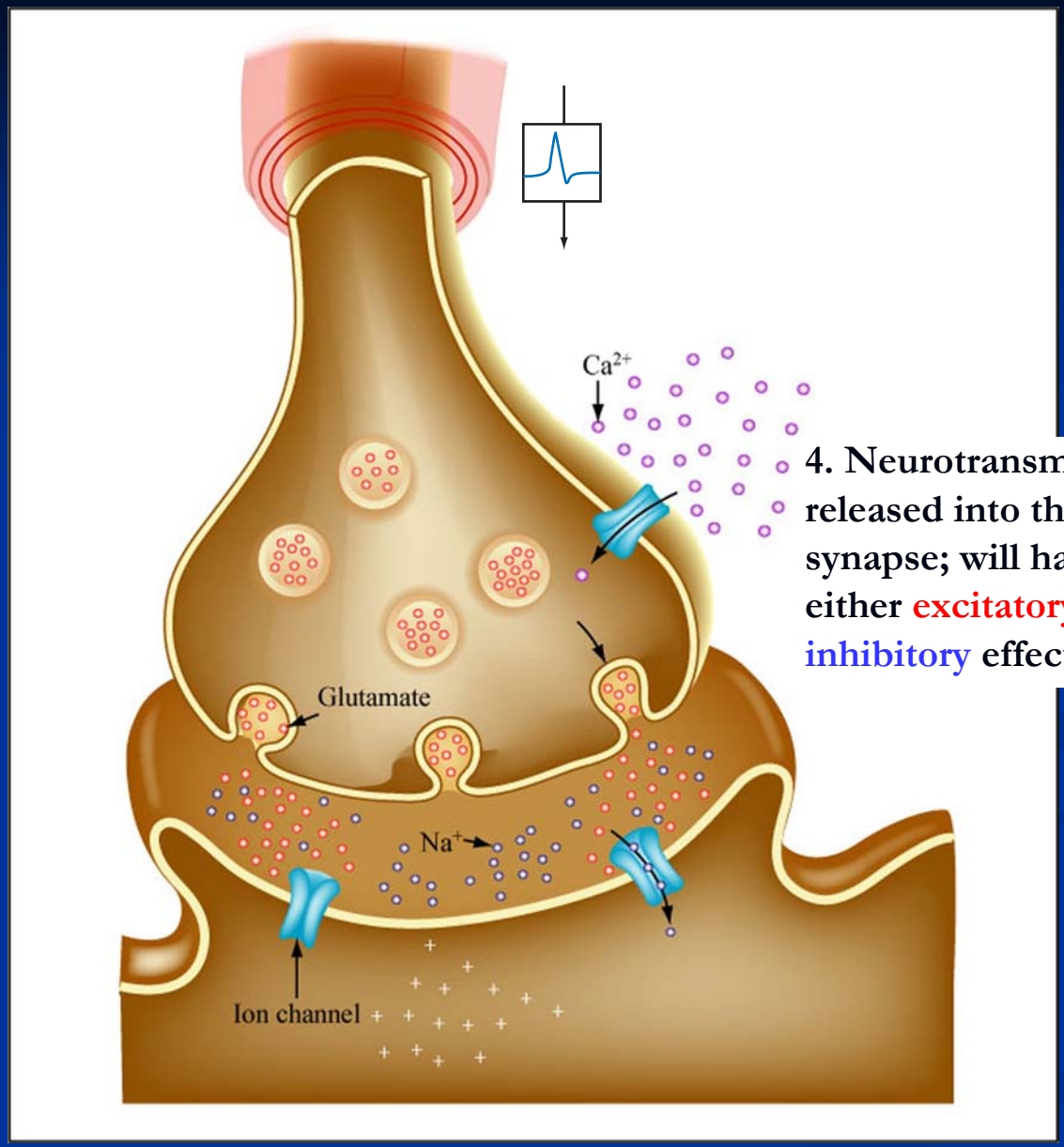
Figure by MIT OpenCourseWare.

Neurotransmitter-filled vesicles populate the distal end of the axon



3. Ca^{++} flows into cell, causing neurotransmitter-filled vesicles to fuse with presynaptic membrane

Figure by MIT OpenCourseWare.



4. Neurotransmitter is released into the synapse; will have either excitatory or inhibitory effects

Figure by MIT OpenCourseWare.

An excitatory or inhibitory effect depend on both neurotransmitter and receptor type

Glutamate is an abundant NT that primarily has excitatory effects

GABA is an abundant NT that primarily has inhibitory effects

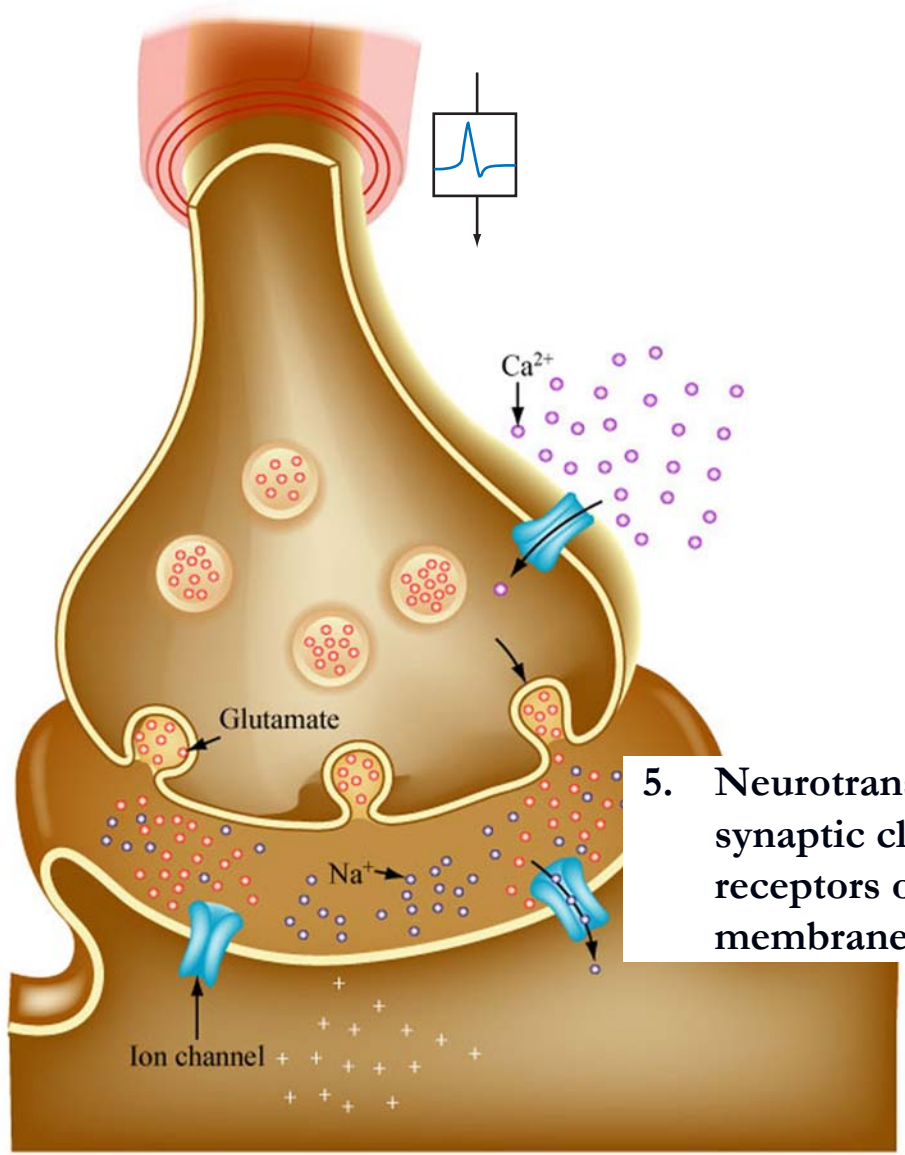
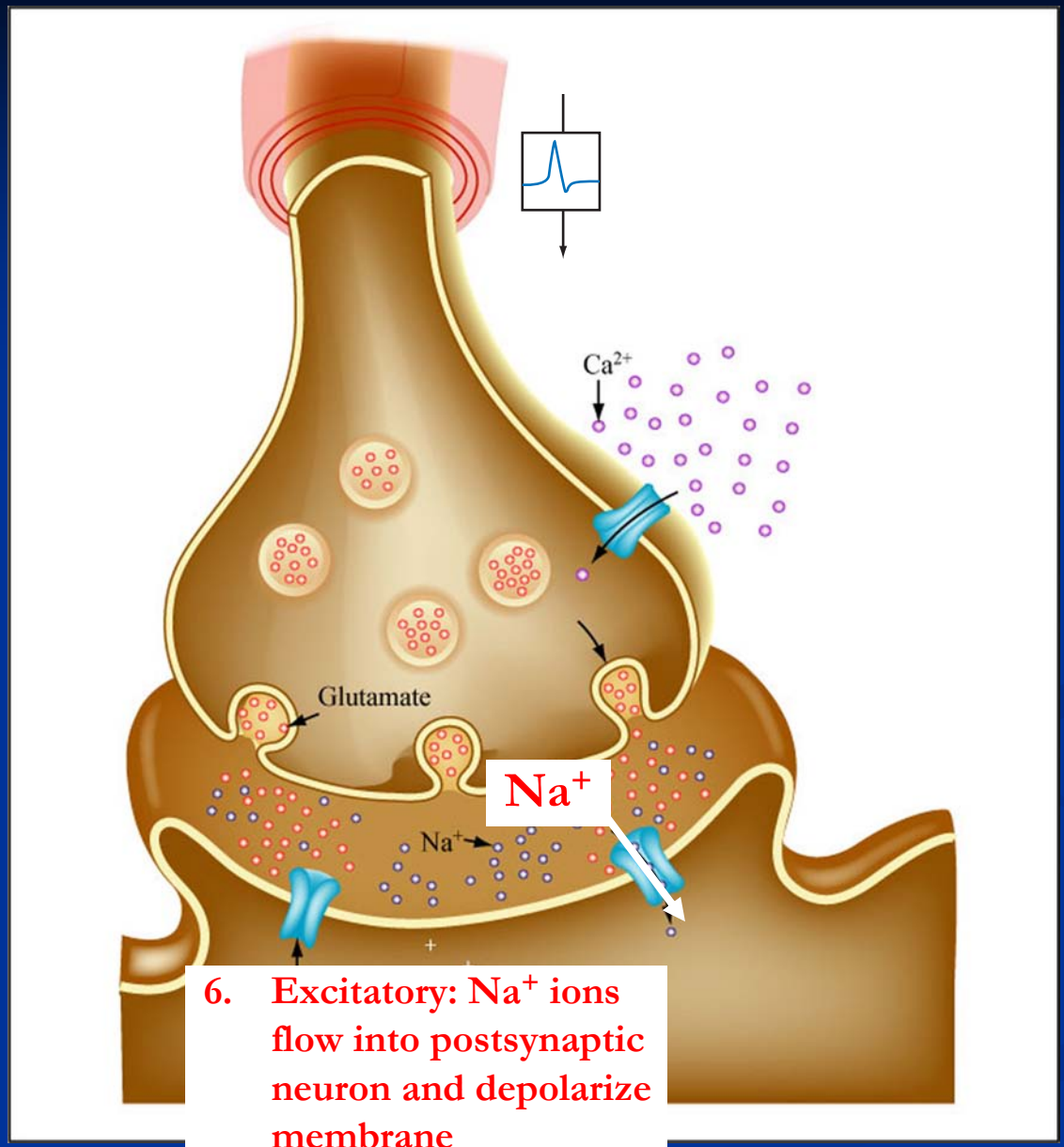


Figure by MIT OpenCourseWare.

Neurotransmitter with excitatory effects binds to receptors on Na^+ channels

Neurotransmitter with inhibitory effects bind receptors on Cl^- or K^+ channels

5. Neurotransmitter diffuses across synaptic cleft and binds with receptors on postsynaptic membrane; opens ions channels



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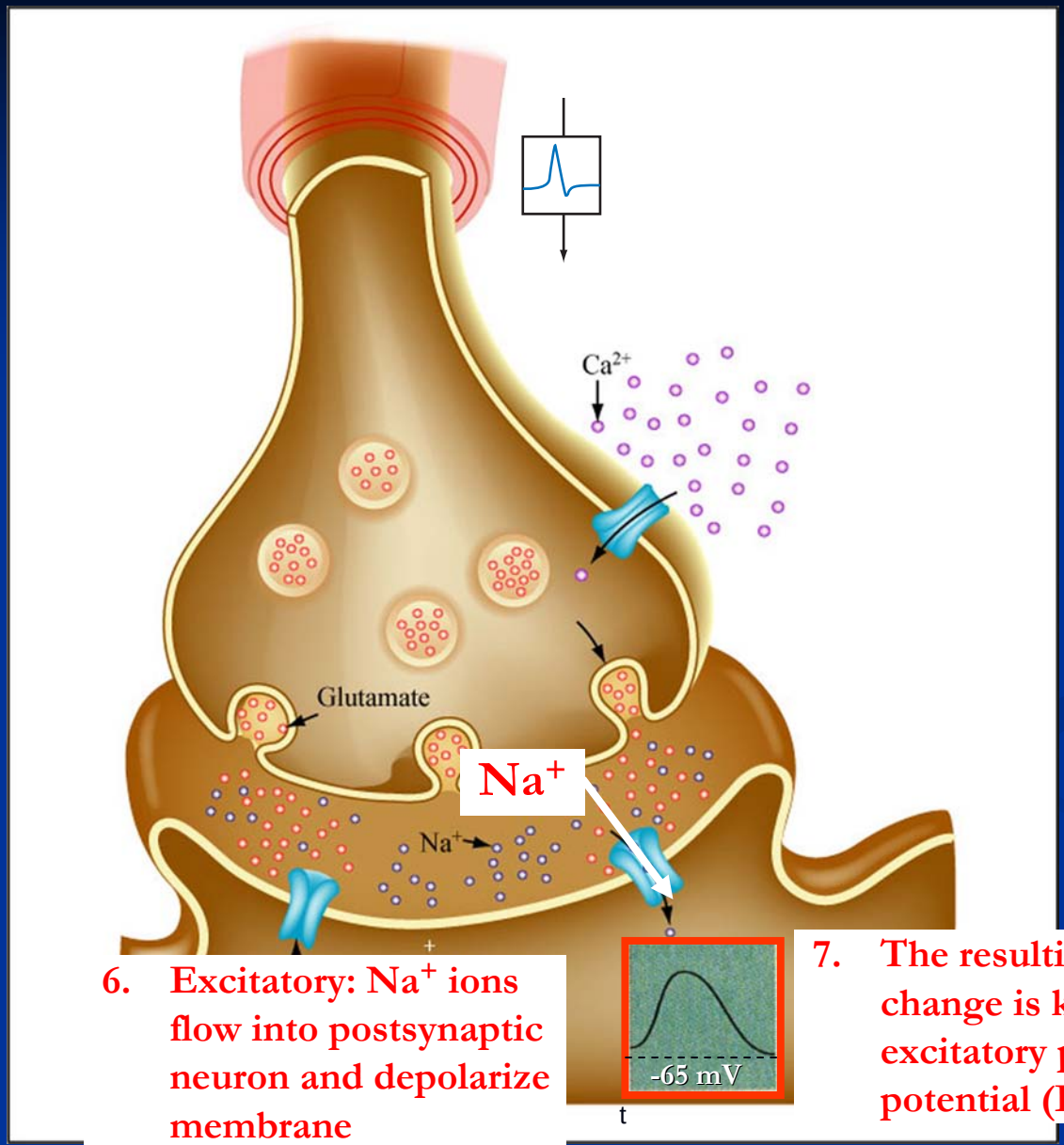
Excitatory **effect leads to *Depolarization:***

Local decrease in the electrical potential between the inside and outside of the membrane



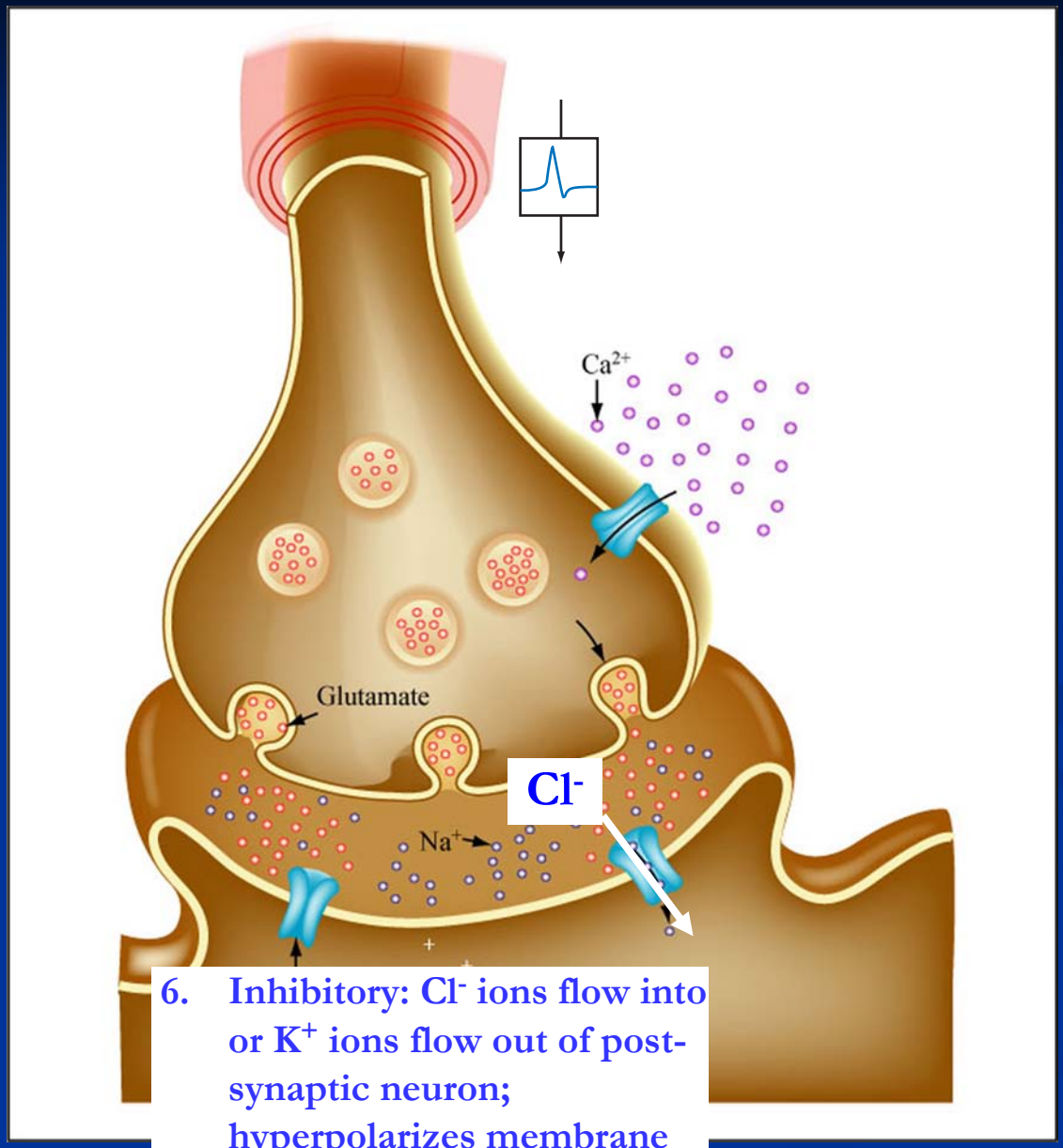
6. Excitatory: Na^+ ions flow into postsynaptic neuron and depolarize membrane

7. The resulting potential change is known as an excitatory post-synaptic potential (EPSP)

Excitatory **effect leads to *Depolarization:***

Local decrease in the electrical potential between the inside and outside of the membrane

EPSPs ***increase*** **probability that receiving cell will fire action potential**

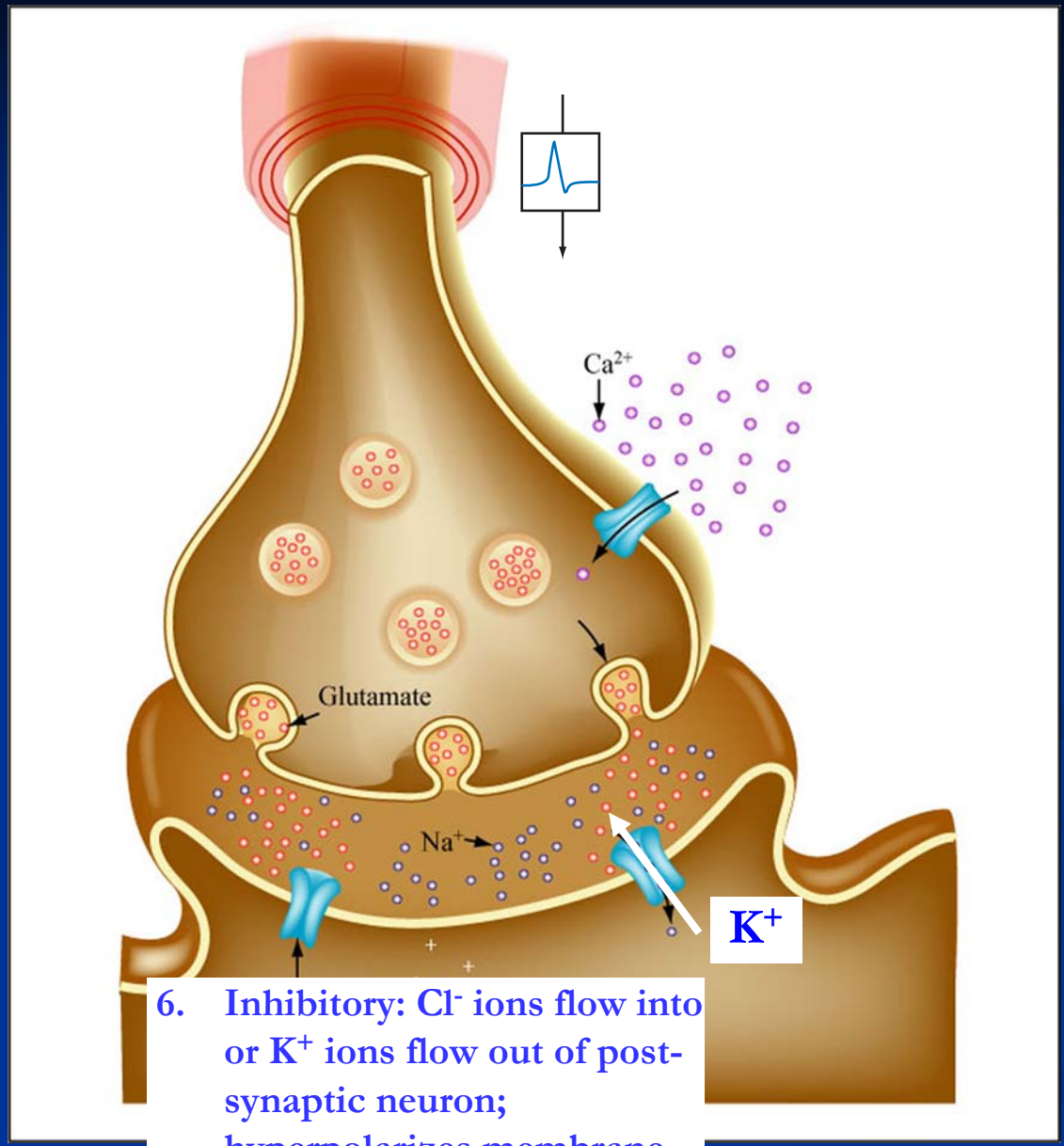


6. Inhibitory: Cl^- ions flow into or K^+ ions flow out of post-synaptic neuron; hyperpolarizes membrane

Figure by MIT OpenCourseWare.

Inhibitory **effect leads to *Hyperpolarization:***

Local increase in the electrical potential between the inside and outside of the membrane



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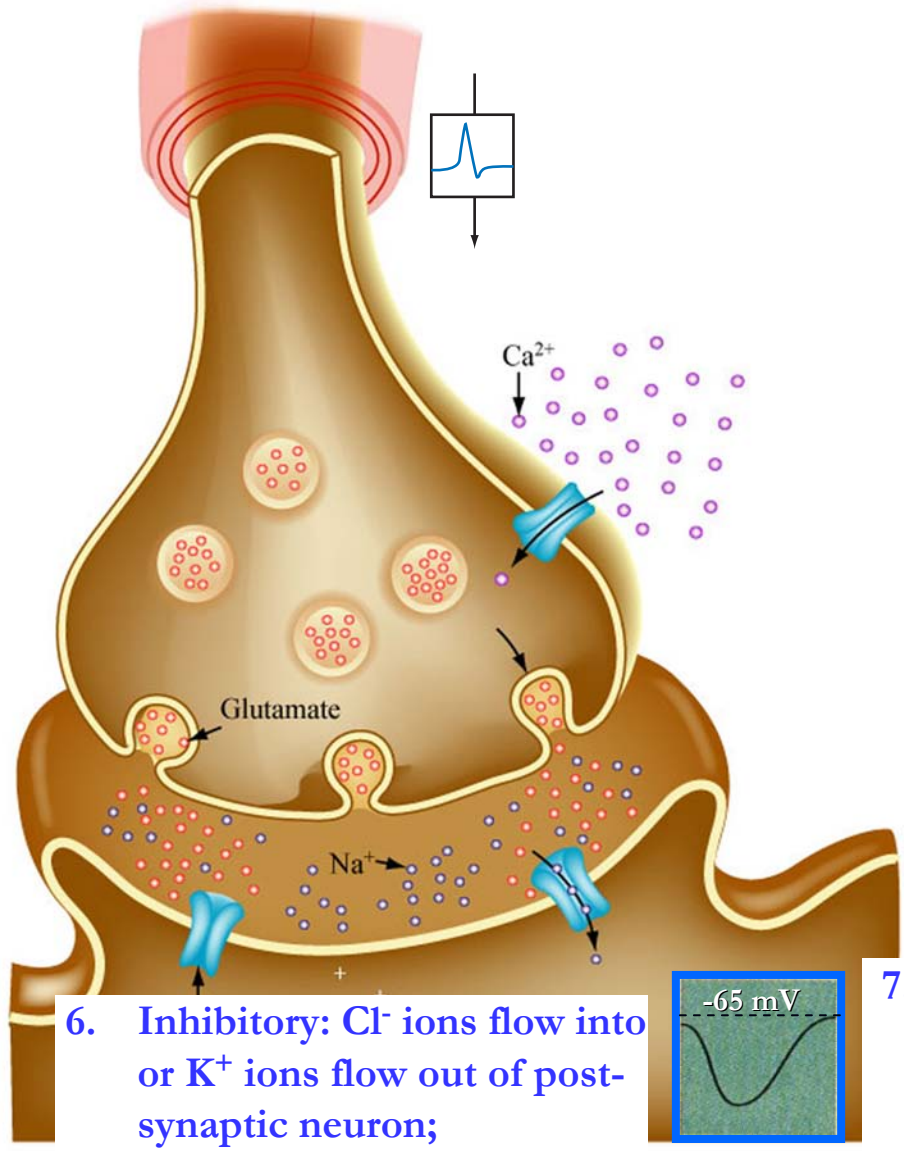
Inhibitory **effect leads to *Hyperpolarization:***

Local increase in the electrical potential between the inside and outside of the membrane



6. Inhibitory: Cl^- ions flow into or K^+ ions flow out of post-synaptic neuron; hyperpolarizes membrane

7. The resulting potential change is known as an inhibitory post-synaptic potential (IPSP)

Inhibitory **effect leads to *Hyperpolarization:***

Local increase in the electrical potential between the inside and outside of the membrane

IPSPs *decrease* probability that receiving cell will fire action potential

Integration leads to signaling

- Thousands of IPSPs and EPSPs are received by dendrites;
- **Integration** is the summation of these of these PSPs
- If the resultant voltage is beyond a threshold, an axon potential is elicited to continue **signaling**

Summary of neural information processing

- Information processing is thus the combination of neuronal ***integrative*** and ***signaling*** roles
- ***Integration:*** The summation of EPSPs *(depolarizations)* and IPSPs *(hyperpolarizations)* from all incoming axons
  - Integration is affected by unique spatiotemporal characteristics of EPSPs and IPSPs
- ***Signaling:*** If summation results in a threshold potential being reached, a new action potential is elicited and sent down axon

Overview

- Brain “activity” can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion

Energy requirements

- Postsynaptic potential (EPSPs, IPSPs) and action potential generation depend on electrochemical gradients, ion flow, & neurotransmitter release
- As signaling proceeds, the driving force behind AP/PSP generation is lost, as ion and neurotransmitter stores are depleted
- ***For neuronal signaling to continue:***
  1. ***Ion concentrations & electrochemical gradients must be re-established for continued ion flow, and***
  2. ***Neurotransmitter must be recycled returned to neuron***
- ***These processes require energy; the primary source of free energy in the brain is ATP!***

Generation of ATP in the brain

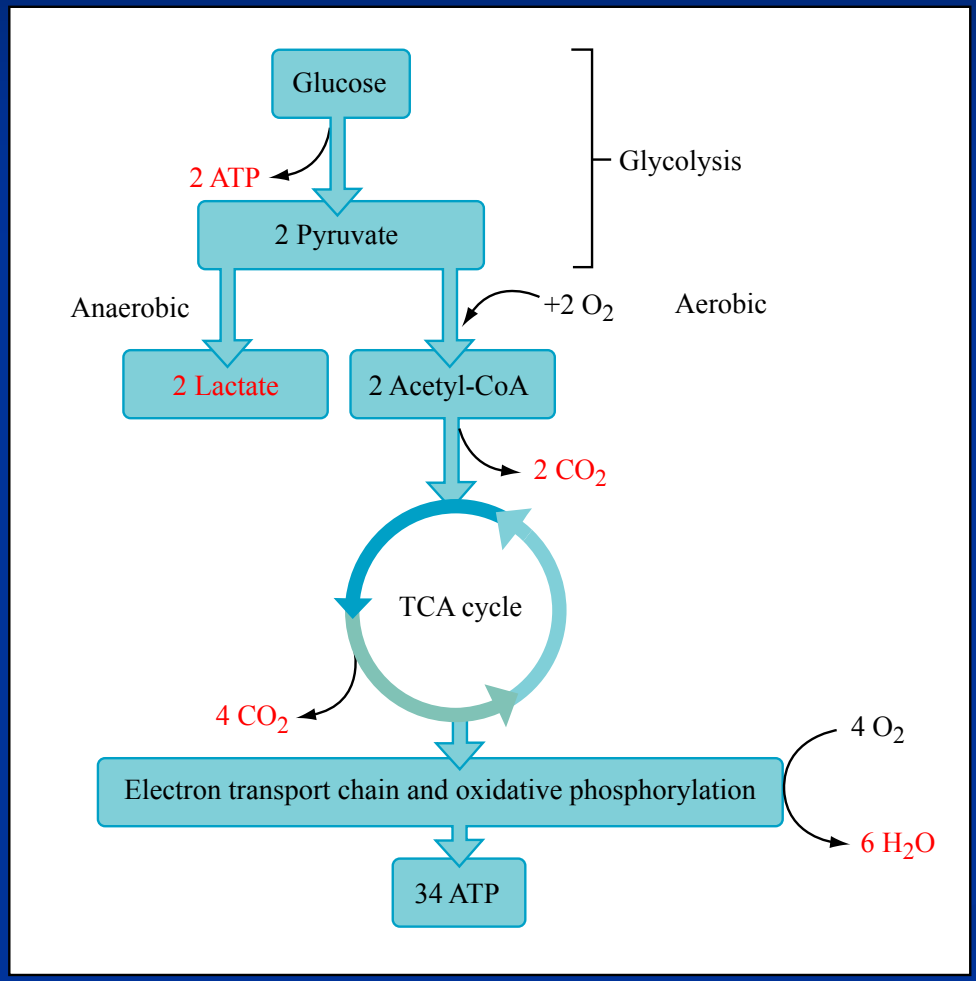
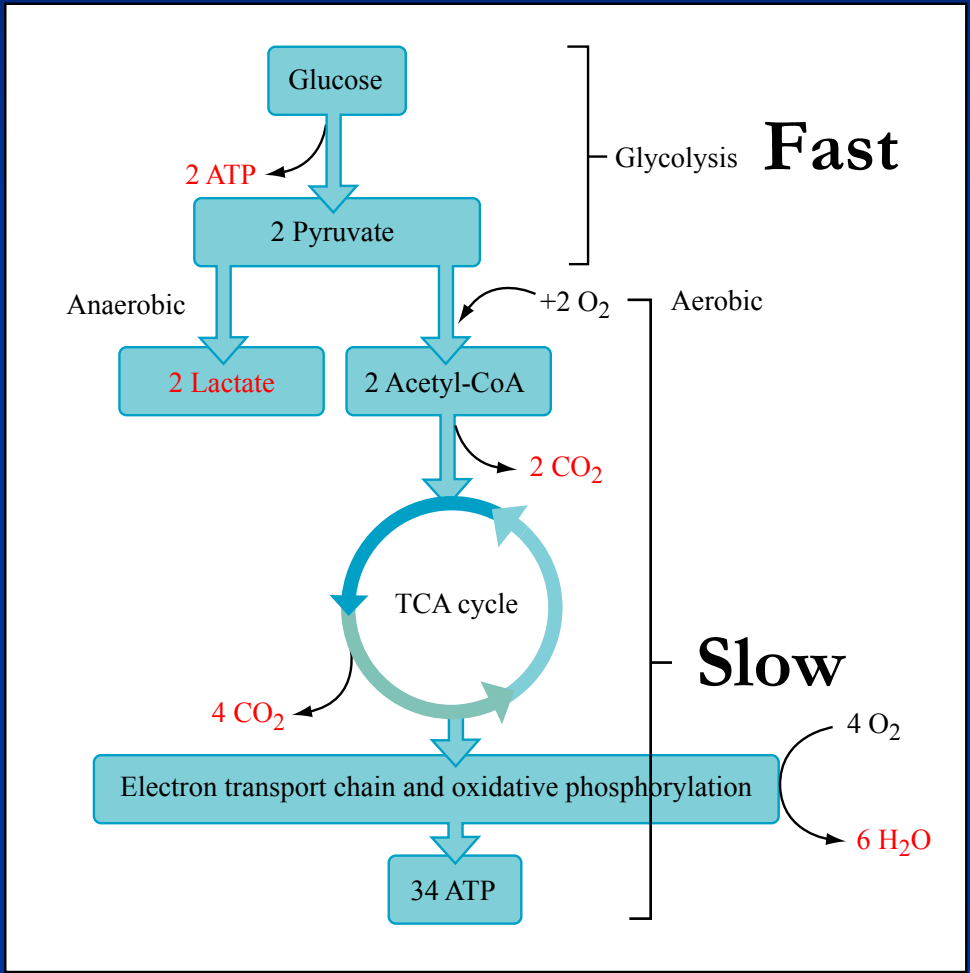


Figure by MIT OpenCourseWare.

- **Glycolysis**
  - Consumes glucose,
  - Produces 2 ATP, Acetyl CoA if O_2; lactate if no O_2
- **TCA Cycle/ Ox Phos**
  - Consumes O_2
  - Produces CO_2, water and **LOTS of ATP**

Generation of ATP in the brain



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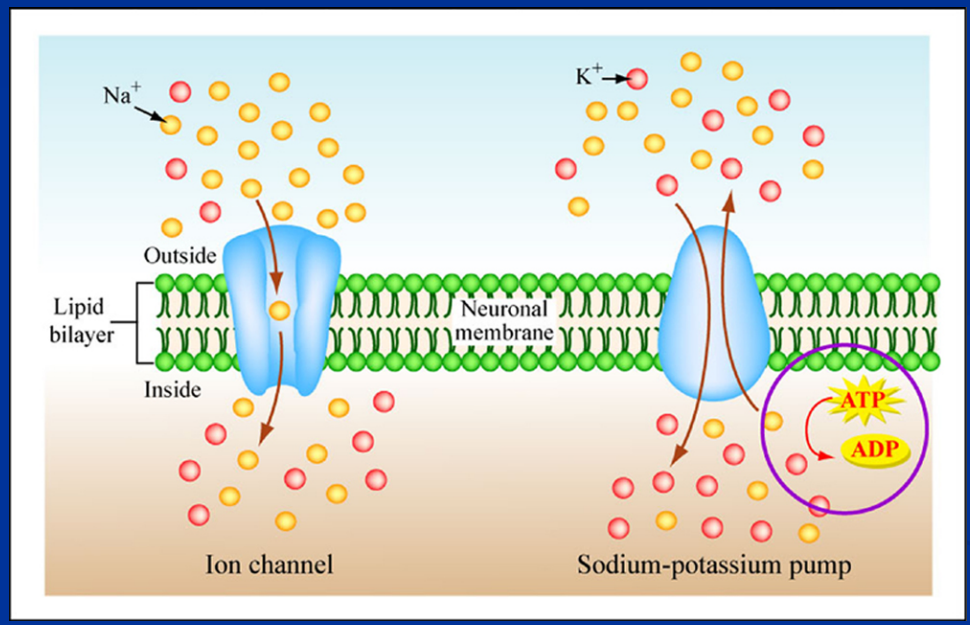
- **Aerobic Respiration:** Requires oxygen, produces 34 ATP, *slow* process
  - Byproducts are CO_2 and H_2O
- **Anaerobic Respiration:** Does not require oxygen, produces only 2 ATP, but very *fast* process
  - Lactate is major byproduct

Reestablishing ion concentrations & electrochemical gradients: Ion pumps

- Signal transduction requires ion flow
- As ions flow, intracellular and extracellular ion concentrations change
- Electrochemical gradient which drives ion flow gets depleted
- For signaling to continue, ion concentrations must be restored for
- This is done via ***ion pumps***

Ion Pumps

- Ion pumps restore electrochemical gradient by pumping ions into or out of neuron



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- Occurs in both presynaptic and postsynaptic neurons
- **This is a process that requires ATP**

Neurotransmitter Recycling*

- Neurotransmitter glutamate is released into synapse during most excitatory signaling processes
- At this point two things must happen:
  1. Glutamate must be quickly removed to stop excitatory activity
     - Specific timing and duration of activity is critical for propoer information processing
     - Unchecked stimulation is neurotoxic
  2. Glutamate must be returned to presynaptic neuron for future signaling
- ***Astrocyte-Neuron Lactate Shuttle*** is a model that could explain glutamate cycling

*** Will focus on glutamate; other NT beyond scope of lecture**

Neurotransmitter Recycling: Astrocyte-Neuron Lactate Shuttle

See Magestretti et al, Science, 1999

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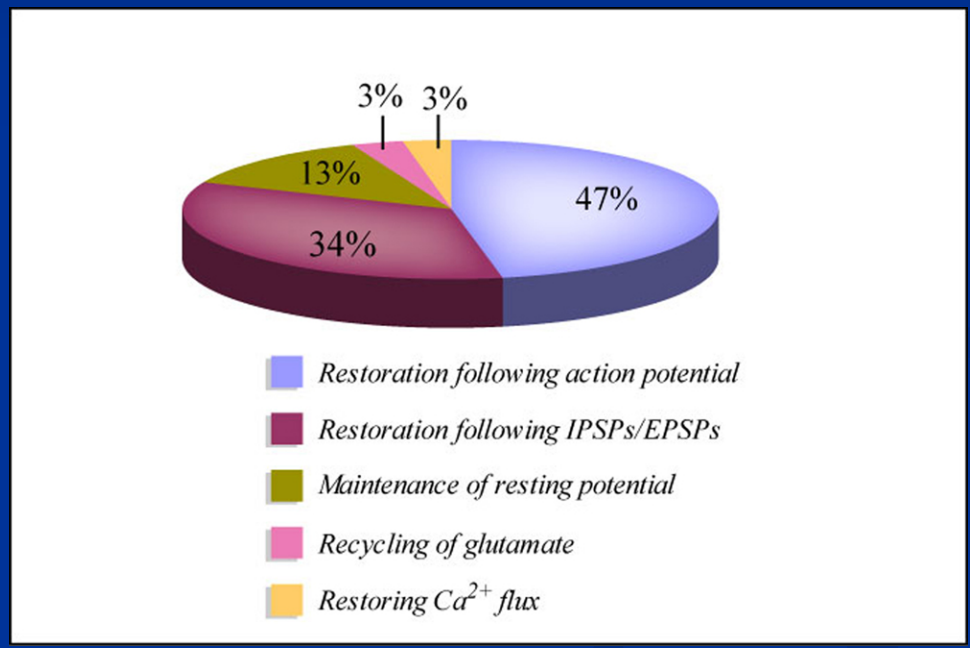
From *fMRI*, Huettel, Song, McCarthy, Sinauer Associates, 2004

- NT glutumate is released into synapse after AP
- Na^+/Glutamate co-transporter on astrocyte *passively* removes glutamate from synapse
- *Anaerobic* glycolysis generates 2 ATP without O_2
- **One ATP** powers Na^+/K^+ pump to maintain membrane potential
- **One ATP** converts glutamate to inactive glutamine
- Glutamine is returned to neuron

Astrocyte is a *glial cell*, historically considered as primary neuronal support cell*

Energy budget in the brain*

- Restoring presynaptic membrane ion concentrations following AP consumes **47%** of total energy expenditure
- Restoring postsynaptic membrane ion concentrations following PSPs consumes **34%**
- Glutamate cycling: **3%**



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* Data from rodent brain; Atwell & Laughlin, JCBFM 2001

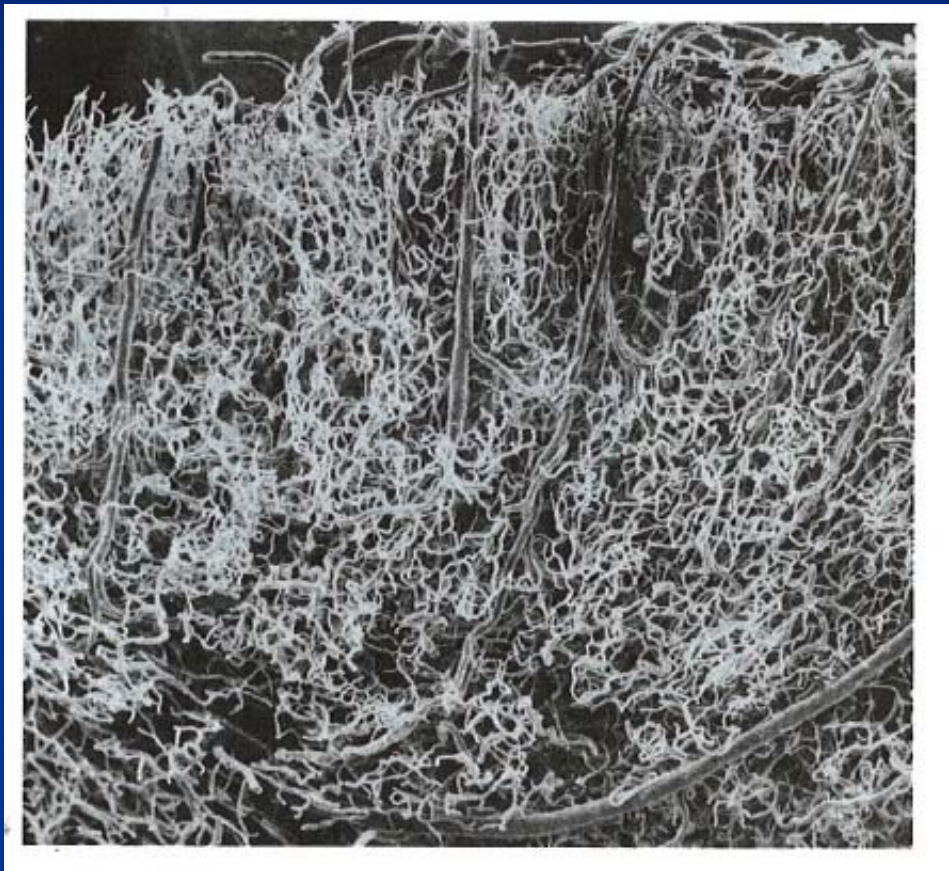
Overview

- Brain “activity” can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion

Cerebral Blood Flow (CBF)

- Supplies ***oxygen, glucose,*** and other nutritive elements to the brain, as needed for neuronal activity and energy metabolism
- Removes ***CO_2***, ***heat***, other byproducts and toxins
- Despite being only 2% of body's weight, the brain receives 20% of its blood flow
- Vascular architecture and macrovascular flow were described in detail in Block I
- Focus on *microvascular CBF* and *perfusion* in this block

*Micro*vascular structure



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- Vessels with radius ~3 um - ~500 um
- Capillaries
- Arterioles
- Venules

Devernoy, Delon, Vannson. "Cortical blood vessels of the human brain." *Brain Research Bulletin* 7, no. 5 (November 1981): 519-579.

Definition of terms
(in the context of fMRI)

- ***Perfusion*** describes nutritive delivery of arterial blood to a capillary tissue bed
- ***CBF*** is the rate of delivery of arterial blood to capillary beds of particular mass (or volume)
- ***CBV*** (cerebral blood volume) is the faction of the tissue volume occupied by microvessels
- ***Mean transit time*** (τ) is the time it takes blood to flow through a defined volume; τ = CBV/CBF

MRI definition of CBF

- Conventional definition of flow:

$$flow = \frac{volume}{time} = CS\ area \cdot velocity$$

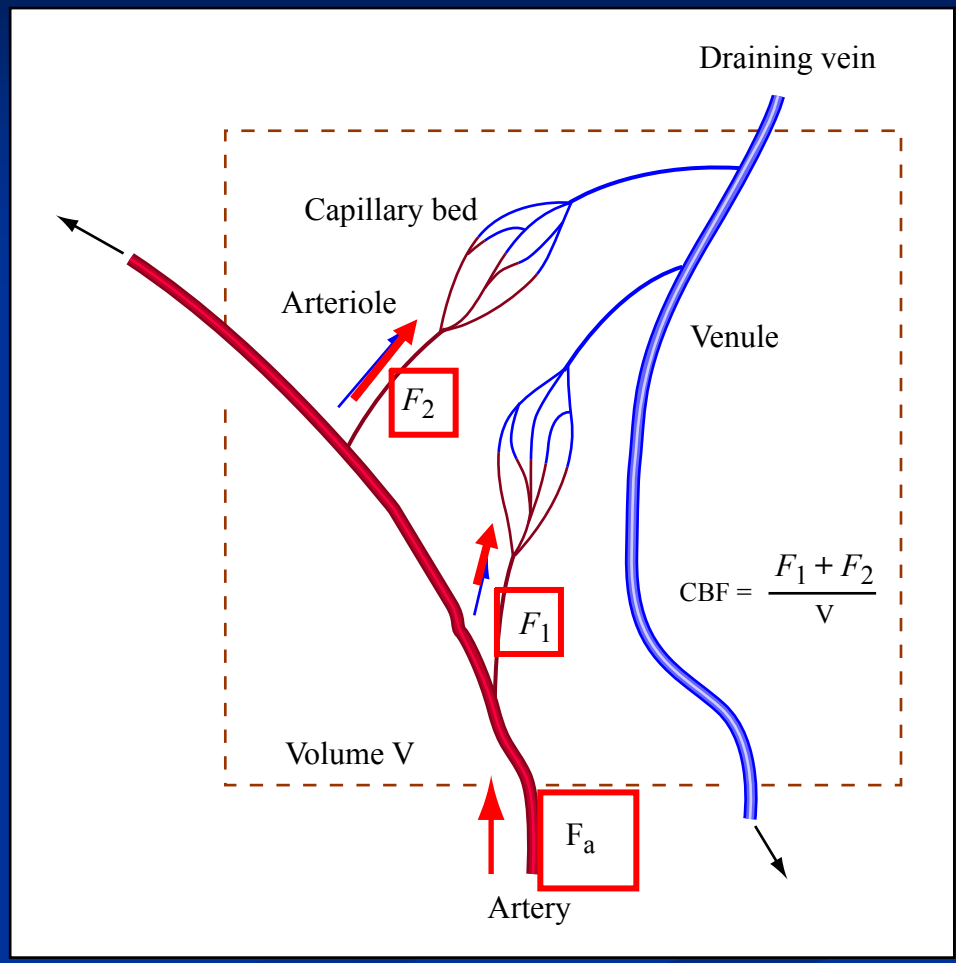


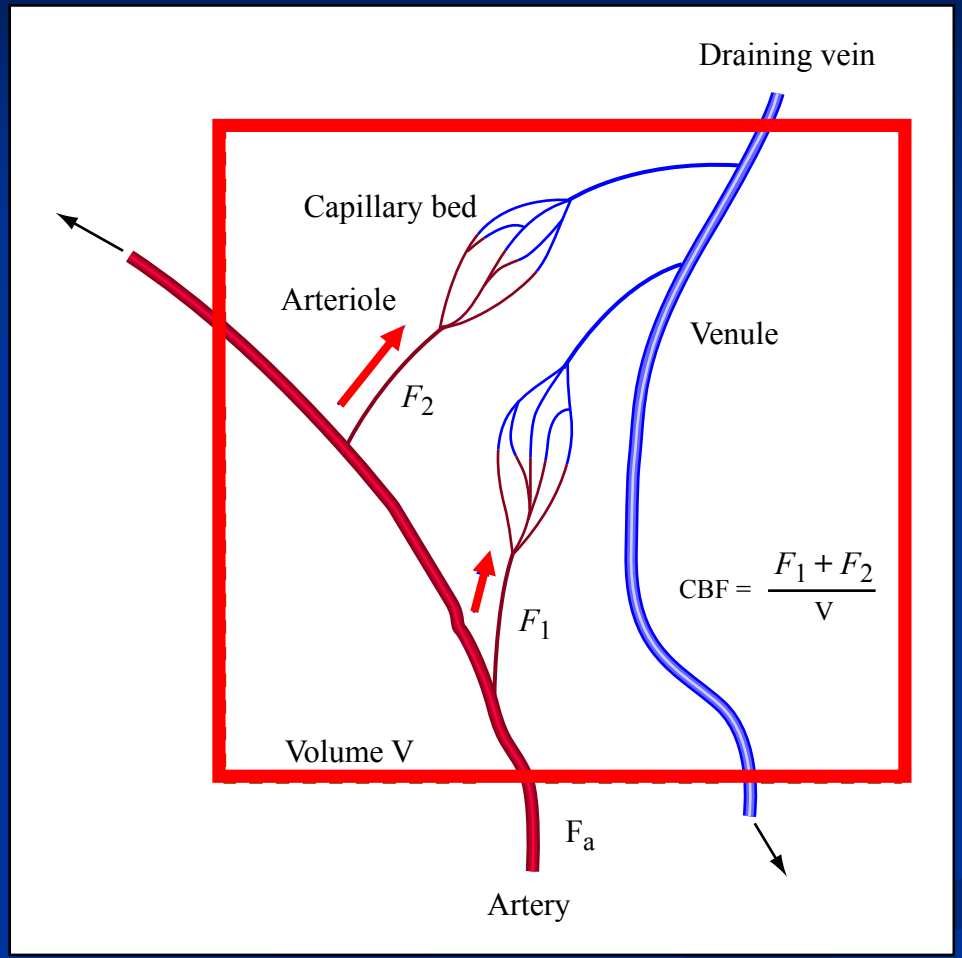
Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

MRI definition of CBF

- Conventional definition of flow:

$$flow = \frac{volume}{time} = CS\ area \cdot velocity$$

- MRI definition of CBF slightly different;
- *CBF* does not report flow ***through*** a vessel, but rather flow ***to*** capillaries in an imaging volume
- MRI CBF depends on:
  1. Total flow ***to capillaries*** in **imaging voxel**
  2. Volume of imaging voxel



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After Buxton, *Introduction to fMRI*, 2002.

MRI definition of CBF

- MRI CBF depends on:
  1. Total flow to ***capillaries*** in **imaging voxel**
  2. Volume of imaging voxel
- $$CBF = \frac{Total\ flow\ to\ caps}{Voxel\ volume}$$

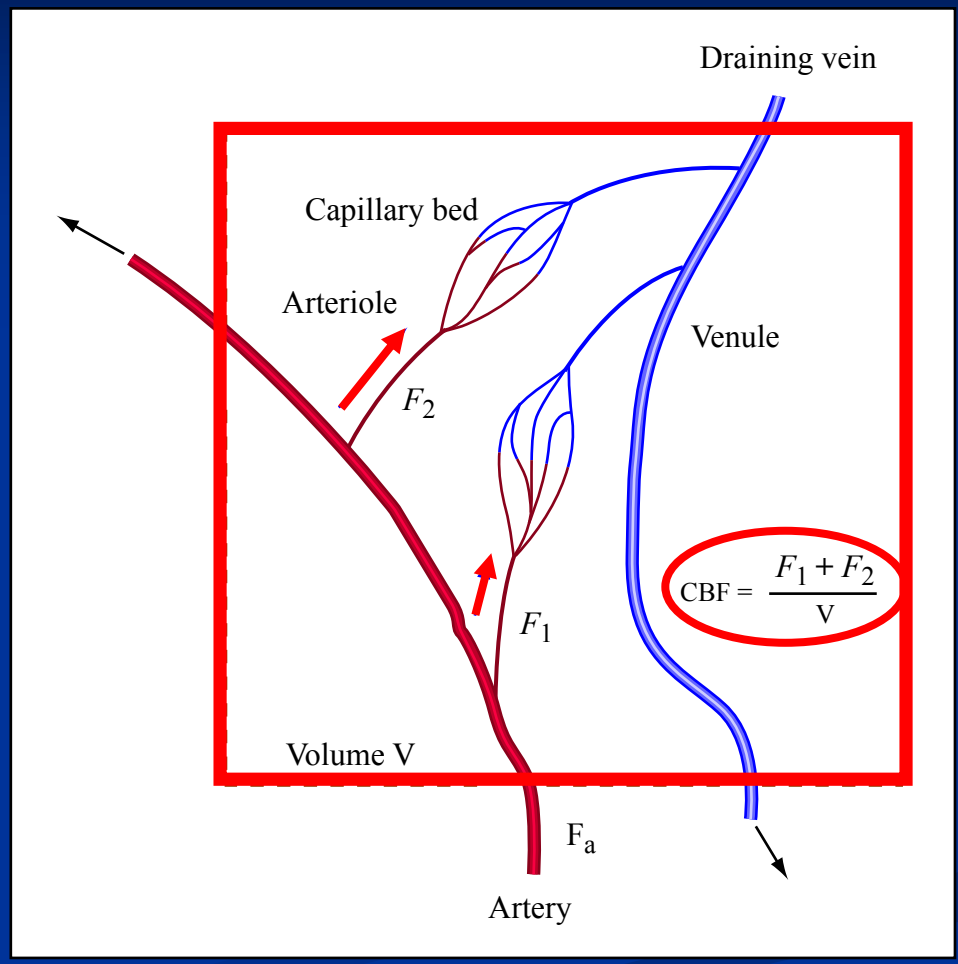
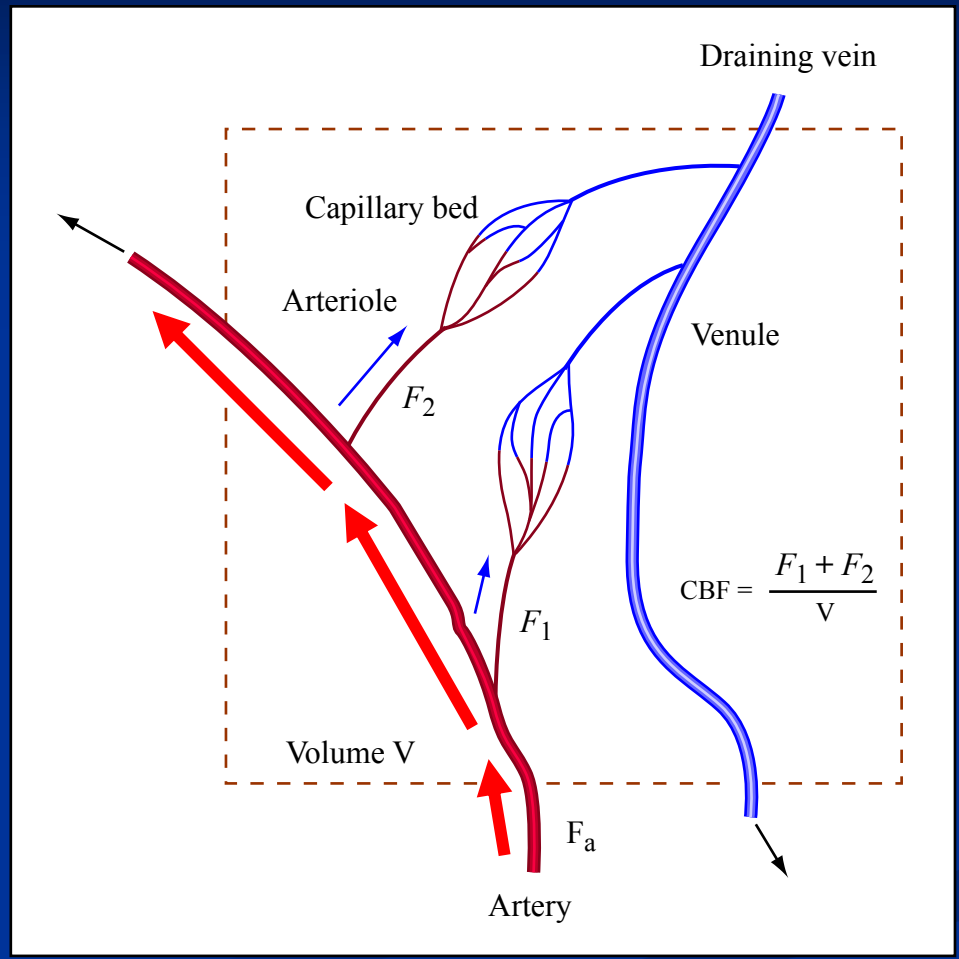


Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

MRI definition of CBF

- MRI CBF depends on:
  1. Total flow to ***capillaries*** in **imaging voxel**
  2. Volume of imaging voxel
- $$CBF = \frac{Total\ flow\ to\ caps}{Voxel\ volume}$$
- Blood that flows *through* the imaging voxel does not count towards CBF!!
- This blood is destined for capillaries in other voxels and will contribute to CBF for that voxel



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MRI definition of CBF

- Units of CBF:

$$\frac{ml}{ml\ of\ tissue - min}$$

- Density of brain tissue is ~1 gram/ ml
- More common units of CBF:

$$\frac{ml}{g\ of\ tissue - min}$$

- Typical gray matter CBF is 60 ml/(100g – min)

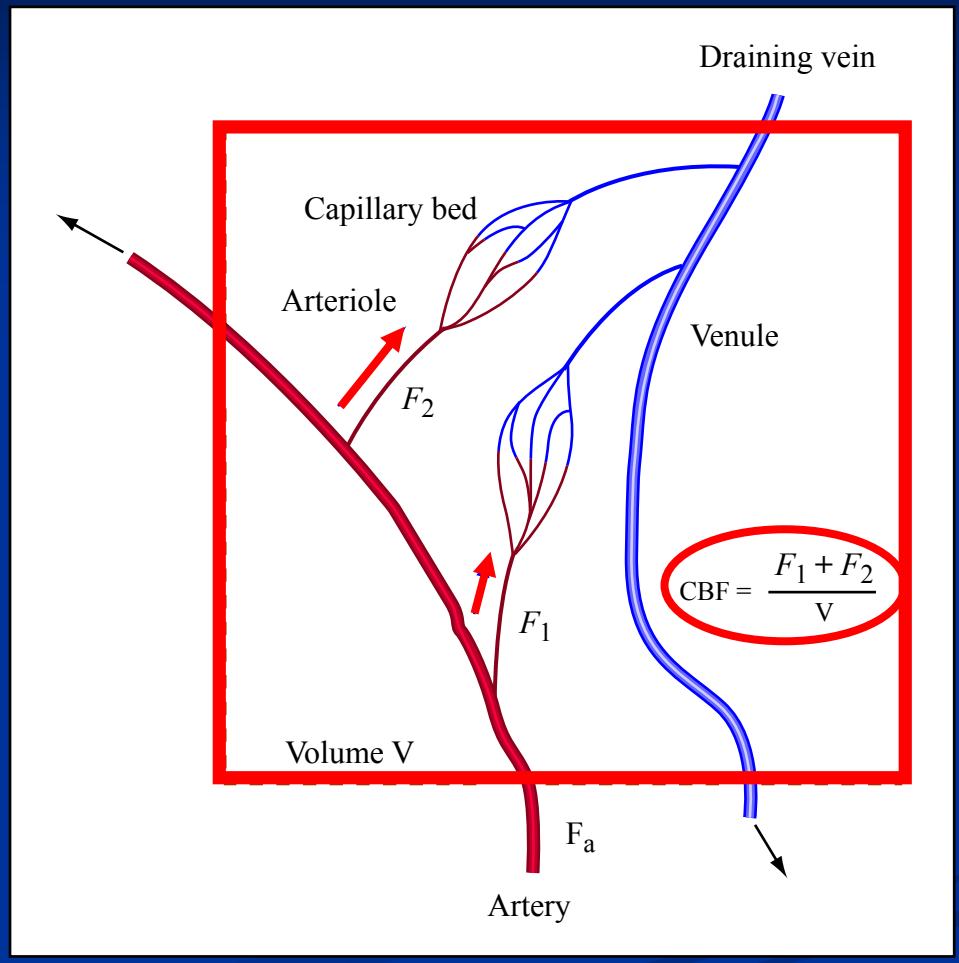
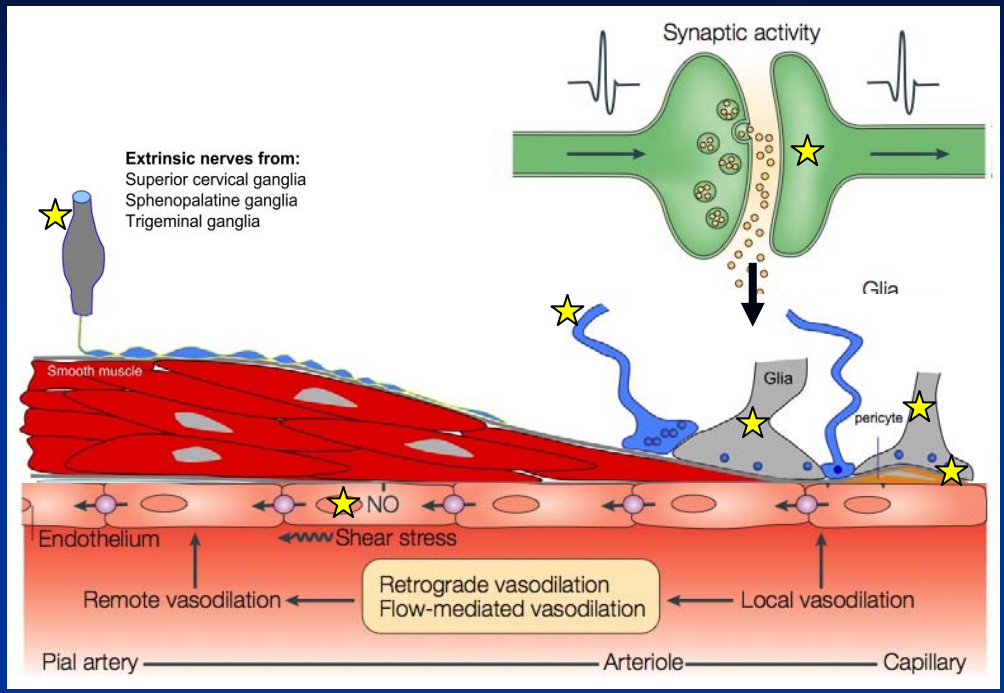


Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

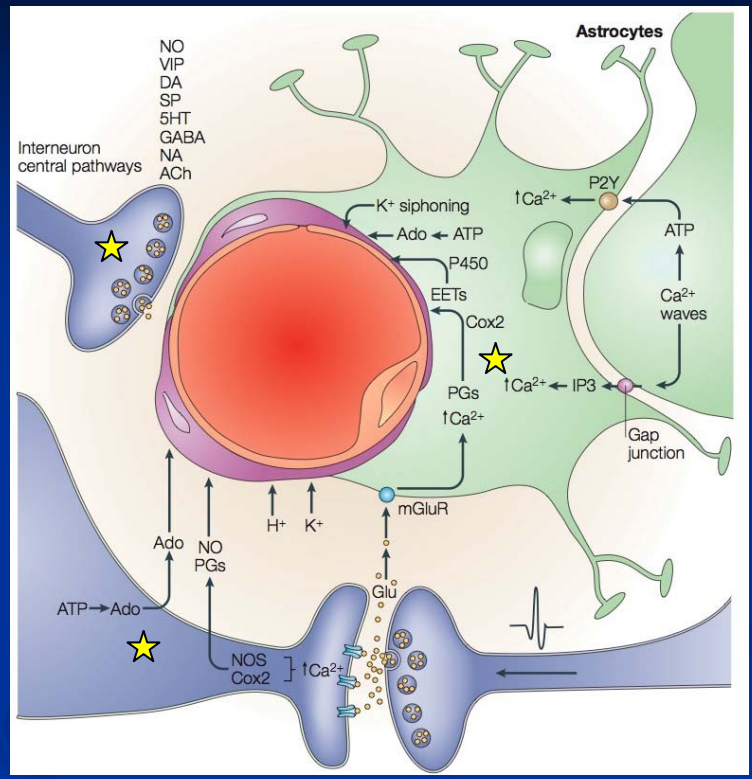
Regulation of CBF

- Modulation of vascular diameter (primarily arteriolar)
  - Vasodilatory substances (NO, CO_2, K^+, adenosine) bind with smooth muscle receptors and cause relaxation
  - Smooth muscle relaxation causes an increase in vessel radius; this increases flow by changing vascular resistance
  - **CBF is proportional to r^4**
- Secretion of vasodilatory substances by neuron during energy metabolism
- Direct neural innervation by afferents & interneurons
- Indirect control via astrocyte endfeet
- Pericyte constriction at capillary level
- ***Mechanisms of CBF regulation a highly active area of research!***

Regulation of CBF



- Direct afferent & interneuron innervation
- Indirect innervation via NT
- Glial (astrocyte) endfeet
- Capillary pericytes
- NO excreted by SM endothelial cells (retrograde vasodilation)



- Vasodilators secreted from neuron after energy metabolism
- Direct neurotransmitter action
- Indirect neurotransmitter action (via astrocyte)

From Iadecola, Nat Rev Neurosci, 2004

MRI definition of CBV

- Fraction of tissue volume occupied by microvessels

Image removed due to copyright restrictions.
Figure 1a in van Zijl, P. C. M., et al.
"Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging." *Nature Medicine* 4, no. 2 (February 1998): 159 - 167. doi:10.1038/nm0298-159.

- Typically 4% in the brain (CBV = 0.04)
- Dimensionless number (ml of blood vessel/ ml of tissue)

MRI definition of CBV

- Can divide CBV into capillary, arterial, and venous volumes

Image removed due to copyright restrictions.
Figure 1b in van Zijl, P. C. M., et al.
"Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging." *Nature Medicine* 4, no. 2 (February 1998): 159 - 167. doi:10.1038/nm0298-159.

Relating CBF to CBV

- CBV and CBF are independent physiological parameters, but are linked since CBF regulation occurs by dilating arterioles
- Grubb's Law, with alpha = 0.38:

$$\frac{V}{V_0} = \left(\frac{F}{F_0}\right)^{\alpha=0.38}$$

- **Implies that a only a small ΔCBV is required for a large ΔCBF (since CBF ∝ r^4)**
- *Does not consider venous volume*; total ΔCBV may be larger since distention in veins might accompany an increase in CBF

Mean Transit Time (τ)

$$\tau = \frac{CBV}{CBF}$$

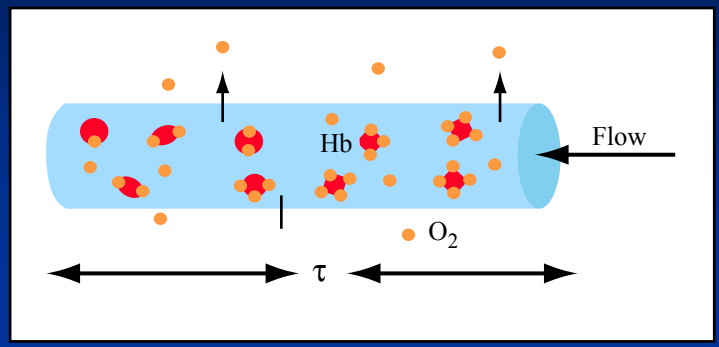


Figure by MIT OpenCourseWare.
From Introduction to *fMRI*, Buxton, Cambridge University Press, 2002

- Qualitatively: time it takes to cross vascular region
- Increasing flow, *decreases* transit time, since *velocity* increases
- A decrease in capillary transit time may result in decreased oxygen delivery to tissue

Mean Transit Time (τ)

$$\tau = \frac{CBV}{CBF}$$

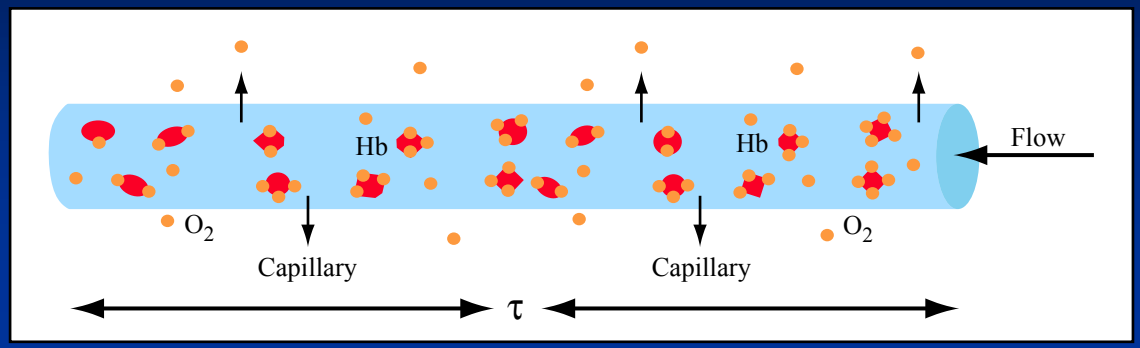


Figure by MIT OpenCourseWare.
From Introduction to *fMRI*, Buxton, Cambridge University Press, 2002

- Qualitatively: time it takes to cross vascular region
- Increasing flow, *decreases* transit time, since *velocity* increases
- A decrease in capillary transit time may result in decreased oxygen delivery to tissue
- Increasing volume *increases* transit time
- Increased τ can indicate regions with delayed blood flow

Summary of Vascular Activity

- ***Hemodynamic*** properties (relating to blood flow, volume, MTT, etc.) are of critical importance to fMRI, as this is what we can readily image

Image removed due to copyright restrictions. See figure at http://www.cfin.au.dk/menu74-en, "Oxygen Delivery in Acute Stroke," by Christine Sølling, M.D.

- It is much more difficult to image neural activity or cellular metabolism directly
- These properties and how they change under evoked activity will be an integral part of the next lecture

Summary

- Three general categories of physiological parameters govern brain function
  - Electrical activity at the neuronal level
  - Energy metabolism at the cellular level
  - Hemodynamics at the microvascular level
- While these parameters are intimately related, they have *very* different spatiotemporal dynamics
- We will focus on these dynamics in upcoming lectures
- **UP NEXT: Evoked activity in the brain**