

Hypoxia and Ischemia

Cerebral perfusion · energy failure · excitotoxicity · tissue fate

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Learning objectives

- Explain the metabolic dependence of the brain on uninterrupted oxygen delivery.
- Distinguish reduced oxygen availability from inadequate cerebral blood flow.
- Trace ischemic ATP depletion, calcium dysregulation, and excitotoxicity.
- Interpret collateral perfusion, tissue at risk, and the double-edged effect of reperfusion.

Where hypoxia–ischemia fits within cerebrovascular disease

Ischemic mechanism

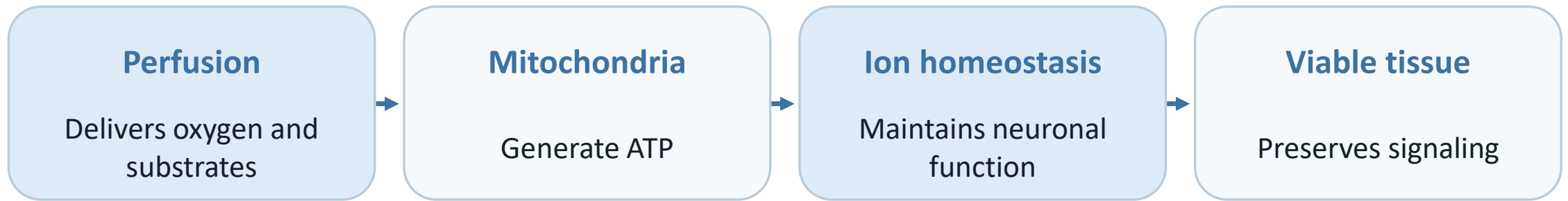
- Impaired oxygenation or blood supply
- May be focal or widespread
- Can lead to tissue infarction

Hemorrhagic mechanism

- Blood escapes from ruptured CNS vessels
- Distinct initial vascular event
- Secondary tissue ischemia can accompany injury

Mechanistic point: Different vascular insults converge on CNS dysfunction and tissue injury.

Neural tissue requires continuous oxidative metabolism



Interrupting this chain threatens high-demand neurons.

The brain's disproportionate metabolic demand

1–2%

Of body weight

≈15%

Of resting cardiac output

≈20%

Of total oxygen use

A small organ receives high perfusion because its aerobic energy demand is continuous.

Why cerebral metabolic dependence is distinctive

- The brain has disproportionately high oxygen consumption relative to its mass.
- Constant energy requirements arise from neuronal and glial cellular functions.
- Strict reliance on aerobic metabolism for sustained demand.

Two routes to insufficient cerebral oxygen supply

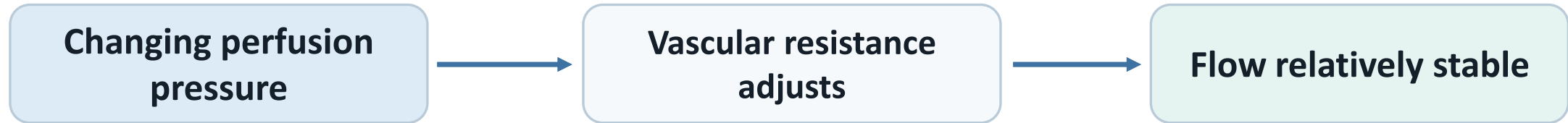
Reduced blood oxygen availability

- Blood flow may be maintained
- Less oxygen is delivered per unit of blood
- Tissue hypoxia can occur without occlusion

Reduced cerebral perfusion

- Blood delivery decreases to affected tissue
- Oxygen and substrate delivery both decline
- Washout of metabolic products is compromised

Autoregulation stabilizes cerebral blood flow



Autoregulation

- Active regulation of vascular resistance
- Buffers changes in blood pressure and intracranial pressure

Limits

- Flow can fall when compensation is insufficient
- Vascular occlusion can defeat local regulation

What autoregulation does—and does not—guarantee

- Vascular resistance adjusts over a range of blood and intracranial pressures.
- The goal is relatively steady cerebral blood flow despite pressure variations.
- Autoregulation cannot guarantee adequate flow during severe hypotension or occlusion.

Cerebral ischemia: Inadequate blood flow

- Inadequate cerebral perfusion is the defining hemodynamic defect.
- Reduced perfusion pressure, arterial occlusion, or both can be responsible.
- Downstream tissue receives an insufficient oxygen and nutrient supply.

Hypoxia and ischemia are related but not identical

Hypoxia

- Primary limitation: Available oxygen
- Perfusion and glucose delivery may persist
- Partial anaerobic ATP formation remains possible

Ischemia

- Primary limitation: Blood supply
- Oxygen and fuel availability fall together
- Waste metabolite removal also deteriorates

Why ischemia is more damaging than isolated hypoxia

Hypoxia with flow preserved

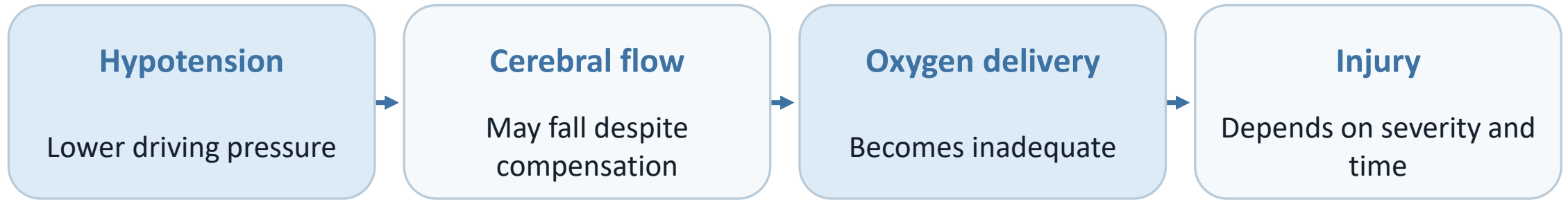
- Oxygen availability falls
- Some substrate delivery persists
- Anaerobic glycolysis can continue temporarily

Ischemia

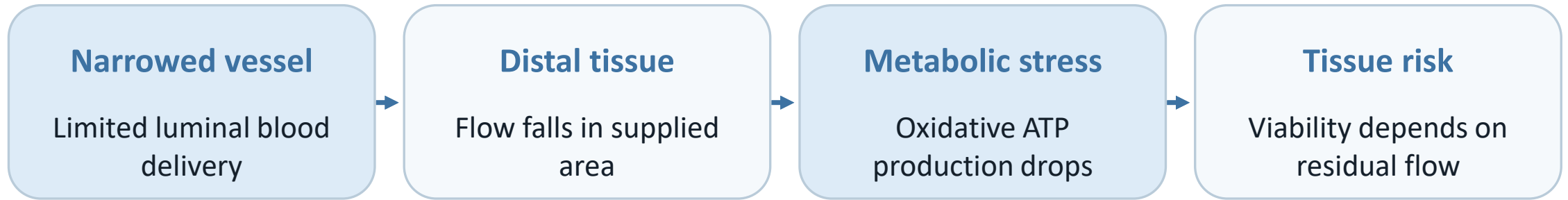
- Oxygen supply declines
- Glucose delivery is limited
- Metabolites are poorly cleared

Consequence: Energy failure usually progresses more rapidly in ischemia.

Reduced perfusion pressure can produce ischemia



Arterial occlusion produces a downstream perfusion deficit



Small and large vessels can both be involved

- Both small-vessel and large-vessel occlusion as sources of reduced perfusion.
- The vascular territory shapes the distribution of injury.
- The functional deficit follows the anatomic distribution of damaged tissue.

Perfusion-pressure failure versus vessel occlusion

Pressure-driven deficit

- Reduced systemic or regional perfusion pressure
- Affects flow by diminishing the driving gradient
- May be prominent during severe hypotension

Occlusion-driven deficit

- Physical limitation within a vascular lumen
- Territory distal to blockage becomes vulnerable
- Collateral routes may partly compensate

Determinants of tissue fate during flow reduction

Collateral flow

Alternate route for oxygen and nutrients

Duration

Length of threatened perfusion

Magnitude

Severity of flow decline

Rapidity

How abruptly flow is lost

Together: They determine lesion site, size, and neurologic deficit.

Collateral circulation modifies ischemic injury

- Alternative vascular routes can continue to supply a threatened territory.
- The amount of remaining flow influences whether tissue survives.
- Limited collateral pathways increase vulnerability when the primary route fails.

Autoregulation and collateralization serve different roles

Autoregulation

- Adjusts resistance within the arterial circulation
- Buffers pressure variation
- Acts to preserve flow through existing vessels

Collateralization

- Provides alternative routes around compromised supply
- Determines residual supply to threatened territory
- May limit the extent of infarction

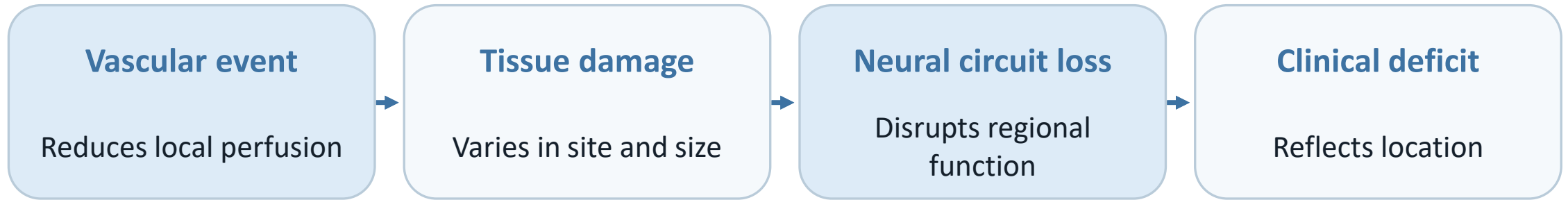
Ischemia duration is biologically decisive

- Brief hypoxic or ischemic episodes may cause reversible functional injury.
- Longer exposure raises the probability of irreversible cellular damage.
- Duration must be interpreted together with severity and collateral flow.

Magnitude and rapidity also determine outcome

- A deeper fall in blood flow restricts oxidative ATP production more severely.
- An abrupt reduction gives less opportunity for compensatory adjustments.
- Magnitude and rapidity separately among determinants of survival.

Cerebral ischemia links vascular injury to clinical deficit



The same vascular mechanism can produce different deficits depending on where it occurs.

Focal and global insults: Two spatial patterns

Cerebral oxygen / flow failure

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graph TD; A[Cerebral oxygen / flow failure] --> B[Focal]; A --> C[Global];
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Focal

- Region supplied by a compromised vessel
- Extent depends on duration and collateral supply

Global

- Generalized perfusion/oxygen-delivery failure
- Potentially widespread neuronal involvement

This lecture covers shared mechanisms; Focal and global patterns have separate Robbins units.

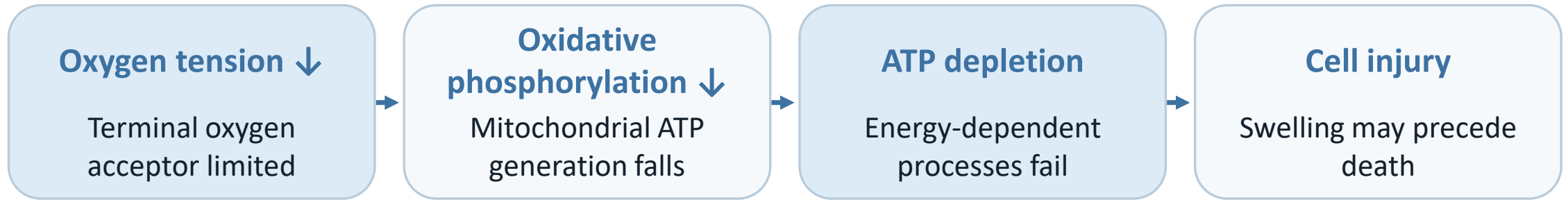
Focal ischemia: Localization matters

- Partial or complete arterial occlusion reduces flow to a defined region.
- The anatomic territory and collateral supply influence lesion configuration.
- Sustained severe focal flow loss may progress to infarction.

Global hypoxic–ischemic injury: Diffuse exposure

- Marked systemic hypotension or cardiac arrest reduces cerebral perfusion generally.
- Reduced oxygen-carrying capacity is another route to widespread cerebral hypoxia.
- The extent of injury is determined in part by insult duration and severity.

How oxygen loss becomes cellular energy failure



Mitochondrial oxidative phosphorylation is central

- Brain cells rely heavily on mitochondrial generation of ATP.
- Hypoxia directly compromises the oxygen-dependent process.
- Mitochondrial damage itself can reinforce subsequent ATP failure.

Why anaerobic glycolysis is insufficient in ischemia

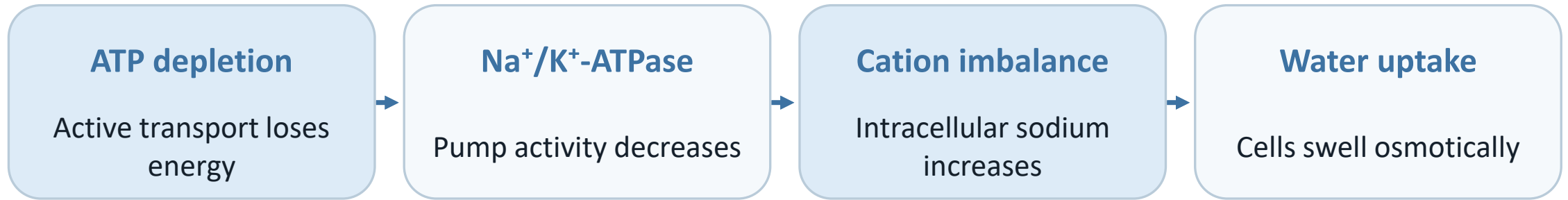
Some oxygen-deficient states

- Perfusion can continue to deliver glucose
- Anaerobic glycolysis can contribute limited ATP
- Metabolites may still be cleared

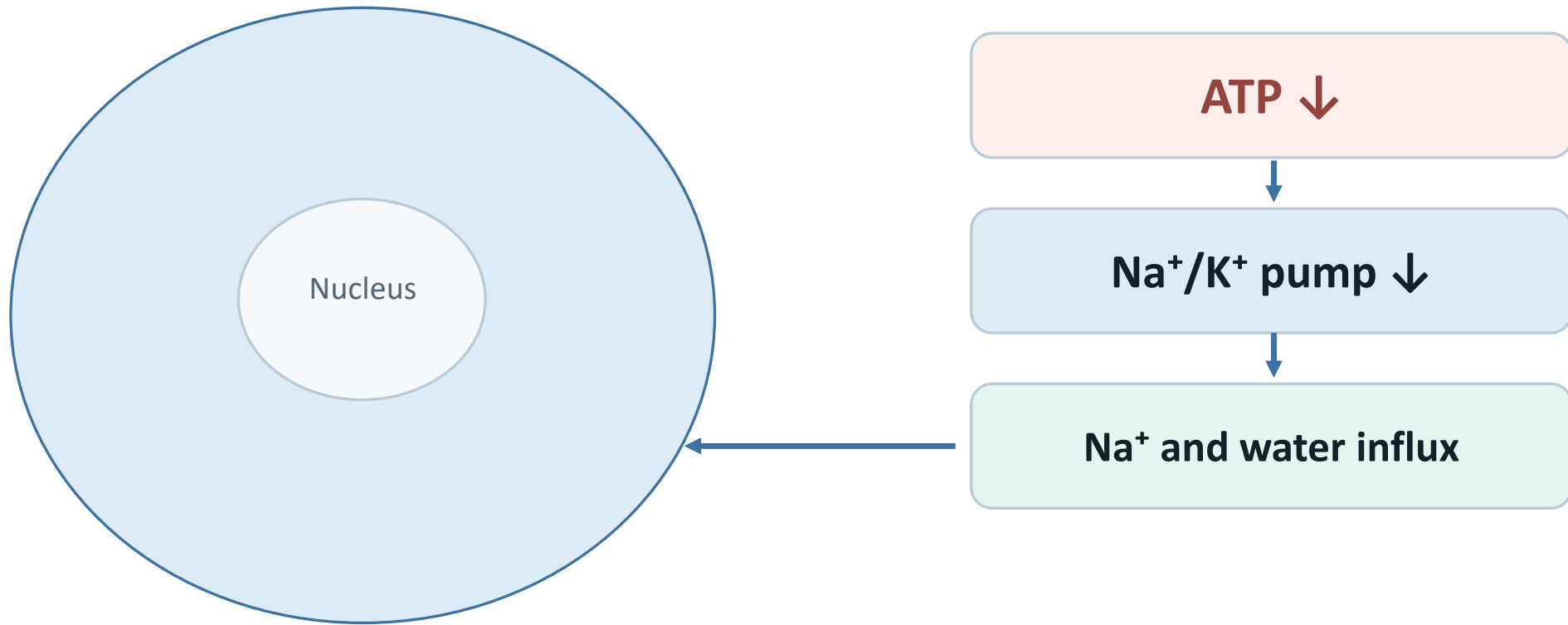
Sustained ischemia

- Substrate delivery is interrupted
- Metabolites accumulate locally
- Anaerobic energy formation becomes inadequate

Loss of ATP disrupts ion gradients



ATP depletion produces cytotoxic cell swelling



Osmotic water accumulation explains reversible cell and organelle swelling.

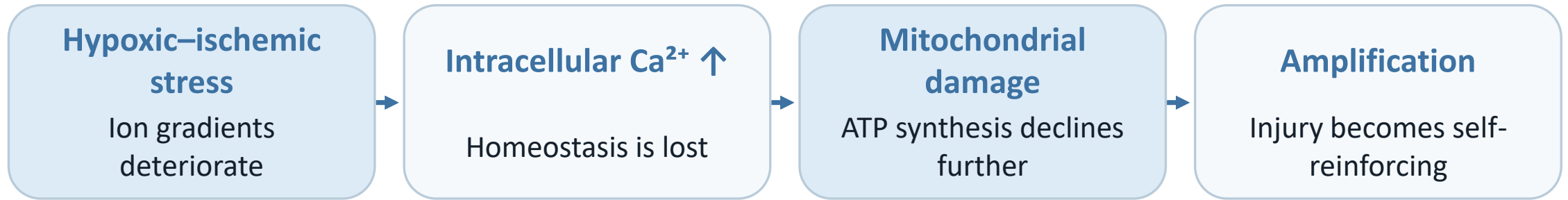
Cytotoxic swelling is an early energy-failure response

- Transport failure produces intracellular sodium accumulation.
- Osmotically driven water entry enlarges the cell and its organelles.
- At this stage, the injury may remain reversible if the insult abates.

Severe or sustained ATP failure advances to necrosis

- Persistent energy depletion compromises multiple cellular systems.
- Membrane failure and irrecoverable mitochondrial injury can follow.
- Necrosis as a terminal result of sufficiently severe ischemic injury.

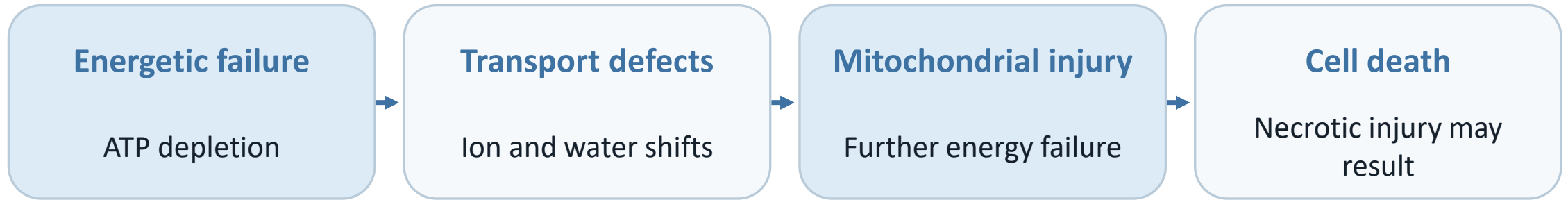
Calcium dysregulation amplifies cellular injury



Mitochondrial permeability transition and ATP loss

- Calcium overload can favor opening of the mitochondrial permeability transition pore.
- Loss of mitochondrial membrane potential further limits oxidative phosphorylation.
- ATP depletion thus becomes both a cause and an effect of injury.

Multiple injury pathways interact rather than act alone



An injured neuron is not governed by one isolated biochemical pathway.

Reversible injury and irreversible tissue injury

Potentially reversible

- Residual cellular integrity
- Swelling and dysfunction may subside
- Restored substrate delivery can aid recovery

Irreversible

- Persistent severe biochemical failure
- Loss of membrane/mitochondrial integrity
- Necrosis leaves tissue loss

Hypoxic stress can trigger adaptive transcription

- Induction of hypoxia-inducible factor-1 (HIF-1).
- HIF-1 supports angiogenic, survival, and glycolytic responses.
- An adaptive response does not guarantee neuronal preservation during severe ischemia.

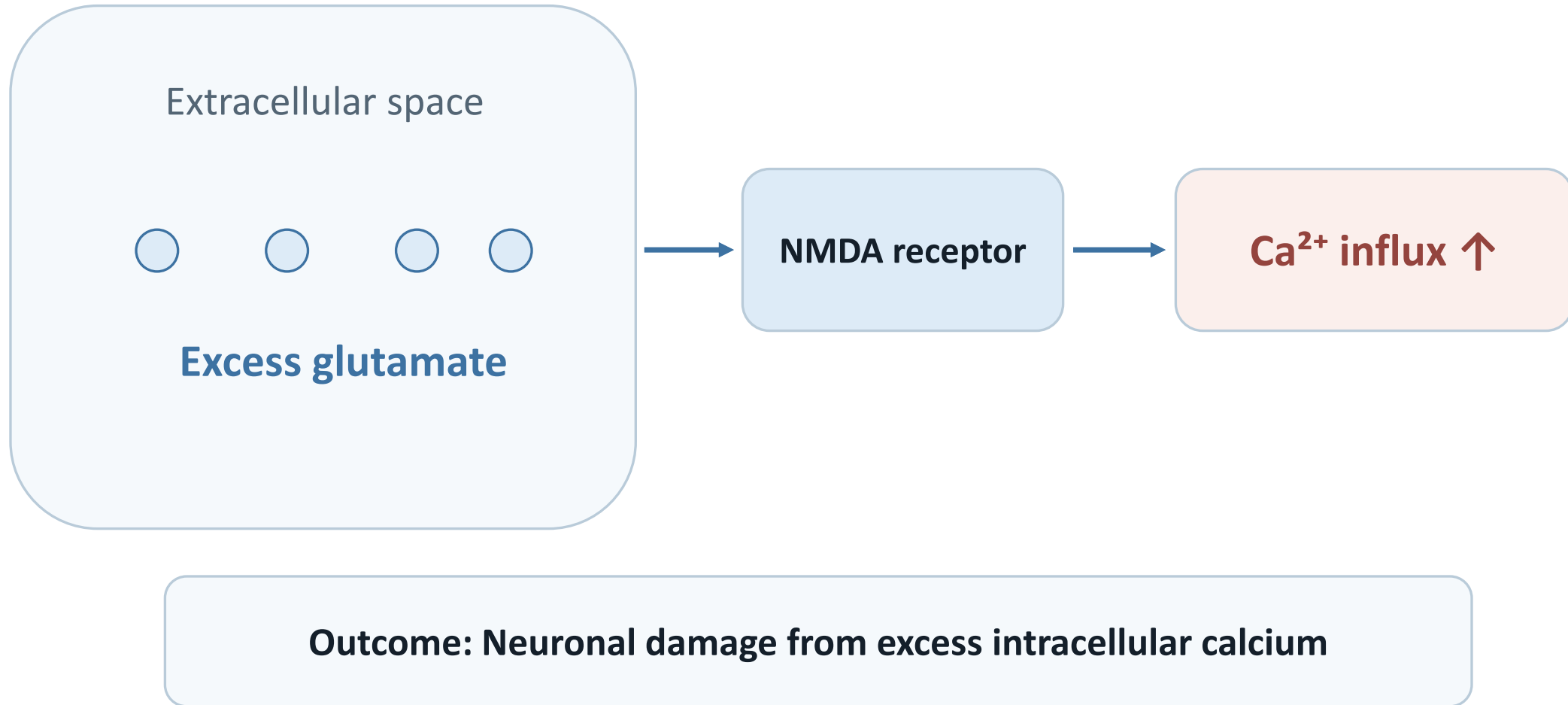
Adaptation has limits in a high-demand organ

- Protective responses require time and surviving metabolic capacity.
- The brain's continuous aerobic demand makes protracted deprivation hazardous.
- Injury severity reflects the balance between inadequate supply and available compensation.

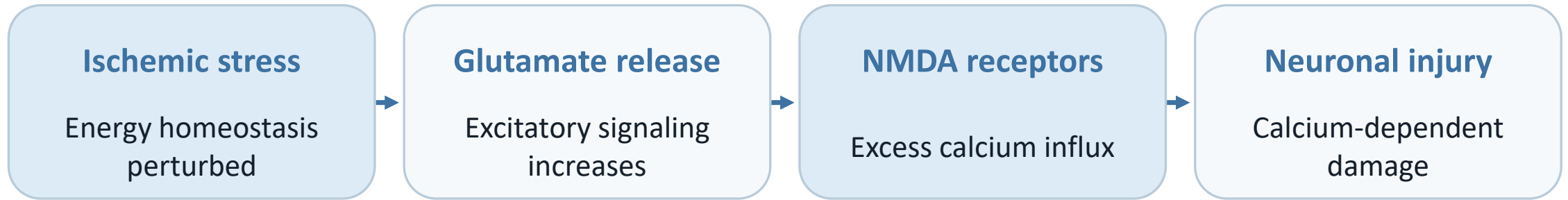
Excitotoxicity is a CNS-specific amplification mechanism

- Ischemia can provoke inappropriate release of excitatory amino-acid neurotransmitters.
- Glutamate is the example highlighted.
- The resulting receptor-mediated calcium influx can injure neurons.

Glutamate–NMDA receptor excitotoxicity



Excitotoxicity connects neurotransmission to cell injury



Energetic failure and excitotoxicity are complementary

Primary energetic failure

- Oxygen-limited ATP generation
- Failure of ion pumps
- Cell swelling and metabolic collapse

Excitotoxic amplification

- Excess extracellular excitatory transmitter
- NMDA-type glutamate receptor activation
- Calcium influx further injures neurons

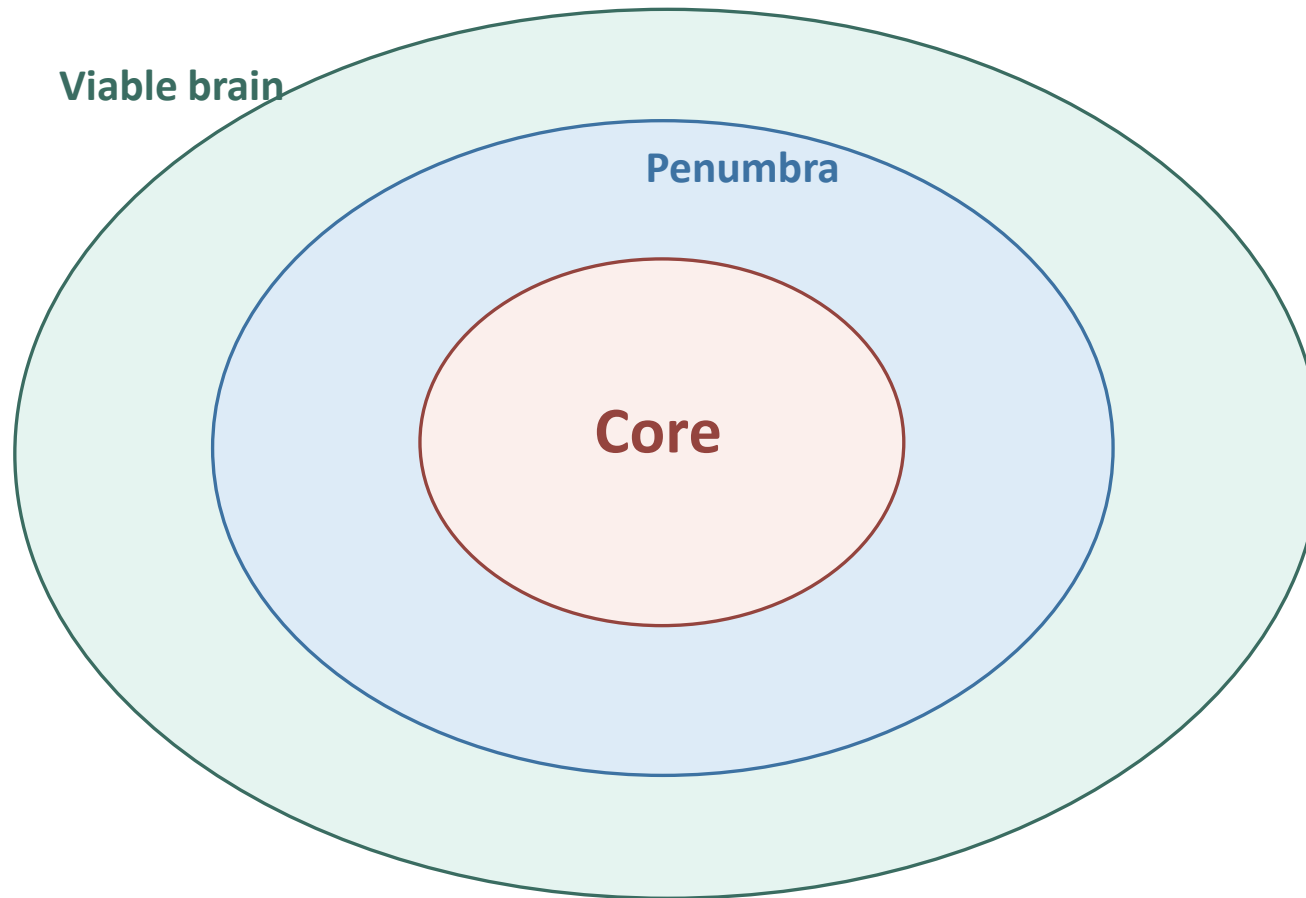
Excess calcium is a biochemical convergence point

- Calcium overload is implicated in both general ischemic injury and neuronal excitotoxicity.
- Mitochondria are vulnerable to cytosolic and mitochondrial calcium elevation.
- This reinforces the connection between signaling failure and energy depletion.

One insult may induce more than one route to cell death

- The penumbral discussion recognizes both necrosis and apoptosis in ischemic neurons.
- Animal-model rescue by antiapoptotic interventions supports an apoptotic component.
- This observation does not mean all ischemic neurons die by apoptosis.

Core, penumbra, and adjacent viable brain



Interpretation

- Core: Critically injured tissue
- Penumbra: Threatened but potentially recoverable
- Outside: Tissue with adequate perfusion

Schematic: Nested zones show a concept—not a fixed anatomic boundary.

The ischemic penumbra is threatened—not necessarily dead—tissue

- The penumbra at the transition from necrotic to relatively normal brain.
- It is described as an area of brain at risk rather than established infarct.
- Its potential reversibility provides the biological rationale for rescue.

Core and penumbra are different biological states

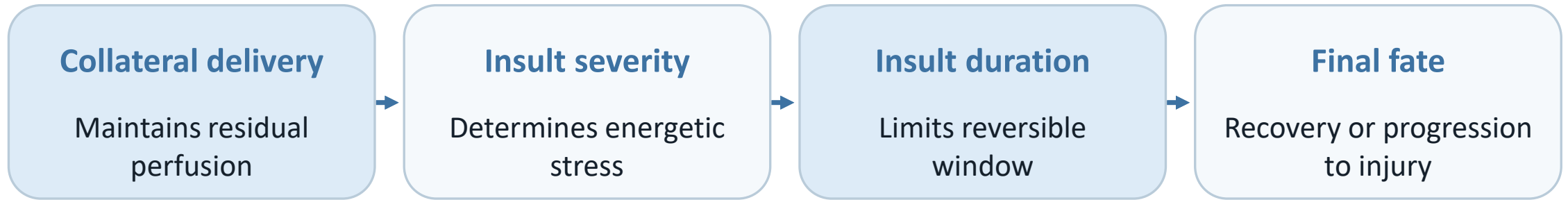
Necrotic core

- Injury has exceeded tissue viability
- Restoration of flow may not reverse cell death
- Infarction represents established tissue loss

Penumbra

- Neurons remain vulnerable to worsening flow failure
- Some tissue may recover if conditions improve
- Potential survival is not guaranteed

What determines whether the penumbra survives?



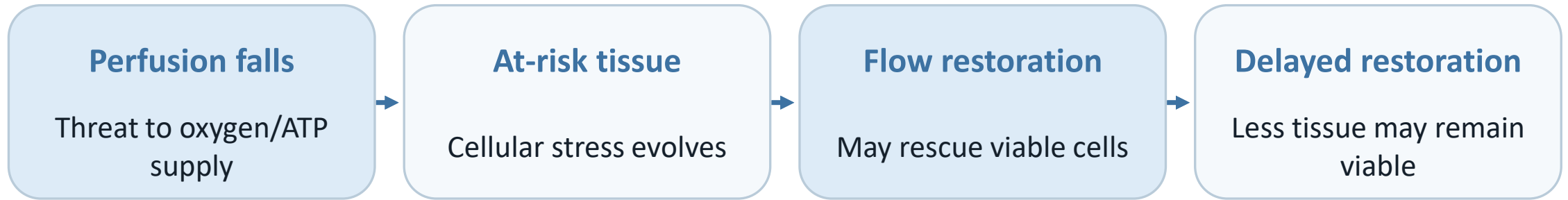
Why rescue of penumbral tissue is plausible

- A transition zone implies an intermediate state between normal and necrotic brain.
- In experimental models, various antiapoptotic manipulations can rescue cells.
- Clinical translation of experimental rescue is not established by this passage alone.

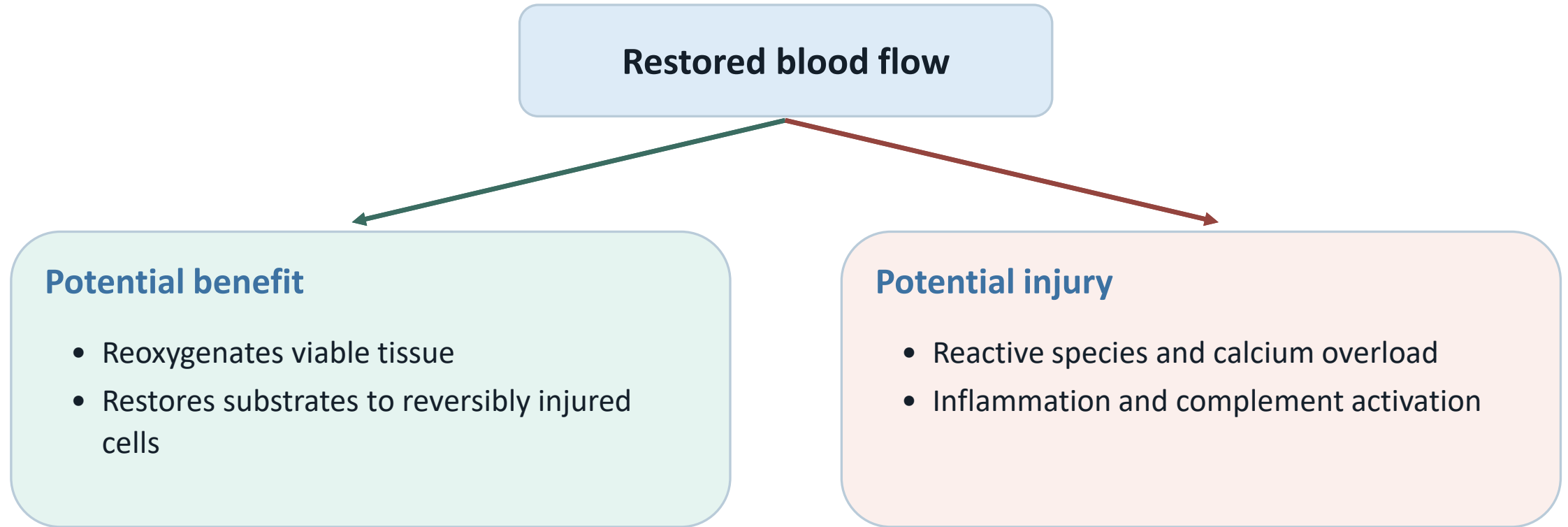
Tissue at risk is dynamic, not a fixed ring

- The conceptual penumbra is defined by viability, not by a standard thickness.
- Blood-flow duration, severity, and alternative supply can change tissue fate.
- An illustrative diagram must not be mistaken for a measured patient-specific border.

The time-sensitive logic of ischemic tissue rescue



Reperfusion has competing effects

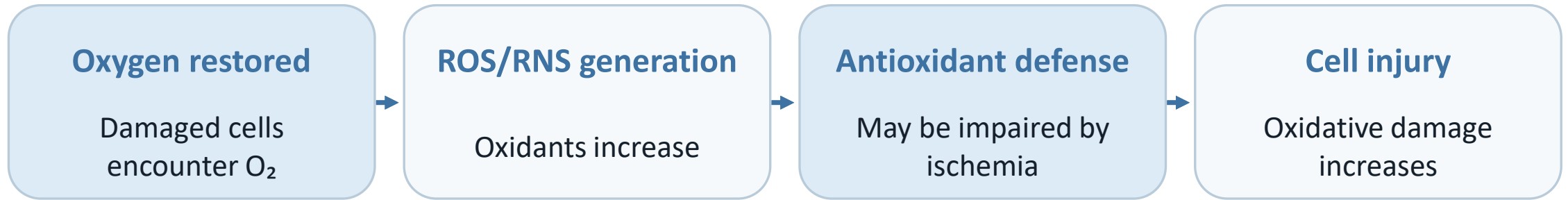


Clinical principle: Salvage and reperfusion injury are both possible.

Reoxygenation is not invariably harmless

- Resuming perfusion can revive cells whose injury is reversible.
- Reoxygenation may initiate additional damaging reactions.
- The total injury can therefore include ischemic and reperfusion components.

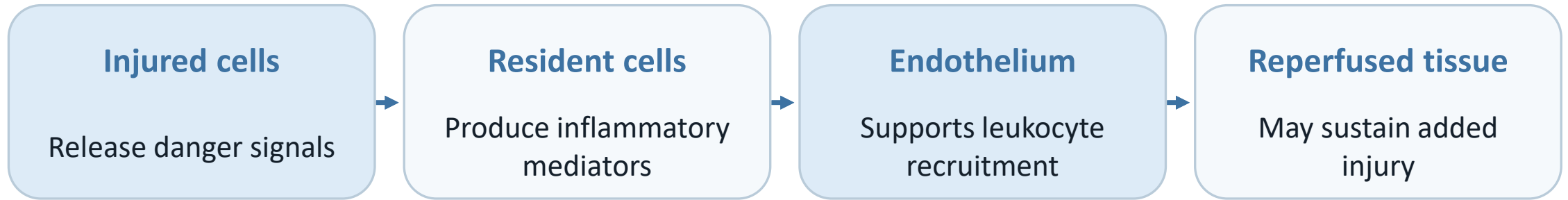
Oxidative stress during reperfusion



Calcium overload can worsen after flow restoration

- Acute ischemia initiates intracellular and mitochondrial calcium loading.
- Reperfusion can exacerbate calcium entry across damaged membranes.
- Mitochondrial permeability transition may intensify ATP failure.

Inflammation adds an injury pathway



Complement can contribute to reperfusion injury

- Complement activation among proposed mechanisms.
- Some IgM deposits in ischemic tissue may interact with complement after flow returns.
- The resulting response can amplify inflammation and parenchymal injury.

Major biochemical pathways: Integrated comparison

Pathway	Initiating change	Consequence
ATP depletion	Reduced oxidative phosphorylation	Pump failure, swelling, necrosis
Excitotoxicity	Excess glutamate / NMDA activation	Neuronal Ca ²⁺ overload
Oxidative stress	Reactive species on reperfusion	Additional macromolecular injury
Inflammation	DAMPs and leukocyte recruitment	Secondary tissue damage
Complement	Activation after reperfusion	Amplification of injury

Regional tissue injury explains neurologic manifestations

- The site and size of ischemic injury to the clinical deficit.
- Localization reflects the affected vascular territory and the functions of that neural tissue.
- The hemodynamic mechanism alone does not define a single stereotyped presentation.

Nonhemorrhagic and hemorrhagic infarction: Boundary concept

- An arterial infarct can initially be nonhemorrhagic.
- Secondary hemorrhage may accompany subsequent reperfusion of damaged small vessels.
- Detailed infarct morphology and hemorrhagic transformation belong to the focal ischemia lecture.

Application: Low oxygen availability

Clinical vignette

A patient develops reduced blood oxygen availability while cerebral arterial perfusion remains present.

Which mechanism is primarily impaired?

Reasoning: This is principally an oxygenation defect; Flow-dependent glucose delivery may initially persist.

Application: Occluded cerebral artery

Clinical vignette

An arterial branch becomes obstructed, reducing flow in its distal territory.

Which variables predict tissue survival?

Reasoning: Collateral supply, duration, magnitude, and rapidity of flow reduction govern tissue fate.

Application: Return of blood flow

Clinical vignette

A threatened region is reperfused after a transient period of severe ischemia.

Why can reperfusion have two effects?

Reasoning: Viable cells may recover, while oxidant, calcium-mediated, and inflammatory injury may add damage.

Synthesis: Determinants and mechanisms

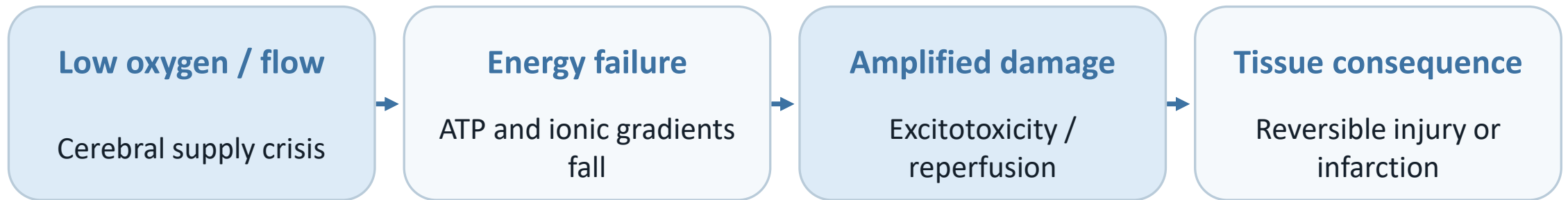
Hemodynamic determinants

- Oxygen availability and cerebral blood flow
- Collateral supply and perfusion pressure
- Magnitude, rapidity, and duration of reduction

Cellular mechanisms

- Failure of oxidative phosphorylation and ATP
- Ion-pump failure, swelling, mitochondrial injury
- Glutamate excitotoxicity and reperfusion pathways

From vascular compromise to clinical injury



Tissue fate—and therefore neurologic outcome—depends on the residual viability of the affected region.

Concept check: Three noninterchangeable terms

- Hypoxia: Tissue oxygen availability is insufficient.
- Ischemia: Blood flow is inadequate, restricting oxygen, substrates, and clearance.
- Penumbra: Threatened peri-infarct tissue that may still be recoverable.

Interpretation: Excitotoxicity is a cellular mechanism, not a synonym for infarction.

Reference and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 28, pp. 1136–1137.
- Foundational mechanisms drawn from Chapter 2, pp. 45–51 (ATP failure and reperfusion injury).
- Focal and global cerebral ischemia are introduced only as context; each has a separate, more detailed topic.