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PATHOLOGICAL NEURONAL DEPOLARIZATION AND NEUROINFLAMMATION A BIDIRECTIONAL CYCLE OF NEURONAL INJURY

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Abstract
Neuronal depolarization is essential for normal neuronal communication but becomes harmful when excessive or sustained. During cerebral ischemia, traumatic brain injury, and epilepsy, metabolic failure and disruption of ion gradients cause pathological depolarization, excessive glutamate release, calcium influx, mitochondrial dysfunction, oxidative stress, and excitotoxic neuronal death. Damaged neurons release danger-associated molecular patterns that activate microglia and astrocytes. These glial cells produce inflammatory cytokines, reactive oxygen species, and other mediators that further impair ion homeostasis and glutamate clearance. Neuroinflammation can therefore increase neuronal excitability and promote additional depolarization, creating a self-amplifying cycle of neuronal injury. This review summarizes the mechanisms linking neuronal depolarization, calcium overload, excitotoxicity, glial activation, and neuroinflammation and discusses their relevance to ischemic stroke, epilepsy, traumatic brain injury, and neurodegenerative diseases.

Keywords: Neuronal depolarization; neuroinflammation; excitotoxicity; microglia; astrocytes; calcium signaling; neurological disorders.

Introduction

Neuronal depolarization is a fundamental electrophysiological process required for action potential generation and synaptic transmission. Under physiological conditions, changes in membrane potential are brief and tightly regulated by voltage-gated ion channels and active ion transport. Pathological conditions such as ischemia, hypoxia, seizures, and traumatic brain injury can disrupt these mechanisms and produce sustained depolarization.

Historically, neuronal electrical dysfunction and neuroinflammation were considered relatively independent processes. Current evidence demonstrates that they are closely interconnected.

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Pathological depolarization causes ionic imbalance, calcium overload, excitotoxicity, and cellular damage, which activate microglia and astrocytes. In turn, inflammatory cytokines and reactive molecules impair glutamate clearance, modify ion channels, and increase neuronal excitability.

Thus, neuronal depolarization and neuroinflammation form a bidirectional feedback loop. Understanding this interaction is important for explaining tissue injury in both acute and chronic neurological disorders and for developing therapies that target several components of the pathological cascade simultaneously.

2. Physiological and Pathological Neuronal Depolarization

The resting membrane potential of most adult CNS neurons is approximately −70 mV. It is maintained by unequal distributions of Na+, K+, Cl−, and Ca2+ across the plasma membrane, together with selective membrane permeability and the activity of the Na+/K+-ATPase. This pump transports three Na+ ions out of the cell in exchange for two K+ ions.

During physiological depolarization, excitatory input shifts the membrane potential toward the threshold for voltage-gated sodium channels. Rapid Na+ influx produces the depolarizing phase of the action potential, followed by channel inactivation and K+ efflux through voltage-gated potassium channels. Repolarization normally occurs within milliseconds.

Pathological depolarization occurs when these homeostatic mechanisms fail. During ischemia or severe hypoxia, ATP production rapidly decreases, impairing Na+/K+-ATPase activity. Na+ and Cl− accumulate intracellularly, while extracellular K+ rises. When extracellular K+ reaches approximately 20–30 mM, neighboring neurons may undergo synchronized spreading depolarization (Dreier, 2011).

Ion gradient collapse also causes cellular swelling because water follows intracellular Na+ and Cl− accumulation. Sustained depolarization can further impair sodium-dependent transport systems and may reverse the direction of the Na+/Ca2+ exchanger. These changes progressively convert normal neuronal signaling into a destructive process.

3. Depolarization, Calcium Overload, and Excitotoxicity

Calcium overload is one of the major mechanisms connecting pathological depolarization with neuronal death. Cytosolic Ca2+ is normally maintained at approximately 100 nM, whereas extracellular concentrations are around 1.2 mM. Depolarization activates voltage-gated calcium channels and promotes excessive glutamate release.

At the same time, energy failure reduces the activity of astrocytic glutamate transporters, allowing extracellular glutamate to accumulate. Excess glutamate activates AMPA and NMDA receptors. Depolarization removes the normal Mg2+ block of NMDA receptors, permitting substantial Ca2+ entry.

The effects of NMDA receptor activation depend on receptor localization and subunit composition. Physiological synaptic NMDA signaling can activate survival pathways, whereas excessive extrasynaptic activation is associated with mitochondrial dysfunction and cell death (Hardingham & Bading, 2010).

Excess intracellular Ca2+ is taken up by mitochondria, where it disrupts electron transport, increases reactive oxygen species production, and can promote opening of the mitochondrial permeability

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transition pore. Loss of mitochondrial membrane potential reduces ATP production and may promote the release of pro-apoptotic factors such as cytochrome c and apoptosis-inducing factor (Bano & Ankarcrona, 2018).

Calcium also activates destructive enzymes, including calpains, phospholipases, and neuronal nitric oxide synthase. These enzymes damage cytoskeletal proteins, cellular membranes, DNA, and other essential structures. Nitric oxide can react with superoxide to produce peroxynitrite, further increasing oxidative injury.

The combined effects of calcium overload, mitochondrial dysfunction, oxidative stress, and enzymatic degradation ultimately result in necrotic or apoptotic neuronal death (Choi, 1988).

4. Neuroinflammation and Glial Activation

Neuroinflammation is primarily mediated by microglia and astrocytes. Although glial activation can initially support tissue repair and homeostasis, prolonged activation may contribute to neuronal injury.

4.1 Microglia

Microglia are the resident immune cells of the CNS and continuously monitor the extracellular environment (Nimmerjahn et al., 2005). Damaged neurons release DAMPs such as ATP, HMGB1, heat shock proteins, and DNA fragments. These molecules activate microglial pattern-recognition and purinergic receptors, including TLR2, TLR4, P2X7, and P2Y12 (Block et al., 2007; Salter & Stevens, 2017).

Activated microglia undergo morphological and transcriptional changes and can produce inflammatory cytokines, including TNF-α, IL-1β, and IL-6, together with nitric oxide and reactive oxygen species. Activation of the NLRP3 inflammasome promotes maturation of IL-1β and IL-18. Excessive production of these mediators creates a cytotoxic environment that can damage nearby neurons.

4.2 Astrocytes

Astrocytes maintain extracellular K+ levels, remove glutamate, provide metabolic support, and contribute to blood-brain barrier integrity (Giaume et al., 2010; Sofroniew, 2015).

Following injury, astrocytes undergo reactive astrogliosis. Inflammatory signals from microglia, including IL-1α, TNF-α, and C1q, can induce neurotoxic reactive states associated with impaired neuronal support (Liddelow et al., 2017). Reactive astrocytes may reduce expression of the glutamate transporter GLT-1/EAAT2, resulting in extracellular glutamate accumulation. Impaired K+ buffering, including reduced Kir4.1 activity, can also increase extracellular K+ and promote neuronal depolarization.

Therefore, astrocytic dysfunction provides an important connection between inflammation and persistent neuronal hyperexcitability.

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5. Bidirectional Interaction Between Depolarization and Neuroinflammation

The relationship between neuronal depolarization and neuroinflammation is bidirectional. Depolarization and neuronal injury activate glia, while inflammatory mediators subsequently increase neuronal excitability.

IL-1β can enhance NMDA receptor-mediated calcium influx through Src-dependent phosphorylation of receptor components. It can also interfere with potassium currents, prolonging neuronal depolarization (Viviani et al., 2003).

TNF-α can modify synaptic receptor composition by increasing the surface expression of calcium-permeable AMPA receptors while reducing inhibitory GABA-A receptor availability. These changes shift the excitatory-inhibitory balance toward neuronal hyperexcitability.

Reactive oxygen and nitrogen species generated by activated microglia can additionally impair astrocytic glutamate transporters. Reduced glutamate clearance prolongs NMDA and AMPA receptor activation, maintaining neuronal depolarization and calcium influx.

ATP released from injured neurons provides another feedback mechanism. Extracellular ATP activates microglial P2X7 receptors and promotes inflammatory signaling, including IL-1β maturation. Microglial responses can therefore amplify the effects of neuronal injury.

Interestingly, homeostatic microglia can normally limit excessive neuronal activity by regulating extracellular ATP and neuronal excitability. Loss of these protective functions during inflammatory activation may further destabilize neuronal networks (Szalay et al., 2016).

Overall, the interaction can be summarized as a pathological cycle: depolarization causes ionic imbalance and calcium overload; excitotoxicity produces neuronal damage; damaged neurons release DAMPs; glia become activated; inflammatory mediators impair glutamate and ion regulation; and these changes promote further depolarization.

6. Clinical Relevance

Cerebral ischemia rapidly reduces oxygen and glucose availability. ATP depletion leads to failure of ion pumps and severe depolarization. In the ischemic core, this process can become irreversible within minutes, whereas the surrounding penumbra may experience recurrent spreading depolarizations (Dirnagl et al., 1999; Dreier, 2011).

These depolarizations increase metabolic demand and can contribute to expansion of ischemic injury. DAMP release activates microglia and promotes inflammatory signaling, while cytokines such as IL-1β and TNF-α can further impair neuronal and astrocytic function (Iadecola & Anrather, 2011).

Epileptic seizures involve excessive and synchronized neuronal activity. Increased firing promotes K+ accumulation, glutamate release, and intracellular Ca2+ loading. Prolonged seizures can activate microglia and astrocytes, leading to production of IL-1β and TNF-α.

Inflammatory signaling can reduce seizure thresholds, alter NMDA and GABA-A receptor function, and impair glutamate clearance. This interaction may contribute to persistent network hyperexcitability and epileptogenesis (Vezzani et al., 2011; Vezzani et al., 2019).

Traumatic brain injury causes immediate mechanical disruption of neuronal membranes followed by excessive ion flux, glutamate release, calcium overload, and mitochondrial dysfunction. Damaged cells rapidly activate microglia and astrocytes.

Although early inflammation may support repair, persistent neuroinflammation can interfere with neuronal recovery and contribute to chronic excitotoxicity. Long-term consequences include post-traumatic epilepsy and progressive neurodegenerative changes (Simon et al., 2017).

Chronic neurodegenerative diseases such as Alzheimer's and Parkinson's disease involve persistent low-level excitotoxicity and neuroinflammation. In Alzheimer's disease, amyloid-β can disrupt glutamatergic signaling and promote abnormal NMDA receptor activity, while amyloid-β and tau can activate microglial inflammatory pathways.

Chronic production of inflammatory mediators may impair astrocytic glutamate clearance and alter synaptic receptor function, contributing to progressive synaptic dysfunction and neuronal loss (Heneka et al., 2015; Ransohoff, 2016).

7. Therapeutic Perspectives

Because neuronal depolarization and inflammation reinforce each other, targeting only one pathway may provide limited protection. Experimental NMDA receptor antagonists such as MK-801 demonstrated strong neuroprotection in animal models but produced significant adverse effects that limited clinical use (Hardingham & Bading, 2010).

More selective approaches include low-affinity NMDA receptor blockers such as memantine, which preferentially inhibit excessive receptor activity while preserving more physiological neurotransmission.

Anti-inflammatory strategies are also being investigated. NLRP3 inflammasome inhibitors such as MCC950 can reduce IL-1β maturation, while IL-1 receptor antagonism may attenuate inflammatory signaling. P2X7 receptor antagonists represent another potential method for interrupting ATP-mediated microglial activation.

Enhancing astrocytic GLT-1/EAAT2 activity may additionally reduce extracellular glutamate and limit excitotoxicity. Future therapies will likely require combinations targeting calcium homeostasis, neuronal excitability, astrocytic function, and neuroinflammation.

An important challenge is determining the correct timing of treatment. Early glial activation can have protective and reparative functions, whereas prolonged activation may become harmful. Therefore, effective therapies must distinguish beneficial from pathological inflammatory states.

8. Conclusion

Pathological neuronal depolarization initiates a cascade involving ion gradient failure, calcium overload, excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuronal death. The resulting release of DAMPs activates microglia and astrocytes, producing inflammatory cytokines and reactive molecules.

Neuroinflammation subsequently worsens neuronal excitability by increasing calcium permeability, impairing potassium and glutamate homeostasis, and altering excitatory and inhibitory receptor function. This creates a self-amplifying cycle linking electrical instability with inflammation.

This mechanism is relevant to ischemic stroke, epilepsy, traumatic brain injury, and neurodegenerative diseases. Future neuroprotective strategies should therefore address both sides of the pathological process by stabilizing neuronal excitability, limiting calcium overload, preserving astrocytic homeostasis, and controlling excessive neuroinflammation.

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