*Review Article*

# Vasopressin Hypersecretion-Associated Brain Edema Formation in Ischemic Stroke: Underlying Mechanisms

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*Background:* Brain edema formation is a major cause of brain damages and the high mortality of ischemic stroke. The aim of this review is to explore the relationship between ischemic brain edema formation and vasopressin (VP) hypersecretion in addition to the oxygen and glucose deprivation and the ensuing reperfusion injury. *Methods:* Pertinent studies involving ischemic stroke, brain edema formation, astrocytes, and VP were identified by a search of the PubMed and the Web of Science databases in January 2016. Based on clinical findings and reports of animal experiments using ischemic stroke models, this systematic review reanalyzes the implication of individual reports in the edema formation and then establishes the inherent links among them. *Results:* This systematic review reveals that cytotoxic edema and vasogenic brain edema in classical view are mainly under the influence of a continuous malfunction of astrocytic plasticity. Adaptive VP secretion can modulate membrane ion transport, water permeability, and blood–brain barrier integrity, which are largely via changing astrocytic plasticity. Maladaptive VP hypersecretion leads to disruptions of ion and water balance across cell membranes as well as the integrity of the blood–brain barrier. This review highlights our current understandings of the cellular mechanisms underlying ischemic brain edema formation and its association with VP hypersecretion. *Conclusions:* VP hypersecretion promotes brain edema formation in ischemic stroke by disrupting hydromineral balance in the neurovascular unit; suppressing VP hypersecretion has the potential to alleviate ischemic brain edema. **Key Words:** Aquaporin-4—astrocytes—brain edema formation—ischemic stroke—neuroendocrine—vasopressin.


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Received December 14, 2015; revision received January 21, 2016; accepted February 1, 2016.

This work is sponsored by the National Natural Science Foundation of China (Grant No. 31471113) and the Higher Education Talents Funds of Heilongjiang Province (Grant No. 002000154).

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1052-3057/$ - see front matter



http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.02.002

## Introduction

A stroke or cerebrovascular accident is the sudden death of brain cells and the rapid disruption of all or parts of brain functions due to a reduced blood flow or ischemia. Among all types of stroke, ischemic stroke accounts for ~80% cases and thus is the focus of both basic and clinical studies. In ischemic stroke, following a sequence of ischemia and then reperfusion, a series of pathological events occur, such as the upregulated expression of water channel protein aquaporin (AQP)4 (2 hours), microvascular narrowing resulting from swollen astrocytic endfeet (2-6 hours), infarct and edema progression, blood–brain barrier (BBB) disruption (6-24 hours), and the activation of inflammatory reactions (24 hours) as shown in a mouse model of middle cerebral artery occlusion (MCAO).[1] Among the aforementioned pathological events, the most dramatic and critical is the increased brain water content, which can lead to an increase in intracranial pressure, further reduction of cerebral blood flow, cerebral herniation, and even death.[2] To reduce brain damages in ischemic stroke, it is essential to understand the pathogenic process of brain edema formation.

Both human and animal studies over the past decades indicate that oxygen and glucose deprivation and reperfusion or reoxygenation (OGD/R) injury as well as vasopressin (VP) hypersecretion play primary roles in ischemic brain edema formation.[3] However, the pathogenesis involving VP is not fully understood. These issues are reviewed in this paper.

## Brain Edema Formation in Ischemic Stroke

Brain edema formation during ischemic stroke involves swelling of individual cells and ischemic brain regions due to disturbance of the integrity of neurovascular unit.

### *Neurovascular Unit and Hydromineral Balance*

Brain hydromineral balance is based on fluid exchanges across both cellular membrane and the BBB in the neurovascular unit. This unit is composed of capillary endothelial cells, neurons, extracellular matrix, and non-neuronal cells such as pericytes, astrocytes, and microglia.[4] In brain parenchyma, there is a bidirectional volume transfer across cell membranes driven by osmotic gradients in association with extracellular volume transmission.[5] When high intracellular or low extracellular osmotic pressure occurs, water gets into cells via AQPs.[6] Conversely, if low intracellular or high extracellular osmotic pressure forms, water flows out of cells.[7] Noteworthy is that cells also have some autoregulatory capacity to maintain homeostasis of their intracellular environment, particularly in astrocytes. After exposure to a hypotonic solution, cultured astrocytes swell within 30 seconds and subsequently undergo a regulatory volume decrease (RVD); when exposed to a hypertonic solution, the astrocytes shrink and then exhibit a regulatory volume increase.[8] This morphological plasticity endows astrocytes with a unique capacity to keep brain volume stability.

In general, osmotic gradients across cell membranes are an essential force driving water transport and their establishment involves coordinated activities of numerous ion transport organelles. As recently reviewed,[9] these organelles include (1) channels such as epithelial $Na^+$ channels, voltage-gated $Na^+$ channels, transient receptor potential channels, $Ca^{2+}$ release-activated $Ca^{2+}$ channels, and voltage-gated $K^+$ channels; (2) carriers including $Na^+$, $Cl^-$ cotransporters, $Na^+$, $K^+$, $2Cl^-$, and water cotransporters (NKCCs), $Na^+/H^+$ exchangers (NHEs), $Na^+$/glucose cotransporters, glutamate transporters (GLTs); and (3) $Na^+/K^+$-dependent ATPase (or sodium pump). In the brain, many of these ion transport organelles have also been found to play important roles in the hydromineral balance of the neurovascular unit, and disorders of their activities underlie brain edema formation in ischemic stroke.

Relative to the volume change in individual cells, which does not alter brain volume directly, water transmission across the BBB influences brain volume dramatically. The BBB is composed of the highly specialized endothelial cells and their underlying basement membrane, pericytes, perivascular antigen-presenting cells, an ensheathment of astrocytic endfeet, and associated parenchymal basement membrane.[10] The direction and amount of water transfer between brain parenchyma and the blood are determined by BBB permeability to osmolytes and hydrostatic/osmotic pressures across the BBB. Thus, increased brain water can be transferred to blood directly through astrocyte endfeet and indirectly through the cerebrospinal fluid, whereas extracellular hypertonicity or high blood pressure can move water from the blood into the brain.[11] Under physiological conditions, water transport across cell membranes and the BBB is kept in a balanced state and brain volume is relatively stable. However, brain edema occurs once this hydromineral homeostasis is disrupted under pathological conditions.

### *Cytotoxic and Vasogenic Brain Edema*

In general, cerebral brain edema can be divided into cytotoxic or intracellular edema and vasogenic or extracellular edema. The former primarily occurs in ischemic gray matter and involves neurons, astrocytes, and endothelial cells, prominently astrocytes; the latter mainly occurs in the white matter as demonstrated in cats.[12] Theoretically, pure cytotoxic edema cannot cause apparent brain edema because of a compensatory reduction of extracellular space during cell swelling; however, cytotoxic edema does promote brain swelling because of the inherent volume regulatory features of astrocytes and changes in the permeability and integrity of the BBB following