Possible new mechanism underlying hypertonic saline therapy for cerebral edema

CEREBRAL EDEMA IS A SIGNIFICANT cause of mortality in patients with traumatic brain injury and ischemic or hemorrhagic stroke. Yet our understanding of the cellular and molecular mechanisms underlying this condition is rather limited, and new treatments showing promise in laboratory studies have frequently been found ineffective in clinical practice. Two types of edema, namely vasogenic and cellular/cytoxic, occur in brain injury. Vasogenic edema is predominantly associated with the expansion of the extracellular space caused by the disruption of the blood-brain barrier (BBB), whereas cellular edema refers to the intracellular accumulation of water. With the paucity of currently available treatments, hyperosmotic therapy is a strategy of choice to cope with increased brain water content. Mannitol is the osmotically active agent most commonly employed in clinical practice; however, there has been an increasing interest in using hypertonic saline (HS) instead of mannitol for osmotherapy (9). Indeed, HS has been shown to be effective in patients who did not respond to mannitol. Unlike mannitol infusions, HS therapy does not appear to be associated with the risk of renal insufficiency, and thus HS may be used to produce higher plasma osmolalities without serious adverse effects.

Creation of an osmotic force that draws water from brain tissue into the intravascular space is by no means the only mechanism underlying the beneficial effects of HS infusions. Although these mechanisms are still incompletely understood, there is good evidence that the decrease in hematocrit and blood viscosity, and possibly the dehydration of erythrocytes and cerebrovascular endothelium, play an important role in improving blood flow and, consequently, reducing ischemic injury and edema. The study by Chang et al. (3) in this issue of the Journal of Applied Physiology suggests yet another mechanism by which HS may reduce brain edema. The authors used a rat model of transient focal ischemia produced by the occlusion of the middle cerebral artery. With a several-hour delay following reperfusion, the animals were continuously infused with 7.5% HS that significantly decreased brain water content 3 days after the insult. This therapy was more effective than mannitol infusions. The most important and novel finding reported by Chang et al. was the reduction in serum arginine-vasopressin (AVP) levels in response to HS, which, as proposed by the authors, may represent an “additional mechanism by which osmotherapy attenuates the edema associated with ischemic stroke.”

AVP has long been postulated to play a role in promoting the formation of edema in various forms of brain injury. Animal experiments have demonstrated the efficacy of AVP subtype 1a receptor (AVP1A) antagonists in decreasing the permeability of the BBB and reducing edema after injury, consistent with augmented AVP1A expression in the injured brain (10). These laboratory findings are consistent with the increased serum AVP concentrations previously observed in patients with ischemic stroke (7) and now also found by Chang and colleagues in a rat model of cerebral ischemia. The mechanisms by which AVP exacerbates cerebral edema remain unclear, but the ability of this neuropeptide to stimulate the activity of the Na⁺-K⁺-2Cl⁻ cotransporter, an important cell volume regulator, and its ability to affect the function of the ATP- and calcium-sensitive K⁺ channels, may play a role in the formation of cellular edema. Consistent with this concept, a 50% reduction in brain water content has been shown in Na⁺-K⁺-2Cl⁻ cotransporter knockout mice subjected to middle cerebral artery occlusion (4). The AVP-mediated disruption of the BBB may, in turn, be related to the ability of AVP to promote the formation of stress fibers, an action likely amplified by the increased AVPR1A expression seen in cerebral microvessels after injury.

This new mechanism suggested by Chang et al., by which HS infusion would alleviate cerebral edema, is possible; however, further studies are needed to test this hypothesis. At a first glance, the decrease in serum AVP levels in response to HS, a potent stimulus for AVP synthesis and release, appears paradoxical. These observations are, however, consistent with previous studies in patients who underwent coronary bypass surgery, or had burn injuries, and were treated with HS solutions (5, 6). In these patients, no correlation was found between plasma osmolality and AVP levels. It is thus possible that the normal hyperosmotic regulation of AVP synthesis and release is impaired under conditions of injury or stress. Unfortunately, Chang et al. do not provide an explanation of why, in ischemic rats, the serum AVP levels drop after HS infusion.

The authors opted for a continuous 3-day infusion rather than multiple bolus injections of HS. Such an approach leads to a gradual intracellular accumulation of organic osmolytes, a part of brain adaptation to chronic hyperosmolality, and consequently, carries a risk of rebound edema after the end of HS infusion. In fact, brain areas where the BBB is intact and that are, therefore, the most responsive to HS are also the most susceptible to rebound edema. Therefore, an effective strategy for weaning from chronic HS infusion has to be developed before this mode of osmotherapy could safely be used in humans. Another important variable that requires further study is the timing of the initiation of HS therapy. Indeed, the same group has previously demonstrated that, when HS infusion is started immediately after reperfusion, it can have deleterious effects (1). Finally, a potential risk of myelinolysis associated with HS therapy should be taken into consideration. Although demyelination has traditionally been associated with the rapid correction of hyponatremia, several cases of pontine and extrapontine myelinolysis have also been reported in hypernatremic patients (2, 8).

In summary, the study by Chang and colleagues provides further evidence to support the use of HS solutions to combat cerebral edema. The authors also give us a hint about a potential novel mechanism by which osmotherapy may control edema formation. However, as with any clinically important problem, this report leaves us with many questions that require answers before HS can become commonly accepted for clinical use.

REFERENCES

Invited Editorial

HYPERTONIC SALINE THERAPY FOR CEREBRAL EDEMA


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