Hydroxyethylstarch revisited for acute brain injury treatment

Abstract
Infusion of the colloid hydroxyethylstarch has been used for volume substitution to maintain hemodynamics and microcirculation after e.g., severe blood loss. In the last decade it was revealed that hydroxyethylstarch can aggravate acute kidney injury, especially in septic patients. Because of the serious risk for critically ill patients, the administration of hydroxyethylstarch was restricted for clinical use. Animal studies and recently published in vitro experiments showed that hydroxyethylstarch might exert protective effects on the blood-brain barrier. Since the prevention of blood-brain barrier disruption was shown to go along with the reduction of brain damage after several kinds of insults, we revisit the topic hydroxyethylstarch and discuss a possible niche for the application of hydroxyethylstarch in acute brain injury treatment.

Key Words: acute subarachnoid hemorrhage; astrocyte; chronic kidney disease; delayed cerebral ischemia; microglia; neurovascular unit; osmotic pressure; pericyte; stroke; traumatic brain injury

The Colloid Hydroxyethylstarch for Volume Substitution
Since the 1960s, hydroxyethylstarch (HES) has commonly been used as a safe artificial colloid for volume substitution to restore hypovolemia and microcirculation after e.g., severe blood loss. HES is a branched and variegated molecule based on glucose, which is modified by hydroxyethylation (mainly) at the C2 and C6 carbon atoms in order to prevent rapid hydrolysis by available α-amylase in the plasma and enable long lasting effects in vivo. HES is a polydisperse solution, and the nomenclature of e.g. 130/0.4 HES stands for an average mean molecular weight of 130 kDa. 0.4 means that 40% of the glucose subunits are modified by hydroxyethylation (Jungheinrich and Neff, 2005). Currently, HES 130/0.4 or HES 130/0.42 with carrier solution either 0.9% sodium chloride (NaCl) or a balanced solution are applied in clinical routine. Alternatively to colloid solutions such as HES or albumin, crystalloid solutions such as saline, Ringer’s solution or Sterofundin® ISO could be used for volume substitution.

PubMed and Google Scholar were used as databases using topic related key words such as HES, hydroxyethylstarch, blood-brain barrier, brain endothelial cells, stroke, brain injury, TBI, traumatic brain injury, SAH.

The microvasculature volume expansion by HES, being essential for its beneficial effects, was explained by the Starling equation that tried to describe the fluid exchange between intravascular space and the interstitium with hydraulic conductivity of the endothelium, surface area, hydrostatic pressure and the osmotic pressure (OP) in the capillary. The OP was measurable and built the theoretical construct to develop colloid solutions to increase the OP, and therefore bind water intravascularly and/or trace water back from the interstitium to the bloodstream to resuscitate hypovolemia. This volume expanding effect of HES is well measurable in young and healthy patients, however, in the case of critical ill patients the starling equation is under discussion. The propagated volume effect of HES (four times higher than the effects of crystalloids) seems to be overestimated in critically ill patients when advanced hemodynamic monitoring is used. A major drawback for the application of HES in the clinical routine was the VISEP study (Brunkhorst et al., 2008), which reveals a negative effect of HES 200/0.4 on kidney function in septic patients. In regard to this, we and others figured out in the last ten years, that HES is incorporated in the proximal tubules cells of the kidney and can induce acute kidney injury (AKI). This effect is not dependent from the size of HES nor its origin (corn- or potato-derived HES) or its carrier solution, just the total applied amount of HES was found to be the key parameter (Bruno et al., 2014). Even in healthy animals, we showed that HES alone induced AKI, which may not be seen in human, because of the lack of e.g nephrobiopsy in routine pathological processes. Nowadays and in the last decade, superiority of HES over crystalloids was not confirmed, but studies with HES revealed its negative

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Acute Brain Injury and Hydroxyethylstarch

Acute subarachnoid hemorrhage (SAH) exhibits a lethality of 35% and survivors show only 30% of regain self-dependence. In this context, we differentiate between "early brain injury", manifesting during the first 3 days after bleeding, and "delayed cerebral ischemia (DCI)". DCI is a syndrome after SAH, caused by cerebral vasospasms and cerebral hypoperfusion. Another devastating acute disease in the brain is ischemic stroke that remains the second leading cause of death and disability worldwide (Vos et al., 2015). Within the ischemic cerebrovascular bed, there are two major zones of injury: the core ischemic zone and the "Ischemic penumbra" (ischemic, but still viable cerebral tissue). In the core zone, which is an area of severe ischemia, the loss of oxygen and glucose results in rapid depletion of energy stores. Severe ischemia can result in necrosis of neurons and also of supporting cellular elements (glial cells) within the severely ischemic area. Brain cells within the penumbra, a rim of mild to moderately ischemic tissue lying between tissue that is normally perfused and the area, in which infarction is evolving, may remain viable for several hours (Thirugnanachandran et al., 2018). That is because the penumbral zone is supplied with blood by collateral arteries Anastomosing with branches of the occluded vascular tree. However, even cells in this region will die, if cerebral edema occurs and reperfusion is not established during the early hours, since the diffusion length for oxygen remains too long and collateral circulation is inadequate to maintain the permanent neuronal demand for oxygen and glucose indefinitely (Heiss, 2012; Wu et al., 2018).

The protection or stabilization of the blood-brain barrier (BBB) might play the key role to reduce neuroglial deficiency after cerebral ischemia induced by vasospasms after SAH and to reduce edema in the penumbra after stroke. To prevent DCI, the so called “triple H-therapy” has been established: Hypervolemia, hypertension and haemodilution. To establish the triple-H goals, HES has been used extensively in these patients. Interestingly, critical ill patients with neurological disorders show different results in regard to HES induced AKI. For example, despite of the enormous amounts of administered HES (> 1 L HES/patient per day) to prevent cerebral vasospasm in the treatment of SAH, no increased incidence of AKI was detected (Kunze et al., 2016; Bercker et al., 2018). However, no benefit in the neurological outcome of this therapy of SAH patients was detectable (Vergouwen, 2011). On the contrary, in the SAFE-T study, the volume substitution with another colloid (albumin) in patients with traumatic brain injuries resulted in a higher mortality rate compared to crystalloids (Myburgh et al., 2007). The use of HES for critically ill patient are contradicted or highly restricted by different agencies like Federal Drug Agency, the European Medicines Agency or Health Canada.

In this context, finding answers to following questions would be essential: (1) How are the pharmacokinetic properties of HES within the brain, can HES be uptaken by glial or neuronal cells? (2) Is HES capable of protecting the BBB and thus reduces the neurological damage during SAH/DCI or stroke? (3) Is there a cross-talk between the kidney and the BBB? (4) Is it justifiable to apply HES under SAH/DCI or stroke conditions to stabilize the microvasculature in the brain, although the risk of HES for AKI is known?

Blood-Brain Barrier Functionality and Hydroxyethylstarch

In general, only few data are available about the effects of HES on BBB functionality. With regard to the effects of HES on the BBB and its permeation into the central nervous system (CNS), some reports support the idea that HES does not permeate across the BBB, but can stabilize the function of the BBB in comparison to detrimental effects of physiological 0.9% NaCl solution (Gerhartl et al., 2020a). Some animal studies showed that BBB leakage by different stimuli such as hyperosmolar mannitol treatment, sepsis induction by cecal ligation and puncture, temporary middle cerebral artery occlusion, severe brain injury or hyperthermia was prevented by HES. Additionally, the inhibition of neutrophil migration by HES may be an advantage in DCI (Trentini et al., 2019). One study using transmission electron microscopy revealed with morpH Colour analysis of HES 16.4% solution vs. 0.9% NaCl solution in rat brain capillaries that HES increases the leakage of neurovascular unit cells as pericytes or astrocytes (Somova et al., 2013). This led to the hypothesis, that HES does not reach the brain parenchyma. In this regard, HES could not be found in brains of healthy animals after its injection. Moreover, even in patients with defect BBB function after SAH or head trauma, no HES was found in the cerebrospinal fluid, supporting the assumption that HES cannot enter the brain tissue (Dietrich et al., 2003).

In order to assess, whether HES can protect the BBB and subsequently the CNS in case of acute brain injury, the underlying mechanisms need to be better understood. In Figure 1, we have illustrated some mechanisms that may be related to the restorative effect of HES on the BBB. During acute brain injury, brain capillary endothelial cells experience an increase in intracellular calcium levels and reactive oxygen species (ROS) associated with the activation of kinases such as ERK1/2 and signaling pathways that ultimately lead to the break-up of tight junctions and increased autophagy (Neuhau et al., 2017; Andjelkovic et al., 2020; Kim et al., 2020; Orellana-Urzúa et al., 2020). Appropriately, we measured that HES can reduce ROS formation in kidney proximal tubules cells and thus may have had an influence on autophagy activity by reducing ROS levels under the threshold necessary for autophagocytotic processes (unpublished data). With regard to the calcium level, we found that the plasma calcium level was significantly reduced after application of HES during pediatric neurosurgery even postoperatively on the intensive care unit (retrospective study; HES: 16.4 ± 9.2 μmol/L, not yet published). Thus, HES might interact with calcium levels, but the detailed mechanisms are still unknown. However, these data could be of high relevance, considering that the calcium level in plasma and that of the interstitial fluid in the CNS are in a dynamic equilibrium, and that one major task of the BBB is the maintenance of the homeostasis between blood and brain. In this regard, Sharma et al. (2017) reported that the serum calcium level correlated positively with neuropsychological and cognitive performance suggesting that a plasma calcium level modulating effect by HES might also affect neuronal function in the CNS (Lam et al., 2016; Sharma et al., 2017). Although there are no further mechanistic studies on the effects of HES on the BBB directly, experiments about the influence of HES on cell-cell junction regulating mediators could be used to discuss possibly related underlying mechanisms. For example, HES was able to diminish brain edema formation in a rat model of severe brain injury (Somova et al., 2013). Moreover, it was shown that HES attenuated NO formation in capillaries during severe TBI, and inhibited NO production is linked to reduced cognitive performance suggesting that a plasma calcium level modulating effect by HES might also affect neuronal function in the CNS (Lam et al., 2016; Sharma et al., 2017). However, no further mechanistic studies on the effects of HES on the BBB directly, experiments about the influence of HES on cell-cell junction regulating mediators could be used to discuss possibly related underlying mechanisms. For example, HES was able to diminish brain edema formation in a rat model of severe brain injury (Somova et al., 2013). Moreover, it was shown that HES attenuated NO formation in capillaries during severe TBI, and inhibited NO production is linked to reduced short-term tight junction dysfunction (Shi et al., 2016; Choi et al., 2019). In addition, HES blocked neuroinflammation in a rat sepsis model (Feng et al., 2010) which coincided with less Evans Blue permeability into the CNS. Since cytokines can increase BBB permeability (Harazin et al., 2018) and HES decreased proinflammatory cytokine levels, HES might restore BBB tightness by mildening the neuroinflammatory process. In this regard, HES also reduced intercellular adhesion molecule-1 expression – an essential surface protein for cell adhesion – which could contribute to less immune cell penetration into
Figure 1 | Summary of proposed mechanistic processes responsible for blood-brain barrier (BBB) breakdown during cerebral ischemia and hypotheses about effects of hydroxyethylstarch (HES) in BBB restoration.

(A) In the healthy BBB brain capillary endothelial cells form the main component of the barrier. Intercellular gaps are sealed by tight junction strands, which prevent an unspecific permeation of mainly hydrophilic compounds into the central nervous system (CNS). A huge array of mechanisms control the transcellular transport across the BBB and subsequent entry of substances into the CNS. Transporter proteins could be classified in ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters with 48 or almost 400 member proteins, respectively. These transporters regulate the transcellular permeation of compounds by preventing (efflux) or enabling their entry (influx). Most prominent efflux transporters are ABCB1 (P-gp, P-glycoprotein), ABCG2 (BCRP, breast cancer resistance protein) and ABCCs (MRPs, multidrug resistance associated proteins), whereas especially nutrient transporters such as SLC2A1 (GLUT-1) or SLC7A5 (LAT-1) belong to the best studied influx carriers. Bigger molecules such as peptides, proteins, particles or even cells can use receptor- or adsorption mediated transcytosis (RMT, AMT) pathways. Microenvironmental stimuli can strongly regulate the function of brain capillary endothelial cells. These stimuli could be molecules secreted, for example, by neighboring cells such as astrocytes (AC) or pericytes (PC) or physical forces such as shear stress induced by blood flow. Brain capillary endothelial cells share the same basal lamina (BL) with pericytes, whereas astrocytes are separated by an additional extracellular matrix layer and cover the majority of the surface of blood capillaries from the CNS side (Abbott et al., 2006, 2010). Within the neurovascular unit the interaction of brain capillary endothelial cells is also proposed with further CNS cells such as microglia (MC), oligodendrocytes (OD) and neurons (N), whereas the interplay with cells in blood such as red blood cells (RBC), macrophages (MP), neutrophils (NP) or platelets (P) is recognized as important but understudied. (B) During cerebral ischemia it was shown that BBB permeability is increased in several phases based on different mechanisms. It is proposed that BBB disruption is causally linked to brain edema formation and development of sequelae after stroke and traumatic brain injury. Therefore, it was hypothesized that the BBB could be a promising target for therapeutic strategies against brain injuries (Thal and Neuhaus, 2014). Some of the mechanisms include opening of the tight junctions which could be linked to phosphorylation of the myosin-light chains, increase of intracellular calcium (Ca2+), and formation of reactive oxygen species (ROS). But also active transporter systems are regulated leading to an altered transcellular permeability, pericytes can lose their close contacts to brain capillary endothelial cells which is proposed to be correlated with an increased transcellular transcytosis rate, and immune cell entry is enabled preferentially at the post-capillary venules. Released tissue-type plasminogen activator (t-PA) and subsequently activated matrix metalloproteinases (MMPs) degrade proteins including tight junction proteins such as Occludin. Due to the lowered availability of glucose during cerebral ischemia, brain endothelial cells upregulate the expression and functionality of glucose transporters such as SLC2A1 (Glut-1) which can also contribute to brain edema formation by the suggested co-transport of water molecules (MacAulay and Zeuthen, 2010). Moreover, ion channel functionality is changed disturbing ion and water homeostasis (O’Donnell, 2014). Concordantly to these detrimental processes autophagy in brain endothelial cells is increased under ischemic conditions (Kim et al., 2020). (C) In relation to these adverse molecular mechanisms at the BBB under ischemic conditions, data of effects of HES (symbolized with pink circles) in different in vitro and in vivo models suggest that HES might have the potential to counteract BBB damage. For example, HES can decrease activity of mitochondrial dehydrogenases (mDHs), ROS formation and stabilize paracellular permeability (Gerhartl et al., 2020a). Yet unpublished data from our own lab suggested that autophagy or single steps of autophagy could be modified by HES. Another important point, which should be investigated in detail in the near future, is the interplay of HES with glucose dependent processes. HES is based on modified glucose units, and thus possibly interact with uptake and metabolic pathways of glucose maybe competing about the same interaction and binding sites with glucose itself. This might lead to an altered glucose uptake and/or metabolism such as glycolysis or subsequent respiratory chain which is also linked to the formation of ROS. Moreover, the interplay of AMP-activated protein kinase (AMPK) as intracellular energy sensor within the cell and the mechanistic target of rapamycin (mTOR) could be concerned and presents a link to autophagy. However, the detailed mechanisms and interactions have still to be resolved.

In addition to the acute processes during a cerebral ischemic insult, the processes following reperfusion must also be considered in order to evaluate a therapeutic strategy. Various cellular and molecular mechanisms are involved in the complex process of reperfusion injury, including e.g., activation and modulation of the complement, immune and coagulation systems. It is known that all these systems can be influenced in different ways by the application of HES. In the last decades experimental animal studies revealed that HES can reduce reperfusion injury by reduction of leucocytes adherence and therefore e.g., reduction of vascular injury (Kaplan et al. 2000). However, clinical trials were not able to recapitulate these beneficial experimental results or revealed even adverse neurological outcome (Mast and Marx, 1991). In this context it is important to consider the respective HES dosage in the interpretation of the outcomes. Generally, it can be postulated that high HES concentrations might lead to vascular instability in vivo. The indication of the above mentioned clinical study for HES application was mainly hemodilution, and to investigate whether adjusting this parameter with HES can reduce cerebral damage after stroke. It is now well known that volume substitution with significant amounts of HES can reduce the vascular glycocalyx (Hippensteel et al., 2019; Li et al., 2020) and therefore induce vascular instability (Alphonson and Rodseth, 2014). Therefore, it could be postulated that the applied HES concentrations were too high in order to be successful in stroke therapy. Another endothelium-stabilizing
possible mechanism mediated by HES could be the inhibition of the plasmatic coagulation system (Rasmussen et al., 2016) and the coating of platelets (Deusch et al., 2003). By coating platelets HES could decrease the attachment of neutrophils and monocytes, and therefore attenuate their increased production of e.g., superoxide after attachment to platelets, which was shown to be more than twice of the amount without attachment. This kind of diminution of ROS formation might contribute to a stabilized endothelial barrier (Rodrigues and Granger, 2015). In summary, it could be speculated that all these known adverse side effects of HES may be superior in case of TBI or stroke to reduce microembolism, stabilize the vascular endothelium and may prevent or reduce damages to the BBB and consequently also to neurons or glial cells.

Possible Cross-Talk between Kidney and the Blood-Brain Barrier

When considering the use of HES in acute brain injury, the possible cross-talk between kidney and the BBB should be included. In the case that HES treatment damages the kidney and at the same time rescues the BBB, later detrimental sequelae effects that are triggered in the kidney can abolish the beneficial effects on the BBB. In this context, it is known that patients with chronic kidney disease or AKI show frequently neurological disorders, such as cerebrovascular disease, cognitive impairment and neuropathy. This indicates that there is a substantial cross-talk between the kidney and the brain (Lu et al., 2015). For example, patients with chronic kidney disease show an increased prevalence of microbleeds in the brain compared to age-matched controls. The presence of microbleeds elevates the risk of cognitive decline and stroke. AKI is characterized by abrupt reduction of kidney function, systemic inflammation, oxidative stress and dysregulation of sodium, potassium and water channels. Systemic factors can affect the endothelial cells of the brain and lead to changes in the BBB integrity (Lu et al., 2015). Several studies on BBB function in kidney disease have been published (O’Kane et al., 2006; Nongnuch et al., 2014). It was shown that acute kidney injury leads to inflammation, BBB disruption and functional changes in the mouse brain (Liu et al., 2008). Another study showed that brains of rats with surgical 5/6 nephrectomy (rat model of chronic renal failure) as well as rat brain endothelial cells incubated with serum from nephrectomised rats showed a significant decrease of influx and efflux drug transporters at mRNA and protein levels (Naud et al., 2012). Nevertheless, BBB integrity and function was not changed due to this chronic renal failure as the brain permeability for drugs was unchanged (Naud et al., 2012). Ischemia/reperfusion injury is a major cause of AKI. To gain more insights into the cross-talk between kidney and brain, we constructed an in vitro co-culture model based on human proximal tubule kidney cells and brain microvascular endothelial cells (BMECs). Human kidney cells underwent oxygen/glucose deprivation for 4 hours and then were cultured along with BMECs. In addition, BMECs were left untreated or were treated with kidney injury toxins, indole-3-acetic acid and indoxyl sulfate. To validate this in vitro model of kidney-brain interaction, we isolated brain microvessels from mice subjected to bilateral renal ischemia (30 minutes)/ reperfusion (24 hours) injury and measured the mRNA and protein expression as in the in vitro studies described above. Both in vitro and in vivo systems showed similar changes in the expression of drug transporters, cellular receptors and tight junction proteins (unpublished results, Förster, Burek, personal communication).

Administration of Hydroxyethylstarch at Acute Brain Injury

In this regard, the question arose for which kind of neurological diseases the stabilization of the BBB by HES treatment could be most beneficial and practically feasible, because especially the controlled delivery of HES to the BBB would be a major factor for the success. A lot of disease states, that compromise the brain, have a preserved vessel architecture and a challenged endothelial layer of the capillaries with changes in BBB integrity in common: Stroke, traumatic brain injury, ischemia-reperfusion after cardiopulmonary resuscitation and severe bleedings, neurosurgery, radiotherapy, systemic inflammation, and all entities of severe hypoxia. However, the challenge remains, to apply HES locally in the vasculature of interest and to benefit from the protective qualities on the BBB integrity without having to deal with the systemic disadvantages of HES in critically ill patients (i.e., kidney injury, coagulopathy etc.). In this context, stroke seems to be the ideal model and disease state to investigate the effect of HES. Acute ischemic stroke is caused by the sudden shut down of the perfusion of a confined brain region. Modern therapies aim to apply mechanical thrombectomy as soon as possible to re-open the vessel of interest and reduce the penumbra area (Sarraj et al., 2020). With the intervention catheter being in the vasculature of interest, it would be easy to apply HES locally in order to reduce brain oedema in the penumbra after the elapsed ischemia-reperfusion injury and to restore BBB integrity in the compromised brain region.

Conclusion

In summary, the discussed data confirmed that kidney injury is a factor influencing BBB functionality which should not be neglected when thinking of HES treatments to stabilize the BBB. A lot of in vitro (e.g., based on oxygen/glucose deprivation) and in vivo (e.g., temporary middle cerebral artery occlusion) models are well established, which could be used to investigate the effects of HES on BBB integrity in stroke (Kleinschnitz et al., 2013; Neuhaus et al., 2017; Gerhardt et al., 2020b), before the straightforward translational transfer in human treatment will be possible. But despite evidence on the adverse effects of HES on the kidney, the well-documented contraindications and warnings, and the overall recommendation from scientific and regulatory bodies that the use of HES should be avoided in the intensive care unit or operating room, Gerhardt et al. (2020a) showed so far unexpected potential benefits for its use demonstrating tightening effects on the BBB in vitro. If confirmed in translational approaches, the use of HES to tighten the BBB might represent a niche for its use in specific cases, especially in diseases where no adverse effects of HES are reported. Nevertheless, to date the use for HES in neurological disorders should be subjected only to clinical trials.

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