The Radical Scavenger Edaravone Improves Neurologic Function and Perihematomal Glucose Metabolism after Acute Intracerebral Hemorrhage

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Oxidative injury caused by reactive oxygen species plays an important role in the progression of intracerebral hemorrhage (ICH)-induced secondary brain injury. Previous studies have demonstrated that the free radical scavenger edaravone may prevent neuronal injury and brain edema after ICH. However, the influence of edaravone on cerebral metabolism in the early stages after ICH and the underlying mechanism have not been fully investigated. In the present study, we investigated the effect of edaravone on perihematomal glucose metabolism using ^{18}F-fluorordeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). Additionally, the neurologic deficits, brain edemas, and cell death that followed ICH were quantitatively analyzed. After blood infusion, the rats treated with edaravone showed significant improvement in both forelimb placing and corner turn tests compared with those treated with vehicle. Moreover, the brain water content of the edaravone-treated group was significantly decreased compared with that of the vehicle group on day 3 after ICH. PET/CT images of ICH rats exhibited obvious decreases in FDG standardized uptake values in perihematomal region on day 3, and the lesion-to-normal ratio of the edaravone-treated ICH rats was significantly increased compared with that of the control rats. Calculation of the brain injury volumes from the PET/CT images revealed that the volumes of the blood-induced injuries were significantly smaller in the edaravone group compared with the vehicle group. Terminal Deoxynucleotidyl Transferase-mediated dUTP Nick End Labeling assays performed 3 days after ICH revealed that the numbers of apoptotic cells in perihematomal region of edaravone-treated ICH rats were decreased relative to the vehicle group. Thus, the present study demonstrates that edaravone has scavenging properties that attenuate neurologic behavioral deficits and brain edema in the early period of ICH. Additionally, edaravone may improve cerebral metabolism around the hematoma by attenuating

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Received May 18, 2014; revision received July 29, 2014; accepted August 22, 2014.

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The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

This research was supported by the Natural Science Fund (No.11ZR1423000; 14ZR1426000) and a Medical Guide grant (No.114119a8500) from the Science and Technology Commission of Shanghai Municipality.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.08.021

apoptotic cell death after ICH. **Key Words:** Intracerebral hemorrhage—edaravone—cerebral metabolism—apoptosis—positron emission tomography/computed tomography.

Intracerebral hemorrhage (ICH) is a medical emergency with high rates of mortality and morbidity and is considered to be the most serious subtype of stroke. The evidence that oxidative stress contributes to ICH-induced secondary brain injury by causing massive oxidative damage to proteins, nucleic acids, carbohydrates, and lipids via the generation of reactive oxygen species is increasing.[1-4] Brain tissue is susceptible to the oxidative damage due to its rapid oxidative metabolic activity, high polyunsaturated fatty acid content, relatively low antioxidant capacity, and inadequate neuronal cell repair activity.[5,6] Thus, the oxidative damage induced by extravasated blood components after ICH disrupts mitochondrial energetics and leads to the death of adjacent brain cells.[7-10] Oxidative stress appears to play a prominent role in the pathogenesis of ICH.

The causal relationship between free radicals and ICH injury has been confirmed by the efficacy of antioxidants as therapeutic agents. Free radical scavengers, such as dimethylthiourea, α-phenyl-N-tert-butyl nitrone, deferoxamine, or edaravone (3-methyl-1- phenyl-2-pyrazolin-5-one) significantly reduce brain injury in animal models of ICH.[11-15] Among these agents, edaravone has widely been used in patients with acute ischemic stroke.[16,17] Previous studies have demonstrated that edaravone may prevent injury to the membranes of neurons and endothelial cells, suppress neuronal death and brain edema by scavenging free radicals, such as a peroxy- and hydroxyl radicals, and inhibit lipid peroxidation.[18-22] Although the neuroprotective mechanism of edaravone has been investigated extensively, to the best of our knowledge, no report describes the therapeutic effects of edaravone on cerebral metabolism in the early period after ICH and the underlying mechanism. The purposes of the present study were to examine whether systemic edaravone improves perihematomal glucose metabolism using ^{18}F-fluorordeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and to examine the relationships between cerebral glucose metabolism, neurologic deficits, and brain edema. Additionally, we hypothesized that cell death following ICH may have an important influence on decreases in cerebral metabolism in the brain tissues surrounding the hematoma.

Materials and Methods

Animals

Animal care and procedures were performed in accordance with the Laboratory Animal Care Guidelines and approved by the Laboratory Animal Ethics Committee of Shanghai Jiao Tong University School of Medicine. Male Sprague–Dawley rats (300-350 g) were purchased from the Experimental Animal Center of the Chinese Academy of Sciences, Shanghai, China. The rats were housed in temperature- and humidity-controlled animal quarters on a 12 hours light/dark cycle for at least 7 days before the initiation of the experiment and allowed free access to food and water.

Induction of ICH and Drug Administration

The animals were anesthetized with chloral hydrate (.35 g/kg intraperitoneally.), and the right femoral artery was catheterized to sample blood for intracerebral infusion. Heart rate and rectal temperature were monitored, and the rectal temperature was maintained at 37 ± .5°C with a feedback-controlled heating pad. The rats were positioned in a stereotaxic frame (Benchmark; Leica, Nussloch, Germany), and a cranial burr hole (1 mm) was drilled on the right coronal suture 3.5 mm lateral to the midline. After collection of blood from right femoral artery, the microinjector was inserted stereotaxically into the right striatum (.2 mm anterior, 5.5 mm ventral, and 3.5 mm lateral to bregma). The mount of 100 μL nonheparinized, fresh, autologous, whole blood was infused at a rate of 20 μL/minute. Sham controls received only needle insertion. After the infusion, the needle was left in place for 5 minutes to optimize localization of the hemorrhage and then slowly withdrawn. The burr hole was plugged with bone wax, and the skin incision was closed with sutures. After the operation, the rats were returned to their cages, and the room temperature was maintained at 23 ± 1°C. Edaravone (Simcere Pharma Corporation, Nanjing, China) was administered subcutaneously at a dose of 10 mg/kg immediately after intrastriatal injection once daily for 3 days thereafter.

Experimental Groups

This study was performed in 3 parts. Part 1 investigated the therapeutic effects of edaravone on brain edema and neurologic deficits 3 days after ICH. Sixteen rats were treated with either edaravone or vehicle (n = 8 per group) for 3 days; another 8 rats received a sham operation. Part 2 evaluated the effect of edaravone on perihematomal cerebral metabolism. Sixteen rats were treated with either edaravone or vehicle (n = 8 per group) for 3 days and then studied with ^{18}F-FDG-PET/CT. Part 3 examined the effect of