Rehabilitation Augments Hematoma Clearance and Attenuates Oxidative Injury and Ion Dyshomeostasis After Brain Hemorrhage

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Background and Purpose—We assessed the elemental and biochemical effects of rehabilitation after intracerebral hemorrhage, with emphasis on iron-mediated oxidative stress, using a novel multimodal biospectroscopic imaging approach.

Methods—Collagenase-induced striatal hemorrhage was produced in rats that were randomized to enriched rehabilitation or control intervention starting on day 7. Animals were euthanized on day 14 or 21, a period of ongoing cell death. We used biospectroscopic imaging techniques to precisely determine elemental and molecular changes on day 14. Hemoglobin content was assessed with resonance Raman spectroscopy. X-ray fluorescence imaging mapped iron, chlorine, potassium, calcium, and zinc. Protein aggregation, a marker of oxidative stress, and the distribution of other macromolecules were assessed with Fourier transform infrared imaging. A second study estimated hematoma volume with a spectrophotometric assay at 21 days.

Results—In the first experiment, rehabilitation reduced hematoma hemoglobin content \( (P=0.004) \) and the amount of peri-hematoma iron \( (P<0.001) \). Oxidative damage was highly localized at the hematoma/peri-hematoma border and was decreased by rehabilitation \( (P=0.004) \). Lipid content in the peri-hematoma zone was increased by rehabilitation \( (P=0.016) \). Rehabilitation reduced the size of calcium deposits \( (P=0.040) \) and attenuated persistent dyshomeostasis of Cl\(^-\) \( (P<0.001) \) but not K\(^+\) \( (P=0.060) \). The second study confirmed that rehabilitation decreased hematoma volume \( (P=0.024) \).

Conclusions—Rehabilitation accelerated clearance of toxic blood components and decreased chronic oxidative stress. As well, rehabilitation attenuated persistent ion dyshomeostasis. These novel effects may underlie rehabilitation-induced neuroprotection and improved recovery of function. Pharmacotherapies targeting these mechanisms may further improve outcome. (Stroke. 2017;48:195-203. DOI: 10.1161/STROKEAHA.116.015404.)

Key Words: cell death ■ intracerebral hemorrhage ■ oxidative stress ■ stroke

After intracerebral hemorrhage (ICH), tissue surrounding the hematoma is subjected to chronic injury and dysfunction. Rehabilitation improves functional outcome and reduces chronic tissue loss after ICH, but mechanisms are incompletely understood.\(^1\)-\(^3\) Known mechanisms include increased neurotrophic factors\(^4\) and reduced atrophy.\(^3\) Greater mechanistic knowledge of rehabilitation-induced recovery and neuroprotection would enhance treatment protocols and guide development of new therapies.

Neurotoxic blood components cause chronic damage to peri-hematoma tissue, resulting in additional injury for days and weeks after ICH.\(^5\)-\(^6\) In particular, lysed erythrocytes release hemoglobin and redox-active iron that contribute to nondiscriminant oxidative injury by producing reactive oxygen species through Fenton reactions.\(^6\) Accordingly, intraparenchymal infusion of FeCl\(_2\) causes protracted tissue loss.\(^7\) Because of the deleterious nature of intraparenchymal blood, hematoma clearance may lessen chronic injury and improve outcome.\(^8\),\(^9\) Indeed, iron chelation therapies can reduce cell death and improve outcome,\(^8\) but benefits are not consistent.\(^10\)

Clinical efficacy of pharmacologically accelerated hematoma clearance is being tested.\(^11\) In addition to causing cell death, stroke impairs function of surviving neurons.\(^12\) Previous studies have shown dyshomeostasis of K\(^+\), Cl\(^-\), and Na\(^+\) 24 hours post ICH.\(^13\) At this acute stage, ionic changes are thought to reflect edema. However, ion dyshomeostasis may persist after edema resolves, as occurs after other nervous system injury.\(^14\) Disturbed ion balance...
disrupts proper neural function. Thus, iron dyshomeostasis in the peri-hematoma zone (PHZ) may underlie neurological impairments and impede activity-dependent recovery processes. Importantly, exercise after spinal cord injury normalizes spinal activity by attenuating iron dyshomeostasis. 

Rehabilitation after ICH may have similar effects. 

Biospectroscopic imaging allows for high-resolution elemental and biochemical analysis of tissue in situ. We previously validated the use of resonance Raman spectroscopy, x-ray fluorescence imaging (XFI), and Fourier transform infrared imaging (FTIRI) to analyze the distribution of hemoglobin, iron, and aggregated proteins 1 day after ICH. Here, we used biospectroscopic imaging to investigate mechanisms of rehabilitation, consisting of skilled reaching and environmental enrichment, after collagenase-induced ICH. We have repeatedly shown that this therapy improves long-term functional recovery and reduces cell death, even when treatment is delayed 7 days. We assessed the effect of rehabilitation on the distributions of hemoglobin, biochemical markers of oxidative stress, and various elements including iron, chlorine, and potassium.

Methods

Subjects

Protocols conformed to Canadian Council of Animal Care Guidelines and were approved by the Biociences Animal Care and Use Committee at the University of Alberta. Sixty-four male Sprague-Dawley rats (200–225 g; 7 weeks old) were obtained from the University of Alberta’s Biosciences colony. Animals were housed (4 per cage) in standard polycarbonate cages or enriched environments consisting of skilled reaching and environmental enrichment, after collagenase-induced ICH. We have repeatedly shown that this therapy improves long-term functional recovery and reduces cell death, even when treatment is delayed 7 days.

We assessed the effect of rehabilitation on the distributions of hemoglobin, biochemical markers of oxidative stress, and various elements including iron, chlorine, and potassium.

Skilled Reach Training

Animals were trained to reach for sugar pellets (45 mg; BioServ, Flemington, NJ) in the staircase test, a skilled reaching task. Training took place twice per day, 15 minutes per trial, 5 days per week for 4 weeks. Animals that did not successfully reach a minimum of 8 pellets per trial (possible maximum of 21) during the last 3 days of training were excluded from the analysis. Nonetheless, these excluded animals were subjected to all procedures (except imaging) to maintain the original cages conditions. This avoided confounds (eg, change in number of cagemates).

Intracerebral Hemorrhage

ICH was induced by striatal infusion of collagenase. Hemorrhage was induced contralaterally to the preferred paw, as determined by the number of successful reaches during the final 3 days of staircase training. Animals were anaesthetized with isoflurane (4% induction, 1.5% to 2% maintenance, in 60% N2O, balance O2). Rectal temperature was maintained at 37 °C with a heated water blanket. A burr hole was drilled 3.5 mm lateral and 1.0 mm anterior from Bregma. Intracerebral Hemorrhage

Enriched Rehabilitation

Beginning 1 week after ICH, animals in the REHAB group were subjected to skilled reaching practice and environmental enrichment. Practice occurred 4 times per day for 7 days with a modified staircase apparatus designed to increase the number of reaches beyond the typical staircase task. Only the impaired limb was trained. From 5:00 am to 8:00 am, REHAB animals were housed in multilevel cages with novel objects that were changed biweekly. CONTROL animals received equivalent handling and sugar pellets and were group housed in standard cages. In a second experiment, animals were subjected to treatment from days 7 to 20 and euthanized on day 21.

Tissue Preparation

Animals were anaesthetized and quickly decapitated 14 days post ICH. To prevent postmortem biochemical alterations, heads were rapidly frozen in isopentane cooled with liquid N. Brains were removed from skulls over dry ice. Serial coronal sections (10 µm for FTIRI and Cresyl violet staining and 20 µm for XFI and Raman spectroscopy) were taken at the center of the hematoma. Sections for FTIRI were mounted on CaF2 discs (Crystran Ltd, Poole, UK). Sections for Cresyl violet were mounted on glass slides. Sections for XFI and Raman spectroscopy were mounted on metal-free Thermonox coverslips (ThermoScientific).

Resonance Raman Spectroscopy

Hemoglobin was mapped within 24 hours of sectioning. Regions of interest were selected from bright-field images to include hematoma and peri-hematoma regions. Samples were imaged at 20×20 µm resolution with an InVia confocal Raman microscope and spectrometer (50x objective; Renishaw, Mississauga, Ontario, Canada), using streamlining mapping. Tissue was excited with an Ar+ laser (ModuLaser, Centerville, UT) emitting at 514.4 nm, 100% laser power. Raman spectra were collected with a 1200 mm line grating from 1200 to 1800 cm-1. Semi-quantitative maps of hemoglobin distribution were generated with Renishaw WiRE software (version 3.3). Spectra were integrated from 1535 to 1590 cm-1, including bands indicative of oxy- and deoxyhemoglobin. Custom software converted maps to allow for region of interest analysis with Sam Microanalysis Toolkit (version 1.1). Intensity was averaged from identifiable regions of hematoma, corroborated with bright-field images, Cresyl violet histology, and XFI iron maps (described below). Nonhematoma regions were avoided.

X-Ray Fluorescence Imaging

Maps of Ca, Cl-, Cu, Fe, Mn, K+, and Zn were collected using synchrotron light at beamline 10–2 at the Stanford Synchrotron Radiation Lightsource. Samples were mounted at a 45° angle to the incident beam. Tissue was exposed to a 13450 eV x-ray beam through a 50 µm pinhole aperture for 200 ms per 30 µm step. Emissions spectra were detected with a 4-element vertex silicon drift detector. Spectra were also collected from standards of known concentration for quantitative analysis. Quantified channels were generated with Sam Microanalysis Toolkit and reformatted with custom software for spatial analysis with Imaged (version 1.48; National Institutes of Health, Bethesda, MD). Elemental concentrations of Fe, Cl-, and K+ were determined over distance from the hematoma in peri-hematoma striatum. As verified previously and in the present study, a sharp decrease in Fe concentration demarcates the hematoma/peri-hematoma boundary. Average elemental concentration was measured in adjacent 6×6 pixel bins (180×180 µm) moving away from the hematoma edge to 1260 µm (3 regions of interest per section). In the contralateral hemisphere, average elemental concentrations were determined in the entire striatum. Potassium concentration was expressed as a change from contralateral striatum because of a large difference in potassium counts between imaging runs. Depots of calcium (often also containing zinc) are associated with pathological cell death. In sections with identifiable calcium deposits, average concentration and size of deposits was determined with ImageJ. Because of the small number of animals with zinc deposits, zinc was not formally analyzed.
Fourier Transform Infrared Imaging

FTIR images were collected on the Mid-IR 01B1-1 beamline at the Canadian Light Source (Saskatoon, Saskatchewan, Canada). Blank background images were collected immediately before each sample. Effective pixel size was 21.4 µm, approximated as 20 µm for spatial comparisons. Spectra were collected in the range from 900 to 3850 cm⁻¹. Images were generated using Cytospec software (version 2.00.01). To generate maps of lipid ester, spectra were integrated from 1710 to 1755 cm⁻¹. Total protein was determined by integrating the amide I band (1610–1690 cm⁻¹). Second derivative intensity at 1625 cm⁻¹ was used to generate aggregated protein maps after spectra were vector-normalized to the amide I band, and second derivatives were calculated from normalized spectra using a Savitsky-Golay 13-point smoothing average. Images were exported from Cytospec and spatially analyzed with ImageJ as per XFI images, except 9x9 pixel binning was used to yield 180x180 µm bins. Because of beamline time limitations, only a random subset of sections was imaged (final N=7 per group).

Spectrophotometric Hemoglobin Assay

In the second experiment, brains were removed and assayed to determine blood volume in each hemisphere immediately after decapitation. Hematoma volume was calculated as ipsilateral–contralateral blood volume.

Statistical Analysis

Data were analyzed with GraphPad Prism software (version 6.0; GraphPad Software, Inc, La Jolla, CA). Two-way ANOVA was used to assess group and distance main effects. Fisher least significant difference was used for post hoc comparisons to minimize type 2 errors. Note that choice of post hoc test did not affect our

**Table. Group Sizes, Exclusions, and Number of Samples Not Imaged**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Initial n (CONTROL, REHAB)</th>
<th>Excluded</th>
<th>Not Imaged</th>
<th>Final n</th>
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<td>XFI</td>
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<td>6, 7</td>
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<tr>
<td>Hemoglobin</td>
<td>assay</td>
<td>16, 16</td>
<td>0, 1</td>
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</table>

CONTROL indicates control animals; FTIRI, Fourier transform infrared imaging; REHAB, rehabilitation animals; and XFI, x-ray fluorescence imaging.

**Figure 1.** Relative hemoglobin content in the hematoma measured by resonance Raman spectroscopy was lessened by rehabilitation (REHAB; A, n=8 CONTROL; n=10 REHAB). B, Illustrative Raman images. Black boxes correspond to region of Raman images. Hematomas in Raman images are outlined in white. Measurements of hemoglobin content only included the hematoma; peri-hematoma tissue and holes were avoided. Hemoglobin assay at 21 d post-intracerebral hemorrhage (ICH) confirmed Raman findings (C; n=15 REHAB, n=16 CONTROL). *P<0.05. **P<0.01.
conclusions. Unpaired Student t tests were used for comparison of 2 independent means. Assumptions of equal variance were tested with Brown–Forsythe or F tests. In cases where variance was not equal, appropriate corrections were applied (ie, Welch t tests). Proportions were compared with Fisher exact test. Statistical significance was defined as P<0.05. All data are mean±SD.

Results

Mortality and Exclusions
Group sizes and exclusions are summarized in Table. In the imaging experiment, 1 animal died from surgical error (cage later randomized to CONTROL group). Three animals per group failed to meet the minimum criteria in the staircase task. An additional 6 animals were excluded from spatial analysis of XFI and FTIRI maps because of insufficient residual striatum for analysis (4 REHAB and 2 CONTROL). One CONTROL animal was excluded from FTIRI analysis because of detector malfunction. One REHAB and 2 CONTROL animals were excluded from Raman analysis because of problems with image collection. One REHAB animal was excluded from the hemoglobin assay experiment because of a surgical error.

Figure 2. Rehabilitation (REHAB) lessened peri-hematoma iron, especially near the hematoma (A; n=10 CONTROL; n=9 REHAB). B, Comparison of x-ray fluorescence imaging (XFI), Cresyl violet (CV) staining, and Raman spectroscopy in serial sections. Iron concentration in the hematoma quantified by XFI was correlated with hemoglobin content measured by Raman spectroscopy (C; n=8 CONTROL; n=9 REHAB). *P<0.05. **P<0.01.
Multimodal Determination of Hemoglobin

REHAB decreased relative hemoglobin content within the hematoma at 14 days (Figure 1A and 1B; P=0.002). This was confirmed with a spectrophotometric assay in separate animals at 21 days (Figure 1C; P=0.024).

X-Ray Fluorescence Imaging

Total Fe was highest at the hematoma border and decreased with distance from the hematoma (Figure 2A and 2B; P<0.001, distance main effect). REHAB decreased peri-hematoma Fe (P<0.001, group main effect), especially nearest to the hematoma (P=0.002). Linear regression between relative hemoglobin content and average Fe content in the hematoma revealed a significant relationship (Figure 2C; P=0.007; r²=0.394), although not all iron within the hematoma is contained in hemoglobin because hemoglobin breakdown is ongoing at this time.

Hemorrhage caused persistent ion dyshomeostasis in peri-hematoma tissue. Specifically, Cl⁻ concentration was increased and K⁺ concentration was decreased in the PHZ compared with contralateral striatum (Figure 3A and 3B; P<0.001). The magnitude of these effects normalized with distance from the hematoma (Figure 3A; P<0.001, distance main effect). REHAB attenuated Cl⁻ dyshomeostasis (Figure 3A and 3C; P<0.001, group main effect), but not K⁺ dyshomeostasis (Figure 3A and 3C; P=0.060, group main effect).

Calcium deposits were found in 6 out of 10 CONTROL animals and 7 out of 10 REHAB animals (no difference in occurrence, P=1.000). These deposits were smaller in the REHAB than CONTROL group (Figure 4A and 4B; P=0.040). Average Ca concentration within deposits was not different between groups (Figure 4A; P=0.092). Calcium was commonly colocalized with Zn (Figure 4C). There were no group differences in elemental concentration in contralateral striatum (Figure 4D; P≥0.491).

Fourier Transform Infrared Imaging

We detected a highly localized increase in protein aggregation (oxidation) surrounding the hematoma that was attenuated by REHAB (Figure 5A through 5D; P=0.004). Lipid content did not change with distance from the hematoma (Figure 5A and 5C; P=0.878, distance main effect) but was higher in the REHAB group (P=0.016, group main effect). Also, there was a loss of total protein content in the PHZ that was decreased by REHAB (Figure 5A and 5C; P=0.001, group main effect). There were no group differences in lipid, total protein, or aggregated protein content in corpus callosum or contralateral striatum (P≥0.230).
Enriched rehabilitation improves functional outcome after stroke by reducing lesion size, increasing dendritic complexity, and upregulating growth factors, among other beneficial effects. Here, we describe novel mechanisms that may underlie how rehabilitation reduces cell death and improves function after ICH. We found that REHAB improved clearance of hemoglobin and iron and concomitantly decreased oxidative stress at the hematoma/PHZ interface, a site of chronic injury. Furthermore, REHAB attenuated ion dyshomeostasis in the PHZ. These findings identify potential therapeutic targets and provide insights into the mechanisms of REHAB, perhaps some of which are unique for intracranial bleeds.

Chronic lesion expansion occurs after ICH and can be reduced by REHAB. As the lesion expands, the hematoma/PHZ interface advances outwards and damages surviving cells as they come into proximity with the hematoma. Using FTIRI, we found a localized region of aggregated (oxidized) protein at the hematoma/PHZ interface, the same region with the greatest accumulation of nonhemoglobin iron. Therefore, it seems that continued oxidative injury at this time is because of remaining blood components. Notably, REHAB decreased this localized tissue oxidation, indicating that this therapy limits chronic oxidative damage. Additionally, REHAB preserved lipid and protein content in residual striatum, suggesting less macromolecular damage or improved repair processes (eg, dendritic growth and axonal remyelination).

Figure 4. Rehabilitation (REHAB) decreased the average size of calcium deposits (A and B; N=6 CONTROL; N=7 REHAB). A, There was no difference in the average concentration of calcium in deposits. C, Deposits were distant from the hematoma and also commonly contained zinc. Arrow indicates hematoma. Arrowheads indicate calcium/zinc deposit. REHAB did not affect elemental concentrations in contralateral striatum (D; n=11 per group). *P<0.05.
We also report the novel finding that REHAB augments clearance of hemoglobin and iron after ICH. We found that iron concentration was highest at the hematoma/PHZ interface and declined with distance from the hematoma, suggesting that the high concentration of iron at the hematoma border underlies localized oxidative stress. Improved clearance of hemoglobin and iron seems to be a mechanism by which REHAB decreases ongoing tissue oxidation and lesion expansion. We previously found that REHAB does not affect ferritin or transferrin after ICH, suggesting limited effects on iron...
sequestration. Here, we found no group differences in iron, copper, manganese, or zinc concentrations in contralateral striatum, indicating a lack of bulk removal of transition metals from the brain. Additional study of iron sequestration in the immediate PHZ is needed but is technically challenging.

Hematoma resolution occurs over weeks through several pathways. For example, CD47 inhibits erythrocyte phagocytosis and limits hematoma clearance. By contrast, accumulation of CD163 and HO-1 microglia/macrophages and membrane attack complexes are associated with improved hemoglobin clearance. In addition, the NrF2 pathway mediates erythrocyte phagocytosis and increases antioxidant production. Notably, exercise upregulates NrF2. We speculate that REHAB upregulates proclearance pathways (eg, NrF2) and downregulates anticlearance pathways (eg, CD47) to hasten hematoma removal and limit secondary injury.

We previously reported distinct deposits of calcium and zinc near the lesion after ICH and ischemic stroke. In addition, cation accumulation has been observed after other brain pathologies, such as ischemia and seizure, and is linked with cell death and inflammation. We found that deposits tended to be smaller in REHAB animals. However, it is unclear whether such deposits are a result of or contributor to nervous system injury. Accordingly, smaller deposits could reflect reduced injury or could be another protective mechanism of REHAB. Because cation accumulation occurs across several insult types, it is likely an important process to nervous system injury in general and should be studied further.

Dyshomeostasis of Cl−, K+, and Na+ occurs acutely post ICH and is associated with edema. Here, we show that increased Cl− and decreased K+ concentrations persist to 14 days post ICH. Na+ could not be assessed with our methods. In contrast to the highly localized oxidative injury observed at this time, ion homeostasis is impaired throughout a large region of the PHZ. We note that this is a region where widespread dendritic atrophy occurs after ICH, and this atrophy can be reduced by REHAB. The impact of altered ion concentrations on neural function has not been assessed after ICH. Nonetheless, we speculate that neural activity in the PHZ would be markedly impaired and that ion dyshomeostasis likely contributes to behavioral impairment. Indeed, reflex function is impaired after spinal cord injury, but function is improved by reducing ion dyshomeostasis with rehabilitation or pharmacotherapy. Additionally, bumetanide, a sodium–potassium–chloride cotransporter antagonist, improves behavioral outcome after focal ischemia in rodents. Furthermore, altered tonic and phasic GABA (gamma aminobutyric acid) (Cl−) signaling has been reported to occur after stroke, and targeted treatments provide behavioral benefit. Taken together, these findings indicate that ion homeostasis is impaired after nervous system injury with functional consequences, and therapies that normalize ion concentration or signaling, including rehabilitation, can be beneficial. However, it should be noted that beginning such treatments soon after stroke can be harmful (eg, increased lesion size).

REHAB normalized dyshomeostasis of Cl− but not K+. Imbalances in Cl− homeostasis can reverse the polarity of GABA signaling by altering expression of ion transporters (eg, KCC2 [potassium–chloride cotransporter] and sodium–potassium–chloride cotransporter). A shift in the reversal potential of Cl− causes hyperexcitability. For example, impaired Cl− homeostasis after spinal cord injury is associated with hyperreflexia. Interestingly, this excitatory switch occurs after stroke as well and could underlie post-ICH seizures. REHAB seems to normalize Cl− homeostasis and improve behavioral recovery by modulating expression of Cl− transporters, although we did not assess this. Future studies will assess whether therapies targeted to normalize ion concentrations (eg, bumetanide) provide benefit after ICH.

Our methodology had several limitations. First, we were unable to determine the chemical state of iron using XFI. This could provide direct evidence that iron contributes to chronic oxidative stress after ICH. Second, we did not assess the functional significance of ion dyshomeostasis or whether the changes were intra- or extracellular. Another limitation was that we imaged one coronal section per animal. Imaging multiple sections might improve consistency but was not feasible given the onerous nature of the study and limited imaging time. Finally, we did not correlate elemental and biochemical changes induced by REHAB with behavioral improvement, although we have repeatedly shown such improvement in this model with this therapy. Future studies will assess subcellular changes in biochemistry and ionic concentration after ICH. Also, the electrophysiological and behavioral effects of ion dyshomeostasis will be examined.

In summary, we demonstrate that REHAB beginning 1 week after ICH improves hematoma clearance and decreases accumulation of iron in surrounding tissue. Perhaps, the most parsimonious explanation is that accelerated hematoma clearance underlies rehabilitation-mediated neuroprotection by limiting chronic oxidative injury at the hematoma–PHZ interface. In addition, REHAB normalizes Cl− dyshomeostasis, presumably lessening impairments and enhancing activity-dependent recovery processes. Many patients experience persistent deficits despite onerous rehabilitative therapy. Further exploration of these novel mechanisms of rehabilitation-mediated recovery will aid the development of cotherapies and improve rehabilitation protocols.

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Disclosures

None.

References


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