Delayed Neuroprotective Effect of Insulin-Like Growth Factor-I After Experimental Transient Focal Cerebral Ischemia Monitored With MRI

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Background and Purpose—Insulin-like growth factor (IGF) treatment has been shown to have trophic and neuroprotective effects in vitro and in vivo in different lesion models. IGF-I has potent neuroprotective effects after hypoxic-ischemic injury and global ischemia. The role of IGF-I in focal cerebral ischemia is only partially understood. Therefore, in the present study, we evaluated, by applying MRI monitoring, whether a clinically relevant systemic administration of IGF-I can achieve a long-lasting neuroprotective effect.

Methods—Male Wistar rats underwent transient occlusion of the right middle cerebral artery for 1 hour by using the suture occlusion model. Animals then were intraventricularly treated with 33.33 μg IGF-I/d for 3 days (group A, the IGF-I group [n=13]; group B, the placebo group [n=14]) or subcutaneously treated with 200 μg IGF-I/d for 7 days (group D, the IGF-I group [n=10]; group E, the placebo group [n=10]). Groups C and F served as sham-operated controls (n=5 and n=3, respectively). Treatment was begun 30 minutes after occlusion of the middle cerebral artery. Subcutaneously treated animals underwent MRI studies (diffusion-weighted imaging, perfusion imaging, and T2-weighted imaging) beginning 60 minutes after vessel occlusion at 6 hours and at days 1, 2, 5, and 7 after ischemia. The animals were weighed and neurologically assessed daily (rating scale ranged from 0, indicating no deficit, to 5, indicating death). On the third day (intraventricular trial) and on the seventh day (subcutaneous trial), animals were euthanized, and brain sections were stained with triphenyltetrazolium chloride.

Results—The mean infarct volume was 52.9±25.2 mm³ in intraventricularly treated animals versus 146.4±62.2 mm³ in control animals (P<0.01) and 42.2±17.9 mm³ in subcutaneously IGF-I–treated animals versus 73.1±38.1 mm³ in control animals (P<0.05). Apparent diffusion coefficient–derived lesion volume at 60 minutes after occlusion was 40.4±23.7 mm³ versus 38.3±19.3 mm³ (P=NS), increased to 168.3±49.55 mm³ versus 105.5±33.8 mm³ (P<0.05) at 24 hours, and then decreased to 55.8±30.3 mm³ versus 23.3±20.2 mm³ (P<0.05) for control and IGF-I–treated animals, respectively. The T2-weighted–derived ischemic lesion volume at 24 hours after occlusion was 236±49.2 mm³ versus 115.9±56.8 mm³ (P<0.05) and decreased to 115.9±26.2 mm³ versus 75.7±35.8 mm³ (P<0.05) at day 7 for control and IGF-I–treated animals, respectively. The relative regional cerebral blood volume was reduced to 50% before reperfusion in all regions of interest except for region of interest 1 (vessel territory of anterior cerebral artery), recovered during reperfusion, but was not different between the control and the growth factor–treated group at any imaging time point. There was no significant difference in weight loss. There was less neurological deficit after ischemia in intraventricularly and subcutaneously IGF-I–treated animals compared with control animals (P<0.05).

Conclusions—Continuous treatment with intraventricularly and subcutaneously administered IGF-I achieved a long-lasting neuroprotective effect as early as 24 hours after ischemia as measured by MRI. Therefore, IGF-I may represent a new approach to the treatment of focal cerebral ischemia.

Key Words: cerebral ischemia, focal ★ growth factors ★ magnetic resonance imaging ★ rats

Insulin-like growth factor (IGF)-I and IGF-II are polypeptide growth factors that mediate anabolic and somatogenic effects of growth hormone and are synthesized and secreted by numerous cell types. Like many growth factors, IGFs are present in the brain, are involved in brain development, and are reactivated after brain insults.2–4 Brain injury triggers the expression of IGFs and expression of the IGF receptor and increases IGF binding proteins (IGFBPs), which bind IGFs with high affinity and inactivate them by limiting their interaction with receptors.5–9 Concentrations of IGF-1 and...
IGFBPs in the peripheral blood were significantly lower in patients with acute ischemic stroke than in control subjects, suggesting an increased demand for the growth factor. IGFBPs have been shown to protect cultured embryonic or adult hippocampal, cerebellar, septal, cortical, and hypothalamic neurons after diverse forms of injury (glucose deprivation and calcium-induced, oxidative, and β-amyloid-induced damage). In vivo particularly, IGF-I has potent neuroprotective effects after hypoxic-ischemic injury and global ischemia in both the developing and adult rat brain. The role of IGF-I in focal cerebral ischemia is only partially understood. Only one study suggests that intraventricular IGF-I is neuroprotective, as measured by 2,3,5-triphenyltetrazolium chloride (TTC) staining 24 hours after transcranial middle cerebral artery (MCA) occlusion.

Diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PI) are novel imaging technologies that are sensitive for the early detection of focal brain ischemia. DWI is based on the random translational movement of water in biological tissues. Ischemia causes a rapid decrease in water diffusion, and ischemic regions appear hyperintense on DWI minutes after the induction of focal cerebral ischemia, whereas conventional MRI techniques such as T2-weighted imaging do not disclose any changes during the initial several hours of ischemia. Cerebral perfusion can be evaluated by using PI and enables the quantification of the relative mean transit time (rMTT), the relative regional cerebral blood volume (rCBV), and the cerebral blood flow index. These imaging techniques are ideally suited to monitor in vivo the evolution of the lesion and to study neuroprotective treatment effects after acute focal cerebral ischemia.

In the present experiment, we evaluated whether a clinically relevant systemic administration of IGF-I can achieve a long-lasting neuroprotective effect and improve neurological outcome after transient focal cerebral ischemia in rats. We have applied MRI monitoring to study brain perfusion and evolution of the lesion and to follow ischemia through the period of 1 week.

Materials and Methods

Experimental Groups

Male Wistar rats (Boehringer Ingelheim, Biberach, Germany) weighing 300 to 315 g were allowed to have food and water ad libitum. All animals were randomly assigned before surgery to one of the following groups: For the intraventricular experiment, treatment was initiated 30 minutes after occlusion and continued for 3 days by use of an osmotic minipump. Groups for this treatment were as follows: group A, IGF-I–treated group (n = 13); group B, placebo-treated group (n = 14); and group C, sham-operated group (n = 5). For the subcutaneous experiment, treatment was initiated 30 minutes after occlusion by bolus injection and was continued for 7 days as a daily bolus injection. Groups for this treatment were as follows: group D, IGF-I–treated group (n = 10); group E, placebo-treated group (n = 10); and group F, sham-operated group (n = 5). The rats were then weighed and intraperitoneally anesthetized with chloral hydrate (400 mg/kg). The left femoral artery was cannulated with PE-50 polyethylene tubing for continuous monitoring of arterial blood pressure and blood sampling for analysis of arterial blood gases and blood glucose. Core temperature was maintained at 37°C during surgery by use of a heating lamp connected to a rectal temperature probe.

Growth Factor Application

IGF-I (a generous gift from Cephalon Inc, Westchester, Pa) was obtained as a concentrated stock solution (15.2 mg/mL) and stored at 6°C before use. For the intraventricular experiment, an osmotic minipump (model 1003D, Alzet) was filled with 6.6 μL of the stock solution (equivalent to 0.10 mg IGF-I) and 86 μL sterile artificial cerebrospinal fluid. IGF-I was delivered intraventricularly at a rate of 33.33 μg/d with a pump rate of 1.29 μL/h (1.4 μg/h). The total amount of IGF-I delivered in the intraventricular trial was 100 μg. Control rats received similar infusions of the vehicle (artificial cerebrospinal fluid) alone. Preparation and implantation of the infusion was performed under sterile conditions. The osmotic minipumps were primed in 37°C sterile isotonic saline 4 hours before implantation to guarantee a prompt delivery. Sham-operated rats received the intraventricular growth factor treatment without occlusion of the MCA. For the subcutaneous experiment, 13.2 mL of the stock solution (200 μg IGF-I) was dissolved in sterile isotonic saline (1 mL) for daily bolus applications. The total amount of IGF-I delivered in the subcutaneous trial was 1400 μg. Control rats received similar infusions of the vehicle (saline) alone. Sham-operated rats received the subcutaneous growth factor treatment without occlusion of the MCA.

Surgery

For mini osmotic pump implantation, the rats were placed in a stereotactic head holder. The dorsal surface was exposed by midline incision, and a burr hole (1 mm) was drilled over the right lateral ventricle (1.6 mm lateral and 0.8 mm posterior to the bregma). A stainless-steel cannula was inserted stereotactically into the ventricle to a depth of 4 mm beneath the surface of the skull, connected with polyethylene tubing to a mini osmotic pump (model 1003D, Alzet), and subcutaneously implanted in the back. Dental cement was used for fixation of the pump on the skull and connected to the screw for stability. The wound was closed with a 3-0 silk suture.

Transient occlusion of the MCA was induced by using the suture occlusion technique. Briefly, the right common carotid artery and the right external carotid artery were exposed through a midline neck incision. A 0-0 monofilament nylon suture (Ethicon) coated with silicon (Bayer) was inserted through an arteriotomy in the common carotid artery, gently advanced into the internal carotid artery, and positioned ~17 mm from the carotid bifurcation. By use of this technique, the tip of the suture occludes unilaterally the proximal anterior cerebral artery, the origins of the MCA, and the posterior communicating artery. A large infarct in the territory of the MCA is typically produced. Reperfusion was performed by withdrawal of the occluder filament 1 hour after vessel occlusion. Sham-operated animals underwent the same experimental procedures as described above, but the nylon filament was merely inserted into the common carotid artery and not advanced, so that no infarction occurred. After surgery and magnetic resonance measurements, the catheters were removed, and the animals were allowed to recover from the anesthesia and were given food and water ad libitum.

MRI Protocol

The animals were examined in a 2.35-T scanner (BioSpec 24/40, BRUKER Medizintechnik). An actively shielded gradient coil with a 120-cm inner diameter was used. This coil was driven by the standard 150-V/100-A gradient power supply. In this configuration, 180 mT/m could be reached in 180 ms. As a radiofrequency coil, we used a home-built birdcage resonator with a 40-mm inner diameter. Magnetic resonance examination started at 60 minutes after vessel occlusion and was repeated at 6 hours and at days 1, 2, 5, and 7 after ischemia. The animals were kept in the same position throughout imaging. In each animal, we performed DWI by using a spin-echo echoplanar-imaging sequence (repetition time [TR] 3 seconds, echo time [TE] 67.7 ms, number of averages [NA] 3, different β values from 0 to 1260 s/mm², diffusion time 50 ms, duration of diffusion...
gradient 5, field of view [FOV] 4.5 cm x 4.5 cm, matrix 128 x 64, 6 slices, slice thickness 2 mm), T2-weighted MRI by using a rapid acquisition with refocused echoes sequence (TR 3 seconds, TE 87 ms, NA 4, FOV 4.5 cm x 4.5 cm, matrix 256 x 256, 6 slices, slice thickness 2 mm), and PI by using a gradient-echo echoplanar-imaging sequence (TR 1 second, TE 12 ms, NA 1, FOV 4.5 cm x 4.5 cm, matrix 128 x 64, 4 slices, slice thickness 2 mm, number of repetitions 20, time resolution 1 second). For perfusion-weighted MRI, a bolus of 0.5 mmol/kg body wt Gd-DTPA (Omniscan, Schering AG) was injected before acquisition of the fifth image data set.

Image data were then transferred to a SUN-Sparcstation 10 (SUN Microsystems). From the T2-weighted magnetic resonance images, we calculated the volume of infarction. From the diffusion-weighted images, we calculated the apparent diffusion coefficient (ADC) as described in Heiland and Sartor. A side-by-side difference of ADC value from homologous pixels (ie, the ischemic and normal hemispheres that best define the ischemic lesion volume in vivo) of 29%, highly correlating with postmortem infarct volume, was used to define abnormal ischemic pixels. From the PI data, we calculated the rCBV and the rMTT as described by Heiland et al.

The animals were weighed and neurologically assessed daily with the researcher (R.K.) blinded to the treatment given (rating scale: 0, no neurological deficit; 1, failure to extend the left forepaw; 2, decreased grip strength of the left forepaw; 3, circling to the left by pulling the tail; 4, spontaneous circling; and 5, death). On the third day (intraventricular trial) and on the seventh day (subcutaneous trial), the animals were reanesthetized with chloral hydrate (400 mg/kg) and decapitated. The brains were removed and inspected for subarachnoid hemorrhage. The brains were then coronally sectioned into five 2-mm coronal slices, incubated for 30 minutes in a 2% solution of TTC at 37°C, and fixed by immersion in a 10% buffered formalin solution. TTC-stained brain sections were photographed by using a charge-coupled device camera (EDC-1000HR Computer Camera, Electrim Corp; slices 1 to 5 equal bregma coordinates +2.4, +0.4, −1.6, −3.6, and −5.4, respectively). The infarct volumes were calculated with the researcher (R.K.) blinded to the treatment given, and in each of the 5 slices, the infarct size was quantified by using an image-processing software package (Bio Scan OPTIMAS). To compensate for the effect of brain edema, the corrected infarct volume was calculated as previously described in detail: corrected infarct area=left hemisphere area−right hemisphere area−infarct area.

The values presented in the present study are mean±SD. After acquiring all the data, the randomization code was broken. ANOVA and subsequent post hoc Fisher protected least significant difference tests were used to determine the statistical significance of differences in continuous variables, such as physiological parameters and diffusion-, perfusion-, and T2-derived infarct volumes. The t test was used for comparison of postmortem infarct volumes. The Mann-Whitney U test was performed for nonparametric data, such as mortality rate and neurological score. A value of P<0.05 was considered statistically significant.

For histological study, 3 animals of the intraventricular group were transcardially perfusion-fixed with 4% paraformaldehyde in 0.1 mol/L phosphate buffer. The brains were removed from the skull, fixed overnight in 4% paraformaldehyde at 4°C, and then sectioned at the level of the anterior commissure, hippocampus, and substantia nigra. Slices of 10 μm were obtained from paraffin blocks and stained with hematoxylin and eosin (H&E). Other sections from these brains were cut at 30 μm and immunostained for glial fibrillary acid protein (GFAP) by using the avidin-biotin peroxidase complex method. H&E-stained brain sections and a corresponding TTC-stained brain slice at the level of the anterior commissure were compared for extent of stratal and cortical infarct volume, with the researcher blinded to the treatment given. H&E- and GFAP-stained brain sections were then inspected for morphology.

Follow-Up Assessment

Figure 1. Infarct volumes of intraventricularly treated animals 3 days after focal cerebral ischemia and infarct volumes of subcutaneously treated animals 7 days after focal cerebral ischemia. Bar graphs of infarct volume are shown (in mm3). Bar indicates SD. The mean infarct volume was significantly smaller in the IGF-I–treated groups than in the control groups (*P<0.05 and **P<0.001, t test).

Figure 2. Serial changes in evolution of ADC-derived ischemic lesion volume over 1 week in subcutaneously IGF-I–treated animals (stippled squares) and control animals (solid diamonds) (n=10 per group). Values are mean±SD (*P<0.05, ANOVA and Fisher test), with time given nonlinearly in days (x-axis).

Figure 3. Serial changes in the evolution of T2-derived ischemic lesion volume over 1 week in subcutaneously IGF-I–treated animals (stippled squares) and control animals (solid diamonds) (n=10 per group). Values are mean±SD (*P<0.05, ANOVA and Fisher test), with time given nonlinearly in days (x-axis).
Results

IGF-I achieved a potent neuroprotective effect in both intraventricular and subcutaneous application routes when delivered after focal cerebral ischemia. Mean infarct volume was $52.9 \pm 25.2 \text{ mm}^3$ in intraventricularly IGF-I–treated animals versus $146.4 \pm 62.2 \text{ mm}^3$ in the control group ($P < 0.01$, Figure 1). Mean infarct volume was $42.2 \pm 17.9 \text{ mm}^3$ in subcutaneously IGF-I–treated animals versus $73.1 \pm 38.1 \text{ mm}^3$ in the control group ($P < 0.05$, Figure 1).

The ischemic lesion volumes in vivo for all subcutaneously treated animals were calculated by using ADC maps derived from the DWI data and T2-weighted images. DWI-derived ischemic lesion volumes at 60 minutes after occlusion and 30 minutes after growth factor injection were $40.4 \pm 23.8 \text{ mm}^3$ for the control group and $38.3 \pm 19.2 \text{ mm}^3$ for the IGF-I–treated group ($P = \text{NS}$). The DWI-derived ischemic lesion volumes increased to $108.2 \pm 40.6 \text{ mm}^3$ and $71.8 \pm 26.1 \text{ mm}^3$ ($P = \text{NS}$) at 6 hours and to $168.3 \pm 49.5 \text{ mm}^3$ and $105.5 \pm 33.8 \text{ mm}^3$ ($P < 0.05$) at 24 hours after occlusion for control and IGF-I–treated animals, respectively. T2-weighted–derived lesion volumes then decreased to $115.9 \pm 26.2 \text{ mm}^3$ and $75.7 \pm 35.8 \text{ mm}^3$ ($P < 0.05$) at day 7 for control and IGF-I–treated animals, respectively (Figure 3 and 4).

Cerebral blood flow was calculated for each region of interest (ROI) at each of the 3 PI time points on the basis of the rrCBV and rMTT data, and values were compared between the 2 experimental groups ($n = 8$ control rats, $n = 9$ IGF-I–treated rats). rrCBV was reduced to 50% before reperfusion in all ROIs except for ROI 1 (vessel territory of the anterior cerebral artery), recovered during reperfusion, but was not different between the control and the growth factor–treated group at any imaging time point (Table 1).

In correspondence with reduced infarct volumes in growth factor–treated animals, there was less neurological deficit after ischemia in both intraventricularly and subcutaneously IGF-I–treated animals compared with control animals ($P < 0.05$, Table 2). There was no significant difference in weight loss between treated and untreated animals (Table 3). In the intraventricular group, 1 control animal died 24 to 48 hours after occlusion.

Figure 4. Evolution of focal cerebral ischemia as measured by DWI (top panel) and T2-weighted imaging (middle panel) in placebo-treated animals (upper rows) and IGF-I–treated animals (lower rows) through 1 week after vessel occlusion. Postmortem TTC staining at day 7 is shown in the bottom right panel. Scale indicates millimeters. Note the long-lasting (7-day) neuroprotection achieved by IGF-I treatment, which is effective as early as 24 hours after vessel occlusion.
hours after MCA occlusion, whereas no animals in the IGF-I–treated group died (P=NS). In the subcutaneous group, 2 control animals died 48 to 72 hours after MCA occlusion, whereas 1 animal in the IGF-I–treated group died 72 to 96 hours after occlusion (P=NS). No differences occurred in physiological parameters during surgery between IGF-I–treated and control animals (Table 4).

In H&E-stained brain sections of the intraventricular groups, the ischemic lesion was clearly discernible from the surrounding brain and involved the basal ganglia, a portion of the thalamus, and, in part, the cortex. Pannecrosis and reabsorption were most prominent in the supraoptic area. Red and ghost neurons, ghost astrocytes, and infiltration by inflammatory cells were found in particular at the margins of the lesion in both groups. Infarcts were, on average, smaller in IGF-I–treated animals compared with control animals. Moreover, examination of H&E- and GFAP-stained brain sections showed no apparent differences in vascular or glial proliferation at the borders of the ischemic lesion in IGF-I–treated and control animals. Examination of H&E- and GFAP-stained brain sections in sham-operated animals showed no abnormal histological findings.

**Discussion**

The results of the present study demonstrate that continuous treatment with intraventricularly and subcutaneously administered IGF-I after induction of transient focal cerebral ischemia achieved a significant infarct-reducing effect and improved neurological outcome. As shown in the present study, first in vivo by MRI, neuroprotection after systemic administration of the growth factor was of delayed fashion, was begun as early as 24 hours after ischemia, and remained effective throughout the entire experiment. These findings are supported by Tatlisumak et al., who measured ADC-derived lesion volumes during intravenous basic fibroblast growth factor (bFGF) treatment in the first 4 hours of ischemia. There was no infarct-reducing effect at the early time points, but there was a significant effect at 24 hours after ischemia. Taken together, these data suggest that the growth factor–mediated neuroprotective effect after stroke is of

<table>
<thead>
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<th>TABLE 1. Results of Pi in Subcutaneously Treated Animals</th>
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<td>ROI 1</td>
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Values are mean±SD. Differences among groups were not statistically different. ROI 1 indicates anterior cerebral artery–supplied cortex; ROI 2, parietal cortex; ROI 3, temporal cortex; ROI 4, basal cortex; and ROI 5, caudoputamen.
delayed fashion. Therefore, growth factors may have a much longer time window compared with other neuroprotective agents, such as \( N \)-methyl-D-aspartate (NMDA) antagonists, which are effective for 1 week. The delayed fashion of neuroprotection is ischemia, as monitored by in vivo MRI, and remained significant neuroprotective effect as early as 24 hours after ischemia, as shown in the present study and as measured by MRI, IGF-I treatment did not reduce systemic blood pressure or ever, as shown in the present study and as measured by MRI, IGF-I treatment did not reduce systemic blood pressure or change cerebral perfusion compared with the control condition.

In conclusion, systemic administration of IGF-I achieved a significant neuroprotective effect as early as 24 hours after ischemia, as monitored by in vivo MRI, and remained effective for 1 week. The delayed fashion of neuroprotection of the growth factor suggests a longer time window and could be of interest for a potential clinical use. Clearly, further

### Table 2. Daily Neurological Score After Intraventricular and Subcutaneous Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<tr>
<td>Intraventricular</td>
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<tr>
<td>IGF-I–treated rats</td>
<td>3.3±0.4*</td>
<td>3.4±0.5*</td>
<td>2.9±0.5*</td>
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<tr>
<td>Control rats</td>
<td>3.8±0.4</td>
<td>4.0±0.4</td>
<td>3.6±0.6</td>
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<td>...</td>
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<tr>
<td>Subcutaneous</td>
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<tr>
<td>IGF-I–treated rats</td>
<td>3.3±0.4*</td>
<td>3.4±0.5</td>
<td>3.0±0.6*</td>
<td>2.9±0.8*</td>
<td>2.7±0.9*</td>
<td>2.5±0.9*</td>
<td>2.5±0.9*</td>
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<tr>
<td>Control rats</td>
<td>3.8±0.4</td>
<td>3.9±0.5</td>
<td>4.1±0.5</td>
<td>3.7±0.8</td>
<td>3.6±0.8</td>
<td>3.5±0.8</td>
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Values are mean±SD.

*P<0.05 by Mann-Whitney U test.

### Table 3. Weight Loss in Percentage of Initial Weight After Intraventricular and Subcutaneous Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<tbody>
<tr>
<td>Intraventricular</td>
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<td></td>
</tr>
<tr>
<td>IGF-I–treated rats</td>
<td>81.8±5.2</td>
<td>77.4±4.0</td>
<td>73.0±3.5</td>
<td>...</td>
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<tr>
<td>Control rats</td>
<td>80.4±4.3</td>
<td>75.2±3.9</td>
<td>70.4±3.7</td>
<td>...</td>
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<tr>
<td>Subcutaneous</td>
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<tr>
<td>IGF-I–treated rats</td>
<td>79.0±3.9</td>
<td>72.7±5.9</td>
<td>70.7±5.8</td>
<td>70.0±4.3</td>
<td>70.3±4.2</td>
<td>69.6±4.0</td>
<td>70.9±5.5</td>
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<tr>
<td>Control rats</td>
<td>79.8±3.9</td>
<td>68.9±5.3</td>
<td>66.7±4.6</td>
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<td>66.1±3.8</td>
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Values are mean±SD. Differences among groups were not statistically different.
TABLE 4. Physiological Parameter in Intraventricularly Treated Animals

<table>
<thead>
<tr>
<th>Control Rats (n=14)</th>
<th>IGF-I–Treated Rats (n=13)</th>
<th>Sham Operated Rats (n=5)</th>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>Glucose, mmol/L</td>
<td>8.1±1.3</td>
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<td>pH</td>
<td>7.35±0.08</td>
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<td>PCO2, mm Hg</td>
<td>37.2±4.0</td>
<td>38.8±3.4</td>
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<tr>
<td>P02, mm Hg</td>
<td>121.0±5.2</td>
<td>115.7±4.9</td>
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<tr>
<td>MABP, mm Hg</td>
<td>75.1±6.8</td>
<td>79.8±9.5</td>
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<tr>
<td><strong>30 min after ischemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>8.0±2.1</td>
<td>8.3±1.9</td>
</tr>
<tr>
<td>pH</td>
<td>7.30±0.04</td>
<td>7.32±0.09</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>45.0±4.4</td>
<td>43.3±5.8</td>
</tr>
<tr>
<td>P02, mm Hg</td>
<td>114.2±6.0</td>
<td>117.8±5.5</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>79.2±6.1</td>
<td>78.8±10.2</td>
</tr>
<tr>
<td><strong>90 min after ischemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>9.7±1.8</td>
<td>10.3±1.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.30±0.05</td>
<td>7.31±0.08</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>44.7±5.3</td>
<td>39.5±4.0</td>
</tr>
<tr>
<td>P02, mm Hg</td>
<td>115.3±5.6</td>
<td>120.2±6.2</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>81.9±10.3</td>
<td>85.3±9.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. MABP indicates mean arterial blood pressure. Differences among groups were not statistically different.

Acknowledgments

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References


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Wolf-R. Schäbitz, Tobias T. Hoffmann, Sabine Heiland, Rainer Kollmar, Jürgen Bardutzky, Clemens Sommer and Stefan Schwab

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