Intravenous Administration of Bone Morphogenetic Protein-7 After Ischemia Improves Motor Function in Stroke Rats

Chen-Fu Chang, MD; Shinn-Zong Lin, MD, PhD; Yung-Hsiao Chiang, MD, PhD; Marisela Morales, PhD; Jenny Chou, BS; Pamela Lein, PhD; Hui-Ling Chen, MS; Barry J. Hoffer, MD, PhD; Yun Wang, MD, PhD

Background and Purpose—We and others have previously reported that bone morphogenetic protein-7 (BMP-7), given before middle cerebral artery occlusion (MCAO), reduces ischemic injury in brain. Recent studies have indicated that receptors for BMP are upregulated after brain ischemia. It is possible that this upregulation may facilitate endogenous neurorepair in the ischemic brain. The purpose of this study was to determine the neuroregenerative effects of BMP-7 given parenterally after ischemia/reperfusion injury.

Methods—Adult Sprague-Dawley rats were anesthetized with chloral hydrate. The middle cerebral artery was transiently occluded by a filament inserted through the right internal carotid artery. The filament was removed after 60-minute ischemia to allow reperfusion. Some animals were killed 24 hours after MCAO to examine BMP-7 mRNA expression. Other animals received a single dose of intravenous BMP-7 or vehicle at 24 hours after MCAO and were used for subsequent behavioral studies and BMP-7 immunostaining.

Results—BMP-7 mRNA was upregulated 24 hours after MCAO in untreated animals. BMP-7 immunoreactivity was dose-dependently increased on the ischemic side of the hippocampus/dentate on day 6 after MCAO in animals receiving intravenous injection of BMP-7. Animals receiving BMP-7 also showed a decrease in body asymmetry from day 7 to day 14 and an increase in locomotor activity on day 14 after MCAO.

Conclusions—Our data indicate that BMP-7, given parenterally after stroke, can pass through the blood-brain barrier on the ischemic side and induce behavioral recovery in stroke animals at longer testing times. (Stroke. 2003;34:558-564.)

Key Words: bone morphogenetic proteins ■ growth factors ■ nerve regeneration ■ stroke

Bone morphogenetic protein-7 (BMP-7), a protein in the transforming growth factor-β superfamily, was initially considered to be a trophic factor mainly for nonneuronal tissue. BMP-7 increases proteoglycan synthesis and initiates formation of cartilage and differentiation of bone.1 Bone morphogenetic proteins (BMPs) are highly expressed in adult kidney during ischemia, as well as in fetal kidney during development.2 Systemic application of BMP-7 reduced ischemia-induced infarction and density of apoptotic cells in kidney.3 Recent studies, however, have indicated that effects of BMPs are not limited to the skeletal or urinary system. BMP-7 is also expressed in perinatal neuronal tissues, including hippocampus, cortex, and cerebellum. Exogenous application of BMP-7 to rat mesencephalic cell cultures increases both the number of tyrosine hydroxylase–positive cells and dopamine uptake.4 Receptors for BMP are also expressed in neuronal tissue. BMP receptors can be upregulated in the granule cells of dentate gyrus after transient global cerebral ischemia5 and brain contusion.6 Moreover, intraperitoneal injection of BMP-7 before general hypoxia reduces brain infarction volume and mortality in neonatal rats.7

We have previously found that intracerebral administration of BMP-7, given before middle cerebral artery (MCA) ligation, reduces stroke injury in adult rats.8 Besides its neuroprotective effect, BMP-7 also induces neurorepair in stroke animals. Intracisternal administration of BMP-7 1 day after focal cerebral infarction induces an enhanced recovery of sensorimotor function in the impaired limbs.9,10 Taken together, these data suggest that BMP-7 and its cognate receptor are involved in neuronal protection and restoration of function during ischemia. The purpose of the present study was to determine whether a procedure more relevant to

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From the National Institute on Drug Abuse, National Institutes of Health, Baltimore, Md (C-F.C., M.M., J.C., H-L.C., B.J.H., Y.W.); Tri-Service General Hospital (C-F.C., S-Z.L., Y-H.C.) and Graduate Institute of Life Sciences (H-L.C.), National Defense Medical Center, Taiwan, Republic of China; and Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, Md (P.L.).

Correspondence to Yun Wang, MD, PhD, National Institute on Drug Abuse, Intramural Research Program, 5500 Nathan Shock Dr, Baltimore, MD 21224. E-mail ywang@intra.nida.nih.gov

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clinical stroke, involving systemic administration of BMP after focal ischemia, induces functional improvement.

Materials and Methods

Animals and Surgery

Adult male Sprague-Dawley rats (average body weight, 269.8 ± 4.1 g) were used for this study. Animals were divided into 3 groups. Animals in group A (n = 12) were killed on day 6 after MCA occlusion (MCAO) (see below) or day 5 after intravenous administration of BMP-7 for immunohistochemical study. Animals in group B (n = 46) were used for behavioral and mortality studies up to 50 days after MCAO and BMP-7 administration. Group C animals (n = 16) were killed 24 hours after MCAO or sham surgery for BMP-7 mRNA measurements. Animals in group C did not receive BMP-7 injection. Nonstroke controls for RNA study were anesthetized and cut open but did not receive stroke surgery.

MCA Occlusion

Animals were anesthetized with chloral hydrate (0.4 g/kg IP initially and 0.1 g/kg every hour). The use of chloral hydrate has been approved by our Animal Care and Use Committee and allowed a more rapid postoperative recovery. Microfilament (4-O Monosof monofilament nylon, USSC) was coated with rubber-base impression material (Omniflex, GC American Inc). The external diameter of the filament, after coating, was similar to that of a 26-gauge needle. The coated filament was inserted from the right external carotid 2 × 10^{-3} m distal to the carotid bifurcation. The distal end of the filament was placed in the internal carotid 15 to 17 × 10^{-3} m above the bifurcation to block the blood flow to the right MCA. The filament was removed after 60 minutes of ischemia. Core body temperature was monitored with a thermistor probe and maintained at 37°C with a heating pad during anesthesia. After recovery from the anesthesia, body temperature was maintained at 37°C with a heat lamp.

Systemic Administration of BMP-7

Rats were individually placed into plastic restraints (Harvard Apparatus) 24 hours after MCAO. BMP-7 (1.0, 0.1, and 0.01 g/L × 10^{-3} L/kg body wt or 10^{-3}, 10^{-4}, and 10^{-5} g/kg) was injected into the tail vein at a speed of 1.5 × 10^{-3} L/h with a syringe pump. Control animals received vehicle (acetate in 50 g/L mannitol buffer solution, 10^{-2} L/kg), at the same speed, 24 hours after MCAO. There was no significant difference in body weight for rats in any treatment group.

Behavioral Measurements

Two behavioral tests were performed blindly: body asymmetry and locomotor activity.

Body Asymmetry

Body asymmetry was quantitatively analyzed with the use of the elevated body swing test.\(^\text{11}\) Briefly, rats were examined for lateral movements/twisting when their bodies were suspended 10^{-3} m above the testing table by lifting their tails. The frequency of initial turning of head or upper body contralateral to the ischemic side was counted in 20 consecutive trials and was normalized, as follows: % recovery = [1 – (lateral turns in 20 trials/10) × 100%.

Locomotor Activity

Animals were placed in an Accuscan 42 × 42 × 31 × 10^{-3}-m activity monitor for 60 minutes of behavioral recording. The monitor contained 16 horizontal and 8 vertical infrared sensors spaced 2.5 × 10^{-3} m apart. The vertical sensors were placed 10^{-3} m from the floor of the chamber. Motor activity was calculated by the number of beams broken by the animals after placement in the chamber. Three parameters of vertical movement over 60 minutes were analyzed: (1) vertical activity (the total number of beam interruptions that occurred in the vertical sensors); (2) vertical time (the time that animals spent in vertical movement); and (3) vertical movements (the frequency of animals rearing up).

BMP-7 Immunoreactivity in Brain

Six days after MCAO, experimental and control rats that received intravenous administration of varying doses of BMP-7 or vehicle, respectively, were anesthetized with chloral hydrate (0.4 g/kg IP) and perfused transcardially with 0.5 L of 40 g/L paraformaldehyde (0.1 L/min) in 0.1 mol/L phosphate buffer, pH 7.3. Brains were then removed, postfixed for 2 hours at 4°C, rinsed with phosphate buffer, and sequentially transferred to 100-, 120-, and 150-g/L sucrose solutions. Brains were then frozen on dry ice and sectioned on a cryostat to obtain coronal sections 30 × 10^{-3} m thick.

Sections were rinsed with phosphate buffer before processing for immunocytochemistry. Nonspecific binding sites were blocked by incubating sections for 1 hour in phosphate buffer supplemented with 40 g/L bovine serum albumin and 3 g/L Triton X-100. After blocking, sections were incubated in a 1:1000 dilution of a well-characterized anti–BMP-7 monoclonal antibody (1B12, from Curis, Inc) for 24 hours at 4° C.\(^\text{12,13}\) After they were rinsed for 30 minutes in phosphate buffer, sections were processed with an ABC kit (Vector,) and the peroxidase reaction was developed with 0.5 g/L 3,3-diaminobenzidine-4 HCl and 0.3 g/L hydrogen peroxide. All microscopic observations were made by blinded observers. The immunoreactivity of BMP-7 in hippocampus/dentate was quantified with the use of Scion Image 4.02 (PC version of NIH Image).

BMP-7 mRNA Expression

BMP-7 mRNA expression in the cortex and striatum/hippocampus was compared between ischemic and control animals by reverse transcription–polymerase chain reaction (RT-PCR) with the use of 18S rRNA as an internal control. Eight hours after MCAO, the brain tissues were dissected free and frozen on dry ice. Total RNA was extracted with the use of Trizol (Life Technology). RNA samples (5 × 10^{-6} g) were reverse transcribed with the use of random primers at an annealing temperature of 65°C (You-Prime-the-First-Strand kit, Amersham). The resultant cDNA was amplified by PCR (DNA Engine Tetrad Thermocycler, MJ Research) for 26 one-minute cycles at an annealing temperature of 55°C and a denaturing temperature of 94°C. As a negative control, samples were amplified by PCR without prior RT. Primers used for amplification of BMP-7 cDNA were designed to unique sequences of rat BMP-7 with the use of the Primer3 program (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi). The specific primer sequences were BMP-7 sense 5′-ATTTCCAGGCTGGAGCAGACG-3′ and BMP-7 antisense 5′-TGGAGATCAACCCCGGAGAC-3′. The primer sequences used to analyze 18S rRNA were sense 5′-GTAACCCGTTGAAACCCTT-3′ and antisense 5′-CCATCCTAATCGGTAGTACCCG-3′. After synthesis, PCR products were assessed by gel electrophoresis (10 g/L agarose) and quantified by densitometry (Stratagene Eagle Eye II) by means of computerized image analysis (Scion).

Statistical Analysis

Statistical analyses were performed with the χ^2 test and 1-way or 2-way ANOVA, and post hoc Newman-Keuls test was used for statistical comparison. Significance was inferred at P < 0.05. Data are presented as mean ± SEM.

Results

Mortality

Animals were used for behavioral studies up to 50 days after MCAO. We found that BMP-7 treatment did not alter the mortality rate (Table; \(P = 0.891\)).

Motor Behavior

Body Asymmetry

An elevated body swing test was used to evaluate body asymmetry before MCAO and on days 1, 7, 10, 14, 21, and 50 after MCAO. All animals developed significant body asymmetry 1 day after MCAO (\(P < 0.05\), 1-way ANOVA; Figure
Mortality Animals With Different Doses of BMP-7 Posttreatment Within 50 Days After Stroke

<table>
<thead>
<tr>
<th>Dose (g/kg)</th>
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<th>Animals That Died Within 50 Days After Stroke, n</th>
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<tr>
<td>0</td>
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$P=0.891$, chi-square test.

1A). There was a spontaneous improvement in body asymmetry in vehicle control animals after MCAO (Figure 1). Intravenous administration of a high dose ($10^{-2}$ g/kg) of BMP-7 significantly reduced body asymmetry after MCAO (Figure 1A; $P<0.05$, 2-way ANOVA plus Newman-Keuls test). Animals receiving a high dose ($10^{-2}$ g/kg) of BMP-7 had an earlier onset of behavioral normalization on day 7 after MCAO (Figure 1), while animals receiving lower doses ($10^{-3}$ and $10^{-4}$ g/kg) of BMP-7 developed significant reductions in body asymmetry between days 7 and 14 after MCAO ($P<0.05$, 1-way ANOVA plus Newman-Keuls test).

**Locomotor Activity**

Locomotor activity was examined before MCAO and on days 7, 14, 21, and 50 after MCAO. All stroke animals developed a significant reduction in vertical movement on day 7 after stroke improvement from days 7 to 14 (*$P<0.05$, 2-way ANOVA). Similar to the body asymmetry test, there was a spontaneous improvement in locomotor activity in stroke animals that received vehicle. Animals receiving BMP-7 at a dose of $10^{-4}$ g/kg had significantly enhanced locomotor activity compared with the vehicle-treated controls on day 14 after MCAO (Figure 1C and 1D; $P<0.05$, 2-way ANOVA). These behavioral parameters were not significantly enhanced in animals receiving higher doses of BMP-7 ($10^{-3}$, $10^{-2}$ g/kg).

**BMP-7 Immunohistochemistry**

A total of 12 animals (n=3 per group), given various doses of BMP-7 (0, $10^{-4}$, $10^{-3}$, $10^{-2}$ g/kg IV), were killed 6 days after MCAO. There was a dose-dependent increase in BMP-7 activity on the lesioned side of the hippocampus and dentate after exogenous application of BMP-7; the greatest increase was found in the stroke animals receiving $10^{-2}$ g/kg BMP-7 (Figure 2A to 2D). The density of BMP-7 immunoreactivity in the lesioned side of the hippocampus/dentate was quantified in all slices and then normalized by comparison with the activity in the corresponding area in the contralateral hemisphere. We found that there is a good linear correlation between the increase in BMP-7 density and dose of BMP-7 applied (BMP-7 activity=$107.252+49.718\times$[dose in $10^{-2}$ g/kg of BMP-7]; $P<0.05$, $r=0.665$). At higher magnification, BMP-7–labeled neurons were detected in the stratum pyramidale (Figure 3) and stratum oriens in CA3 (Figure 3) on the ischemic side. No

**Figure 1.** Systemic administration of BMP-7 1 day after stroke improved body asymmetry and locomotor activity after MCAO. Animals received MCAO on day 0 and intravenous BMP-7 or vehicle injection on day 1. A, Body asymmetry was measured by the frequency of swinging the upper body to the side contralateral to the lesion in 20 consecutive trials on days 1, 7, 10, 14, 21, and 50. The recovery in body asymmetry was calculated according to the following formula: % recovery=$[1-($lateral turns in 20 trials$-10)/10]\times100\%$. The open bars on the far left of panels A to D represent behavioral values in nonstroke animals. All animals developed body asymmetry on day 1 after stroke ($P<0.05$ vs nonstroke animals, 1-way ANOVA plus Newman-Keuls test). There was a spontaneous improvement in body asymmetry in vehicle control animals. Treatment with BMP-7, at a dose of $10^{-2}$ g/kg, significantly augmented the recovery in body asymmetry after MCAO ($P<0.05$). Among all treatments (0, $10^{-2}$, $10^{-3}$, $10^{-4}$ g/kg), animals that received a high dose ($10^{-2}$ g/kg) of BMP-7 showed significant behavioral improvement from days 7 to 14 ($P<0.05$). B to D, Animals were placed in activity chambers on days 7, 14, 21, and 50 after stroke for locomotor activity measurement. B, Vertical activity, the total number of beam interruptions that occurred in the vertical sensors in the activity chambers over 60 minutes, was significantly reduced in all stroke animals on day 7 after MCAO ($P<0.05$ vs nonstroke animals, 1-way ANOVA). Low doses of BMP-7 ($10^{-4}$, A, g/kg) significantly enhanced vertical activity ($P<0.05$ vs vehicle group, 2-way ANOVA). C, Animals receiving BMP-7 also spent significantly longer time moving vertically after MCAO. D, Vertical movement, the frequency of animal rearing up over 60 minutes, was also significantly enhanced in stroke animals receiving BMP-7 ($P<0.05$ vs vehicle group, 2-way ANOVA). Unlike the improvement in body asymmetry, animals receiving a low dose ($10^{-4}$ g/kg) of BMP-7 developed significant locomotor behavioral improvement (B to D) on day 14 ($P<0.05$, 1-way ANOVA plus Newman-Keuls test).
BMP-7–positive cells were found in the ipsilateral hippocampus/dentate in the stroke animals receiving vehicle (Figure 2E) or in the contralateral nonlesioned hippocampus/dentate in animals receiving BMP-7 (Figure 3).

Expression of BMP-7 mRNA
A total of 16 animals (8 stroke, 8 nonstroke controls) were used to assess the effects of ischemia on expression of BMP-7 transcripts and 18S rRNA in the striatum/hippocampus and

Figure 2. Dose-dependent increase in BMP-7 immunoreactivity in hippocampus/dentate in animals receiving exogenous BMP-7. Animals were injected with BMP-7 (A, vehicle; B, $10^{-4}$ g/kg IV; C, $10^{-3}$ g/kg IV; D, $10^{-2}$ g/kg IV) through the tail vein 24 hours after MCAO. Animals were killed on day 6 after MCAO. There was a dose-dependent increase in BMP-7 immunoreactivity in the lesioned side of the hippocampus and dentate (A to D). At higher magnification, BMP-7–positive cells can be found in the dentate in an animal receiving BMP-7 ($10^{-2}$ g/kg). E. No BMP-7–positive cell was found in the hippocampus/dentate in the animals receiving vehicle (E).

Figure 3. BMP-7 immunoreactivity in hippocampus after MCAO and intravenous injection of $10^{-2}$ g/kg BMP-7. A, At low magnification, BMP-7 immunoreactivity was detected in all subdivisions of the hippocampus and dentate gyrus (DG) on the ischemic side (brown label) but not on the contralateral side. B to E, At intermediate (B) and higher (D) magnifications, labeled neurons were detected in the stratum pyramidale (SP; small arrows in E) and stratum oriens (SO; large arrows in E) in CA3 on ischemic side. C and E, Lack of BMP-7 immunoreactivity in CA3 on the nonischemic side. Bar=425×$10^{-6}$ m in A; bar=75×$10^{-6}$ m in B and C; bar=38×$10^{-6}$ m in D and E.
In this study we found that parenteral administration of BMP-7 1 day after MCAO reduced body asymmetry and enhanced locomotor activity in stroke animals. Previous studies have indicated that maximal cerebral infarction can be achieved 24 hours after reperfusion and that BMP-7, given intracerebroventricularly 1 day after MCAO, does not attenuate the volume of infarction. On the other hand, we found that there is a behavioral improvement in animals receiving poststroke BMP-7 injection. Such behavioral normalization is therefore probably not related to the changes in the volume of cerebral infarction. We and others previously reported that BMP-7, given centrally, did not alter blood pressure, blood gas, and electrolytes. It has also been demonstrated that intravenous administration of BMP-7 did not alter serum electrolytes. We also found that BMP-7, at doses between $2.5\times10^{-3}$ and $2.5\times10^{-1}$ g/kg, did not alter blood Na$^+$, K$^+$, Ca$^{2+}$, hemoglobin, cholesterol, glucose, total protein, bicarbonate, GOT, or creatinine levels (data not shown), suggesting that improvement in behavior is not secondary to the indirect changes in liver, pancreatic, or kidney function.

We found that there is a dose-dependent decrease in body asymmetry after BMP-7 treatment starting from day 7 after ischemia. The long latency of this BMP-7-mediated behavioral recovery may be related to several factors. First, in relation to the pharmacodynamic properties of BMP-7, it has been reported that BMP-7 stimulates bromodeoxyuridylate incorporation into glial cells, resulting in proliferation of immature glial cells and increasing astrocyte numbers in vitro. Inhibition of bromodeoxyuridylate incorporation into the glial cells abolishes BMP-7–induced trophic effects on midbrain dopamine neurons. These data suggest that BMPs have trophic effects that are indirectly mediated through activation of glial-derived factors. Supporting this hypothesis are reports that BMPs selectively promote the differentiation of oligodendroglial-astroglial progenitor cells into astrocytes. It is thus possible that the effects of BMP-7 are indirectly mediated through the activation of astroglia, which would delay its onset of action. Second, our preliminary data have indicated that BMP-7 can elicit new neurite outgrowth. The behavioral normalization may thus also depend on the generation of new neuronal connections, which would require several days.

We found that there was a spontaneous improvement in locomotor function that occurred 3 weeks after MCAO in vehicle controls. There was a significant increase in vertical locomotor activity. Similar non–dose-dependent responses were reported with BMP–induced neuroprotection in primary cortical cultures and BMP–mediated ureteric bud development. The reason for this disparity of dose dependency between body asymmetry and locomotor behavior is not clear. Previous studies have indicated that intracisternal injection of BMP-7, given on days 1 and 3 after MCAO, reduced forelimb use asymmetry but did not induce significant improvement in the adhesive removal test, a sensory function test. It has been suggested that recovery in certain motor functions can be affected by muscle strength in the cortex. The expression levels of 18S rRNA were not altered by MCAO (Figure 4A), nor were PCR products detected in samples amplified without prior RT (data not shown). The level of BMP–7 in each animal was normalized by comparison with that of 18S rRNA (Figure 4B and 4C). We found that MCAO caused significant increase in BMP–7 mRNA expression in the ischemic and nonischemic sides of the cortex as well as in striatum/hippocampus ($P<0.05$, 1-way ANOVA).

**Discussion**

In this study we found that parenteral administration of BMP-7 1 day after MCAO reduced body asymmetry and enhanced locomotor activity in stroke animals.
MCA-occluded rat.\textsuperscript{22} It is also possible that high doses of BMP-7 may affect locomotor scores through indirect motor or sensory functions.

Previous studies have indicated that the blood-brain barrier is open transiently after ischemia. This occurs within 0 to 4 hours after the onset of reperfusion. There is a second phase of reopening starting 22 hours after MCAO.\textsuperscript{23,24} In this study we injected BMP-7 at 24 hours after stroke. We found that BMP-7 immunoreactivity was present on the ischemic side in cortex, striatum, and hippocampus. No BMP-7 immunoreactivity was found in the contralateral hemisphere. These data suggest that the increase in BMP-7 immunoreactivity is specifically related to the ischemia-induced blood-brain barrier opening. We also found that the increased BMP-7 immunoreactivity in the ischemic hippocampus was dose dependent.

There was no significant increase in BMP-7 immunoreactivity in the ipsilateral hippocampus in vehicle-treated animals 6 days after MCAO. We found that there was a much greater increase in BMP-7 immunoreactivity in stroke animals given systemic BMP-7. These data suggest that the BMP-7 immunoreactivity detected in this study was mainly derived from exogenous application. Previous studies have indicated that receptors for BMP are upregulated after ischemic brain injury\textsuperscript{6} and brain contusion.\textsuperscript{6} We found that pyramidal neurons in the ischemic hippocampal CA3 regions showed marked BMP-7 immunoreactivity. It is possible that ischemia upregulates BMP receptors and thus increases the effects of exogenous BMP-7 on these neurons.

Our RT-PCR data indicate that BMP-7 mRNA in cortex and striatum/hippocampus is upregulated 24 hours after MCAO and suggest that there is an upregulation of endogenous BMP-7 expression early after stroke. As noted above, we also found enhanced BMP-7 immunoreactivity in the ipsilateral hemisphere 6 days after stroke, indicating that there is also an accumulation of exogenously administered BMP-7 protein in the lesioned hemisphere. Since BMP receptors are upregulated after ischemia,\textsuperscript{5} the binding of exogenous BMP-7 protein to its receptors in the ischemic hemisphere may be enhanced in stroke animals.

We found that there is also an upregulation of BMP-7 mRNA in the contralateral hemisphere after stroke. Several reports indicate that the contralateral hemisphere can compensate for the functions of the lesioned hemisphere after stroke. For example, electrophysiological excitability was increased in the neocortex contralateral to infarction after MCAO.\textsuperscript{25,26} Intracerebral injection of basic fibroblast growth factor enhanced recovery of sensorimotor function and immunoreactivity of growth-associated protein 43 (GAP-43), a molecular marker of axonal sprouting, in the intact sensorimotor cortex contralateral to cerebral infarcts.\textsuperscript{27} The early contralateral upregulation of BMP-7 mRNA and/or other factors suggests that endogenous neuroreparative processes can be activated from the nonischemic hemisphere after stroke via these trophic factors.

We have previously demonstrated that pretreatment with BMP-7\textsuperscript{1} or BMP-6\textsuperscript{19} reduces ischemia/reperfusion-induced cerebral infarction and reduces behavioral deficits, suggesting that BMPs may have neuroprotective effects against brain ischemia. In this study we found that BMP-7 has additional neurorestorative function. Parenterally administered BMP-7, given after stroke, entered into the ischemic brain areas and reduced abnormal motor behavior in stroke animals. These data may have clinical implications insofar as systemic administration of BMP-7 after stroke could improve behavior outcomes in such patients.

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