Resolution of Stroke Deficits Following Contralateral Grafts of Conditionally Immortal Neuroepithelial Stem Cells

Tina Veizovic, MSc; John S. Beech, PhD; R. Paul Stroemer, PhD; William P. Watson, PhD; Helen Hodges, PhD

Background and Purpose—Grafts of MHP36 cells have previously been shown to reduce dysfunction after global ischemia in rats. To test their efficacy after focal ischemia, MHP36 cells were grafted 2 to 3 weeks after transient intraluminal middle cerebral artery occlusion (tMCAO) in rats.

Methods—MHP36 cells were implanted into the hemisphere contralateral to the lesion, with 8 deposits of 3 μL of cell suspension (25 000 cells per microliter). Sham grafted rats received equivalent volumes of vehicle. Three groups, sham-operated controls (n=11), MCAO+sham grafts (n=10), and MCAO+MHP36 grafts (n=11), were compared in 3 behavioral tests.

Results—In the bilateral asymmetry test, MCAO+MHP36 grafted rats exhibited neglect before grafting but subsequently showed no significant dysfunction, whereas MCAO+sham grafted rats showed stable sensorimotor deficits over 18 weeks relative to controls. MCAO+sham grafted rats demonstrated spontaneous motor asymmetry and increased rotational bias after injection of dopamine agonists. MCAO+MHP36 and control groups exhibited no bias in either spontaneous or drug-induced rotation. In contrast to motor recovery, MCAO+MHP36 grafted rats showed no improvement relative to MCAO+sham grafted rats in spatial learning and memory in the water maze. MCAO produced large striatal and cortical cavitations in both occluded groups. Lesion volume was significantly reduced (P<0.05) in the MCAO+MHP36 grafted group. The majority of MHP36 cells were identified within the intact grafted hemisphere. However, MHP36 cells were also seen in the cortex, striatum, and corpus callosum of the lesioned hemisphere.

Conclusions—MHP36 cells may improve functional outcome after MCAO by assisting spontaneous reorganization in both the damaged and intact hemispheres. (Stroke. 2001;32:1012-1019.)

Key Words: behavior, animal ■ stem cell transplantation ■ middle cerebral artery occlusion, transient ■ stroke, experimental ■ rats

Transplantation of fetal tissue into the brain of adult animals has been shown to have therapeutic effects in a variety of neurological disorders. Fetal tissue is available at embryonic stages when the brain is most plastic and susceptible to the influence of exogenous cell transplantation. Fetal brain tissue provides a possible donor source for grafts, and might require both cortical and striatal dissections of different gestational ages. Use of laboratory-grown, immortalized cells might require homotypic replacement of damaged tissue and would be expected to overcome these difficulties. Borlongan et al., using grafts of the NT2N cell line developed from human teratocarcinoma, showed improvements in passive avoidance and body swing tests after permanent MCAO in rats. However, the provenance of these cells may pose difficulties for their development for large-scale clinical use. Our approach is to generate conditionally immortalized human stem cell lines by incorporating an immortalizing oncogene into fetal stem cells and creating clonal lines.

As “proof of principle,” we have investigated the functional efficacy of the MHP36 conditionally immortalized
TABLE 1. Timetable of the Experiment

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Murine stem cell line derived from the H-2Kb-tsA58 transgenic mouse neuroepithelium, which constitutively expresses the temperature-sensitive tsA58 oncogene.11 MHP36 cells are capable of unlimited expansion to generate cells for grafting under permissive low (33°C) temperature in vitro, but they cease dividing and develop into mature neurons and glia on implantation into the higher temperature of the brain (37°C). They have been shown to improve outcome in several models of impairment, including hippocampal ischemia induced by 4-vessel occlusion, lesions to cholinergic forebrain projections, and old age.11–15 MHP36 grafts are well suited to repair the indiscriminate cell loss that occurs with MCAO because (1) they have the capacity to develop into neurons, glia, or oligodendrocytes in response to host signals and (2) they migrate to and engraft areas of damage in the host brain.13–15

The present experiment investigated the efficacy of MHP36 grafts placed within the intact cortex and striatum, contralateral to the lesion cavity, to alleviate behavioral deficits induced by 60 minutes of tMCAO. The intact side was chosen to avoid exposing the cells to the poorly vascu-
larized, inflammatory environment of the developing ischemic lesion, in the process of forming a fluid-filled cyst.16 Rats were tested in tasks of sensorimotor (tape removal), motor (rotation), and cognitive (spatial learning) function to provide stable measures of several long-term deficits.17–19 Histological examination sought to provide preliminary evidence regarding whether migration to the areas of damage and/or enhancement of local reorganization in the intact hemisphere might contribute to functional effects.

Materials and Methods

The time course of the experiment is described in Table 1.

Animals

Thirty-six male Wistar rats (Charles Rivers, Maidstone Kent, UK) were used, weighing 280 to 320 g before surgery and 560 to 630 g at the end of behavioral testing. They were housed 4 to a cage, fed ad libitum, and maintained on a 12-hour light/dark schedule (lights on 9 AM). Procedures accorded with the UK Scientific Procedures Act of 1986 and the Ethical Review Committee of the Institute of Psychiatry.

tMCAO Surgery

Twenty-one rats were subjected to left tMCAO under halothane anesthesia (4% induction, 3% maintenance in 70%/30% NO2/O2). A 3.0-mm polypropylene (Prolene) filament coated at the tip with silicon (instant gasket, Halfords Ltd) was inserted 18 to 20 mm up the exposed left MCA to the junction of the circle of Willis and tied in place for 60 minutes. Anesthetic was discontinued, and the rat was tested for neurological deficit (contralateral paw flexion and circling) to establish the presence of ischemia. After 60 minutes the filament was retracted to the external carotid stump under anesthesia, where it was left in place, the excess was trimmed off, and the wound was sutured. Body temperature was maintained at 37±1°C during surgery by rectal probe and heating pad. The rats were kept warm by heating lamps for approximately 2 hours after surgery and then placed in single cages in the postoperative room for recovery. Neurological and health status was monitored for a week until normal feeding was seen and postoperative weight was regained. Control rats (n=11) were sham operated by exposure of the left internal carotid artery only.

Transplant Surgery

Transplant and sham graft surgery was undertaken 2 to 3 weeks after occlusion or sham surgery, which (1) allowed for full recovery; (2) enabled rats to be assigned to stroke-only and graft groups on the basis of equivalent neurological deficit; and (3) enabled pregraft baseline deficits in tape removal to be established. Rats were anesthetized with Immobilon (etorphine hydrochloride, 0.074 mg/mL, and methotrimeprazine, 18 mg/mL; 0.01 mL/100 g IM) after pretreatment with midazolam (Hynovel; 0.03 mL/100 g IM) and placed in a stereotaxic frame. Holes were drilled in the right side of the skull to allow the penetration of a 10-μL Hamilton syringe by the following coordinates (mm) derived from bregma, with the skull in the flat position (−3.2 mm): anteroposterior, −0.3; lateral, −3.5; ventral, −4.5, −6.0; lateral, −5.5; ventral, −4.0; −5.5; anteroposterior, −1.3; lateral, −3.0; ventral, −5.0; −6.5; lateral, −5.5; ventral, −5.0, −6.5. Three microliters of suspension (25 000 cells per microliter) was infused over 2 minutes at each of the 4 sites (2 deposits/descent), and the cannula was left in place for an additional 2 minutes to allow diffusion from the tip. Controls received vehicle infusions to control for surgical and volume effects. Coordinates targeted somatosensory cortex (lateral sites) and striatum (medial sites) to ensure wide seeding of the area homologous to the region of stroke damage assessed in pilot animals. After transplantation, rats were injected with diprenorphine (Reviron; 0.272 mg/mL; 0.01 mL/100 g IM) and single housed in the recovery room until normal feeding, grooming, and weight gain were seen. Grafted rats received cyclosporin A (Sandimmun, Sandoz: 10 mg/kg IM mixed with Cremophor EL, Sigma, in a volume of 1:3) immediately after surgery and 3 times a week for 2 weeks, a regimen effective for MHP36 graft survival in rats with 4-vessel occlusion ischemia or lesions,11–14 which maintains stable blood cyclosporin A levels above the therapeutic minimum of 100 mg/dL.

Behavioral Tests

Bilateral Asymmetry Test

Strips of tape (1×5 cm) were wound around each forepaw in random order. Animals were placed in an observation cage and timed for latency to contact and to remove each tape. Random use of a second observer established that interrater reliability was >90%. Rats were tested before surgery and during the week before grafting to establish preoperative and postoperative baselines. One session of 4 tests of 3 minutes was performed weekly for 12 weeks, commencing approximately 6 weeks after transplantation, to assess long-term recovery.

Water Maze Acquisition

Approximately 26 weeks after transplantation, rats were trained to find a submerged platform (9 cm) in a large (200-cm-diameter) pool filled to a depth of 25 cm with water maintained at 24±2°C. Two trials of 60 seconds (10-minute intertrial interval) were given daily for 16 days, followed by a probe trial (60 seconds) with the platform removed. Rats that failed to find the platform within 60 seconds were guided to it by the experimenter. Animals remained on the platform for 10 seconds before being removed and placed in a holding cage or returned to the home cage. The swim path was recorded by an image

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analysis system (HVS Image) that computed path length, latency to mount the platform, and percentage of time spent in each of 4 quadrants and 3 annuli into which the maze was calibrated for analysis of swimming patterns and heading angle, a measure of divergence from a straight path to the platform.

Rotation
Spontaneous and drug-induced rotation were measured approximately 38 weeks after transplantation in an 8-bowl rotameter (TSE GmbH) in which rats were harnessed to swivels for 30 minutes at 30 minutes after injection. Swivels enabled turns to left or right to be recorded. Rats were tested for response to saline (baseline). They were then tested once a week, on alternate weeks, with either amphetamine (2.5 mg/kg; Sigma) or apomorphine (0.5 mg/kg; Sigma) on 3 occasions over a period of 6 weeks. All injections were given in a volume of 1.0 mL/kg IP.

Histology
At the end of behavioral testing, rats were overdosed with pentobarbital sodium (Sagatal, Rhone Merieux) and transcardially perfused with heparinized saline followed by 4% paraformaldehyde. Brains were placed in 30% sucrose (Sigma) for 24 hours, blocked, and mounted on a cutting stage with embedding compound. Brains were held at 22°C to 24°C in a cryostat (Leica CM 1900), and 50-μm coronal sections were cut and collected at 500-μm intervals from 6.3 to 3.7 mm before bregma.20 Images of left and right hemispheres were taken with a Leica stereo microscope. Datacell image capture software (Pro-Plus) was used by an operator blind to the rats’ identity for the automated estimation of lesion volume by region of interest and slice interval using Simpson’s rule. Total lesion volume was obtained by subtracting the volume of the lesioned from the intact hemisphere. Intervening serial sections were processed by immunocytochemistry for reactivity to β-galactosidase (β-gal), the protein product of the LacZ gene expressed by grafted cells. β-Gal immunocytochemistry was chosen in preference to in situ hybridization or X-gal histochemistry to recognize LacZ or β-gal because (1) pilot studies indicated that it yielded good bright-field and confocal images; (2) in contrast to in situ hybridization, it permitted further processing for histology; and (3) it was more stable and reliable than X-gal.

Statistical Analysis
Sham grafted controls (n=11), ischemic rats with sham transplants (MCAO+sham; n=10), and ischemic grafted rats (MCAO+MHP36; n=11) were compared in the water maze and bilateral asymmetry tests by repeated-measures ANOVA, with groups as the between-subjects factor and days or weeks as the within-subjects factor. Weekly rotameter scores for baseline and drug-induced rotation and lesion volumes were analyzed by 1-way ANOVA. Group means were compared by Fisher’s least significant difference test.
Bilateral Asymmetry Test
Before occlusion, rats did not show a mean difference in paw use as judged by the latency to contact and remove tapes from left and right paws (Figure 1). After sham surgery the controls continued to show no preference. However, rats subjected to tMCAO showed marked paw disparity, with the right paw contacted and the tape removed significantly more slowly than the left, indicative of contralateral sensorimotor impairment ($F_{1,64}=19.72$, $P<0.001$; Figure 1B). This robust and stable deficit persisted throughout testing. In rats with MHP36 grafts, the stroke-induced forepaw disparity was not significant by 8 weeks after transplantation, and this improvement persisted through the 12 weeks of testing, so that there was no difference between paws ($F_{1,64}=1.15$, $P=\text{NS}$; Figure 1C). Hence, grafted rats did not differ from controls (compare Figure 1A and 1C) since both groups showed paw equivalence.

Water Maze Acquisition
There was a substantial difference between groups in latency to find the submerged platform ($F_{2,29}=47.8$, $P<0.0001$) because the 2 stroke groups, with and without transplants, were both impaired relative to controls ($P<0.001$; Figure 2). There was no difference between groups in speed of swimming, minimizing the effects of a motor deficit on performance. Ischemic groups were also impaired relative to controls on all other measures, such as in the percentage of time spent in the platform quadrant and annulus. During the probe trial, in which the platform was removed, stroke rats exhibited impaired recall of their precise position by spending less time in the correct location and crossing the platform position less often than controls. MHP36 grafts, therefore, did not ameliorate the marked deficit in spatial learning and memory induced by tMCAO.

Spontaneous and Drug-Induced Rotation
Baseline (spontaneous) rotation was mildly asymmetric in stroke rats without grafts (Figure 3A), which turned more to the right than the left, whereas control and grafted rats showed comparable turning in both directions ($F_{2,30}=3.59$, $P<0.05$ for the difference between groups). However, in response to amphetamine on weeks 2, 4, and 6 of testing, stroke rats without grafts showed marked leftward turning, toward the lesioned side, indicative of increased dopamine release on the intact side (Figure 3B). Group differences were very substantial ($F_{2,30}=5.71$, 8.23, and 7.31, $P<0.01$ for weeks 2, 4, and 6, respectively), and the nongrafted group differed significantly ($P<0.01$) from the grafted and control groups, which did not show a turning bias, apart from the grafted group on week 2. In all groups the number of turns was lower in response to saline than to the dopamine agonists.
However, all groups showed similar activation, so that drug-induced increases in bias in the nongrafted group were not associated with differences in activity.

Histology

Lesion Volume
tMCAO resulted in severe cavitation, amounting to approximately 26% of total brain volume, so that groups differed significantly in brain tissue volume ($F_{2,23}=9.68$, $P<0.01$; Table 2). Ventricles on the lesion side were enlarged, so that only a thin strip of striatal tissue separated the lateral ventricle from the lesion. Ventricles were also enlarged to a lesser extent on the intact side. Distortion, possibly via tissue loss, had pushed the midline toward the lesion side (Figure 4). In grafted animals lesion size was significantly reduced to approximately 16% of total brain volume, and therefore the area of degeneration was only 35.8% ($P<0.05$) of that seen in nongrafted stroke rats (Table 2).

Distribution of Grafted Cells

MHP36 cells, identified by $\beta$-gal immunocytochemistry, were seen at the injection site in the middle of the intact striatum (Figure 5). Cells were also seen caudally and laterally throughout the striatum and entering the parietal cortex. However, approximately a third of $\beta$-gal–positive cells had moved away from the side of implantation and were seen in abundance in the corpus callosum, straddling the midline, and within the lesioned hemisphere. Some cells were seen in the residual strip of striatum, adjacent to the lesion, and some had left the corpus callosum to enter somatosensory cortex. Neuronal or glial phenotype of grafted cells cannot be identified in the absence of double labeling, but cells showed bipolar and multipolar morphologies of several types, including neuron-like cells, of pyramidal and medium spiny neuron appearance, and glial-like cells, suggesting a diverse pattern of differentiation.

Discussion

The experiment examined effects of grafts of conditionally immortal MHP36 cells on the promotion of functional recovery from stroke damage when placed in the intact hemisphere, contralateral to the lesion cavity. Previous studies have shown MHP36 cell survival, migration, differentiation, and efficacy in cognitive tasks after 4-vessel occlusion in the rat and hippocampal lesions in the marmoset, which resulted in circumscribed CA1 cell loss. In the present study we sought to determine whether MHP36 grafts also promoted recovery...
from MCAO, which affects several brain regions, many types of cells, and both motor and cognitive function, with assessments performed during an unusually long period of 10 months after transplantation.

**Bilateral Asymmetry**
The bilateral asymmetry test, as described by Schallert et al., resolves within 1 month after stroke. Our modification of wrapping tape around the forelimbs required both sensory cortex and striatal integrity and revealed a robust behavioral deficit over 18 weeks in sham-grafted stroke animals. Grafted animals showed a comparable deficit before transplantation, but when testing resumed at 6 to 7 weeks after graft (approximately 8 weeks after tMCAO), grafted rats showed no difference in the time to remove the tape from the affected and unaffected paws throughout testing, indicating long-term improvement in a test in which no spontaneous recovery occurred.

Primary fetal grafts have been shown to improve motor performance after cortical infarction or striatal lesions, but this may only be significant when grafts have been paired with enriched environments or training, pointing to a role for experience-dependent neuronal plasticity in recovery. Indeed, Grabowski et al. found that an enriched environment was as functionally effective as fetal neocortical grafts, with no additive effects apparent. The mechanisms are not well understood, although Mayer et al. suggest that training enables animals to learn how to use their transplants. This evidently was not the case with the recovery from bilateral asymmetry, since animals showed immediate improvement when testing was resumed 6 weeks after implantation. Recovery from sensorimotor neglect may therefore be more dependent on graft-enhanced corticospinal pathway reorganization in the lesioned or intact side of the brain than on experiential factors.

**Spatial Learning in the Morris Water Maze**
The failure of the MHP36 grafts to improve spatial learning in the water maze in this MCAO model suggests that the grafts (1) do not provide enough tissue or appropriate connectivity to promote recovery and/or (2) may be more effective in sensorimotor than in cognitive tasks. Other studies with fetal grafting after distal MCAO also failed to show improvements in this test. However, Aihara et al. found that striatal fetal grafts improved spatial learning in the water maze, but not the radial maze, in rats with MCAO, suggesting that grafts can in some circumstances reduce spatial deficits after stroke. We have recently found that intraventricular MHP36 grafts improved water maze learning in rats subjected to 60 minutes of tMCAO, while rats with intraparenchymal grafts showed no recovery, as in the present study. Thus, graft placement may influence connectivity or transmitter release and facilitate specific behaviors, despite the marked migratory capacity of MHP36 cells.
Rotation
Stroke rats displayed mild spontaneous rotation to the right, possibly reflecting a stronger push by the unaffected left paw, whereas dopamine agonist drugs induced marked rotation to the left, consistent with activation of dopamine receptors on the intact side of the brain. Neither asymmetry was evident in grafted rats. Increased release of dopamine from grafted cells, as occurs with fetal nigral grafts in rats with unilateral nigrostriatal lesions, is not likely to account for reduced bias because MHP36 cells rarely present as tyrosine hydroxylase positive and do not reduce bias in rats with unilateral nigrostriatal lesions (S.B. Dunnett, PhD, unpublished data, 1999). Since the majority of grafted cells remained on the intact side of the brain, asymmetry would have been amplified had they adopted a dopaminergic phenotype. Alternatively, the large volume of cells infused may have damaged the intact side, so that the dopaminergic agonists were ineffective on both sides of the brain. However, equally large infusions of vehicle in sham grafted stroke animals did not eliminate bias, and dopamine agonists increased activity comparably in all groups, indicating that grafted rats were not subsensitive to their motor stimulant effects. Normalization of rotation bias may therefore have involved either enhanced thalamic function or recruitment of a normally silent corticospinal pathway on the intact side of the brain, as discussed below.

Lesion Volume
The reduction of lesion volumes in the brains of the MHP36 grafted group seen 11 months after transplantation is probably due to the reduction of secondary degeneration and atrophy, distant to the original lesions. It would not be possible for infusions of 24 µL (600 000 cells) to fill out cavities averaging 260 mm³, particularly since only a third of the cells migrated to the lesion side. Moreover, cells were scattered in the parenchyma and did not infiltrate the lesion, in contrast to fetal grafts, which have been used to fill out cortical cavities. Release of trophic factors from relatively few grafted cells might conceivably have contributed to prevention of delayed secondary degeneration, since neuroepithelial stem cells have been shown to express a variety of cytokines and growth factor receptors. Environmental factors may also be implicated, since Mattson et al found that fetal grafts in cortical cavities reduced thalamic atrophy and improved behavior only when animals were also exposed to an enriched environment. Possibly our extensive behavioral testing offered comparable stimulation. Reduced lesion volume appears to a delayed effect because we have not seen a reduction in rats examined 3 months after transplantation of MHP36 grafts, which exerted positive effects on bilateral asymmetry. A time course study is therefore essential to compare the evolution of lesion size in grafted and nongrafted animals after 60 minutes of MCAO and to relate volume change to behavioral outcome and to expression of trophic factors in MHP36 cells.

Cell Placement and Migration: Implications for Graft Mechanisms
MHP36 cells were infused in the intact hemisphere because stroke lesions might not have provided a sufficiently well-vascularized matrix to support their survival. Hadani et al found that fetal cortical grafts survived in the penumbra but not in the lesion core. A key finding was that MHP36 cells not only dispersed within the intact cortex and striatum but also migrated to the damaged hemisphere, probably via the densely populated corpus callosum, to colonize somatosensory cortex and residual striatum. Approximately two thirds of grafted cells remained within the side of implantation, while one third migrated to the contralateral hemisphere. We have subsequently confirmed this impression by detailed counts of grafted cells in regions of interest and found that similar proportions (ie, 30% to 35%) of cells migrate to the contralateral hemisphere, whether implanted in the lesioned or intact side of the brain. Increased nerve growth factor expression induced by MCAO both in perilesion regions and in the homologous contralateral cortex, which has lost innervation, may guide implanted stem cells to both hemispheres after stroke.

In addition to location, the identity of grafted cells is crucial to understanding the mechanisms of their effects. This preliminary study examined only cell distribution and lesion volume. Subsequently we have shown that up to 40% of grafted cells were neuronal by double labeling of PKH26, the fluorescent marker incorporated into cells before grafting, and the neuronal marker NeuN. Most of the remaining grafted cells were astrocytes (PKH26 and glial fibrillary acidic protein [GFAP] positive). There were more grafted neurons in the intact striatum, which harbored more cells than the lesioned striatum, but the proportions of neurons and glia were similar whether grafts were initially placed in the intact or lesioned hemisphere or in the ventricles. Grafted cells were found to adopt striatal phenotypes (positive for somatostatin, parvalbumin, calretinin, and choline acetyltransferase), but work is ongoing to quantify cell types in regions of interest (M. Modo, MSc, unpublished data, 2000) and to look for relationships with behavior.

Functional recovery after implantation distal to stroke damage found in this study provides some pointers to the possible mechanisms involved. Two possibilities are (1) that grafted cells migrated to the area of damage and reconstituted local circuits that were sufficient to sustain some functions and (2) that grafts augmented spontaneous reorganization on the intact side sufficient to undertake, or compensate for, some lost contralateral functions. Evidence from imaging studies suggests that both possibilities are reasonable. The contralateral hemisphere undergoes substantial plastic changes after stroke, suggesting the “unmasking” of ipsilateral corticospinal projections. Thus, Cramer et al found both enhanced activation in the intact side of the brain and foci of activation on the rim of the infarct in response to finger tapping in patients recovered from hemiparesis, while Dettmers et al found bilateral representation of movement in cortical motor association areas of stroke patients. The present results indicate that the majority of grafted cells dispersed within the side of implantation, and therefore a major contribution to recovery may have occurred through reinforcement of normally suppressed host ipsilateral corticospinal pathways. We subsequently showed that cells migrate to the opposite side whether placed ipsilaterally or contralaterally to stroke damage. Unexpectedly, apolipoprotein E (apoE) was upregulated in the intact striatum of rats with both ipsilateral and contralateral grafts, but not in sham-grafted controls, where it was confined to the lesion.
Conclusions

The results suggest that MHP36 grafts contralateral to site of stroke damage exert positive functional effects and reduce lesion volume. These findings provoke an investigation of novel graft mechanisms, which will increase our knowledge of how grafts may be used to harness and augment brain plasticity in response to stroke damage. Stem cell grafts may serve to augment constitutive and inducible mechanisms of plasticity rather than to “fill the hole.” These results may increase the flexibility of transplant surgery, so that grafts may be placed at a distance from stroke damage in brain regions that are more favorable to their survival and integration.

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References

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