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Permalink

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Journal

Stroke, 46(6)

ISSN

0039-2499

Authors

Barbay, Scott
Plautz, Erik J
Zoubina, Elena
et al.

Publication Date

2015-06-01

DOI

10.1161/strokeaha.114.008088

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Effects of Postinfarct Myelin-Associated Glycoprotein Antibody Treatment on Motor Recovery and Motor Map Plasticity in Squirrel Monkeys

Scott Barbay, PhD; Erik J. Plautz, PhD; Elena Zoubina, PhD; Shawn B. Frost, PhD; Steven C. Cramer, MD; Randolph J. Nudo, PhD

Background and Purpose—New insights into the brain's ability to reorganize after injury are beginning to suggest novel restorative therapy targets. Potential therapies include pharmacological agents designed to promote axonal growth. The purpose of this study was to test the efficacy of one such drug, GSK249320, a monoclonal antibody that blocks the axon outgrowth inhibition molecule, myelin-associated glycoprotein, to facilitate recovery of motor skills in a nonhuman primate model of ischemic cortical damage.

Methods—Using a between-groups repeated-measures design, squirrel monkeys were randomized to 1 of 2 groups: an experimental group received intravenous GSK249320 beginning 24 hours after an ischemic infarct in motor cortex with repeated dosages given at 1-week intervals for 6 weeks and a control group received only the vehicle at matched time periods. The primary end point was a motor performance index based on a distal forelimb reach-and-retrieval task. Neurophysiological mapping techniques were used to determine changes in spared motor representations.

Results—All monkeys recovered to baseline motor performance levels by postinfarct day 16. Functional recovery in the experimental group was significantly facilitated on the primary end point, albeit using slower movements. At 7 weeks post infarct, motor maps in the spared ventral premotor cortex in the experimental group decreased in area compared with the control group.

Conclusions—GSK249320, initiated 24 hours after a focal cortical ischemic infarct, facilitated functional recovery. Together with the neurophysiological data, these results suggest that GSK249320 has a substantial biological effect on spared cortical tissue. However, its mechanisms of action may be widespread and not strictly limited to peri-infarct cortex and nearby premotor areas. **(*Stroke*. 2015;46:1620-1625. DOI: 10.1161/STROKEAHA.114.008088.)**

Key Words: FAM168B protein, human ■ haplorhini ■ neuronal plasticity ■ neurophysiology ■ recovery of function ■ stroke

Pharmacological treatments to improve functional outcomes after stroke remain limited beyond the use of thrombolytic agents during the first few hours. As our understanding of regenerative mechanisms that underlie the recovery of function matures, it is expected that approaches to target long-term recovery will receive increasing attention.[1] This study focuses on GSK249320, a monoclonal antibody that blocks the axon outgrowth inhibition molecule, myelin-associated glycoprotein (MAG). Brain levels of MAG spontaneously increase after a stroke.[2] The putative mechanism of action for this MAG antibody is the disinhibition of neurite sprouting and growth, thus allowing new neuronal connections to be formed.[3]

Many neurophysiological and neuroanatomical events related to behavioral recovery have been described in the days to weeks after a stroke. After focal ischemic infarct in primary motor cortex (M1) in both rodents and nonhuman primates, motor representations in spared cortical areas undergo functional reorganization in parallel with motor recovery.[4,5] Furthermore, growth-promoting and growth-inhibiting genes are upregulated in spared neural tissue both adjacent to the infarct and in more remote areas connected with infarct.[2,6,7] Finally, axonal sprouting and the formation of new cortico-cortical connections occur after focal cortical infarcts.[8,9] Thus, it is reasonable to presume that pharmacological agents that

Received November 22, 2014; final revision received February 23, 2015; accepted March 16, 2015.

From the Department of Molecular and Integrative Physiology, Landon Center on Aging, University of Kansas Medical Center (S.B., E.J.P., E.Z., S.B.F., R.J.N.); and Department of Neurology and Department of Anatomy and Neurobiology, University of California, Irvine (S.C.C.).

Current address for E.J.P.: Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas.

Current address for E.Z.: Department of Neurology, Harvard Medical School, Boston, MA.

Guest Editor for this article was Miguel Perez-Pinzon, PhD.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.008088/-/DC1.

Correspondence to Randolph J. Nudo, PhD, University of Kansas Medical Center, Landon Center on Aging, MS 1005, 3901 Rainbow Blvd, Kansas City, KS 66160. E-mail rnudo@kumc.edu

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promote neurite sprouting and growth might amplify these events and thereby increase the extent of behavioral recovery during this period.

Previous studies in rodents have demonstrated that a MAG antibody can neutralize MAG-mediated inhibition and promote neurite outgrowth associated with improved behavioral recovery after injury to the cerebral cortex.[3,10] A study in 47 healthy human subjects found GSK249320 to be well tolerated in doses ≤25 mg/kg body weight.[11] A recent clinical trial enrolled 42 patients 24 to 72 hours after stroke onset and found GSK249320 to be safe.[12] The primary goal of this study was to evaluate the efficacy of GSK249320 for enhancing recovery of skilled use of the forelimb in a nonhuman primate model of focal cortical ischemia and to determine whether its effects are evident in the organization of movement representations in spared cortical areas.

Methods

Nine adult male squirrel monkeys were used in this study. All experiments were conducted in accordance with institutional and federal guidelines for care and use of experimental animals and with approval from the Institutional Animal Care and Use Committee. A procedural timeline is presented in Figure 1. Monkeys were assigned randomly to 1 of 2 groups, differing only with regard to whether they received postinfarct injections of GSK249320 (experimental group) or vehicle (control group). One investigator was wholly responsible for animal behavioral training and postinfarct testing and was blind to the treatment condition. Each monkey underwent preinfarct training on a pellet retrieval task for 10 days, and then probe trials were conducted once per week for 2 weeks.[13] Next, monkeys underwent the first of 2 surgical procedures. In the first procedure, the distal forelimb (DFL) representations in primary motor cortex (M1), dorsal premotor cortex (PMd), and ventral premotor cortex (PMv), as well as the surrounding proximal representations, were identified by intracortical microstimulation mapping techniques. Then, a cortical infarct that targeted 80% of the M1 DFL was created by electrocoagulation of surface vasculature (Figure 2). After recovery from anesthesia, monkeys were returned to their home cages.

The active drug, identified as GSK249320 and supplied by GSK, United Kingdom, is an antibody to MAG. It binds with human MAG or its monkey ortholog with similar affinity (data on file). GSK249320 (30 mg/kg per dose; experimental group) or vehicle (control group) was administered intravenously every 7 days for 7 weeks, beginning 24 hours after infarct. Postinfarct behavioral performance on the retrieval task was assessed weekly on days after the injections. Then, in a second surgical procedure, intracortical microstimulation mapping was repeated to verify the extent of the infarct and to determine whether motor representations were altered. After a 2-week survival period, animals were humanely euthanized and the brains were removed for histological analysis.

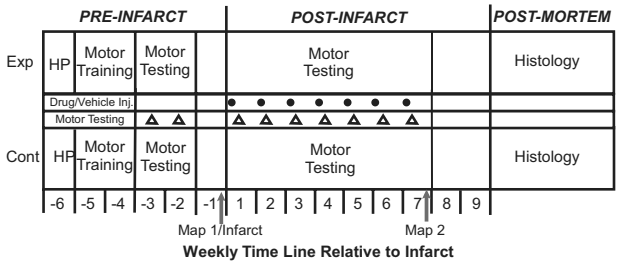

Figure 1. Timeline of experimental procedures. In the figure and throughout the text, experimental (Exp) time periods are referenced to the number of days or weeks relative to the infarct; that is, week -6=6 weeks before infarct. Baseline behavioral performance was defined by 2 motor testing sessions during weeks -3 and -2. After an intracortical microstimulation mapping procedure and infarct (time, 0), each monkey received 7 weekly injections of GSK249320 or vehicle beginning 24 hours post infarct. Behavioral testing occurred weekly beginning on day 3; filled circle: drug or vehicle injection and open triangles: behavioral testing session. Cont indicates control; and HP, hand preference testing.

The primary end point was a function of the number of finger flexions required to retrieve a pellet (flexions per retrieval performance index) measured during probe sessions. Secondary end points included retrieval success rate, time required to perform different phases of the retrieval task, and frequency of aiming errors, again measured during the probe sessions. Statistical tests included repeated-measures ANOVA and Bonferroni post hoc comparisons maintaining α-level at 0.05. Group averages are reported as mean+SEM. Additional details can be found in the online-only Data Supplement.

Results

Infarct Size and Location

The mean extent of the infarct across the cortical surface was 12.03±1.04 mm2 in the experimental group and 10.97±1.07 mm^2 in the control group. There was no statistically significant difference between groups in the absolute lesion size: $t_{(5)}$=0.69; P=0.52 (Figure 3). The M1 DFL damage relative to each monkey's baseline DFL was 81.5±1.61% for the experimental group and 79.1+0.98% for the control group, closely in line with our 80% target (Figure 2). There was no statistically significant difference between groups in the relative lesion size: $t_{(5)}$=1.136; P=0.31. As intended, all infarcts spared DFLs at the rostral edge of the M1 DFL, as well as a small portion located medial and lateral to the infarct region. No damage was evident in PMd or PMv.

Behavioral Assessment of Skilled Hand Use

There was a significant effect of group (F[1,5]=12.732; P=0.001), time (F[8,40]=15.696; P<0.0001), and group X time interaction (F[8,40]=5.899; P<0.0001) in the primary end point, flexions per retrieval performance index. Bonferroni multiple comparison tests revealed significant group differences on days 3 (t[1,40]=6.95; P=0.009) and 9 (t[1,40]=3.86; P=0.018). That is, performance was better in the experimental group on day 3 (experimental group=1.55+0.22; control group=3.44+0.73) and day 9 (experimental group=1.01+0.06; control group=1.92+0.60). On day 3, there was no overlap between the groups. There were no differences between groups before the infarct or on day 16 through 44 (Figure 4A).

With respect to secondary end points, there was a significant effect of group (F[1,5]=8.48; P=0.01), time (F[3,15]=5.54; P=0.0092), and group X time interaction (F[3,15]=6.537; P=0.0048) for time in well. Bonferroni multiple comparison test revealed that the experimental group required significantly more time (3.17±0.71) than the control group (0.93±0.22) on day 3 only (t[1,15]=5.70; P<0.0004; Figure 4B). Assessing reach and retrieval times separately, there was a significant effect of time for both reach (F[3,15]=8.217; P=0.0018) and retrieval (F[3,15]=12.904; P=0.0002) but there was no effect of group nor group X time interaction. Bonferroni comparisons indicate that time to reach was significantly greater on day 3 than on preinfarct day 1 (t[1,15]=4.39; P=0.003) and day 2 (t[1,15]=4.03; P=0.0066), as well as day 9 (t[1,15]=3.57; P=0.0168). Retraction time was greater on days 3

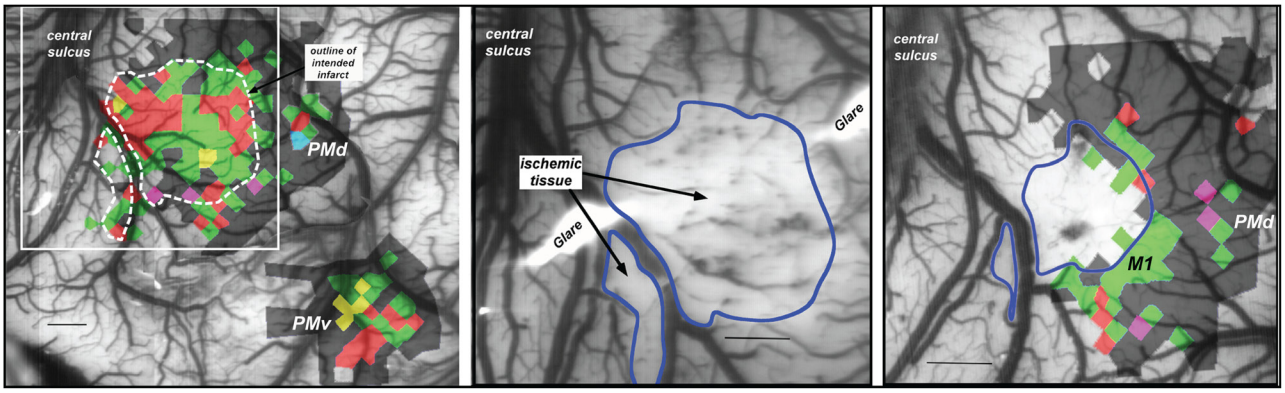

Figure 2. Sequence of photographs of surface vasculature in frontal cortex before (**left**), immediately after (**middle**), and 7 weeks after (**right**) an ischemic infarct in M1 distal forelimb (DFL; case control [Cont]-1). **Left**, Vascular pattern with superimposed movement representations in M1, dorsal premotor cortex (PMd), and ventral premotor cortex (PMv). M1 DFL (≈80%) was targeted for the infarct based on intracortical microstimulation (ICMS) maps of evoked movements (movement coding: red=digit; green=wrist/forearm; purple=proximal+wrist/forearm; yellow=digit+wrist; and grey=proximal). Dashed white line indicates intended infarct territory. In the case illustrated here, a large vein that bisected the DFL was intentionally spared but not its branches. White box encloses the enlarged region shown in middle and right images. **Middle**, Ischemic region in M1 DFL several minutes after the infarct was completed. The ischemic area is readily distinguishable because of blanching of the tissue. Visual glare is because of the presence of saline on the brain surface during the procedure. This infarct technique produces sharply defined borders between ischemic and normally perfused tissue (indicated by blue boundary) and creates an infarct through all 6 layers of cerebral cortex but spares the underlying white matter. **Right**, Photograph of ischemic region 7 weeks after the infarct in M1 DFL. As intended, the perimeter of the M1 DFL, as well as PMd and PMv (not shown), was spared by the infarct, as evidenced by ICMS-evoked movements. Scale bar, 500 μm.

and 9 compared with preinfarct days 1 and 2. Other significant differences included day 3 versus preinfarct day 1 (t[1,15]=4.69; P=0.0018) and preinfarct day 2 (t[1,15]=5.16; P=0.0006); day 9 versus preinfarct day 1 (t[1,15]=3.42; P=0.0228) and preinfarct day 2 (t[1,15]=3.90; P=0.0084). Days 3 and 9 were not significantly different: (t[1,15]=1.27; P>0.9999).

There was also a significant effect of time for aiming errors (F[3,15]=12.904; P=0.0028). Bonferroni comparisons indicated that the average aiming errors for all monkeys were greater than preinfarct measures on days 3 and 9. There was no significant effect of group nor group X time interaction in aiming errors: day 3 versus preinfarct day 1 (t[1,15]=3.0; P=0.054) and preinfarct day 2 (t[1,15]=3.60; P=0.0156). Day 9 versus preinfarct day 1 (t[1,15]=3.60; P=0.0156) and preinfarct day 2 (t[1,15]=3.626; P=0.0150). Days 3 and 9 were not significantly different: (t[1,15]=0.022; P>0.9999).

Postinfarct Changes in Spared Motor Representations

Forelimb movements typically were evoked throughout the peri-infarct M1, PMd DFL, and PMv DFL at low current levels (Figure 2). In addition, forelimb movements could be evoked from sites along the border of the infarcted territory. However, because these sites were typically no >250 μm from the border and current thresholds were relatively high (often 25–30 μA), these sites were eliminated from the analyses because the evoked movements were likely due to current spread into the spared tissue. In 3 of the intracortical microstimulation mapping procedures, proximal but not DFL movements were evoked in PMd (baseline maps: Exp-3, Cont-3; postinfarct maps: Cont-3). This lack of distal movements at threshold current levels is not unusual in PMd of squirrel monkeys, and thus, these data were retained for the statistical analyses. DFL movements were observed at threshold currents in each of the PMv mapping procedures.

Area means (±SEM) for the DFLs before and after the infarct are presented in Table. In the peri-infarct M1 DFL, there were no statistically significant differences between groups (group effect: F(1,5=0.0068, P=0.9374; time effect: F(1,5)=2.0365, P=0.2129; group X time interaction: F(1,5)=0.21374, P=0.6633). In the PMd DFL, there were no statistically significant differences between groups (group effect: F[1,5]=2.7294, P=0.1594; time effect: F[1,5]=3.0600, P=0.1407; group X time interaction: F[1,5]=1.0144, P=0.3601). It should be noted though that PMd DFL increased in each of the 4 monkeys in the experimental group but in only one of the 3 monkeys in the control group (χ^2=9.561; P=0.002). In PMv, there was no group (F[1,5]=0.5553; P=0.4897) nor time effect (F[1,5]=0.1821; P=0.6873), but there was a significant group X time interaction (F[1,5]=11.0953; P=0.0208). Bonferroni multiple comparison tests revealed a decrease in PMv DFL in the experimental group after the infarct (experimental pre- versus experimental postinfarct area), but this difference was not significant [t(1,5)=2.87; P=0.07]. There was also no significant difference between the pre- and post control group maps (t[1,5]=1.92; P=0.112; Figure 5).

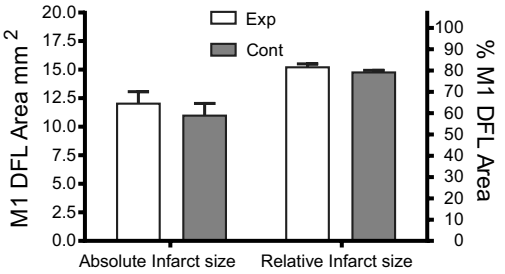

Figure 3. Lesion size in experimental (Exp) and control (Cont) groups. There were no statistical differences in either absolute or relative lesion size between groups. DFL indicates distal forelimb.

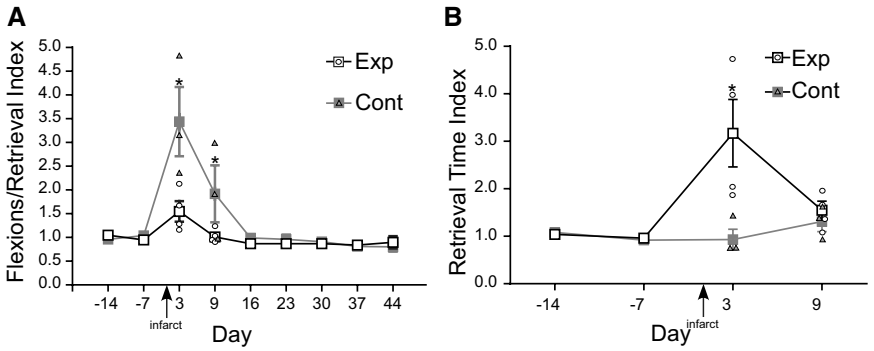

Figure 4. Motor performance. **A**, Flexions per retrieval performance index. The control (Cont) group was significantly more impaired than the experimental (Exp) group on days 3 and 9. **B**, Retrieval time index. The Exp group took more time to retrieve food pellets from the Klüver board on postinfarct day 3 than the Cont group. The infarct had no significant effect on flexion time for a successful retrieval for the Cont group. *Indicates significant difference between groups (post hoc test, $P<0.05$). Small circles (Exp) and triangles (Cont) correspond to individual case data. Individual data are shown only for days 3 and 9 as the variance was small on the other days, and small circles would overlap. Error bars, mean±SEM.

Because of the significant interaction effect in PMv and the potential for differential effects between PMv and PMd in experimental versus control groups, we also examined PMv–PMd difference scores. A 2-way ANOVA revealed a significant group X time interaction ($F[1,5]=8.75$; $P=0.0308$). Bonferroni adjusted multiple comparisons showed that for the experimental group, the baseline PMv–PMd difference scores were greater than the postinfarct difference scores ($t[1,5]=3.678$; $P=0.0286$). There was no prepost difference in PMv–PMd difference scores for the control group ($t[1,5]=0.7557$; $P=0.9678$).

Discussion

Loss of function after stroke is due not only to the local ischemic damage, but also to a large extent, a disconnection of functional neural networks throughout the brain. Therefore, investigations into various therapeutic strategies to improve motor function after stroke have targeted interventions thought to promote neural reorganization, restoring functional connectivity within the spared motor networks. Many recent restorative therapies have targeted myelin-associated axon outgrowth inhibition molecules, inhibitors that promote a nonpermissive growth environment after stroke, reducing neurite outgrowth,[14,15] thus constraining neural plasticity and limiting recovery.[16] One current putative intervention strategy is to neutralize such inhibition, thereby promoting axonal growth and sprouting to restore movement-related communication in cortical networks. Of the various myelin-associated inhibitors, MAG is of interest as it has been shown to be upregulated in peri-infarct tissue after ischemic damage in the aged brain.[2] This study examined the efficacy of a new monoclonal antibody, GSK 249320, to MAG (ie, MAG antibody) in squirrel monkeys for recovery after an ischemic infarct in M1. A pilot experiment conducted before this study demonstrated that after cortical infarcts in M1 of squirrel monkeys, MAG antibody was present within the infarcted tissue within hours after a single administration (Figure I in the online-only Data Supplement).

With an infarct targeting of 80% of the M1 DFL, the deficit was transient in both groups. However, GSK249320, initiated intravenously 24 hours after the infarct, facilitated more rapid recovery of DFL motor function, including the primary end point, flexions per retrieval performance index. The experimental group demonstrated superior motor performance on the reach-and-retrieval task on day 3 (2 days after initial treatment) and day 9 (1 day after second treatment). In fact, the deficit was unusually mild in the experimental group even on day 3. This rapid recovery in motor skill is somewhat surprising given the putative effects of MAG antibody on axonal growth promotion. However, evidence from other studies suggests that, in addition to blocking MAG-mediated inhibition of neurite outgrowth, treatment with MAG antibody protects oligodendrocytes from oxidative-stress induced cell death.[3] Because oligodendrocytes play a critical role in axonal integrity and are particularly sensitive to ischemic injury,[17,18] it is possible that treatment with GSK249320 in this study exerted its therapeutic benefits through protection of oligodendrocytes in the vicinity of the infarct. There is also evidence suggesting that MAG antibody may enhance synaptic plasticity. In the mature central nervous system, MAG receptors, such as NgR1 (part of the Nogo receptor family), maintain synaptic stability by inhibiting dendritic changes in morphology and function, such as long-term potentiation.[19,20] Blocking these pre- and postsynaptic inhibitory receptors could account for an immediate activity-dependent modulation of synaptic connections supporting a rapid increase in functional recovery.

Comparing neurophysiological map changes revealed unexpected findings. Given that MAG is known to be upregulated in peri-infarct cortex,[2] it might be expected that GSK249320 would have its greatest effect in the 20% of the

Table. Size of Movement Representations Before and After Infarct (mm²)

	Peri-Infarct M1	Peri-Infarct M1	PMv	PMv	PMd	PMd
Group	Preinfarct	Postinfarct	Preinfarct	Postinfarct	Preinfarct	Postinfarct
Exp	2.65±0.25	3.00±0.41	3.49±0.68	2.75±0.44	0.59±0.28	1.38±0.43
Cont	2.75±0.28	2.93±0.39	2.98±0.67	3.55±0.25	0.41±0.31	0.62±0.33

Cont indicates control; Exp, experiment; PMd, dorsal premotor cortex; and PMv, ventral premotor cortex.

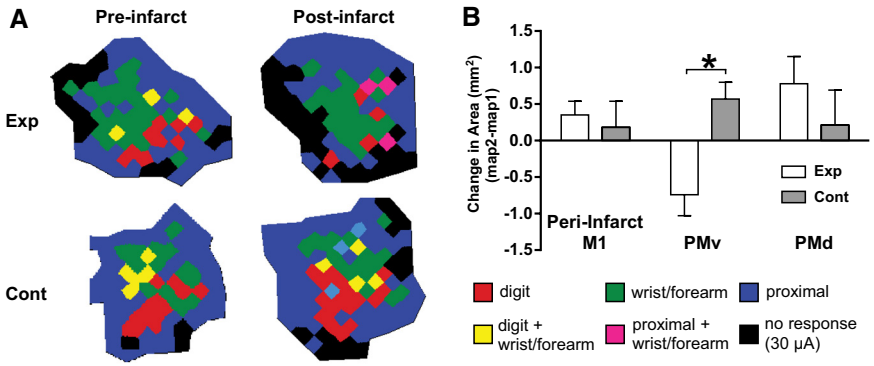

Figure 5. Changes in size of distal forelimb representations. **A**, Ventral premotor cortex (PMv) distal forelimb (DFL) motor maps before and 7 weeks after infarct in representative experimental (Exp) and control (Cont) cases. Movement coding: red=digit, green=wrist/forearm, purple=proximal+wrist/forearm, yellow=digit+wrist; blue=proximal; and black=no response at 30 µA). **B**, Comparison of peri-infarct, PMv, and dorsal premotor cortex (PMd) DFL representations before and 7 weeks after infarct. Bar graphs portray difference scores between postinfarct and preinfarct maps. Means for each time point are shown in the Table. There was a differential effect of treatment on map area in PMv (*P<0.05). Error bars, mean±SEM.

M1 DFL spared by the infarct. However, although the peri-infarct M1 DFL increased slightly in both experimental and control groups (0.35 mm^2 in Exp; 0.18 mm^2 in Cont), there was no significant difference between groups (P=0.93). Thus, if the behavioral benefit seen with GSK249320 is based on expansion of DFL representation in peri-infarct cortex, then it is likely to be due to some other neuroanatomical or neurophysiological change. Similarly, PMd DFL maps did not change significantly, although a larger sample size may yet reveal a group effect since in the present sample, P=0.16, with larger PMd DFL maps in the experimental group (Figure 5).

On the basis of our previous studies demonstrating an increase in PMv DFL after M1 infarct in squirrel monkeys not subjected to postinfarct intervention,[5,8] we expected to see postinfarct expansions in both groups but larger increases in the experimental group. We have also shown in a recent study that spared premotor representations expand as a function of rehabilitative training in a rat model of ischemic infarct.[4] As expected, in this study, PMv DFL increased in size in each of the 3 control monkeys but decreased in size in each of the 4 experimental monkeys. On the basis of our historical data,[5,8] the expected increase in PMv DFL in animals with an 80% infarct in the M1 DFL, but no rehabilitative training, is 33.4% at 3 months post infarct. In this study, the increase in PMv DFL representation in the control group was 17.5% at 7 weeks post infarct. Furthermore, we have shown in other studies that after M1 lesions, spared motor maps first decrease and then increase in size with increasing time after infarct.[4,21] Given the longer survival times in the historical controls, the size of the increase in PMv DFL in control monkeys in this study is within the expected range. However, in the experimental group, PMv maps decreased by 19.2%. We have only observed decreases in PMv DFL when infarcts were <50% of the M1 DFL[8] or were derived at much earlier time points after the infarct (<3 weeks).[4,22] Because there is no evidence that GSK249320 affected lesion size, this result suggests that the drug treatment may have had an unusual effect on cortical motor networks to support recovery of DFL performance compared with what is typically observed during spontaneous recovery alone.

One possible explanation for the discrepant map results in PMv is that monkeys in the experimental group used a particularly successful compensatory reaching strategy. Although movement kinematics were not explicitly examined in this study, some support for a successful compensatory strategy in the experimental group can be derived from examination of the secondary behavioral end point, time in well. Although monkeys in the experimental group demonstrated superior scores on the flexions per retrieval performance index, they also spent more time with their digit(s) in the food well to perform retrievals on day 3. It is possible that slower and more deliberate movements were part of a compensatory strategy that facilitated improvement. Furthermore, if monkeys in the experimental group differentially used proximal arm and shoulder muscles for reaching or stabilization, recovery may have been accompanied by an expansion of proximal forelimb representations at the expense of distal representations in PMv. Consistent with this hypothesis, examination of Figure 5 reveals that at many specific sites, intracortical microstimulation resulted in distal movements in the preinfarct map but proximal movements in the postinfarct map. This observation is most evident in the experimental group. Previous studies from this laboratory using a similar infarct model have shown that a variety of compensatory strategies are used soon after the infarct. The kinematic patterns that are eventually used after recovery often are different than those used before the infarct.[23] Alternatively, compensatory strategies could involve attentional or motivational mechanisms related to a more focused effort leading to more successful retrievals.

In a virtual lesion study in healthy humans using transcranial magnetic stimulation, Davare et al[24] provided evidence for a functional dissociation between PMd and PMv. Their results supported the view that PMv is involved more in the grasping component of a grip-lift task, whereas PMd is involved more in the lifting phase, recruiting more proximal muscles. If the trend toward larger distal representations in PMd and smaller distal representations in PMv with GSK249320 treatment is borne out in larger samples, then it is reasonable to suggest that the differential functional specialization of premotor areas in precision grasping is altered by postinfarct GSK249320. We propose that reorganization of spared cortical networks results in a functional rebalancing of premotor cortical areas, so that

PMd assumes a greater role in the grasp phase and PMv in the lift-retrieval phase of the task.

In the context of the previous literature, the present results narrow the range of possibilities for the mechanisms underlying the functional benefits of GSK249320. Plasticity in peri-infarct M1 DFL is an unlikely candidate, unless a different neurophysiological or neuroanatomical end point is needed to capture the effect of GSK249320. It is likely that compensatory kinematic or attentional strategies, supported by plasticity in premotor cortical areas, contributed to faster recovery in the experimental group. The best case can be made for plasticity in PMv, although PMd is still a potential site. In the future, larger studies should (1) expand on the present results to examine other premotor areas (PMd and the supplementary motor area) and (2) focus on kinematic end points. It would also be interesting to know whether GSK249320 given to normal monkeys would affect the motor map representations in PMv and PMd similarly to what we have shown in the experimental group. As plasticity after neural injury is likely to be a network response, it is also possible that subcortical or contralateral structures are involved. However, it is clear that GSK249320 is safe in a nonhuman primate model of focal cortical ischemia, accelerates functional recovery, and has a significant effect on the neurophysiology of spared motor representations.

Acknowledgments

We thank Robert Cross, Ann Stowe, and Numa Dancause for technical assistance in the study.

Sources of Funding

This study was funded by GlaxoSmithKline.

Disclosures

Dr Nudo has served as a consultant for Gerson Lehrman Group, MicroTransponder, and St. Jude Medical. Dr Cramer has served as a consultant for GlaxoSmithKline, Dart Neuroscience, and MicroTransponder, and is a cofounder of personalRN. The other authors report no conflicts.

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