Mechanisms of Motor Dysfunction After Transient MCA Occlusion
Persistent Transmission Failure in Cortical Synapses Is a Major Determinant

Hayrunnisa Bolay, MD; Turgay Dalkara, MD, PhD

Background and Purpose—Failure of prompt motor recovery after spontaneous recirculation or thrombolytic therapy may be due to an unsatisfactory restoration of synaptic activity within cortex and/or blockade of electrical impulses at the severely ischemic subcortical region.

Methods—Afferent, efferent, and synaptic activities were focally examined within the rat sensorimotor cortex by recording the somatosensory-evoked potential (SEP) and motor area response evoked by stimulation of premotor afferents (PmEP) intracortically and the motor-evoked potential (MEP) generated by stimulation of the forelimb area from the brain stem. The effect of ischemia on electrical activity in the cortex and on axonal conduction in the subcortical region was studied differentially by proximal or distal occlusion of the MCA.

Results—MEP consisted of direct and indirect waves generated by direct activation of pyramidal axons and indirect excitation of pyramidal neurons via cortical synapses, respectively. MEP, PmEP, and SEP disappeared on proximal occlusion. Following reperfusion after 1 to 3 hours of ischemia, the direct wave of MEP readily recovered but the indirect wave showed no improvement, suggesting a restored axonal conduction but impaired cortical synaptic transmission. The synaptic defect, which also caused a poor recovery in PmEP and SEP and on electrocorticogram, was persistent and detected 24 hours after 1 hour of proximal occlusion.

Conclusions—Our data suggest that motor dysfunction is caused by loss of cortical excitability and blockade of motor action potentials at the subcortical level during ischemia. After brief transient ischemia, axonal conduction readily recovers; however, a persistent transmission failure at cortical synapses leads to motor dysfunction. (Stroke. 1998;29:1988-1994.)

Key Words: cerebral ischemia, focal penumbra, ischemic motor cortex evoked potentials transmission, synaptic

Loss of motor power is one of the most devastating outcomes of stroke due to middle cerebral artery (MCA) occlusion. Because most of the motor cortex and pyramidal tract lie within the MCA territory, motor dysfunction intuitively has been considered a natural outcome of MCA ischemia.1,2 This view is valid when the MCA is permanently occluded and the pyramidal fibers and motor cortex inevitably become infarcted. However, mechanisms of motor dysfunction are likely to be more complex in transient MCA occlusion because some parts of the motor cortex are located in the penumbra region, but the pyramidal tract descends through the ischemic core.3-5 In other words, ischemia-sensitive synapses and neuronal bodies located in the motor cortex are exposed to a relatively mild ischemia, whereas pyramidal axons, known to be more resistant to ischemia, encounter a profound ischemia.6-9 Therefore, depending on the duration of ischemia before recirculation, motor dysfunction may arise from loss of cortical excitability and/or blockade of electrical impulses at the subcortical level. These mechanisms may account for failure of motor recovery after spontaneous recirculation of MCA occlusion or thrombolytic therapy. However, there is a paucity of information about the mechanisms of motor dysfunction in transient MCA occlusion, despite an increasing use of thrombolytic therapy.2,10

To elucidate these mechanisms, we have developed a model in which afferent and efferent activity and synaptic transmission were focally examined within the forelimb area of motor cortex along with regional cerebral blood flow (rCBF) in rats subjected to proximal or distal MCA occlusion. Because proximal occlusion causes cortical and subcortical ischemia and the distal occlusion leads to only cortical ischemia, we were able to study differentially the

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The effects of ischemia on electrical activity in the cortex and axonal conduction in the subcortical region. Our data indicate that both cortical and subcortical mechanisms are responsible for motor dysfunction during ischemia. After 1 to 3 hours of ischemia, reperfusion readily restores axonal conduction, but persistent damage to synaptic transmission in the cortex hampers recovery of motor function. The sensitivity of synaptic transmission to ischemia was recognized long ago and was proposed to be one of the factors responsible for motor dysfunction during ischemia. After 1 to 3 hours of ischemia, reperfusion following even a short ischemic period.

Materials and Methods

Experimental Groups

Wistar rats weighing 180 to 210 g were housed under diurnal lighting conditions (12-hour dark/light cycle) and fasted overnight but allowed free access to water before the experiment. Animal housing and care and application of experimental procedures were done in accordance with institutional guidelines. Rats were anesthetized with urethane (1.2 mg/kg IP) and maintained unresponsive to tail pinch by supplements of one fifth of the initial dose. Chloral hydrate (375 mg/kg IP with atropine 0.01 mg/kg IM) was used during induction of anesthesia in all groups. Body temperature was monitored by a rectal probe and maintained at 36.5°C to 37.5°C by a homeothermic blanket control unit (Harvard Apparatus). The left femoral artery was cannulated for continuous arterial blood pressure monitoring to obtain blood samples to determine pH, PCO₂, Po₂, hematocrit, and plasma glucose and for heparinization to achieve a suitable blood flow velocity. Rats were tracheotomized, intubated, and allowed to spontaneously breathe room air mixed with supplemental oxygen. Chloral hydrate (375 mg/kg IP with atropine 0.01 mg/kg IM) was used during induction of anesthesia in all groups. The left femoral artery was cannulated for continuous arterial blood pressure monitoring to obtain blood samples to determine pH, PCO₂, Po₂, hematocrit, and plasma glucose and for heparinization to achieve a suitable blood flow velocity. Rats were tracheotomized, intubated, and allowed to spontaneously breathe room air mixed with supplemental oxygen.

Thirty-six rats were subjected to 1, 2, or 3 hours of distal or proximal MCA occlusion followed by 3 or 24 hours of reperfusion; permanent ischemia in a group of rats that were kept alive after reperfusion. However, to our knowledge, this is the first study demonstrating a persistent defect in synaptic transmission after reperfusion following even a short ischemic period.

Electrophysiological Recordings

A concentric, bipolar, tungsten electrode was inserted into the forelimb area in the right sensorimotor cortex (2.5 to 3 mm lateral and 0.5 to 1.5 mm anterior to bregma). Motor and sensory cortices overlap in the rat, which provided an opportunity to stimulate the motor neurons of the forelimb area and to record its electrical activity in the cortex and subcortical region. After a midline incision was made, the right common carotid artery (CCA) and external carotid artery (ECA) were ligated with a 5-0 silk suture. A 4-0 nylon filament was inserted into the CCA through a small incision 1 to 2 mm proximal to the bifurcation and advanced in the internal carotid artery (ICA) as far as it passed through the carotid canal. The filament was prepared by blunting the tip near a flame, and its distal 5 mm was coated with cyanoacrylate glue. Also, a 0 silk suture was loosely tied around the contralateral CCA.

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Each animal was then placed in a stereotaxic frame, and a craniotomy was made over the right sensorimotor cortex (1 to 4 mm lateral and 0.5 to 3 mm anterior to bregma). An electrode was implanted for electrophysiological recordings (2.5 to 3 mm lateral and 0.5 to 1.5 mm anterior to bregma, depending on localization of the pial vessels), and next to it a needle probe (PF-302 of Periflux PF 2B, Perimed) was placed over the dura, away from large pial vessels, to monitor 

if rCBF values recorded over the sensorimotor cortex were >35% of the control levels after MCA occlusion, the contralateral CCA was additionally occluded by snare ligature. 

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motor cortex was stimulated with square pulses (0.2 ms, 1 mA) at 10 Hz to generate MEP. Stimulation at 10 Hz with trains of 10 to 25 pulses (1 ms, 1 mA) evoked visible forelimb movement. The latter stimulation pattern was used only to verify the electrode position at the beginning of the experiment and to check the paw movement during ischemia and reperfusion. In 14 experiments, another concentric bipolar electrode was inserted into the medial agranular field rostromedial to the one in sensorimotor cortex (1.5 to 2.5 mm anterior and 1 to 2 mm lateral to bregma). The potential evoked by stimulating this area, which is considered the rat equivalent of the premotor cortex,20–22 with square pulses (0.05 ms, 1 mA, 10 Hz) was recorded by the electrode in the sensorimotor cortex (PmEP). The left median nerve was stimulated by 2 needle electrodes at 10 Hz with square pulses (0.2 ms, 10 mA) to evoke SEP.

Signals were amplified and filtered (band width, 1 to 100 Hz for ECoG and 10 to 3000 Hz for evoked potentials) by an AC/DC amplifier (DP-304, Warner Instruments Corp). Amplified signals were digitized, displayed, and stored in a computer by a data acquisition and analysis system (MacLab/8s, ADInstruments). A 100-Hz sampling rate was used for acquisition of the ECoG signal and a 20-kHz rate for evoked potentials.

ECoG, rCBF, and arterial blood pressure were continuously recorded except during evoked potential recordings, which were conducted to the brain stem via the ipsilateral pyramidal tract. The configuration of SEP (Figure 1), which was bipolarly recorded by an intracortical electrode, was different than SEP recordings was the field potential generated by excitation of muscles in the upper limb during median nerve stimulation and thus was resistant to MCA occlusion. The MEP consisted of a D wave and I waves generated by direct and synaptic activation of upper motor neurons, respectively. The D wave completely recovered within minutes on reperfusion after 3 hours of ischemia; however, synaptic activity (I wave) was still not restored 3 hours after reperfusion. The ECoG and SEP were partially recovered 3 hours after reperfusion. Negativity is downward in all recordings.

In line with the latter findings, the D wave never reappeared in rats subjected to 24 hours of permanent MCA occlusion (Table). Contrary to the D wave, I waves did not recover during reperfusion in all groups except a few rats in which a wave with a similar latency but opposite polarity to preschismic I waves appeared.

**Changes in SEP**

The configuration of SEP (Figure 1), which was bipolarly recorded by an intracortical electrode, was different than typical SEP recorded from the rat brain by epidural or subcutaneous electrodes.18,26,27 The first positive component of SEP (peak latency, 2.84±0.05 ms) was possibly generated by volume conduction of the electrical field caused by excitation of muscles in the upper limb during median nerve stimulation because it persisted after severing the spinal cord at the cervicomедullary junction and was resistant to MCA occlusion. This component was followed by a negative wave lasting approximately 25 ms (peak latency 13.94±0.48 ms, peak amplitude, 10±1 μV), (Figure 1). The SEP was sensitive to ischemia and readily disappeared on distal and proximal MCA occlusion. Recovery of the SEP was slow and incomplete during reperfusion (Figure 1), and after 3 hours of reperfusion, the peak amplitude of the negative wave reached to 52±8%, 56±11%, and 56±16% of preschismic amplitude in 1-hour distal and 1- and 3-hour proximal occlusion groups, respectively (Table and Figure 2). The amplitude of SEP was recorded by a concentric bipolar electrode inserted into the forelimb area of sensorimotor cortex; the MEP was evoked by stimulating the same area and was recorded from the brain stem. The ECoG, SEP, and MEP were readily depressed on proximal MCA occlusion. The positive wave with short latency in SEP recordings was the field potential generated by excitation of muscles in the upper limb during median nerve stimulation and thus was resistant to MCA occlusion. The MEP consisted of a D wave and I waves generated by direct and synaptic activation of upper motor neurons, respectively. The D wave completely recovered within minutes on reperfusion after 3 hours of ischemia; however, synaptic activity (I wave) was still not restored 3 hours after reperfusion. The ECoG and SEP were partially recovered 3 hours after reperfusion. Negativity is downward in all recordings.

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**Results**

Physiological variables of the rats studied were within normal limits. Mean arterial blood pressure was 82±3 mm Hg; pH, 7.39±0.02; Po2, 97±7 mm Hg; Pco2, 36±1 mm Hg; hematocrit, 46±1%; and plasma glucose, 118±7 mg/dL. On induction of ischemia, rCBF dropped to 23±3%, 21±5%, 20±5%, and 24±2% in 1-hour distal and 1-, 2-, and 3-hour proximal occlusion groups, respectively (Figure 2). Rapid reperfusion was followed by hyperemia in 1-hour distal and proximal occlusion groups. Reperfusion was slower in 2- and 3-hour ischemia groups.

The MEP consisted of a short latency direct (D) wave and indirect (I) waves generated by activation of pyramidal motor neurons directly (at the initial segment or first nodes of axons) and synthetically (indirectly) via stimulation of interneurons and afferent axons ending on pyramidal neurons.24,25 The peak latency of the D wave was 1.84±0.03 ms, and its peak to peak amplitude was 12±1 μV (Figure 1). D and I waves completely disappeared on proximal MCA occlusion within a few minutes (Figures 1 and 2). In distal MCA occlusion, I waves vanished but the D wave was depressed to 27±1% of its preschismic amplitude within 10 minutes and then recovered to 64±10% (Figure 2). On reperfusion, the D wave totally recovered within 10 minutes, and its amplitude reached to 117±10%, 105±5%, 104±4%, and 99±5% of the preschismic values in 1-hour distal and 1-, 2-, and 3-hour proximal occlusion groups, respectively (Table). The D wave was still preserved after 24 hours of reperfusion in rats subjected to 1 hour of proximal MCA occlusion and had a comparable amplitude to that of the sham-operated group (Table). The preserved activity persisted after destruction of the neighboring frontal areas or contralateral homolog sensorimotor cortex as well as sectioning of the corpus callosum, suggesting that the D wave was conducted to the brain stem via the ipsilateral pyramidal tract.

**Changes in SEP**

![Figure 1. Changes in ECoG, MEP, and median-evoked SEP during ischemia and reperfusion. The ECoG and SEP were focally recorded by a concentric bipolar electrode inserted into the forelimb area of sensorimotor cortex; the MEP was evoked by stimulating the same area and was recorded from the brain stem. The ECoG, SEP, and MEP were readily depressed on proximal MCA occlusion. The positive wave with short latency in SEP recordings was the field potential generated by excitation of muscles in the upper limb during median nerve stimulation and thus was resistant to MCA occlusion. The MEP consisted of a D wave and I waves generated by direct and synaptic activation of upper motor neurons, respectively. The D wave completely recovered within minutes on reperfusion after 3 hours of ischemia; however, synaptic activity (I wave) was still not restored 3 hours after reperfusion. The ECoG and SEP were partially recovered 3 hours after reperfusion. Negativity is downward in all recordings.](http://stroke.ahajournals.org/)

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further decreased 24 hours after reperfusion in rats subjected to 1 hour of proximal MCA occlusion (Table). In 24-hour permanent MCA occlusion, no recovery in the SEP was observed (Table).

**Changes in PmEP**

Stimulation of the rat equivalent of the premotor area evoked a potential in the sensorimotor cortex (PmEP) that consisted of a slow negative wave with a 5.23±0.54-ms peak latency and 332±45-µV peak amplitude (Figure 3). The PmEP readily disappeared on MCA occlusion. After reperfusion, its recovery was slow and incomplete (Figure 3). The PmEP amplitude recovered to 37±6% of its preischemic value 3 hours after reperfusion following 1 hour of distal MCA occlusion (Table and Figure 2). After 24 hours of reperfusion following 1 hour of proximal MCA occlusion, the amplitude of PmEP was only 10±6% of the PmEP values in the sham-operated group (Table). In permanent ischemia, PmEP values did not show any recovery (Table).

**Changes in ECoG**

The amplitude of ECoG was assessed by calculating the root-mean-square (RMS) of 60-minute epochs (RMS function, MacLab/8s, ADInstruments). The ECoG amplitude was depressed to 52±11%, 46±9%, 42±6%, and 46±5% of the preischemic values in 1-hour distal and 1-, 2-, and 3-hour proximal occlusion groups, respectively, within 10 minutes of ischemia (Figures 1 and 2). The recovery of ECoG amplitude on reperfusion was incomplete, and its amplitude reached to 69±4%, 72±8%, 62±6%, and 67±8% of the preischemic values in 1-hour distal occlusion and 1-, 2-, and 3-hour proximal occlusion groups, respectively (Table and Figures 1 and 2). The ECoG amplitude was further depressed (35±2%) 24 hours after reperfusion in rats subjected to 1-hour proximal MCA occlusion (Table). In permanent ischemia, ECoG amplitude was 31±1% of that of the sham-operated rats (Table).

**Discussion**

Recording SEP and PmEP by an electrode inserted into the sensorimotor cortex from which MEP were generated allowed us to study the afferent and efferent activity and synaptic transmission in the cortex with a better resolution than achieved by conventional evoked potential recordings. Vertical placement of two poles of the electrode within the cortex and bipolar recording diminished the effect of neighboring cortical as well as distant electrical fields. Such a feature was essential to study ischemia-induced electrical changes in the sensorimotor cortex, which is situated at the border of the penumbra next to the cortex, an area of normal
electrical activity (ie, the anterior cerebral artery region). Recording of rCBF was indispensable to determine the severity of ischemia, because residual blood flow showed a great deal of variation after MCA occlusion in this penumbral area (see also Reference 28). In fact, occlusion of the contralateral carotid was required to bring flow values below the ischemic threshold in some rats.

We used the recording electrode also for stimulating forelimb area of the motor cortex. Voltage pulses applied generated a current flow between deep and superficial layers of the cortex and stimulated pyramidal motor neurons directly (at the initial segment or first nodes of axons) as well as indirectly (synaptically). MEP recorded at the level of medullary pyramids consisted of a short latency D wave followed by I waves, as described by Amassian and colleagues. Stronger stimulation of the cortex led to movement of only the contralateral forelimb but not other parts of the body, indicating that configuration of the electrode provided a focal stimulation and, hence, MEP reflected the activity in pyramidal fibers descending from the forelimb area of the motor cortex. Persistence of MEP after destruction of the neighboring frontal areas or homolog regions of the contralateral hemisphere. In fact, no D wave could be evoked after 1 hour of ischemia, suggesting a persistent transmission failure at synapses within the motor cortex. Poor recovery in PmEP, which is generated by synaptic activity within the sensorimotor cortex, strongly supports this idea. Latency and duration of the slow negative wave of PmEP suggest that it is a polysynaptic response, although the stimulation pattern used may activate several cortical elements, including afferent and efferent axons and principal and interneurons.

After 1-hour proximal MCA occlusion, synaptic activity continued to deteriorate, and evoked and spontaneous electrical activities were severely depressed 24 hours after reperfusion. The D wave was also (although only a little) impaired at 24 hours, possibly due to dysfunction of some axons at subcortical region. Destruction studies mentioned above argue against the possibility of residual MEP being generated in the neighboring frontal areas or homolog regions of the contralateral hemisphere. In fact, no D wave could be evoked after permanent MCA occlusion. Hence, these findings indicate that pyramidal axons can conduct 24 hours after 1-hour transient ischemia. Accordingly, a rat subjected to 1 hour of proximal MCA occlusion will have motor dysfunction caused by transmission failure within the motor cortex, despite a recovered axonal conduction on reperfusion. A similar mechanism may account for failure of a prompt motor recovery after successful restoration of blood flow by thrombolytic therapy in patients with acute stroke, as a result of MCA occlusion.

SEP recordings also support the above contention. The negative component of SEP essentially reflected the cortical activity induced by median nerve stimulation, because SEP was bipolarly recorded within the forelimb area of the sensorimotor cortex. Cortical ischemia induced by distal MCA occlusion totally abolished the SEP, possibly by inactivating the cortical electrical activity. Blockade of impulses in thalamocortical projections, as previously reported in cats subjected to MCA occlusion, is likely to have contributed to disappearance of SEP during proximal MCA occlusion. Similar recovery rates after distal and proximal occlusions suggest that axonal conduction in sensory fibers is readily restored on reperfusion as in pyramidal fibers. However, even after 1 hour of cortical ischemia, SEP recovery was
incomplete after reperfusion, possibly as a result of a persistent damage to synapses in the sensorimotor cortex.\(^4\)

ECoG recordings from the sensorimotor cortex showed about 55% depression in amplitude even when the CBF dropped below the threshold for failure of electrical activity, indicating that ECoG of the adjacent ACA territory was additionally picked up. In fact, an isoelectric ECoG was recorded when the electrode was moved toward the core region. No such contamination was observed during SEP recordings, possibly because SEP evoked by median nerve stimulation was focally generated within the forelimb area of the sensorimotor cortex.\(^5\) ECoG showed very little recovery after reperfusion (from 55% to 65% of the preischemic amplitude). Even after 1-hour distal MCA occlusion, recovery was poor, suggesting that cortical mechanisms generating ECoG were sensitive to ischemia. Persistent damage to synaptic activity is likely to be a major factor impairing ECoG.

In conclusion, our data demonstrate that pyramidal motor function is rapidly lost on occlusion of MCA as a result of loss of excitability in the cortex and blockade of axonal conduction in the subcortical region. Axonal conduction readily recovers following reperfusion after 1 to 3 hours of ischemia; however, motor dysfunction continues even after 1 hour of ischemia because of a persistent synaptic transmission defect within the motor cortex. The resistance of direct excitability of the initial segment or first nodes of axons of pyramidal neurons to ischemia, contrary to well-known sensitivity of the spontaneous and evoked electrical activities,\(^3,4\) suggests that a persistent defect in synaptic transmission is a major problem causing electrical dysfunction after reperfusion. A persistent synaptic failure and ensuing functional disconnection may also hamper postsynaptic synaptic reorganization in addition to acute dysfunction.\(^2,3\) Studying the mechanisms of lasting synaptic failure after ischemia may help in development of new therapeutic strategies for stroke.

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References

After permanent occlusion of a large intracranial artery, a lapse of several hours exists before panneurosis (or infarction) affects the entire territory supplied by the occluded artery.¹

The most likely, but still hypothetical, explanation for the loss of neuronal function is injury to the synaptic apparatus that presumably is directly related to the energy deficit. Several experiments have demonstrated that reopening the artery, sometimes as late as 4 hours after the initial occlusion, leads to a significant recovery of neurological function.²⁻⁵ Such improvement can be ascribed only to the salvage of a number of the neurons initially affected by the arterial occlusion. As reviewed by Heiss,⁶ the duration of the ischemia that causes irreversible damage to all neurons is still unknown. However, what is well established now is that transient arterial occlusions (≥60 minutes) cause brain lesions that are significantly different from the infarctions that develop after prolonged arterial occlusions. Several features are prominent in the incomplete infarctions caused by transient arterial occlusions: the appearance of neuronal injury in the cortex is delayed by several days, and at this site the lesion involves only a limited number of scattered cells. The death of these neurons is accompanied by microglial activation that does not progress to the stage of macrophage and does not lead to cavitation.⁷

In the ingenious experiments devised by Bolay and Dalkara, the integrity of the axons (in the caudoputamen) and of the cortical dendrites was separately evaluated both during the period of ischemia (MCA occlusion 1 hour in duration) as well as during the period of reperfusion (24 hours). The results show that during the period of arterial occlusion, dendritic as well as axonal dysfunction are easily demonstrable. Reopening the artery leads to restoration of blood flow to normal or supernormal levels with prompt recovery of axonal transmission. In contrast, the recovery of the dendritic function in the cortex was both delayed and incomplete despite the fact that cortical blood flow had returned to preocclusion levels.

These novel findings reinforce the concept that the brain injury secondary to a transient arterial occlusion is different (in terms of its pathogenesis and its features) from that caused by a prolonged arterial occlusion. In addition, the experiments emphasize the differences that exist in the responses observed in 2 regions of the brain (caudoputamen and cortex) when both are simultaneously affected by the occlusion of 1 cerebral artery.

Should the synaptic dysfunction observed in the cortex of these rats be a permanent sequel of a transient ischemic event, and should this loss of dendritic function be a reflection of the death of isolated neuronal groups (ie, selective neuronal necrosis), one would ask whether such “moderate” ischemic injury could be the substrate of the brain damage observed in patients who are cognitively impaired but who do not have neurodegenerative diseases. This issue has been reviewed elsewhere,⁸ and the results of the experiments by Bolay and Dalkara offer additional evidence for the hypothesis that “moderate” ischemia causes mild damage to selected regions of the brain.

**References**

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