MODELING POSTSTROKE EPILEPTOGENESIS BY MIDDLE CEREBRAL ARTERY OCCLUSION: CAN IT WORK?

Occurrence of Nonconvulsive Seizures, Periodic Epileptiform Discharges, and Intermittent Rhythmic Delta Activity in Rat Focal Ischemia

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A significant proportion of neurologic patients have electroencephalographic (EEG) seizures in the acute phase after traumatic or ischemic brain injury, including many without overt behavioral manifestations. Although such nonconvulsive seizures may exacerbate neuropathologic processes, they have received limited attention clinically and experimentally. Here we characterize seizure episodes after focal cerebral ischemia in the rat as a model for brain injury–induced seizures. Cortical EEG activity was recorded continuously from both hemispheres up to 72 hours after middle cerebral artery occlusion (MCAo). Seizure discharges appeared in EEG recordings within 1 hour of MCAo in 13 (81%) of 16 animals and consisted predominantly of generalized 1- to 3-Hz rhythmic spiking. During seizures, animals engaged in quiet awake or normal motor behaviors, but exhibited no motor convulsant activity. Animals had a mean of 10.6 seizure episodes within 2 hours, with a mean duration of 60 seconds per episode. On average, seizures ceased at 1 hour 59 minutes after MCAo in permanently occluded animals and did not occur after reperfusion at 2 hours in transiently occluded animals. In addition to seizures, periodic lateralized epileptiform discharges (PLEDs) appeared over penumbral regions in the injured hemisphere, whereas intermittent rhythmic delta activity (IRDA) recurred in the contralateral hemisphere with frontoparietal dominance. PLEDs and IRDA persisted up to 72 hours in permanent MCAo animals, and early onset of the former was predictive of prolonged seizure activity. The presentation of these EEG waveforms, each with characteristic features replicating those in clinical neurologic populations, validates rat MCAo for study of acutely induced brain seizures and other neurophysiologic aspects of brain injury.

Long-term Functional Consequences of Transient Occlusion of the Middle Cerebral Artery in Rats: A 1-Year Follow-up of the Development of Epileptogenesis and Memory Impairment in Relation to Sensorimotor Deficits

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Poststroke seizures occur in 5% to 20% of patients. Modeling of stroke-induced seizures in animals provides a useful tool for investigating the molecular basis of epileptogenesis and for developing therapies for stroke patients at increased risk for epileptogenesis. The questions addressed in the study were (a) Do rats develop spontaneous seizures after transient occlusion of the middle cerebral artery (MCAO)? (b) Is epileptogenesis associated with impaired hippocampus-dependent spatial learning and memory? (c) Are the functional abnormalities linked to axonal plasticity in the dentate gyrus? (d) Does the sensorimotor impairment induced by MCAO predict the risk of epileptogenesis? Adult male Sprague–Dawley rats were subjected to MCAO for 120 minutes. Development of spontaneous seizures was monitored by 1 week of continuous video-electroencephalographic (EEG) recordings at 3, 7, and 12 months after MCAO. Spontaneous seizures were not detected during 1-year follow-up in ischemic rats. Animals were, however, impaired in the spatial memory task ($P < .001$), which was not associated with altered hippocampal long-term potentiation (LTP) or abnormal mossy fiber sprouting (Timm staining). Animals also had a long-lasting sensorimotor deficit ($P < .05$). The present study indicates that MCAO causes long-lasting sensorimotor and spatial memory impairment but does not induce epileptogenesis or spontaneous seizures.

COMMENTARY

The mechanisms of poststroke epileptogenesis are not known, and development of animal models has been limited (1). Recent studies by two different groups of researchers have investigated the short- and long-term effects of middle cerebral artery occlusion (MCAO) on the potential development of behavioral and electroencephalographic (EEG) seizures. MCAO produces a large cortical/subcortical infarct ipsilateral to the occlusion, and it has been hypothesized that injured neuronal networks within the "ischemic penumbra" surrounding the infarct core may be capable of initiating poststroke epileptogenesis. Despite the widespread use of MCAO in studies focused on the pathophysiology of ischemia, neuroprotection, and functional outcomes, relatively little work has been performed in extending the use of MCAO as a potential model of poststroke seizures and epilepsy.

The report by Hartings et al. complements and extends previous work in the same laboratory that incorporated routine and quantitative EEG analysis of animals studied 1 to 7 days after MCAO (2–5). In the current study, 16 male Sprague–Dawley rats were studied up to 72 hours after transient (with reperfusion) or permanent (no reperfusion) MCAO. The researchers' basic finding was that multiple generalized or ipsilateral EEG seizures occurred within the first 2 hours after MCAO. Interestingly, these ictal discharges were unaccompanied by any behavioral manifestations of seizure activity (e.g., convulsions, motor arrest) in the animals, which were unanesthetized and ambulatory. Additionally, periodic lateralized epileptiform discharges (PLEDs) occurred primarily ipsilateral to the lesion and persisted throughout the end of the 72-hour monitoring period in most of the animals tested. Taken together, these studies substantially improve the available EEG database after MCAO, mirror several electroclinical aspects of the immediate and early phases of human stroke, and suggest the potential for subsequent epileptogenicity to develop in the periinfarct area.

In contrast to the studies by Hartings et al., which examined the acute phase of infarction with or without reperfusion, Karhunen et al. performed transient MCAO by essentially the same technique and assessed five to seven animals for the development of spontaneous seizures by continuous video-EEG for 1 week at 3, 7, and 12 months after lesioning. Disappointingly, they found no evidence of either behavioral or EEG seizure activity in any animal at any of the times studied. This result appears to raise more questions than it may seem to answer. First, and perhaps most important, the result calls into question whether the pathophysiologic mechanisms of ischemia and infarction caused by MCAO in a lissencephalic animal are capable of predisposing injured brain to epileptogenicity. In other words, perhaps the brain, not the technique, is a critical variable. Testing MCAO in an animal with a gyral cortex may be important. Second, although the ages of animals were not specified in either of the two studies reviewed, it is likely that juvenile or young adult animals were used. This raises the possibility that use of aged animals might produce a different result; however, no information exists on whether advanced animal age in this model is necessary or sufficient for epileptogenicity. Third, for the model to produce epileptic seizures, it may need to be a "second hit" superimposed on genetic susceptibility or acquired disease (e.g., diabetes, hypertension, renal insufficiency). In this regard, use of transgenic animals may be of some advantage, whereas use of metabolically compromised animals typically results in unacceptable levels of morbidity and mortality. Fourth, the role of reperfusion in this model, as it relates to potential epileptogenicity, is unknown and requires further evaluation. In summary, the longitudinal study by Karhunen et al. has important implications and may eventually prove to be the springboard, rather than the swan dive, for MCAO as a viable model of poststroke epileptogenesis.

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