UDC 616-005.4+831

Y. ZHANG [1], D. M. HAO[1], X. H. LI[1], Z. H. LIU[1], Y. RONG[1], M. G. LI[1],
Y. Q. TIAN[2], and Y. J. ZENG[1]

CEREBRAL ACTIVITIES IN RATS WITHIN DIFFERENT PERIODS AFTER EXPERIMENTAL UNILATERAL CEREBRAL ISCHEMIA

Received February 1, 2015

A model of cerebral ischemia in the left hemisphere was established in rats by occlusion of the left middle cerebral artery (MCAO). Twenty-five Sprague-Dawley rats were divided into five groups, the control (C) group and animals 4, 24, 48 h and one week (4h, 24h, 48h, and 1w, respectively) after MCAO. The footprint pattern test (FPT) was used to compare the gait in the MCAO groups with that in the C group. Ongoing EEGs were recorded and analyzed (spectral power densities of different rhythms were calculated). Somatosensory evoked potentials (SSEPs) were induced by stimulation of the right median nerve and averaged. Rats of group 4h displayed significantly worse gait parameters compared to those in the C group ($P < 0.01$). The 24h, 48h and 1w groups demonstrated no significant differences from this aspect, as compared with the C group ($P > 0.05$). Compared with the latter group, mean EEG mean powers of the EEG rhythms in the MCAO groups were significantly lower ($P < 0.01$), latencies of the SSEP components were longer, and peak amplitudes were reduced significantly ($P < 0.01$). All EEG and SSEP parameters demonstrated trends toward normal values with increase in the time interval after MCAO but were not restored completely. Therefore, functional behavioral tests, EEG, and SSEP monitoring at different phases after experimental cerebral ischemia can provide valuable information on the states of neural activities, which are well correlated with the motor function recovery.

Keyword: experimental cerebral ischemia, occlusion of the middle cerebral artery (MCAO), gait, EEG, somatosensory evoked potentials (SSEPs).

INTRODUCTION

Stroke is a disease of the high morbidity and mortality in the world. About 80-85% of all stroke cases are of an ischemic nature [1]. Animal models are highly valuable for gaining a comprehensive understanding the mechanisms underlying an ischemic injury after stroke onset, as well as subsequent evolution of changes and recovery of the functions. Different animal models of cerebral ischemia have certain advantages and disadvantages, and various output measures to characterize the consequences of ischemia are used [2, 3]. Preclinical studies demonstrated that cerebral ischemia after occlusion of the middle cerebral artery (MCA), which generates a focal cerebral infarct, closely resembles that found in ischemic stroke patients [4, 5]. Computerized tomography (CT) and magnetic resonance imaging (MRI) are sensitive to ischemic stroke, but these imaging techniques are rather expensive and "massive" (low-resolution). Moreover, the relationship between the post-stroke neurological status and functional outcome lacks a clear interpretation by MRI [6, 7].

As a direct measurement of the cerebral functions, EEG recording can detect subtle changes in mass cerebral electrical activities, which may be interpreted as a response to cerebral ischemia [8]. In animal models of cerebral ischemia, several studies reported that "flat" EEG patterns during global ischemia are observed, and these is followed by poor recovery [9, 10]. Various EEG activities were associated with exacerbated brain injury during focal cerebral ischemia [11, 12]. Such EEG parameters as coherence, synchrony, and entropy of potentials in most brain

[1] College of Life and Bioengineering, Beijing University of Technology, Beijing, China.
[2] State Intellectual Property Office of the P.R.C, Beijing, China.
Correspondence should be addressed to D. M. Hao
(e-mail: haodongmei@bjut.edu.cn or
Y. J. Zeng (e-mail: yjzeng@bjut.edu.cn).

regions are subjected to significant changes after bilateral carotid artery ligation [13]. Oscillation powers within the EEG spectrum bands correlate with different severity of injuries in the rat sensorimotor cortex [14]. EEG measures are highly sensitive to the dynamics of functional changes in brain tissues, and EEG retains a useful approach in evaluation of the processes induced by cerebral ischemia. Nevertheless, relatively few preclinical studies have adopted EEG measures as quantitative surrogate markers for estimation of brain dysfunctions in stroke models. EEG measurements in animals are limited by some significant factors, such as poor source anatomical localization, anatomical specificities, restricted number of EEG electrodes, anesthesia depth, etc.

Somatosensory evoked potentials, SSEPs, reflect sequential activation of neural structures along the somatosensory pathway; estimation of the intactness of somatosensory pathways is commonly used for brain function monitoring. SSEPs have been established as a useful electrophysiological tool for the neurological outcome prognosis in patients with hypoxic/ischemic brain injury [15, 16]. The SSEP waveform is conventionally analyzed by the respective peaks and latencies. Short-latency and long-latency SSEP components were studied during recovery from brain ischemia in a rat model [15]. The peak-to-peak amplitudes of the components of primary somatosensory cortical responses to electrical stimulation of the median nerve were used to predict the neurological outcome [17]. Yet, there is no clear view about mapping of the SSEP peaks with their origins. Some SSEP peaks are so small that they are over-ridden by preceding or subsequent peaks. Definitions of the latencies are relatively subjective, and justifications for such definitions are unclear.

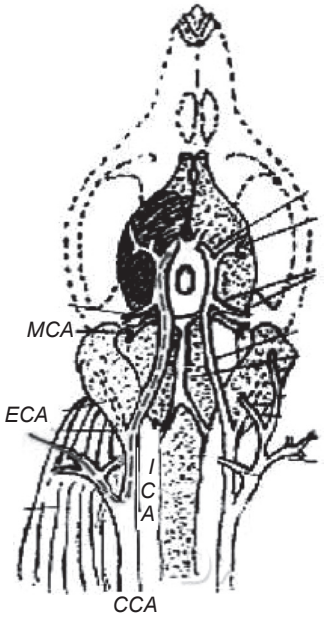
Functional behavioral tests are an essential part of preclinical research to assess the animal's functional status after stroke. These tests have been used to measure the sensorimotor deficits in contralateral forelimbs and hindlimbs [18]. The De Ryck's test was mainly assessed for estimation the forelimb function. The beam walking test was used to assess the stroke rat's hindlimb motor function [8]. Gait analysis is used to analyze the walking ability of humans and animals; so, this technology can be applied for studying locomotion after stroke. Behavioral tests can reflect the functional recovery relatively directly.

There is conflicting evidence regarding to correlations between the deficits in the sensorimotor function and EEG/SEP features after brain ischemia. More investigations are necessary to exploit the diagnostic methods. The purpose of our study was to combine the gait test and analysis of the EEG patterns and SSEP parameters at different post-stroke phases and to find some correlations with functional recovery in the rat stroke model. These measures could provide a more comprehensive method to characterize the consequence of cerebral ischemia.

METHODS

Animals. Two hundred adult male Sprague-Dawley rats (aged 8-10 weeks, weighing 200-250 g) were purchased from the Beijing HFK Bioscience Co Ltd in these experiments (License No. SCXK, Beijing, 2009-0007). They were housed in transparent Makrolon cages during 12/12 h day/night cycle in a temperature-controlled room (25°C) with free access to food and water.

Middle Cerebral Artery Occlusion. The rats were anesthetized by intramuscular injection of 10% chloral hydrate (0.4 ml/100 g, provided by the Dept. of Pharmacology, Peking Union Medical College Hospital) and placed in the prone position in a stereotaxic system (DW-5, Chengdu Taimeng Technology Co Ltd, China). The rat's left carotid region was exposed through a midline cervical incision



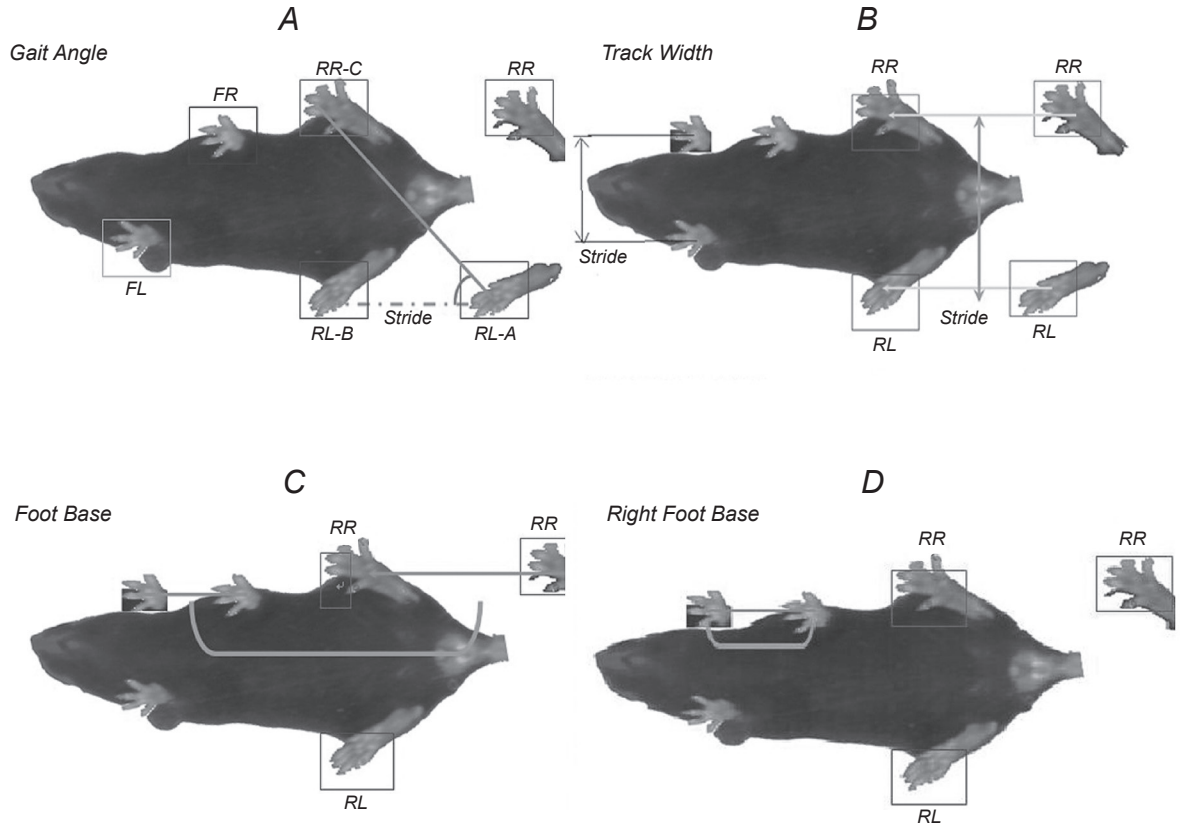
F i g. 1. Topography of the MCAO operation in rats.

Р и с. 1. Топографія MCAO на щурі.

(about 20 mm). The left common, internal, and external carotid arteries (CCA, ICA, and ECA, respectively) were isolated from the surrounding tissues. A nylon suture (product code 2432-50, Beijing ShaDong Biological Technology Co. Ltd.) coated with poly-L-lysine, with its tip shaped round, was inserted into the left ICA and advanced to a point approximately 18-20 mm distal to the bifurcation of the ECA and ICA, thereby occluding the origin of the middle cerebral artery (MCA) (Fig. 1). During surgery, the core temperature of the rat was maintained at 37 ± 1°C by a heating lamp. The state of the "stroke" rat was scored as follows: (0) no neurological deficit was observed, (1) failure to extend the right forepaw, (2) circling to the right side, (3) falling to the right, and (4) inability to walk and a depressed level of consciousness. Only rats with a Longa's score corresponding to 1 or 2 were selected for the EEG study [19].

Groups of Rats. The qualified 25 rats were selected and randomly divided into five groups: control (C), four h after MCAO (4h group), 24 h after MCAO (24h group), 48 h after MCAO (48h group), and one week after MCAO (1w group) with 5 rats in each group.

Gait Test. The footprint pattern test (FPT) was used to compare the gait in the MCAO groups with that in the C group. To obtain footprints, the forelimb and hindlimb feet of the rats were coated with nontoxic paints, like red or blue and green or orange, respectively [20]. The animals were then allowed to walk along a 120-cm-long 25-cm-wide runway (with 45-cm-high walls) into an enclosed box. A fresh sheet of white paper was placed on the floor of the runway for each run. All rats were tested three times. The footprint patterns were analyzed by four step parameters (all measured in centimeters, see Fig. 2). The gait angle (i) was measured between the line of the rear feet on one side during one stride to the middle toe of the opposite rear foot; (ii) the track width was a distance between mid-points of the strides of the feet on the same half (front or rear half); (iii) the foot base was measured as the distance between mid-points of the strides of the pairs of feet on the same side of the animal, and (iv) the right foot base was the horizontal distance of the right forelimbs.



F i g. 2. Measurements of the gait parameters of rats. A) Gait angle; B) track width; C) foot base, and D) right foot base.

Р и с. 2. Вимірювання параметрів локомоції у щурів.

EEG and SSEP Recording. Rats were fixed in a stereotactic frame under 10% chloral hydrate (0.4 ml/100 g) anesthesia. A scalp incision was made above the midline. The skin and underlying tissue layers were dissected to expose the cranium. The frontal cerebral cortex was exposed by making a craniotomy from about 0.5 mm posterior and 2.0 mm anterior to the bregma and from 0.5 to 1.5 mm lateral from the bregma with an electric cranial drill. The dura remained intact, and its surface was covered with 1.5 to 2% agar dissolved in 0.9% saline [21]. The microelectrode was adjusted precisely to the target area by carefully adjusting the position of the micromanipulator and slowly advanced downward to 1.8 mm from the cortex surface. The silver epidural ball EEG electrodes were spaced regularly on the somatosensory cortex of the left forelimb with a grid of penetrations separated by 0.5 mm. The reference electrode was placed at the bregma, and the ground electrode at the inner side of the right ear. EEG signals were recorded using BL-420 biological experimental system (Chengdu Thaimeng Technology Co. Ltd.) with the sampling frequency of 500 sec^{-1}, a bandpass filter of 0.053 to 100 Hz, and gain of $5 \cdot 10^4$.

SSEP Stimulation. Stimulation of the median nerve was achieved through inserting a pair of 1-cm stainless steel needle electrodes into the right forepaw. Direct-current stimulation was applied with the pulse duration of 0.25 msec, 0.8 mA, and 2 sec^{-1} frequency. The recording electrodes were the same as those for EEG recording.

Signal Processing. The EEG data was stored for offline analysis with MATLAB R2010b (Mathworks, USA). Firstly, the power spectra were estimated by the method of averaged periodograms or the Bartlett's method. The signal sequence $x(n)$, $n = 0,1,\ldots,N-1$, was divided into K small overlapping segments, each of the segment had L samples, then $K \cdot L = N$. The existing recorded data were subdivided as: $x_i(n) = x(n + iL)$, $I = 0,1,\ldots,K-1$, $n = 0,1,\ldots,L-1$. Periodograms of the K segments were plotted.

In this study, $N = 15000$, $L = 2500$, and $K = 6$.

Then, the mean powers within the θ frequency band (3 to 7 Hz), α (7 to 15 Hz), β (15 to 30 Hz), and γ (30-45 Hz) were calculated by equation.

$$MP = \frac{1}{M} \sum_{f=f_1}^{f_2} \left| s_x \left(e^{j 2\pi f} \right) \right|^2 ,$$

where f_1 and f_2 represent the low and upper frequencies within the frequency band. M is the number of frequency bins, which is determined by the bandwidth and resolution of the frequency.

Because there is a relatively high amount of electrical noise, while the SSEP amplitude is low, SSEPs should be averaged. Two most important parameters of SSEPs are the amplitude and latency of the peaks. Here, the amplitude and latency were defined as the first peak and its time delay with respect to the stimulus onset.

Statistical Analysis. Experimental measurement data are expressed as means ± s.d. and were statistically processed by SPSS 18.0 software (IBM Corporation, USA) using one-way ANOVA analysis. For intergroup differences, $P < 0.05$ was considered statistically significant.

RESULTS

Footprint Test. Gait abnormalities were assessed by analyzing the footprint pattern of rats when they walked along a narrow corridor. Footprint patterns of the C group and 4h group are illustrated in Fig. 3. It can be seen that the C-group rats walked in a straight line, with a regular even alternating gait, placing the hindpaw precisely at the position where the ipsilateral forepaw had been in the previous step (Fig. 3A). By contrast, 4h-group rats progressively weaved from side to side, while walking along the runway, adopting staggering movements (Fig. 3B). The 24h, 48h, and 1w groups walked approximately in a straight line, just like that Fig. 3A.

The resulting footprint patterns were assessed quantitatively by four measurements (gait angle, track width, foot base, and right foot base; see Table 1). The 4h group displayed a significantly smaller gait angle ($P = 0.0023$, i.e., $P < 0.01$), a shorter track width ($P = 0.0051$, $P < 0.01$), a shorter foot base ($P = 0.0045$, $P < 0.01$) and a shorter right foot base ($P = 0.0041$, $P < 0.01$), compared with the C group. Differences of the indices in groups 24h, 48h and 1w from those in the C group were noticeable but did not reach the significance level ($P > 0.05$).

EEG Mean Spectral Powers. Table 2 shows the EEG mean spectral power within the θ, α, β, and γ frequency bands for the C, 4h, 24h, 48h, and 1w groups. The EEG mean powers in each above band were lower significantly ($P < 0.01$) after MCAO.

T a b l e 1. Gait Parameters

T a б л и ц я 1. Параметри локомоції

Groups	Gait angle, deg	Track width, cm	Foot base, cm	Right base, cm
Control group	30.2 ± 3.0	2.0 ± 0.3	8.7 ± 0.2	2.2 ± 0.3
Group 4h	15.8 ± 0.8*	0.5 ± 0.1*	4.1 ± 0.5*	0.5 ± 0.1*
Group 24h	28.5 ± 1.6	1.8 ± 1.3	7.9 ± 1.3	1.9 ± 0.2

*$P < 0.01$.

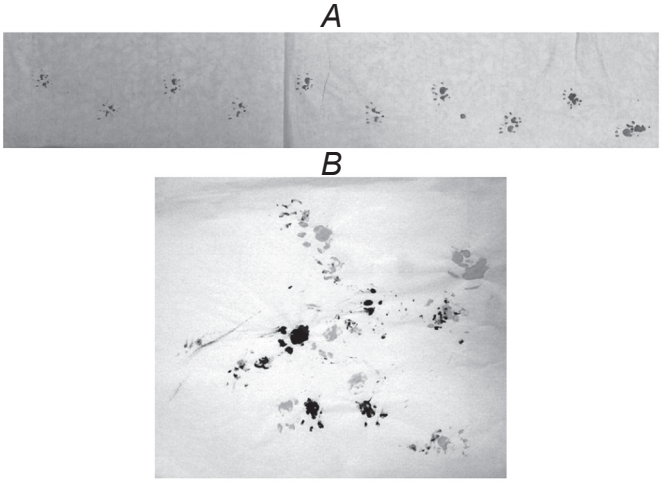
The respective shifts were dramatic at 4 h and gradually decreased within later time periods. The EEG mean powers increased obviously with time after MCAO but did not reached the control values.

SSEP Parameters. SSEPs were obtained by ensemble averaging of 100 successive stimulus-locked sweeps for each rat. The average amplitudes and latencies of SSEPs across five rats in the C, 4h, 24h, 48h, and 1w groups were compared. The amplitudes of SSEPs in the MCAO groups were significantly lower (Fig. 4A), while the latencies were significantly longer (Fig. 4B) than those in the C group. The amplitude and latency values demonstrated returns to those in the C group with time after MCAO but did not reach the control values even in the 1w group.

DISCUSSION

Stroke occurs when the blood flow to a part of the brain becomes inadequate, and this results in sudden death of cerebral cells. EEG is playing an increasingly important role for analyzing brain activities and evaluating the processes induced by cerebral ischemia. The SSEP parameters reflect the integrity and function of the neural transmission paths; these values have been extensively studied for evaluation of the neurological outcome after ischemic injury. Behavioral tests reflect the functional recovery more directly. Therefore, implementation of multimodal and multiparametric techniques in preclinical investigations with animal models would significantly contribute to the elucidation of mechanisms underlying brain impairment and recovery and aid in optimization of the diagnostic methods.

The conventional approach in EEG investigations in preclinical stroke models is to delineate the powers within the EEG spectral bands (rhythms) and to draw relevant inferences from the frequency-dependent changes in EEG oscillations. In our study, the EEG mean powers within the θ, α, β, and γ frequency bands decreased dramatically after MCAO and then increased gradually within later time periods. It is obvious that



F i g. 3. Footprints of rats of the control group (A; red is the forefeet and green is the hindfeet) and of group 4h (B; blue is the forefeet and orange is the hindfeet).

Р и с. 3. Відбитки лап щурів контрольної групи (*A*) та групи 4h (*B*).

T a b l e 2. Mean Spectrals Powers Within the Frequency Bands

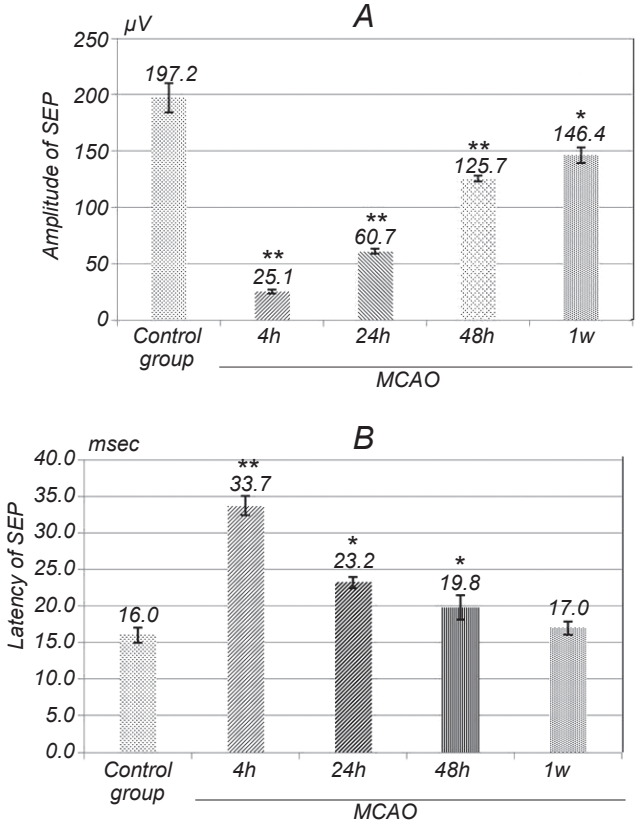
T а б л и ц я 2. Середні значення спектральних потужностей ритмів ЕЕГ

Groups	Powers within the bands (rhythms), μV^2			
	θ	α	β	γ
Control	139367.86 ± 178.66	5389.33 ± 25.55	79.11 ± 4.16	0.30 ± 0.12
4h	2.22 ± 0.40*	0.23 ± 0.01*	0.01 ± 0.01*	0.00 ± 0.00*
24h	625.06 ± 8.89*	21.70 ± 1.44*	0.62 ± 0.14*	0.10 ± 0.02*
48h	5875.45 ± 24.69*	574.19 ± 7.59*	14.81 ± 1.61*	0.15 ± 0.02*
1w	77926.19 ± 78.54*	1256.89 ± 11.20*	46.46 ± 2.37*	0.69 ± 0.03*

*$P < 0.01$.

electrical processes in the brain depend significantly on the cerebral blood flow (CBF) and oxidative metabolism of glucose delivered to the brain tissue via the arterial blood supply. Occlusion of the MCA leads to reduction of CBF in the brain regions supplied by this artery. The insufficient oxygen delivery leads to failure of synaptic transmission, which is supposed to lead to electric silence in the ischemized area [22] and, thus, for severe reduction in the EEG power observed during an acute phase of ischemia in MCAO rats. The degree of the EEG power reduction depends on the model used and on the duration of vessel occlusion [23, 24]. With the establishment of collateral circulation, CBF and oxygen delivered to the brain increase, and the EEG power enhances along with this process but does not reach pre-ischemia values.

The SSEP test is now widely used for evaluation of the somatosensory pathway continuity. The sensory stimulus travels through the peripheral nerve, nerve root, spinal cord, and subcortical brain relay structures to the primary sensory cortex [25]. Unlike ongoing EEG that represents spontaneous activity of the cerebral networks SSEPs represent a compound series of triggered electrophysiological activities. Greater latencies and suppressed amplitudes of the SSEP components in our study correlated with time intervals following MCAO. Longer latencies showed that brain ischemia induces cerebral edema that oppresses nerve fibers and decreases the axon ability of transduction. The neural conductivity is impaired immediately after cerebral ischemia, while the disturbed synaptic connections may have a prolonged effect on sensory pathways [26, 27]. With functional recovery, both the SSEP latencies and amplitude demonstrated clear recovery trend toward normal values, but the latter have not been attained even in the 1w group. Therefore, the peak amplitudes and latencies of SSEPs could act as complementary indicators to shed better insight in the neurophysiology deficit caused by ischemic injury.



F i g. 4. Diagrams of the means of the amplitudes of SSEP components (A) and latencies of their peaks (B) within different periods. $^{**}P < 0.01$, $^{*}P < 0.05$.

Р и с. 4. Діаграми середніх значень амплітуд компонентів соматосенсорних ВП (*A*) та латентних періодів їх піків (*B*) у різні проміжки часу після МСАО.

It is noticed that gait, EEG parameters, and SSEP parameters changed evidently after MCAO and then demonstrate certain return to normal conditions. It should be emphasized that behavioral parameters (gait) demonstrated better recovery dynamics than electrophysiological indices; the EEG and SSEP parameters remained clearly below the normal values even in the 1w group. The MCAO rats demonstrate, in general, the strong self-recovery capability; this is related to the specific features of the vascular net and of the compensatory capabilities of the used animal model species (rat) [3].

A combination of the gait, EEG, and SSEP measures may provide valuable predictive biomarkers for the functional brain tissue status.

Acknowledgments. The authors give special thanks to Dr. Wangsheng Lu for his instruction related to MCAO operation.

This research was partially sponsored by the Beijing Natural Science Foundation (Nos. 7132028 and 7132021) and the National Natural Science Foundation of China (No. 81441053). This study received permission from the Animal Care and Research Committee of Beijing University of Technology, Beijing, China.

All procedures performed in studies involving animals were in accordance with the international ethic norms and with the statements of the local Ethic Commitee.

The authors of this communication, Y. Zhang, D. M. Hao, X. H. Li, Z. H. Liu, Y. Rong, M. G. Li1,Y. Q. Tian, and Y. J. Zeng, confirm the absence of any conflict related to the comercial or financial interests, relation with organizations or person in any way involved in the research, and interrelations of the co-authors.

Я. Жан[1], Д. М. Хао[1], Кс. Х. Лі[1], Ж. Х. Лю[1], Я. Рон[1], М. Г. Лі[1], Ю. К. Тіан[2], Я. Дж. Зен[1]

АКТИВНІСТЬ МОЗКУ У ЩУРІВ У РІЗНІ ПЕРІОДИ ПІСЛЯ УНІЛАТЕРАЛЬНОЇ ЕКСПЕРИМЕНТАЛЬНОЇ ЦЕРЕБРАЛЬНОЇ ІШЕМІЇ

[1] Коледж наук про життя та біоінженірінгу Пекінського Технологічного Університету (Китай).
[2] Державний офіс інтелектуальної власності P.R.C, Пекін (Китай).

Р е з ю м е

Модель церебральної ішемії в лівій півкулі була реалізована на основі оклюзії середньої мозкової артерії (MCAO). 25 щурів лінії Спрег-Доулі були поділені на п’ять груп – контрольну (С) та групи тварин через 4, 24, 48 год та один тиждень після MCAO (4h, 12h, 24h, 48h та 1w відповідно). Тест із реєстрацією відбитків лап (FPT) був використаний для порівняння якості локомоції в групах MCAO з такою в групі С. У щурів відводили та аналізували поточну ЕЕГ, визначаючи спектральну потужність різних ритмів. Усереднені соматосенсорні викликані потенціали (ССВП) реєстрували після стимуляції правого *n. medianus*. Щури групи 4h демонстрували значно гірші параметри локомоції порівняно з такими в групі С ($P < 0.01$). Відмінності цих параметрів у групах 24h, 48h та 1w не досягали рівня статистичної значущості. Порівняно з групою С значення середніх потужностей ритмів ЕЕГ у групах MCAO були істотно нижчими ($P > 0.01$), латентні періоди компонентів ССВП – довшими, а амплітуди цих компонентів – меншими ($P < 0.01$). Характеристики локомоції та параметри ЕЕГ та ССВП зі збільшенням часового інтервалу після MCAO демонстрували тенденцію до повернення до нормальних значень, але нормалізація була частковою. Таким чином, результати поведінкових тестів та моніторингу ЕЕГ та ССВП у різні періоди після церебральної ішемії дають об’єктивну інформацію про стан активності ЦНС, котра добре корелює з відновленням моторних функцій.

REFERENCES

1. M. G. Hennerici, J. Bogousslavsky, and R. L. Sacco, *Stroke*, Mosby, iSBN 07234 33356 (2004).
2. D. W. Howells, M. J. Porritt, S. S. J. Rewell, et al., “Different strokes for different folks: the rich diversity of animal models,” *Cerebr. Blood Flow Metab. J.,* **30**, 1412-1431 (2010).
3. I. M. Macrae, “Preclinical stroke research – advantages and disadvantages of the most common rodent models of focal ischemia,” *Pharmacol. J.,* **164**, 1062-1078 (2011).
4. S. G. Moyanova and R. M. Dijkhuizen, “Present status and future challenges of electroencephalography- and magnetic resonance imaging-based monitoring in preclinical models of focal cerebral ischemia,” *Brain Res. Bull.,* **102**, 22-36 (2014).
5. C. Xing, K. Arai, E. H. Lo, and M. Hommel, “Pathophysiologic cascades in ischemic stroke,” *Int. J. Stroke*, **7**, 378-385 (2012).
6. J. U. Blicher, C. J. Stagg, J. O’Shea, et al., “Visualization of altered neurovascular coupling in chronic stroke patients using multimodal functional MRI,” *Cerebr. Blood Flow Metab. J.,* **32**, 2044-2054 (2012).
7. S. Wegener, R. Weber, P. Ramos-Cabrer, et al., “Subcortical lesions after transient thread occlusion in the rat: T2-weighted magnetic resonance imaging findings without corresponding sensorimotor deficits,” *J. Magn. Reson. Imag.,* **21**, 340-346 (2005).
8. S. J. Zhang, Z. Ke, L. Li, et al., “EEG patterns from acute to chronic stroke phases in focal cerebral ischemic rats: correlations with functional recovery,” *Physiol. Meas.,* **34**, 423-435 (2013).
9. Q. Gu, H. T. Lu, X. H. Lu, et al., “The influence of deep hypothermic global brain ischemia on EEG in a new rat model,” *J. Card. Surg.*, **27**, 612-617 (2012).
10. S. Choi, S. W. Kang, G. J. Lee, et al., “Real-time ischemic condition monitoring in normoglycemic and hyperglycemic rats,” *Physiol. Meas.,* **31**, 439-450 (2010).
11. A. J. Williams, X. C. Lu, J. A. Hartings, and F. C. Tortella, “Neuroprotection assessment by topographic electroencephalographic analysis: effects of a sodium channel blocker to reduce polymorphic delta activity following ischaemic brain injury in rats,” *Fund. Clin. Pharmacol.*, **17**, 581-593 (2003).
12. J. A. Hartings, A. J. Williams, and F. C. Tortella, “Occurrence of nonconvulsive seizures, periodic epileptiform discharges, and intermittent rhythmic delta activity in rat focal ischemia,” *Exp. Neurol.,* **179**, 139-149 (2003).
13. S. N. Kozhechkin, O. C. Koshtoyants, and S. B. Seredenin, “Multiparameter analysis of EEG in old Wistar rats after bilateral carotid artery ligation,” *Bull. Exp. Biol. Med.*, **147**, 573-577 (2009).
14. D. A. Volkova, N. S. Kositzyn, E. V. Goloborodko, et al., “Electrophysiological correlations of morphological

restructuring in experimental local ischemia of different severity in the rat sensorimotor cortex," *Bull. Exp. Biol. Med.*, **155**, 264-267 (2013).
15. D. Wu, B. Anastassios, W. Xiong, et al., "Study of the origin of short- and long-latency SSEP during recovery from brain ischemia in a rat model," *Neurosci. Lett.*, **485**, 157-161 (2010).
16. X. X. Kang, M. Koenig, I. Orukari, et al., "Assessment of post-cardiac-arrest somatosensory evoked potential in rats," in: *Proc. 4th Internat. IEEE/Embs Conf. on Neural Engin.* (2009), pp. 602-606.
17. W. Xiong, M. A. Koenig, J. Madhok, et al., "Evolution of somatosensory evoked potentials after cardiac arrest induced hypoxic-ischemic injury," *Resuscitation*, **81**, 893-897 (2010).
18. T. Schallert, "Behavioral tests for preclinical intervention assessment," *NeuroRx,* **3**, 497-504 (2006).
19. E. Longa, P. Weinstein, S. Calson, and R. Cummins, "Reversible middle cerebral artery occlusion without craniotomy in rats," *Stroke,* **20**, 84-91 (1989).
20. R. J. Carter, L. A. Lione, T. Humby, et al., "Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation," *J. Neurosci.*, **19**, 3248-3257 (1999).
21. J. N. Sanes, S. Suner, and J. P. Donoghue, "Dynamic organization of primary motor cortex output to target muscles in adult rats I. Long-term patterns of reorganization following motor or mixed peripheral nerve lesions," *Exp. Brain Res.,* **79**, 479-491 (1990).
22. J. Hofmeijer and M. J. A. M. van Putten, "Ischemic cerebral damage. An appraisal of synaptic failure," *Stroke*, **43**, 607-615 (2012).
23. B. Lei, S. Popp, C. Capuano-Waters, et al., "Lidocaine attenuates apoptosis in the ischemic penumbra and reduces infarct size after transient focal cerebral ischemia in rats," *Neuroscience,* **125**, 691-701 (2004).
24. S. Moyanova, F. Mastroiacovo, L. Kortenska, et al., "Protective role for type-4 metabotropic glutamate receptors against ischemic brain damage," *J. Cerebr. Blood Flow Metab.,* **31**, 1107-1118 (2011).
25. M. A. Koenig, P. W. Kaplan, and N. V. Thakor, "Clinical neurophysiological monitoring and brain injury from cardiac arrest," *Neurol. Clin.,* **24**, 89-106 (2006).
26. S. Yang, "Cortical evoked potential changes in a rat model of acute ischemic stroke: Detection of somatosensory evoked potentials and motor evoked potentials," *Neural Regen. Res*., **5**, 550-554 (2010).
27. Y. Ma, Y. Hu, N. Valentin, et al., "Time jitter of somatosensory evoked potentials in recovery from hypoxic–ischemic brain injury," *J. Neurosci. Methods*, **201**, 355-360 (2011).