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Review

Present status and future challenges of electroencephalography- and magnetic resonance imaging-based monitoring in preclinical models of focal cerebral ischemia

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ABSTRACT

Animal models are useful tools for better understanding the mechanisms underlying neurological deterioration after an ischemic insult as well as subsequent evolution of changes and recovery of functions. In response to the updated requirements for preclinical investigations of stroke to include relevant functional measurement techniques and biomarker endpoints, we here review the state of knowledge on application of some translational electrophysiological and neuroimaging methods, and in particular, electroencephalography monitoring and magnetic resonance imaging in rodent models of ischemic stroke. This may lead to improvement of diagnostic methods and identification of new therapeutic targets, which would considerably advance the translational value of preclinical stroke research.

Contents

Abbreviations: BOLD, blood oxygenation level-dependent contrast; CBF, cerebral blood flow; CT, computed tomography; DWI, diffusion-weighted imaging; EEG, electroencephalography, electroencephalogram; Et-1, Endothelin-1; fMRI, functional magnetic resonance imaging; MCAO, middle cerebral artery occlusion; MRI, magnetic resonance imaging; PET, positron emission tomography; PWI, perfusion-weighted imaging; rs-fMRI, resting state functional magnetic resonance imaging.

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1. Introduction

Much of the medical progress of understanding the dynamics of diseases, their underlying mechanisms and the development of therapeutic strategies has come from animal studies. Preclinical investigations with animal models of stroke are highly valuable for gaining a comprehensive understanding of brain activity and functions, for characterizing ischemic tissue fate, and for offering new possibilities for reinstatement of lost functions (Braeuninger and Kleinschnitz, 2009). In ischemic stroke in humans, thrombosis or embolism occludes a major cerebral artery, most often the middle cerebral artery (MCA), causing a focal cerebral infarct. Therefore, this brain vessel is the artery mostly targeted to induce focal cerebral ischemia by its occlusion (MCA-occlusion (MCAO) models) in preclinical studies, which have demonstrated that the ischemia-induced changes closely resemble those seen in ischemic stroke patients. The principal mechanisms of ischemia, including complex cellular and molecular cascades, are well established and have been reviewed in detail elsewhere (e.g., Lipton, 1999; Xing et al., 2012). Occlusion of the MCA may be performed in animals by intraluminal insertion of a pro-thrombotic agent or a filament, ligation, cauterization, photothrombosis or extraluminal application of the potent vasoconstrictory peptide endothelin-1 (Et-1). Detailed characteristics, advantages and disadvantages of the different models of MCAO, and various output measures to characterize the consequences of ischemia in these models have been described elsewhere (Carmichael, 2005; Durukan and Tatlisumak, 2007; Braeuninger and Kleinschnitz, 2009; Howells et al., 2010; Macrae, 2011; Liu and McCullough, 2011; Roulston et al., 2012).

Functional behavioral tests are an essential part of preclinical research to assess the animal's functional status after stroke. Behavioral tests that have been used in animal stroke research have been extensively described in previous reviews (e.g., DeVries et al., 2001; Schallert, 2006). These tests have for instance been used to measure unilateral MCAO-induced sensorimotor deficits in contralateral fore- and hindlimbs, including paralysis or weakness, loss of muscle tone and coordination, and lack of response to sensory or proprioceptive stimuli. These behavioral impairments correspond with loss of function in cerebral areas that are supplied by the MCA, i.e., the somatosensory cortex, most of the motor cortex, lateral and medial segments of the caudate-putamen, and the pyramidal tract. There is conflicting evidence regarding a correlation between deficits in sensorimotor functions and the volume of MCAO-induced hemispheric infarction (see references in Hunter et al., 1998). It is believed that damage of specific functional regions better predicts functional outcome than total infarct volume (DeVries et al., 2001). Therefore, for effective and comprehensive examining of consequences of cerebral ischemia as well as for preclinical drug testing, behavioral endpoints should ideally be complemented with neural correlates that can explain functional output.

Nowadays, a bulk of techniques and approaches exists to measure functional changes in the brain after stroke. Electroencephalographic (EEG) and magnetic resonance imaging (MRI) techniques are among the most widely applied in clinical and preclinical research. Despite a long history of EEG application in clinical practice and the important role it has played in studying cerebrovascular diseases (reviews of Faught, 1993; Jordan, 2004; Foreman and Claassen, 2012), relatively few preclinical studies have adopted EEG measures as quantitative surrogate markers for brain dysfunction in stroke models (Table 1). Besides the accumulated knowledge about the complex electrophysiological processes triggered by ischemia at cellular level (Astrup et al., 1981; Hossmann, 1983; Krnjević, 2008), we are not aware of any recent review on changes in the gross intrinsic bioelectrical activity, i.e., EEG, recorded in preclinical models of stroke. On the contrary, a large number of reviews have been published on application, benefits and pitfalls of various MRI techniques in animal models of stroke (Dijkhuizen and Nicolay, 2003; Farr and Wegener, 2010; Denic et al., 2011; Hoehn et al., 2001; Hoehn, 2011; Duong, 2012; Obenaus and Ashwal, 2012). Interestingly, electrophysiological (EEG, local field potentials, unit neuronal activity) and functional MRI (fMRI) measures may be combined in the same experimental setting (Logothetis et al., 2001), which can significantly contribute to improved understanding of (changes in) brain function in health and disease. This has been demonstrated in studies on epilepsy, sleep and cognition (e.g., Duyn, 2012), and recently also after stroke in human patients (Dubovik et al., 2012) or in experimental animal models (van Meer et al., 2012).

The purpose of this literature review is to summarize findings of studies using EEG and MRI measurements in animal models of focal cerebral ischemia, and to speculate on future directions in this field.

2. EEG in preclinical stroke studies

2.1. EEG in rodents

The physiological basis and technical aspects of EEG have been largely reviewed in the literature (e.g., Schaul, 1998; Amzica and Lopes da Silva, 2010). In animal experiments, electrodes can be placed on calvarium (epidurally or subdurally) for recording of electrocorticogram, or inserted into brain structures for recording of local field potentials or electrosubcorticogram. These recordings reflect gross electrical activity emanating from summated extracellular excitatory and inhibitory postsynaptic currents in dendrites of cortical pyramidal cells (e.g., Speckmann and Elger, 1999). The acronym EEG will be used to indicate electro(sub)corticogram, local field potentials and EEG for the remainder of this article, although it is recognized that differences do exist between data obtained from each of these measurements. The EEG in healthy animals, including rodents, exhibits a spectrum of oscillation frequencies and various patterns mostly dependent on the functional state during the different phases of the ultradian cycles of sleep and wakefulness. For example, low-frequency and high-voltage oscillations dominate the slow wave sleep pattern, while during waking state the EEG is asynchronous and with low-voltage oscillations. The intrinsic (background) EEG activity recorded in normal conditions when the animal is awake, quiet and immobile (i.e., in a "resting state"), is regulated by a homeostatic system, involving dynamic interactions among anatomically dispersed brain regions of different brain structures, such as brainstem, thalamus, limbic areas, and cortex, which play an important role in a wide variety of behavioral functions. EEG activity in animal studies has conventionally been described in terms of a set of frequency bands, usually defined as delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). The distribution of the fast Fourier transformation spectrum among these four frequency bands normally is 25–45%, 40%, 12–15% and 3–20%, respectively, in the total frequency band (usually from 1 to 30–32 Hz) (e.g., Lu et al., 2001; Zhang et al., 2013).

A bulk of algorithms have been developed to process the EEG signals, extracting a variety of EEG features in order to obtain reliable alerting indices of possible cerebral pathology. Some of the quantitative EEG .approaches and spectral parameters include: fast Fourier transformation of the EEG signal; absolute power spectral density across the total frequency band; percentage distribution of total power into delta, theta, alpha and beta frequency bands (relative power); alpha-to-delta ratio (Zhang et al., 2013) or ratio between alpha + beta and delta + theta