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Homeostatic changes in neuronal network oscillations in response to continuous hypoperfusion in the mouse forebrain

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ABSTRACT

Neuronal activity is highly sensitive to changes in oxygen tension. In this study, we examined the impact of hypoxic/ischemic conditions on neuronal ensemble activity patterns in the mouse brain using in vivo extracellular electrophysiological recordings from up to 8 sites in the thalamus, dorsal hippocampus, and neocortex, while cerebral hypoperfusion was induced by unilateral carotid artery occlusion. After a few minutes, the occlusion triggered a rapid change in the power of the local field oscillations. In the hippocampus, but not in the neocortex, the absolute power changes at all frequency ranges (relative to the baseline) became less pronounced with time, and no significant changes were observed 30 min after the occlusion-induced hypoperfusion. We also tested whether continuous hypoperfusion induced by the occlusion for up to 1 week alters neuronal activity. In the hippocampus and the thalamus, the chronic occlusion did not lead to a reduction in the power of the local field oscillations. These results indicate that certain neuronal populations have the ability to maintain internal neurophysiological homeostasis against continuous hypoperfusion.

1. Introduction

Normal brain function is maintained by a stable energy supply delivered by continuous blood flow. Certain diseases that cause an insufficient blood supply to the brain, such as cardiac arrest, stroke and head trauma, can result in cerebral hypoxic/ischemic conditions, leading to long-term disability and neuronal death. Numerous studies have revealed signaling pathways and molecular mechanisms underlying the neuronal degeneration observed with hypoxia/ischemia (Eltzschig and Eckle, 2011). However, there is still a lack of information on the pathophysiological basis of ischemia.

In normal physiological states, the mammalian forebrain generates diverse rhythmic activity with a frequency band ranging from approximately 0.1 Hz to 200 Hz. This rhythmic activity is thought to link the firing of single neurons into collective neuronal ensembles and facilitate efficient information processing, including cognition, learning and memory (Buzsaki, 2006). However, only a few experimental studies have examined how decreased blood flow affects ongoing neuronal oscillations (Barth and Mody, 2011; Buzsaki et al., 1989; Monmaur et al., 1986). Unresolved questions include (1) how individual brain regions alter their network activity patterns under hypoxic/ischemic conditions and (2) how ischemia-induced activity patterns undergo further changes during post-ischemic survival periods.

To address these issues, we examined electrical activity patterns following the induction of hypoxia/ischemia using a multi-channel electrical recording system to examine the mouse thalamo-cortico-hippocampal network. The hypoxic/ischemic states were acutely or chronically induced by (i) common carotid artery occlusion (CCAO) (Ohtaki et al., 2005) and (ii) photothrombosis of blood vessels (Barth and Mody, 2011) to induce moderate global hypoperfusion and severe focal ischemia, respectively. Power spectrum analyses of local field potentials (LFPs) revealed the pathophysiological effects of hypoxia/ischemia on the temporal activity patterns of neuronal networks in different brain regions.

2. Materials and methods

2.1. Animals

All experiments were performed with the approval of the experimental animal ethics committee at the University of Tokyo

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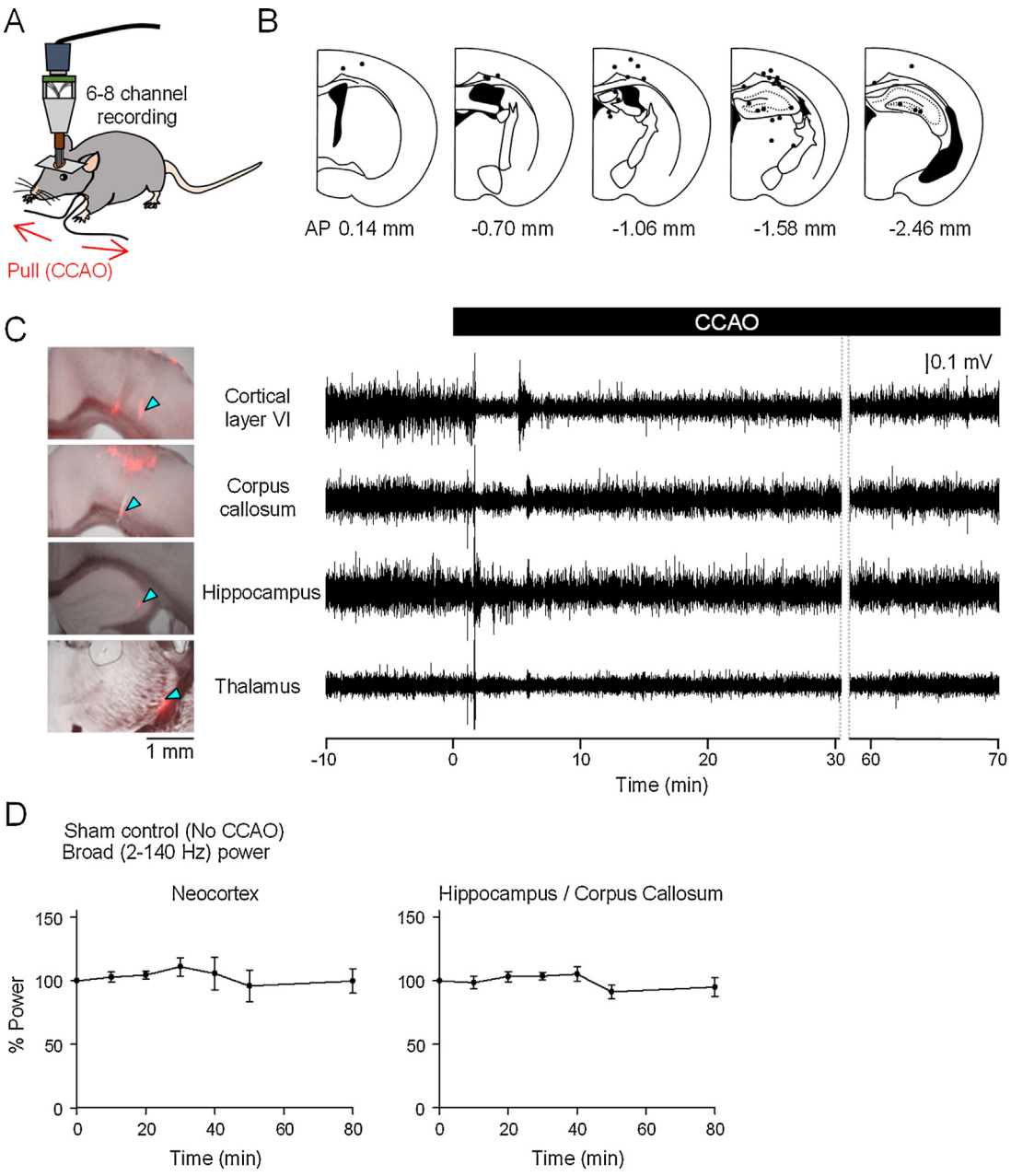

Fig. 1. Simultaneous in vivo electrophysiological recordings from the thalamo-cortico-hippocampal network during the induction of CCAO. (A) Illustration of the set-up used for multichannel recordings of neuronal activity during cerebral hypoperfusion. CCAO was produced by pulling both ends of a string looped around the common carotid artery. (B) Histological verification of the recording sites in sequential coronal brain sections. Black dots indicate the endpoints of electrode tracts from the acute CCAO experiments ($n = 7$ mice). (C) Representative simultaneous recordings of extracellular LFP signals from four brain regions from a mouse. CCAO was induced at time 0 min. The corresponding recording sites are indicated by the blue arrows in the left panels. (D) Time changes in LFP power at a broad frequency (2–140 Hz) band for 80 min in the neocortex (left, $n = 6$ recordings from 4 mice) and hippocampus/corpus callosum (right, $n = 12$ recordings from 4 mice).

(approval number: P24-70) and according to the NIH guidelines for the care and use of animals. A total of 17 male C57BL/6 mice (6–10 weeks old) with a preoperative weight of 18–28 g were used in this study. The animals were maintained on a 12-h light/dark schedule with lights off at 7:00 PM. All animals were purchased from SLC (Shizuoka, Japan). Mice were housed individually following surgery.

2.2. Surgery to induce brain hypoxia/ischemia

One of the following three surgeries was performed on each animal: acute common carotid artery occlusion (CCAO), chronic CCAO, and photothrombosis. For acute CCAO, mice were anesthetized with urethane (1.0 g/kg body weight, intraperitoneal injection). The left common carotid artery was exposed, and an elastic string with a diameter of ~1 mm was used to form a loop (~1-mm wide) surround the artery. Electrophysiological recording was then performed as described below. During recording, the loop was manually closed by pulling both ends of the string (Fig. 1A). For chronic CCAO, mice were first anesthetized with pentobarbital (0.38 g/kg bodyweight, intraperitoneal injection), and the left common carotid artery was ligated with the same type of string used for acute CCAO. The mice were allowed to recover for one week following the surgery, and electrophysiological recordings were performed as described below (Fig. 2). For induction of photothrombosis, mice were anesthetized with urethane (1.0 g/kg