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High incidence of adverse cerebral blood flow responses to spreading depolarization in the aged ischemic rat brain

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ABSTRACT

Spreading depolarizations (SDs) occur spontaneously in the brain after stroke, exacerbate ischemic injury, and thus emerge as a potential target of intervention. Aging predicts worse outcome from stroke; yet, the impact of age on SD evolution is not clear. Cerebral ischemia was induced by bilateral common carotid artery occlusion in young (8–9 weeks old, n = 8) and old (2 year olds, n = 6) anesthetized rats. Sham-operated animals of both age groups served as control (n = 12). Electrocorticogram, direct current potential, and cerebral blood flow (CBF) variations were acquired via a small craniotomy above the parietal cortex. SDs were elicited by KCl through a second craniotomy distal to the recording site. Ischemia and age delayed the recovery from SD. CBF decreased progressively during ischemia in the old animals selectively, and inverse neurovascular coupling with SD evolved in the old but not in the young ischemic group. We propose that (mal)adaptation of cerebrovascular function with aging impairs the SD-related CBF response, which is implicated in the intensified expansion of ischemic damage in the old brain.

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1. Introduction

Aging emerges as a major independent risk factor for the incidence and prevalence of ischemic stroke and predicts poor patient outcomes (Chen et al., 2010; Liu and McCullough, 2012). Considering our aging population, it is becoming ever more urgent to identify targets for therapeutic intervention to restrain the evolution of ischemic brain injury and improve stroke outcome. Much of the primary damage in the acute phase of ischemic stroke may prove irreversible despite prompt intervention, yet the management of secondary pathophysiological processes is more feasible and of fundamental importance to improve the prospect of successful recovery.

Recurrent spreading depolarizations (SDs) spontaneously occur in the cerebral cortex for at least over a week after the surgical intervention for the alleviation of primary injury in subarachnoid hemorrhage, malignant stroke, and traumatic brain injury patients (Dohmen et al., 2008; Dreier et al., 2006; Hartings et al., 2009). Moreover, SD has been recognized to contribute to the progression of delayed ischemic neurological deficit, and it has become increasingly clear that the occurrence of SD predicts worse clinical outcome from neurological casualties (Dreier et al., 2006; Hartings et al., 2011). SD, therefore, emerges as an important secondary pathogenic phenomenon in the injured brain as it has a considerable impact on lesion progression and may become a target of therapeutic strategies.

SD is a wave of intense depolarization that propagates across the cerebral gray matter and is typically followed by local changes in cerebral blood flow (CBF). The characteristic features of SD are a large, transient negative shift in the slow electrical potential (direct current potential), and the simultaneous silencing of brain electrical activity (Hartings et al., 2009; Leão, 1944; Strong et al., 2002). At the level of the nervous tissue, SD is a self-igniting cellular ionic imbalance of a critical mass of neurons and glia cells, which propagates across the gray matter at a rate of 2–6 mm/min (Somjen, 2001). When neurovascular coupling is intact, SD is associated with a CBF response containing an obvious functional hyperemic element (Hansen et al., 1980). Conversely, when neurovascular coupling is compromised (e.g., by ischemia), the SD-related hemodynamic response becomes atypical, shifting to dominant vasoconstriction (Dreier et al., 1998). This atypical CBF variation during ischemia is believed to aggravate metabolic supply-demand mismatch in the tissue (Dreier, 2011; Hoffmann and Ayata, 2013) and is thought to mediate the SD-related expansion of ischemic brain injury.

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Aging was associated with the increased conversion of penumbra into infarction in patients (Ay et al., 2005), more severe ischemia-related neurological impairment in old mice, (Liu et al., 2009), and accelerated infarct development and neuronal degeneration in old rats (Popa-Wagner et al., 2007). Although SD may be implicated in all these events, the impact of aging on SD evolution, and the potential role SD might play in the age-related worsening of stroke outcome, have remained largely unexplored (Farkas and Bari, 2014).

Our group has recently made an important discovery that prolonged SDs and associated hypoperfusion likely compromise cortical tissue exposed to focal ischemia in aged rats (Clark et al., 2014). Following up on our previous work, here, we set out to determine the impact of age on the evolution of SD and the kinetics of the associated changes in local CBF in the intact and ischemic rat brain. We introduce an experimental model in which the degree of cerebral ischemia is highly reproducible, and SDs can be elicited in a planned, controlled fashion. These conditions enable the accurate evaluation of how SD evolves in the old ischemic rat brain with respect to young control.

As an addition, we introduce a detailed analysis of the electrocorticogram (ECoG) to identify specific frequency bands that may be selectively affected by SD, and to test whether spectral analysis of the ECoG can be used as a predictor for SD causing worse recovery from ischemia.

2. Materials and methods

2.1. Surgical procedures

Experimental procedures were performed with the approval of the National Scientific Ethical Committee on Animal Experimentation (updated Law and Regulations on Animal Protection: 40/2013. (II. 14.) Government of Hungary), following the EU Directive 2010/63/EU on the protection of animals used for scientific purposes.

Adult, male Sprague-Dawley or Wistar rats of 2 age groups (2 month olds, and 2 year olds, n = 26) were anesthetized with halothane or isoflurane (1.5%–2.2%, in N_2O:O_2/2:1) and allowed to breathe spontaneously through a head mask. Body temperature was kept between 37.1 °C and 37.3 °C using a heating pad, feedback-controlled by a flexible rectal probe (Homeothermic Blanket System, Harvard Apparatus, Holliston, USA). The left femoral artery was cannulated for the continuous monitoring of mean arterial blood pressure (MABP; RX104A, TSD104A, Biopac Systems, Inc, Goleta, USA). Both common carotid arteries were exposed through a ventral cervical incision. A silicone-coated fishing line used as occluder was looped around each artery for later induction of acute, incomplete, global forebrain ischemia. Animals were placed into a stereotactic frame, and 2 craniotomies were prepared on the right parietal bone (−3 mm caudal −5 mm lateral and −7 mm caudal −5 mm lateral from bregma) with a high precision dental drill (Technobox 810, Bien-Air Dental SA, Bienne, Switzerland). The dura in each craniotomy was carefully incised, and the craniotomies were regularly irrigated with physiological saline.

2.2. Ischemia induction and SD elicitation

Ischemia induction was preceded by a 10-minute baseline period, during which all variables were continuously recorded. Acute global forebrain ischemia was induced by pulling on the occluder lines looped around the common carotid arteries and securing them in place ("two-vessel occlusion", 2VO) in a young and in an old group of rats (young 2VO, n = 8; and old 2VO, n = 6). In an age-matched young group used as control for the surgical procedures, the occluders were in place but not pulled on (young control, n = 6). For the old age-matched control group, acute 2VO was not implemented either; instead, animals had undergone permanent 2VO produced 1-year prior SD elicitation (old control, n = 6).

Recurrent SDs in all groups were triggered by placing a 1M KCl-soaked cotton ball on the exposed cortical surface in the caudal cranial window 10 minutes after 2VO onset. In old rats, 1M KCl often proved insufficient to trigger SD, therefore, either 3M KCl was used, or—if still inefficient—a tiny KCl crystal was placed on the cortical surface to achieve SD elicitation. Experiments were terminated by the overdose of the anesthetic agent.

2.3. Electrophysiology

In the rostral craniotomy, slow cortical or direct current (DC) potential and ECoG were acquired through a glass capillary electrode (20 μm outside tip diameter) filled with saline, implanted 1–1.2 mm deep into the cerebral cortex. An Ag/AgCl reference electrode was placed subcutaneously in the neck. DC potential and ECoG were recorded via a high-input impedance preamplifier (NL102G, NeuroLog System, Digitimer Ltd Welwyn Garden City, Hertfordshire, England), connected to a differential amplifier (NL106, NeuroLog System, Digitimer Ltd) with associated filter and conditioner system (NL125, NL530,Digitimer Ltd, NeuroLog System). Potential line frequency noise (50 Hz) was removed by a high-quality noise eliminator (HumBug, Quest Scientific Instruments Inc, North Vancouver, Canada) without any signal attenuation. Signals were acquired at a sampling frequency of 1 kHz. Analog to digital conversion was performed by a dedicated data acquisition system (MP 150, Biopac Systems, Inc).

Data analysis was assisted by the inbuilt instructions of the software AcqKnowledge 4.2 for MP 150 (Biopac Systems, Inc). For each SD, the amplitudes of depolarization and hyperpolarization were defined as the maximum of the negative and positive shift relative to baseline in DC potential, respectively and were expressed in mV. The maximum rates of depolarization and repolarization were calculated as the respective slopes of the SD-related DC shift given in mV/s. The duration of SD events was measured at half amplitude of the SD-related negative DC shift in seconds.

2.4. Monitoring of local CBF

SD-associated changes in local CBF adjacent to the glass capillary electrode were recorded by using laser-Doppler flowmetry (LDF). A stainless steel needle Doppler probe (Probe 403, connected to Periflux 5000, Perimed UK Ltd, Bury St Edmunds, UK) was positioned at an angle with a micromanipulator close to the penetration point of the glass capillary electrode. Care was taken to avoid large pial vessels. The LDF signal was digitized together with the DC potential and ECoG as described previously (MP 150, Biopac Systems, Inc).

All variables (i.e., DC potential, ECoG, LDF signal, and MABP) were simultaneously acquired, displayed live, and stored using a personal computer equipped with a dedicated software (AcqKnowledge 4.2 for MP 150, Biopac Systems, Inc).

Six types of hemodynamic responses were identified, ranging from dominating hyperemia to prolonged cortical spreading ischemia with intermediate forms. The CBF response to each SD was classified accordingly, and the prevalence of various CBF response types was determined for each experimental group.

SD-associated relative changes in local CBF were calculated based on 100% baseline taken shortly before SD occurrence and residual LDF signal after anesthetic overdose considered as biological zero. The magnitude of each element of the SD-related CBF

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