

The impact of age on the evaluation of spreading depolarization triggered during global forebrain ischemia in the rat

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OBJECTIVES

Spreading depolarizations (SD) spontaneously occur in the ischemic brain, and facilitate cell death. Aging is the most important risk factor for the incidence of ischemic stroke; yet, it is not clear how age alters SD evolution. The aim of the recent study was (i) to compare the typical features of K⁺-evoked SDs during cerebral ischemia in young and aged rats and (ii) to assess the impact of age and ischemia on the electrical threshold of SD elicitation.

METHODS

Adult male Sprague-Dawley rats of various ages were anesthetized with isoflurane in N₂O:O₂. Transient global forebrain ischemia was induced by bilateral occlusion of the common carotid arteries (2VO, in young adult and old rats, from 7-week-old to 2-year-old, n=52). Sham-operated rats (SHAM) served as control (n=11). DC potential and local cerebral blood flow (CBF) were acquired via a small craniotomy. SDs were elicited by topical application of 1 or 3M KCl through a second craniotomy (8-week-old group, n=14; 2-year-old group, n=11), or by electrical stimulation for the determination of SD elicitation threshold (7-30-week-old group, n=38). In the latter case, 3 SDs were evoked during baseline and another 3 SDs during ischemia in each experiment. Blood pressure was continuously monitored and blood gases regularly controlled via a femoral artery catheter.

RESULTS

Ischemia elongated the duration of the SD-related negative DC shift, which was augmented further by age. Old age was also associated with reduced slope of depolarization and amplitude

of repolarization. In animals 7-30 weeks old, brain maturation markedly increased the elicitation threshold of SD, and ischemia significantly elevated the threshold of SD elicitation. CBF decreased progressively during ischemia in the 2-year-old animals, and inverse neurovascular coupling with SD evolved in the old but not in the young ischemic groups. The hyperemic CBF responses to SDs were of smaller amplitude but longer duration under ischemia.

CONCLUSIONS

We propose that (mal)adaptation of cerebrovascular function with aging impairs the SD-related CBF response. As a consequence, the aged ischemic brain has scarcer resources to recover from an SD event, which reflects the increased vulnerability of the aged brain to ischemia- and/or SD-related injury. Finally, the threshold to trigger SDs increases with aging and ischemia. The susceptibility of the brain to SD may be determined by the gray matter's biochemistry and cytoarchitecture that undergo adaptational changes with maturation, and ischemia is suggested to inhibit SD elicitation by decreasing tissue pH.

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