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Spreading Depolarization in the Acute Phase of Experimental Subarachnoid Hemorrhage in Mice

Fach/Eintichtung: Neurochirurgie

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SAH resulting from aneurysmal rupture is a delicate condition frequently leading to a high early as well as late morbidity and mortality. However, until now, the exact causes of early as well as late morbidity and mortality are still the subject of debate. SD is a propagating wave of neuronal and glial depolarization across the cerebral cortex at a velocity of 2 to 5 mm/min. More and more clinical evidence has suggested SD occurs after SAH and is associated with worse patients' outcome. However, the details of SD occurrence and how ischemic brain injury after SAH is aggravated has not been figured out. For this reason, within the frame of this study, the occurrence of SD was detected by IOSI with high spatio-temporal resolution in the mouse model of SAH using the endovascular filament perforation technique. In addition, the effect of subanaesthetic dose of ketamine on SD and brain edema was tested in the acute phase (3 hours after SAH or sham surgery). For induction of SAH, one 5-0 nylon monofilament was introduced into the ECA and advanced into the bifurcation of the MCA and ACA, and then this bifurcation was perforated, which is similar to the rupture of an intracranial aneurysm. Subsequently, the position of animals was changed from supine to prone position. One CCD camera with an optical band pass filter (564 nm), connected with one computer, was mounted above the thinned mouse skull to record SD. Meantime, ketamine or saline (30 mg/kg) was given every half

hour after SAH or sham surgery. For brain edema, mice were killed 3 hours after SAH or sham by decapitation and brain water content was measured by the wet/dry weight method. It was found that 199 SDs occurred after SAH and 30 SDs occurred in sham groups. These SDs originated from different sites: the cerebral cortex affected by the ICP sensor, other areas in the cerebral cortex and even in the olfactory bulb. The majority of SDs initiated with an irregular radial pattern and evolved into semi-planar waves during propagation. They propagated into different directions, forming diverse pathways. The morphology of SD waves was affected by the surface of the cerebral cortex, the presence of ICP sensors and other SDs. When two SD wavefronts encountered each other, they interacted and collided. Moreover, SDs exhibited 4 distinct hemodynamic types: type I (transient increase), type II (transient increase with subsequent plateau), type III (transient increase with subsequent decrease), and type IV (step increase) in the profile of reflectance intensity change, which may imply different blood volume changes in the cerebral cortex. The three most abundant types of hemodynamic response were: monophasic hypoperfusion response, biphasic response (hypoperfusion, then hyperperfusion), and tri-phasic response (initial unapparent hyperperfusion, then predominant hypoperfusion, and a recovery still below the baseline). Obviously, the hemodynamic response to SD is reversed from hyperperfusion to hypoperfusion after SAH, which suggests vascular tone changes from dilatation to constriction. In the current study, compared with the control, the brain water content was significantly higher in the SAH groups. Moreover, the brain water content in ketamine-treated animals was lower than in saline-treated groups, but there was no significant difference. Furthermore, compared with saline, ketamine was capable of reducing the number of ROIs reached by SD and the intensity change of SD, diminishing the cortex area covered by SD, slowing down SD propagating speed, and decreasing the duration of SD intensity change. However, the occurrence of SD was not prevented by ketamine, which means ketamine at this dosage cannot inhibit SD induction after SAH in mice. This might be caused by the low dose or mode of administration. Another explanation might be that the deleterious condition is stronger than the NMDA receptor antagonist, and thus despite the presence of ketamine, SD

still occurs. Our experiments suggest that SD occurs in a high incidence after SAH. These SD waves originate from different places in the mouse brain, display distinct morphologies, and propagate into different directions and pathways. Additionally, the hemodynamic response to SD is inverted from hyperperfusion to hypoperfusion after SAH, which suggests SD contributes to cerebral ischemic injury after SAH. As a NMDA receptor antagonist, ketamine may have therapeutical benefit in inhibiting SDs. However, for human use, an appropriate dosage and route of administration should be studied and established.