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Spreading Depolarization dynamics and pharmacological modulation with ketamine in the gyrencephalic porcine cortex

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Spreading depolarization (SD) corresponds to a self-propagating wavefront of depolarization in the central nervous system with neuronal and glial cell participation. Following its discovery more than 70 years ago, it is only during the past 12 years that its relationship between several neurovascular diseases has been confirmed. Today there is sufficient evidence of SD association with neuronal degeneration and poor clinical outcome after brain injury. However, SD is still an unknown phenomenon and many questions are still unanswered. The fact that the majority of the experimental models are performed in small lissencephalic brains makes the translation of the results to the human pathology problematic. Therefore, the use of larger brains will then provide better models to understand the neuropathological mechanisms in the gyrencephalic brain, and to validate different therapeutic approaches.

The aims of the present work were: to standardize an experimental model for SD study in a large gyrencephalic porcine brain, and to validate an intrinsic optical signal (IOS) imaging system and software for SD analysis. Therefore, a series of three studies were performed. First a pilot test of an IOS imaging setup and its validation with electrocorticography (ECoG) signals was performed; second SD dynamics and propagation patterns using IOS imaging, validated with ECoG and laser-Doppler (LD) were described, and third the dose-dependent effect of ketamine at therapeutic dosages and its impact on SD susceptibility through IOS imaging and ECoG were analyzed.

In the first study, brains were perfused for 5 min once, with an elevated K^+ concentration (7 mmol/l) in standard ringer lactate solution at the beginning of the experiment, as preconditioning procedure. SDs were induced using a 0.5 mm diameter wire with a small drop of KCl (7 mmol/l) at the tip. A mean of 3 SDs per hour were induced during

the 80 h of recording in 4 pigs. The first SDs were detected between 4 and 8 h after preconditioning. The propagation of the SDs increased progressively over the monitoring time. Every SD recorded using ECoG was also observed in IOS imaging. In the second study, the brain surface was immersed for 30-40 min in a standard lactated Ringer's solution with an elevated K^+ concentration (7 mmol/l) at the beginning of the experiment. Fourteen animals were divided into 2 groups, in the first group the cortex was irrigated with NaCl 0.9% to keep the brain hydrated. In the second group a paraffin pool was used to improve image quality. SDs were induced using 3-5 µl of 1 mol/l solution every 30 min. A total of 198 SDs using IOS were monitored. IOS enabled the visualization of SD dynamics and patterns. In this regard, 187 SDs appeared as radial waves that developed semi-planar fronts. The morphology was affected by anatomical structures. Other SD patterns such as spirals and reverberating waves, which have not been described before in gyrencephalic brains, were also observed. In the third study, preconditioning was performed as in the second study, and all brains were covered with a paraffin pool. SD in 12 animals were induced every 30 min 12 times. In 6 animals, stimulations were performed every 15 min 9 times. Animals received ketamine at increasing dosage. Ketamine at 2 mg/kg/h i.v decreased SD spread and had an effect on the amplitude of SD deflections, as well as on duration, and speed. Also a sustained decrease of the hyperemic response following SD was observed in IOS. Only ketamine at 4 mg/kg/h i.v. inhibited SD induction and expansion. When this high-dose was administered as a bolus 1 min after stimulation, SD propagation was blocked abruptly within 1-2 min, and it hindered SD induction and expansion for the following 15-30 min.

Blood volume changes associated with SDs were detected employing IOS imaging in a porcine experimental model of SD *in vivo*. IOS hemodynamic changes correlated with ECoG signals and LD changes. IOS enabled to clearly visualize the induction, propagation, and termination of SDs with a high spatial and temporal resolution within the sub-millimeter range. Using this imaging technique allowed the investigation and analysis of SD dynamics and patterns of expansion. The first spirals and reverberating waves in the gyrencephalic brain were described. A classification of initiation and propagation patterns is proposed. IOS also enabled the study of the spatio-temporal properties of SD modulation with ketamine in the gyrencephalic brain *in vivo*. The results confirm that ketamine effects are dose-dependent and limited to the time of drug administration. After discontinuation, it exerts inhibition only for a brief period of time. Ketamine may be a therapeutically effective option to abort SDs with human dose regimen being effective in a gyrencephalic large animal brain.