Is Spreading Depression Bad for You? Focus on “Repetitive Normoxic Spreading Depression-Like Events Result in Cell Damage in Juvenile Hippocampal Slice Cultures”

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In this issue of the Journal of Neurophysiology (p. x), Pomper et al. report that repeated episodes of spreading depression-like events (SDLEs) caused irreversible injury in hippocampal slice cultures taken from immature brains. Although after the first four or five SDLEs, antidromic population spike and synaptically transmitted potentials recovered, after further repetitions, the response amplitudes progressively and irreversibly decreased. Even more importantly, propidium iodide (PI) added to the bathing medium at the end of the experiment gained access into many more cells in preparations that have undergone SDLEs than in control tissue. The PI test is a reliable diagnostic sign of irreversible cell damage.

The authors are careful to use the phrase “SD-like event” rather than SD, for they find minor differences in their recordings from those seen during SD in other preparations. Similarities outweigh these small deviations, and the underlying mechanism is very probably the same.

An important technical variation was aerating the slice cultures with 20% oxygen instead of the customary 95%. Measured $P_{O2}$ in the tissue was within the normal range for cerebral gray matter, whereas 95% $P_{O2}$ produced hyperoxia. This does, however, bring up a caveat. In brains, in situ SD is associated with increased blood flow and a rise in tissue $P_{O2}$, which does not occur in vitro. Because metabolic rate increases greatly during SD, there is the possibility of transient hypoxia during SDLEs, which could contribute to the neuron injury. This point deserves experimental testing.

The question of the relationship of SD to brain pathology is as old as the discovery of the phenomenon. In his first article, Leão (1944) described the similarity between the ways in which SD and seizures propagate. Later he reported (Leão 1947) that sudden ischemia of the brain is associated with an extracellular voltage shift very similar to that of typical of SD. This gave rise to speculation that SD may be caused by brief ischemic episodes or by temporary energy failure of the cortex. Either or both of these factors may be involved in the mechanisms of SD.

As mentioned by Pomper et al. (2005), in normally circulated and oxygenated healthy adult brains, SD can be provoked many times without obvious harm (Nedergaard and Hansen 1988). In the slice cultures of (Pomper et al. 2005), the SDLE-associated negative shifts of extracellular voltage became progressively longer, and the amplitude of the initial deflection became smaller. A similar progressive prolongation was also seen in normal adult rat hippocampus in situ (Herreras and Somjen 1993b) but without evidence of neuron injury. The group of J. Bureš (1984) made extensive use of SD induced in freely moving rats during behavioral experiments, and Korol’eva and Bureš (1993) concluded that rats “do not experience SD as aversive.” Opinions are divided whether SD could in fact have a physiological function (Bureš et al. 1984) or could perhaps play a neuro-protective role (Kawahara et al. 1995; Kunkler et al. 2004). Recovery after SD appears to depend on the relatively short duration of the successive waves of depolarization, for if neurons are forced to remain depolarized for an extended period, they do succumb. This damage was calcium dependent (Herreras and Somjen 1993a; Jing et al. 1991). The crucial difference between immature and mature cerebral tissue could be that neurons in the former tolerate a longer time in the depolarized, hyper-calcic state than those in the latter. More recently, it has been reported that compounds released during SD into interstitial space activate trigeminal afferents and cause inflammatory reaction, edema and protein extravasation in and around vessels of the dura mater (Bolay et al. 2002). This finding challenges the concept that SD is ever completely innocuous.

While the question whether SD is good or bad for normal cortex remains somewhat uncertain, no doubt remains that SD can occur in cases of migraine, concussion and brain trauma, cerebral hypoxia and stroke, and possibly some types of epilepsy (Gorji 2001). As also discussed by Pomper et al. (2005), in metabolically impaired brain tissue, so called peri-infarct depolarizations (PIDs) cause demonstrable damage. PIDs are SD-like waves that emanate from the edges of cortical infarcts due to ischemia and traumatic injury. In the surrounding penumbra region where blood flow is not zero but reduced, PIDs can cause the growth of the infarct (Gorji 2001; Harris et al. 1981; Hossman 1971; Strong and Dardis 2005).

Pomper et al. (2005) have convincingly shown that in slice cultures of metabolically competent normally oxygenated but immature nervous tissue, repeated SD episodes do cause the death of neurons and probably also of glial cells. If confirmed in intact juvenile brains, this finding is relevant for the pathogenesis of neurological conditions of infants.

REFERENCES


