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AUTOCOMMENTARY

A new direction for spreading depolarization: Investigation in the fly brain

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Spreading depolarization (SD) is a complex neural phenomenon which we still do not fully understand. Fifty years after its initial discovery by Leão,[1] evidence suggested that SD may not occur in humans,[2] however it is now well established that SD underlies a spectrum of human brain pathologies from migraine with aura to stroke and traumatic brain injury.[3] It is characterized by substantial ion currents and the loss of ionic concentration gradients across neuronal and glial membranes but, in spite of intensive and prolonged research effort, it is still unclear which specific channels drive SD and the relative roles of neuronal and glial mechanisms. Now a recent article,[4] co-authored by 2 of us (KES and RMR), describes a different approach to SD using a new model which will allow a molecular genetic dissection of SD mechanisms in the fly brain.

Although most of the work on SD has concentrated on mammalian models, SD has been demonstrated in many non-mammalian species including those as primitive as insects.[5] In the present paper, Spong et al.[4] show that the hallmarks characteristic of SD can be recorded in the fly brain after treatment with ouabain to reduce activity of the Na^+/K^+-ATPase. In addition, using genetic strains of flies that differ in levels of PKG activity, the authors demonstrate that reduction of activity of cyclic GMP-dependent protein kinase (PKG) attenuates SD and suggest that the PKG pathway might have a similar modulatory role for SD in mammals, an idea that has not yet been tested. This new direction for SD research raises 2 important general questions: are findings from the fly brain relevant to human brain pathology and what can we learn from flies?

The weight of evidence, described in an accompanying review,[6] supports a conclusion that the neural mechanisms underlying SD in flies and mammals have a common molecular basis as a result of evolutionary conservation. For example, ouabain also induces SD in the mammalian brain.[7] Nevertheless, some may be skeptical of what the fly can really tell us about mammalian SD due to obvious CNS differences such as the presence in mammals, versus the absence in insects, of a vascular supply within neural tissue. Certainly the influence of the vasculature for providing oxygen and nutrients and for clearing metabolites, to say nothing of the release of modulators, greatly complicates the SD process in the mammalian CNS. However the lack of this complexity in the insect system may actually add value to the fly SD model given that the goal is to understand the fundamental neural underpinnings of the phenomenon. For instance the current paper clearly demonstrates that SD characteristics in the fly brain, despite the absence of a vascular system, are strikingly similar to SD recorded in the mammalian brain meaning that the presence of a vascular system is not a requirement for SD generation. Interruptions in blood flow during SD and the resulting injury that occurs in the mammalian brain need not be considered with the fly model system.

One advantage of invertebrate model systems, such as the fly, is that understanding the evolutionary origins and potential adaptive value of SD could help us

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determine the conditions under which SD is injurious or beneficial. It may be that, in insects, the ability to shut down the nervous system has adaptive value in conserving energy and preventing over-excitation. A similar adaptive role has been proposed for mammalian SD.[8] However, in spite of the observation that a preconditioning cortical SD can be neuroprotective under some circumstances, there is little doubt that repetitive SD in metabolically compromised neural tissue exacerbates brain damage. This apparent paradox presents a conundrum for the clinician who may have to decide under what circumstances to prevent or encourage SD. The fly provides a model that may reveal the evolutionary origins of SD and allows rapid and sophisticated molecular genetic dissection. For instance, experiments to target specific ion channels, pumps and modulatory pathways in various combinations and in a tissue-specific manner can be designed with a reasonable expectation that they can be completed expeditiously.

It is important not to overstate the molecular similarities between insects and mammals. For example, although the Na^+/K^+ATPase has an important role to play in SD of both taxonomic groups, there are 4 isoforms of the α subunit with different tissue distributions in mammals but only one in insects. The paper by Spong et al.[4] is only the first step in a new direction for SD. There is much to be done in the comparative analysis of SD mechanisms and it would not be surprising if the differences are as revealing as the similarities.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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