Review of: "The Ca2+-gated Cl- channel TMEM16A amplifies capillary pericyte contraction reducing cerebral blood flow after ischemia"

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It is controversial whether pericyte contraction can lead to microvascular occlusion during ischemia. This paper shows that a small rise in cytoplasmic Ca2+ concentration ([Ca2+]i) in pericytes activates chloride efflux through the Ca2+-gated anion channel TMEM16A, thus depolarizing the cell and opening voltage-gated calcium channels. This mechanism strongly amplifies the pericyte [Ca2+]i rise and capillary constriction evoked by contractile agonists and ischemia. In a rodent stroke model, TMEM16A inhibition slows the ischemia-evoked pericyte [Ca2+]i rise, capillary constriction and pericyte death, reduces neutrophil stalling and improves cerebrovascular reperfusion. This paper is quite innovative and the experimental methods is decent.

1. During reperfusion, Ani9 reduced the capillary constriction on the arteriole and the venule sides of the capillary bed, and the dependence of diameter on distance from the pericyte soma maintained a steeper negative slope that was significantly different from zero both during and after CCAO(Figure7F). The author can tell about why the capillary is narrower during reperfusion than CCAO. What is the potential mechanism?

2. To test whether the absence of an ET-1 evoked pericyte [Ca2+]i rise and contraction in 0[Ca2+]o was the result of preventing Ca2+ entry via Cav channels, or alternatively a result of depleting internal stores of Ca2+, The author examined the effect of the L-type Cav blocker nimodipine on the ET-1 response in normal [Ca2+]o solution. In addition to the flow of calcium ions in pericyte, the author can measure the effect of the nimodipine on pericyte contraction.

3. TMEM16A inhibition attenuates capillary constriction and pericyte death in ischemia. In addition to OGD in vitro, the author can use the NG2-dsRed mice to perform CCAO, to test the effect of Ani9 on pericyte coverage rate in vivo.

4. TMEM16A block improves CBF, reducing infarction and cerebral hypoxia after ischemic stroke in aged mice. What is the effect of Ani9 on mortality and neurological score in mice after CCAO?

5. The author can discuss about the difference in effect between Ani9 and Nimodipine on pericyte contraction. TMEM16A activation depolarizes pericyte, thus opening voltage-gated calcium channels. Nimodipine is clinically used to treat hypertension. Can nimodipine be used to treat cerebral infarction clinically?