Elevated Ca2+ sparklet activity during acute hyperglycemia and diabetes in cerebral arterial smooth muscle cells. [1]

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Abstract	Ca(+) sparklets are subcellular Ca(2+) signals produced by the opening of L-type Ca(2+) channels (LTCCs). In cerebral arterial myocytes, Ca(2+) sparklet activity varies regionally, resulting in low and high activity, "persistent" Ca(2+) sparklet sites. Although increased Ca(2+) influx via LTCCs in arterial myocytes has been implicated in the chain of events contributing to vascular dysfunction during acute hyperglycemia and diabetes, the mechanisms underlying these pathological changes remain unclear. Here, we tested the hypothesis that increased Ca(2+) sparklet activity contributes to higher Ca(2+) influx in cerebral artery smooth muscle during acute hyperglycemia and in an animal model of non-insulin-dependent, type 2 diabetes: the dB/dB mouse. Consistent with this hypothesis, acute elevation of extracellular glucose from 10 to 20 mM increased the density of low activity and persistent Ca(2+) sparklet sites as well as the amplitude of LTCC currents in wild-type cerebral arterial myocytes. Furthermore, Ca(2+) sparklet activity and LTCC currents were higher in dB/dB than in control myocytes. We found that activation of PKA contributed to higher Ca(2+) sparklet activity during hyperglycemia and diabetes. In addition, we found that the interaction between PKA and the scaffolding protein A-kinase anchoring protein was critical for the activation of persistent Ca(2+) sparklets by PKA in cerebral arterial myocytes after hyperglycemia. Accordingly, PKA inhibition equalized Ca(2+) sparklet activity between dB/dB and wild-type cells. These findings suggest that hyperglycemia increases Ca(2+) influx by increasing Ca(2+) sparklet activity via a PKA-dependent pathway in cerebral arterial myocytes and contributes to vascular dysfunction during diabetes.
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