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Oxidized Calcium Calmodulin Kinase and Atrial Fibrillation

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Abstract

This is a review of a recent work from the laboratory of Mark E. Anderson and associates at the University of Iowa. This laboratory has covered the role of calcium calmodulin II (CaMKII) in calcium signaling and myocardiocyte contraction, as well as signaling in smooth muscle, skeletal muscle, and nerve transmission. There are tissue specific mechanisms of action, partly related to the ryanogen receptor (RyR), and also related to tissue specific isoenzymes of CaMKII. Much ground has been traversed in exploring these mechanisms. This includes the recent discovery of hormone triggering by the release from vesicles at the nerve muscle junction, and much remains open to investigation.

Keywords: Calcium Calmodulin Kinase II (CaMKII), Oxidized Calcium Calmodulin Kinase II (ox-caMKII), Calcium signaling, Myocardiocyte, Atrial fibrillation (Afib), Angiotensin II (Ang II), Isoenzyme ryanogen receptor (RyR), Ca^{2+} sparks, MsrA target, atrial myocytes, blood pressure (BP), cardiac hypertrophy, proarrhythmic, Sinus node, Sarcoplasmic reticulum, Delayed After-Depolarizations (DADs).

Mini Review

This is a review of a recent work from the laboratory of Anderson et al. at the University of Iowa. This laboratory has covered the role of calcium calmodulin kinase II (CaMKII) in calcium signaling and myocardiocyte contraction, as well as signaling in smooth muscle, skeletal muscle, and nerve transmission. There are tissue specific mechanisms of action, partly related to the ryanogen receptor (RYR), and also related to tissue specific isoenzymes of CaMKII. Much ground has been traversed in exploring these mechanisms. This includes the discovery of hormone triggering by the release from vesicles at the nerve muscle junction, and much remains open to investigation.

The recently published work by Mark E. Anderson and associates in Mannheim and Heidelberg, Germany, clarifies the relationship between the oxidized form of CaMKII and the triggering of atrial fibrillation. The following studies show [1-5]:

1. Ang II infusion increased the susceptibility of mice to AF induction by rapid right atrial pacing and established a framework for us to test the hypothesized role of ox-CaMKII in promoting AFib. Ox-CaMKII is critical for AFib.
2. Estalished a critical role of ox-CaMKII in promoting AFib
3. Ang II induced increases in ROS production seen in WT atria were absent in atria from MsrA TG mice suggesting that MsrA sensitive targets represent an important component of Ang II mediated atrial oxidation.
4. The protection from AF in MsrA TG mice appeared to be independent of pressor effects that are critical for the proarrhythmic actions.
5. These findings suggest that NADPH oxidase dependent ROS and elevated ox-CaMKII drive Ang II -pacing-induced AF and that
6. targeted antioxidant therapy, by MsrA over-expression, can reduce or prevent AF in Ang –II infused mice [6].
7. Atrial myocytes from Ang II treated WT mice showed a significant ($p < 0.05$) increase in spontaneous Ca^{2+} sparks compared to atrial myocytes from saline treated control mice
8. In contrast to findings in WT mice, the atrial myocytes isolated from Ang II treated MM-VV mice did not show an increase in Ca2+ sparks compared to saline treated MM-VV mice

9. These data to suggest that in ox-caCMKII-the proarrhythmic effects of Ang II infusion depend upon an increase CaMKII, sarcoplasmic reticulum Ca^{2+} leak and DADs.

10. Enhanced CaMKII-mediated phosphorylation of serine 2814 on RyR2 is associated with an increased susceptibility to acquired arrhythmias, including AFib

11. Proarrhythmic actions of ox-CaMKII require access to RyR2 serine 2814.

12. Mutant S2814A knock-in mice (lacking serine 2814) were highly resistant to Ang II mediated AFib

13. AC3-I mice with transgenic myocardial expression of a CaMKII inhibitory peptide were also resistant to the proarrhythmic effects of Ang II infusion on pacing-induced AFib [7,8].

14. S2814A, AC3-I and WT mice, all developed similar BP increases and cardiac hypertrophy in response to Ang II, indicating that these mice were not resistant to the hemodynamic effects of Ang II, but were nevertheless protected from AFib.

15. selectively targeted antioxidant therapies could be effective in preventing or reducing AFib

16. half of patients enrolled in the Mode Selection Trial (MOST) with sinus node dysfunction had a history of AFib

17. Ang II and diabetes-induced CaMKII oxidation caused sinus node dysfunction by increased pacemaker cell death and fibrosis

18. ox-CaMKII increases susceptibility for AF via increased diastolic sarcoplasmic reticulum Ca^{2+} release

19. clinical association between sinus node dysfunction and AF might have a mechanistic basis because sinus node dysfunction and AF are downstream consequences of elevated ox-CaMKII [9,10].

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