Metabolic signals of arrhythmia

Jason R.B. Dyck[a,b] **and Peter E. Light**[b]
[a]**Cardiovascular Research Group, Department of Pediatrics, Faculty of Medicine and Dentistry,
University of Alberta, Edmonton, Alberta, Canada, and** [b]**Cardiovascular Research Group,
Department of Pharmacology, Faculty of Medicine and Dentistry,
University of Alberta, Edmonton, Alberta, Canada**

Correspondence: Dr Jason R.B. Dyck, Departments of Pediatrics and Pharmacology,
474 Heritage Medical Research Centre, University of Alberta, Edmonton, Alberta, Canada, T6G 2S2.
Tel: +1 780 492 0314; fax: +1 780 492 9753; e-mail: jason.dyck@ualberta.ca

Abstract

Cardiac arrhythmias represent a major cause of mortality in the Western world. Recent research has advanced our understanding of the cellular and molecular mechanisms of arrhythmogenesis and has demonstrated that some of the causes of arrhythmias may occur as a result of perturbations in cardiac energy metabolism. These alterations in cardiac energy metabolism can have direct effects on the activity of ion channels and exchangers involved in ionic homeostasis, which can subsequently promote arrhythmogenesis. In addition, a mutation in AMP-activated protein kinase – a kinase that has a major role in the regulation of cardiac energy metabolism – has been implicated in causing ventricular pre-excitation and/or progressive conduction system disease, further highlighting the involvement of metabolism in contributing to cardiac arrhythmogenesis. Pharmacological modulation of specific metabolic pathways may therefore represent a novel approach for the clinical treatment and prevention of certain types of arrhythmias.
■ *Heart Metab.* 2006;33:5–8.

Keywords: Arrhythmia, cardiac energy metabolism, ion channels, AMPK, PRKAG2

Introduction

The correct conduction of electrical signals within the heart relies on the precise spatial and temporal control of action potential propagation throughout the myocardium. It comes as no surprise that any disruption in this highly orchestrated rhythmic process can potentially lead to life-threatening electrical abnormalities or arrhythmias. Indeed, arrhythmias are one of the major causes of cardiac-related deaths in the Western world.

Depending on the underlying reason, arrhythmias may be generated in many different regions of the heart. The most common type of arrhythmia is atrial fibrillation, which has an incidence of 6% in people older than 65 years [1]; other types of arrhythmia include congenital long QT syndrome and familial Wolff–Parkinson–White (WPW) syndrome [2]. It is now apparent that the underlying trigger for many types of arrhythmias may not be purely electrical in nature, but that alterations in cellular metabolism also contribute to abnormal ionic homeostasis leading to increased susceptibility of the myocardium to arrhythmogenic events. Thus the attenuation of metabolic disturbances may offer a novel therapeutic strategy in several types of arrhythmia, such as those precipitated by ischemia-reperfusion injury and familial WPW syndrome, in which metabolism has a causative role. Because of the relative clinical importance of the proarrhythmogenic events that are probably generated in response to the metabolic disturbances that occur in ischemia-reperfusion and familial WPW

Basic article

Jason R.B. Dyck and Peter E. Light

syndrome, we have focused this review on these two topics.

Ischemic metabolism and arrhythmogenesis

The most common trigger for fatal arrhythmias is the underlying pathology of acute coronary syndrome. Myocardial ischemia has a major role in the pathophysiology of heart disease and is a major health concern worldwide. The slowing or cessation of blood flow to regions of the heart resulting from coronary artery occlusion induces ischemia and provides the ideal conditions for the genesis of arrhythmias. It is now apparent that both ionic and metabolic disturbances act in concert to trigger proarrhythmic activity within the myocardium.

During severe ischemia, oxidative metabolism effectively ceases and ATP is produced primarily from glucose via anaerobic glycolysis. Although the benefit of a continued supply of ATP via glycolysis is essential to myocardial cell function and survival, the hydrolysis of glycolytically derived ATP in the absence of glucose oxidation results in an accumulation of protons and lactate that may cause cardiac dysfunction and/or arrhythmias, either during ischemia or after reperfusion [3,4]. One reason why this dysfunction occurs is that the already diminished supply of ATP is redirected from myocardial contraction towards the clearance of the glycolytic byproducts. If the ischemic episode is too severe, then ATP concentrations may decrease sufficiently to alter ionic homeostasis, leading to proarrhythmic activity. Indeed, the ST-segment elevation often observed on the electrocardiogram in the ischemic heart is believed to result from excess opening of ATP-sensitive potassium channels [5]. A limited supply of ATP may also lead to the impaired clearance of sodium ions via the action of Na^+/K^+-ATPase. Furthermore, upon reperfusion, the accumulated protons are removed from the cardiac myocyte by the $Na^+–H^+$ exchanger NHE1, in exchange for Na^+ ions, which further increases the intracellular Na^+ concentration. This increase in intracellular Na^+ activates the $Na^+–Ca^{2+}$ exchanger in the reverse mode, thus promoting increased accumulation of Ca^{2+} within the cardiac myocyte. The resultant Ca^{2+} overload is believed to be a major cause of contractile dysfunction of cardiac arrhythmias after reperfusion of an ischemic myocardium [6].

In addition to alterations in the supply of ATP during ischemia, there are other metabolic signals that can contribute to arrhythmias. As metabolism is switched from β-oxidation of fatty acids to glycolytic production of ATP during ischemia, an intracellular build-up of lipid metabolites such as lysophosphatidylcholine* has been shown to increase the persistent activity of the normally transient voltage-gated sodium channel [7], which may also contribute to action potential prolongation and Na^+ loading in myocytes. Furthermore, esterified fatty acids such as long-chain acyl coenzyme A also accumulate in the ischemic myocardium, and our recent research (Embo J 2006, in press) suggests that these metabolites increase reverse-mode $Na^+–Ca^{2+}$ exchange activity, further exacerbating Ca^{2+} overload, contractile dysfunction, or cardiac arrhythmias.

Reperfusion of reversibly injured myocardial tissue improves functional recovery, but there are also negative consequences associated with restoring blood flow to the ischemic region. For example, reperfusion of the ischemic myocardium results improved mitochondria function and a rapid production of reactive oxygen species, which further exacerbates existing ionic imbalances [8]. Therefore the metabolic generation of reactive oxygen species is also believed to have a major role in cardiac arrhythmogenesis.

Collectively, the metabolites that are generated during ischemia and/or reperfusion, or both, will alter both sodium and calcium homeostasis and contribute to electrical dysfunction. This resulting heterogeneity of the action potential duration and dispersion of refractoriness will lead to an increased potential for re-entrant-type arrhythmias [9]. Therefore, it is clear that the alterations in cardiac energy metabolism that occur during ischemia-reperfusion have a major impact on many ion channels and exchangers involved in ionic homeostasis, highlighting the importance of metabolism in the control of arrhythmogenesis.

Alterations in AMP-activated protein kinase activity and arrhythmogenesis

In addition to the metabolic disturbances that occur during ischemia-reperfusion, there are also genetic mutations that can alter the function of specific proteins, eventually leading to arrhythmias. A number of these proteins are ion channels [10,11]; however, several mutations in one enzyme that has a major role in the regulation of cardiac energy metabolism have been identified as being a major contributor to ventricular pre-excitation or progressive conduction system disease, or both. This enzyme is AMP-activated protein kinase (AMPK)*. The identification of this key regulator of cardiac energy metabolism as being centrally involved in a specific arrhythmia further supports the notion that metabolism plays a major part in the regulation of arrhythmogenesis.

AMPK is a heterotrimeric protein (consisting of an α–β–γ complex) that regulates both whole-body and cellular utilization of energy [12]. Early reports showed that AMPK is activated by metabolic stresses that

deplete cellular ATP [13] and responds by readjusting energy production and expenditure in order to re-establish the supply of ATP. AMPK has a major role in regulating cardiac energy metabolism [3], but specific mutations in the γ_2 gene of AMPK (PRKAG2)[*] have recently been shown to alter AMPK activity in the heart [14–17]. These PRKAG2 mutations also appear to be directly responsible for a glycogen storage cardiomyopathy characterized by ventricular pre- excitation (WPW syndrome), progressive conduction system disease [18–22], and, in specialized cases, cardiac hypertrophy [23,24]. This triad of cardiac abnormalities has been termed the PRKAG2 cardiac syndrome [23,24].

The exact cause of this ventricular pre-excitation in patients with the PRKAG2 cardiac syndrome has not been firmly established, but it has been suggested that conduction system abnormalities observed in this disease originate from glycogen-filled myocytes causing the formation of pre-excitation muscular bypass tracts between the atrial and ventricular chambers [18,20]. Such tracts are used as a retrograde limb of the re-entrant circuit, and appear to result in a macro-re-entrant arrhythmia. The finding that a mutation in a major regulator of cardiac energy metabolism leads to arrhythmias further supports the concept that alterations in cardiac energy metabolism, independent of ischemia-reperfusion, may be sufficient to signal arrhythmogenic activity.

Although metabolic alterations occurring in response to abnormal AMPK activity clearly produce glycogen-filled myocytes that may act as bypass tracts, there are also other possible mechanisms by which alterations in AMPK activity may contribute to the arrhythmogenic activity. Indeed, we have shown that the cardiac Na^+ channel is also regulated by activated AMPK [2,25], and suggested that there may be other ion channels that are regulated by AMPK, which could contribute to the observed arrhythmogenic activity in patients with some PRKAG2 mutations [25]. Future research will undoubtedly clarify the targets of the mutated form of AMPK and help establish the precise mechanism by which the ventricular pre-excitation and progressive conduction system disease originate in patients who are afflicted with the PRKAG2 cardiac syndrome.

Summary

It is becoming clear that alterations in cardiac energy metabolism can have a major role in the development of cardiac arrhythmias, but it is currently unknown whether pharmacological restoration of cardiac metabolism will be an effective approach to the treatment of arrhythmogenesis. Although the approach of ''metabolic modulation'' for the treatment of cardiac arrhythmias is in its infancy, there is clear evidence that modifications to the downstream effector ion channels, and exchangers, or both, that are disturbed by metabolic alterations may have clear benefit for the treatment of certain arrhythmias. For example, drugs that ameliorate the function of the Na^+–H^+ and the Na^+–Ca^{2+} exchangers are good candidates for novel antiarrhythmic agents [26,27]. In addition, modulation of AMPK activity in patients with the PRKAG2 mutations that cause familial WPW syndrome may help prevent the accumulation of glycogen or prevent the ventricular pre-excitation and progressive conduction system disease. Together, these new strategies may one day lead to improved treatment of patients who develop cardiac arrhythmias that are related to ischemia-reperfusion or the PRKAG2 cardiac syndrome. ∎

[*] See glossary for definition of these terms.

REFERENCES

1. Roberts R. Mechanisms of disease: genetic mechanisms of atrial fibrillation. *Nat Clin Pract Cardiovasc Med*. 2006;3: 276–282.
2. Light PE. Familial Wolff–Parkinson–White Syndrome: a disease of glycogen storage or ion channel dysfunction? *J Cardiovasc Electrophysiol*. 2006;17 (suppl 1):S158–S161.
3. Dyck JR, Lopaschuk GD. AMPK alterations in cardiac physiology and pathology: enemy or ally? *J Physiol*. 2006;574:95–112.
4. Dennis SC, Coetzee WA, Cragoe EJ Jr, Opie LH. Effects of proton buffering and of amiloride derivatives on reperfusion arrhythmias in isolated rat hearts. Possible evidence for an arrhythmogenic role of $Na(^+)$–H^+ exchange. *Circ Res*. 1990;66:1156–1159.
5. Li RA, Leppo M, Miki T, Seino S, Marban E. Molecular basis of electrocardiographic ST-segment elevation. *Circ Res*. 2000; 87:837–839.
6. Piper HM, Meuter K, Schafer C. Cellular mechanisms of ischemia-reperfusion injury. *Ann Thorac Surg*. 2003;75: S644–S648.
7. Shander GS, Undrovinas AI, Makielski JC. Rapid onset of lysophosphatidylcholine-induced modification of whole cell cardiac sodium current kinetics. *J Mol Cell Cardiol*. 1996;28: 743–753.
8. Hool LC. Reactive oxygen species in cardiac signalling: from mitochondria to plasma membrane ion channels. *Clin Exp Pharmacol Physiol*. 2006;33:146–151.
9. Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. *Basic Res Cardiol*. 2001;96:517–527.
10. Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a HuGE review. *Genet Med*. 2006;8:143–155.
11. Bjerregaard P, Gussak I. Short QT syndrome: mechanisms, diagnosis and treatment. *Nat Clin Pract Cardiovasc Med*. 2005;2:84–87.
12. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab*. 2005;1:15–25.
13. Yeh LA, Lee KH, Kim KH. Regulation of rat liver acetyl-CoA carboxylase. Regulation of phosphorylation and inactivation of acetyl-CoA carboxylase by the adenylate energy charge. *J Biol Chem*. 1980;255:2308–2314.
14. Ahmad F, Arad M, Musi N, et al. Increased alpha2 subunit-associated AMPK activity and PRKAG2 cardiomyopathy. *Circulation*. 2005;112:3140–3148.
15. Davies JK, Wells DJ, Liu K, et al. Characterisation of the role of gamma2 R531G mutation in AMP-activated protein kinase in cardiac hypertrophy and Wolff–Parkinson–White syndrome. *Am J Physiol Heart Circ Physiol*. 2006;290:H1942–H1951.

16. Sidhu JS, Rajawat YS, Rami TG, et al. Transgenic mouse model of ventricular preexcitation and atrioventricular reentrant tachycardia induced by an AMP-activated protein kinase loss-of-function mutation responsible for Wolff–Parkinson–White syndrome. *Circulation*. 2005;111:21–29.

17. Zou L, Shen M, Arad M, et al. N488I mutation of the gamma2-subunit results in bidirectional changes in AMP-activated protein kinase activity. *Circ Res*. 2005;97:323–328.

18. Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest*. 2002;109:357–362.

19. Vaughan CJ, Hom Y, Okin DA, McDermott DA, Lerman BB, Basson CT. Molecular genetic analysis of PRKAG2 in sporadic Wolff–Parkinson–White syndrome. *J Cardiovasc Electrophysiol*. 2003;14:263–268.

20. Gollob MH, Seger JJ, Gollob TN, et al. Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. *Circulation*. 2001;104:3030–3033.

21. Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff–Parkinson–White syndrome. *N Engl J Med*. 2001;344:1823–1831.

22. Blair E, Redwood C, Ashrafian H, et al. Mutations in the gamma(2) subunit of AMP-activated protein kinase cause familial hypertrophic cardiomyopathy: evidence for the central role of energy compromise in disease pathogenesis. *Hum Mol Genet*. 2001;10:1215–1220.

23. Gollob MH. Glycogen storage disease as a unifying mechanism of disease in the PRKAG2 cardiac syndrome. *Biochem Soc Trans*. 2003;31:228–231.

24. MacRae CA, Ghaisas N, Kass S, et al. Familial hypertrophic cardiomyopathy with Wolff–Parkinson–White syndrome maps to a locus on chromosome 7q3. *J Clin Invest*. 1995;96:1216–1220.

25. Light PE, Wallace CH, Dyck JR. Constitutively active adenosine monophosphate-activated protein kinase regulates voltage-gated sodium channels in ventricular myocytes. *Circulation*. 2003;107:1962–1965.

26. Ayoub IM, Kolarova J, Yi Z, et al. Sodium–hydrogen exchange inhibition during ventricular fibrillation: beneficial effects on ischemic contracture, action potential duration, reperfusion arrhythmias, myocardial function, and resuscitability. *Circulation*. 2003;107:1804–1809.

27. Gazmuri RJ, Ayoub IM, Hoffner E, Kolarova JD. Successful ventricular defibrillation by the selective sodium–hydrogen exchanger isoform-1 inhibitor cariporide. *Circulation*. 2001;104:234–239.