Editorial

Another layer of ventricular heterogeneity? \(\alpha_1\) agonists prolong repolarization in Purkinje fibers but not M-Cells

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See article by Burashnikov and Antzelevitch ([1], pages 901–908) in this issue.

The heart is a complex organ and grows more so each day. Past research has firmly established the existence of multiple cell types that coexist within the myocardium, each demonstrating a unique electrophysiological identity, regional localization, and coupling relationship with neighboring cells that specify the pattern of the heart beat. Within each cardiac cell type, the action potential waveform is determined by a delicate interplay among a variety of inward and outward currents flowing through distinct ion channels, pumps and transporters. The activity of each of these cellular components can in turn be modulated by drugs, hormones and neural stimulation, or modified by disease. While we are rapidly gaining an appreciation for the molecular and genetic events underlying this complexity, there remain significant gaps in our knowledge about how these events become integrated at the cell and tissue level, in health and disease.

In this issue, Alexander Burashnikov and Charles Antzelevitch add another dimension to an already complex situation by describing dramatic differences in the way ventricular cells respond to \(\alpha_1\)-adrenergic receptor agonists [1]. Using strips of tissue carefully isolated from different regions of the canine myocardium, these investigators studied the effects of \(\alpha_1\)-agonists on action potential duration. For the first time, they demonstrate a major pharmacologic difference between Purkinje fibers and M-cells, the two cell types that figure most prominently in discussions on the mechanism of pause-dependent proarhythmia. Their studies show that activation of the \(\alpha_1\)-receptor by either methoxamine or phenylephrine prolongs repolarization in Purkinje fibers at concentrations and cycle lengths that shorten the action potential in M-cells. This finding carries important implications for understanding how arrhythmias associated with QT interval prolongation, either congenital or induced by drugs, might occur.

1. Basic mechanisms: \(\alpha_1\)-receptors and the heart

Three different \(\alpha_1\)-adrenergic receptors subtypes have been cloned from different species and tissues (\(\alpha_1b\), \(\alpha_1c\), \(\alpha_1d\)) [2] and the existence of a fourth subtype (\(\alpha_1a\)) has been proposed based on a pharmacologic profile that is distinct from each of the cloned receptors. Although \(\alpha_1\)-receptors play a dominant role in smooth muscle contraction, including the control of blood pressure, they are also present in the adult myocardium, where their function has been the subject of intense investigation. Cardiac \(\alpha_1\)-receptors have been suggested to contribute to the generation of ventricular arrhythmia following ischemia and reperfusion [3,4], and to trigger hypertrophic cell growth in vitro [5,6] and in vivo [7]. Their importance in regulating cardiac activity under normal physiological conditions remains less clear, although a number of important repolarization currents appear to be sensitive to \(\alpha_1\)-receptor activation. The literature exploring these electrophysiological effects is thoroughly reviewed by Burashnikov and Antzelevitch [1].

All four \(\alpha_1\)-receptor subtypes are present in the mammalian ventricle [8], but the amount of each is extremely variable from species to species and within different regions of the heart. Rat myocardium is reported to contain a ten-fold greater density of \(\alpha_1\)-receptors than rabbit, with the majority (70%) being the \(\alpha_1b\) subtype and the remainder (30%) \(\alpha_1a\) in both species [9]. Using RT-PCR measurements, Wolf et al. [10] found alpha-1-
receptor mRNA to be distributed non-uniformly throughout the rat heart, with α1b receptor transcripts being most common (>50%), except in papillary muscle and the septal region, which contained a high proportion of α1a receptor message. In human ventricle, α1-1 receptors are considered to be low in density and to mediate only weak second messenger (IP3) signals [11].

Burashnikov and Antzelevitch [1] report that action potential duration is prolonged by alpha-1-agonists in canine Purkinje fibers but shortened in canine M-cells. These two effects appear to be mediated by different receptor subtypes, as evidenced by the ability of the α1b antagonist clorethylclonidine (CEC) to inhibit the shortening in M-cells but not the prolongation in Purkinje fibers. Unfortunately, the data do not permit one to associate these particular electrophysiological effects with a regional distribution of alpha-1-receptor subtypes in these tissues. Nor can one draw clear conclusions about which membrane currents mediate the effects on repolarization time course. Of interest in this regard is the finding that the amount of alpha-1-agonist induced prolongation decreases with increasing rates of stimulation, a phenomenon known in the antiarrhythmic drug literature as ‘reverse use-dependence.’ This suggests that that target for alpha-1-agonist action is a component of repolarization current whose role is minimized at short cycle lengths, e.g. the rapid delayed rectifier current IKr, which is consistent with the conclusion reached by Lee and Rosen in their study of canine Purkinje fibers [12]. The slow delayed rectifier IKs is enhanced by alpha-1-agonists [13], and an offsetting increase in this current may be the basis for the observed shortening of the M-cell action potential in the experiments presented here. The data obtained by Burashnikov and Antzelevitch [1] would suggest that the IKr effect is mediated via α1a receptors, while the IKs effect may depend on α1b receptor activation. The existing literature neither fully supports nor entirely refutes this interpretation, nor does it establish the basis for the differential effect. The authors suggest that cells with weak IKs (e.g. M-cells) may be more likely to have that current enhanced by alpha-1-receptor stimulation than cells with a robust IKs. Whether a robust IKs is characteristic of Purkinje fibers is still unclear. More work is needed at both the molecular and cellular levels to resolve these questions.

2. Clinical implications: alpha-1-receptors and arrhythmogenesis

There is a considerable body of work on alpha-1-receptors and reperfusion arrhythmias [14,15], much of which links arrhythmogenesis to α1a receptor activation [4,16,17]. However, specific blockers of α1a receptors such as UK 52,046 fail to protect against induction of experimental arrhythmias in acutely ischemic myocardium [18]. Alpha-1-receptor activation has also been implicated, albeit indirectly, in the generation of the malignant ventricular arrhythmia torsade de pointes. One of the more consistent and predictive models of drug-induced torsade de pointes involves the pretreatment of rabbits with methoxamine prior to administration of the test compound. In this model, IKr blockers such as dofetilide [19], d-sotalol [20] and almokalant [21] reliably generate QT prolongation followed by a polymorphic ventricular tachycardia. This model has become one that is used by pharmaceutical companies to assess the risk of serious proarrhythmia for drugs that prolongs the QT interval. The results presented by Burashnikov and Antzelevitch [1] raise several interesting points. First, the preferential prolongation by methoxamine of action potential duration in Purkinje fibers versus M-cells suggest that the triggering event in the methoxamine-treated rabbit model may involve the Purkinje system. This is consistent with tridimensional mapping data placing the initiating event for torsade at the subendocardial surface [22]. Moreover, the data clearly establish that methoxamine pretreatment dramatically alters the electrical substrate of the heart, and resets the baseline dispersion of ventricular refractoriness so that it favors an arrhythmic response. This means that the effects of QT-prolonging drugs such as dofetilide, a potent and highly specific blocker of IKr, are not being studied in isolation, but in a complex pharmacologic setting that involves the non-specific and heterogeneous blockade of multiple potassium channel subtypes as background. From the standpoint of drug development in predicting drug safety, one needs to evaluate whether these marked and perhaps non-physiological alterations in electrical substrate effectively capture the clinical conditions under which serious pause-dependent arrhythmias are likely to become manifest.

3. Limitations of the study

The authors leave unresolved a most critical question: why do the effects of alpha-1-agonists differ in Purkinje fibers and M-cells? Except for a pacemaker current and T-type calcium channels in Purkinje fibers, both appear to contain the same complement of electrogenic cell components, and, until now, both have been essentially indistinguishable in their response to drugs. Burashnikov and Antzelevitch cite the possibility that the level of IKs may be critical in determining the magnitude of the change induced by alpha-1-agonists. The implications are that IKs is weak in M-cells and strong in Purkinje fibers, and that a contribution of IKs can completely reverse the effect of reduced IKr on repolarization time course. Neither is known at this time. Another possibility is that the type of alpha-1-receptors present on the surface of the two cells differ, or that there are differences in the post-receptor signaling pathways and/or the effector sites involved. However, a third possibility is that native alpha-receptor
responsiveness in M-cells may have been lost or blunted during the preparation of the tissue samples used in the study. It has been reported that alpha-receptor function can be dynamically regulated by experimental conditions [24]. Without compelling data supporting a contrary position, one cannot exclude that the dissection of M-cell preparations from within the myocardial wall represents an extreme measure that altered the ability of the M-cells to respond to alpha-1-agonists during exposure in vitro.

4. Conclusions

The study generates a critical need for new and detailed information on all the types of heterogeneity that exist within the mammalian ventricle at the protein, transcriptional and functional levels. The demonstration that cell types specific to epicardial, endocardial and mid-myocardial regions may respond differently to a physiologic stimulus such as alpha-1-adrenergic stimulation provides a crucial insight that will enhance our understanding of how serious cardiac arrhythmias can be triggered. However, data on the specific membrane currents affected are needed, as is firm confirmation of the receptor subtype and signaling pathway involved in the response. This having been said, one also needs to confirm that what is measured in vitro actually represents the situation in the intact heart. In this regard, Burashnikov and Antzelevitch have provided an important beginning.

References


