Aldosterone, ion channels, and sudden death: another piece of the circle?

Geoffrey S. Pitt1 and Bertram Pitt2

1Departments of Medicine and Pharmacology and Center for Molecular Cardiology, College of Physicians and Surgeons, Columbia University, New York, New York; and 2Department of Medicine, University of Michigan, Ann Arbor, Michigan, and William Beaumont Hospital, Department of Internal Medicine, Royal Oak, Michigan

Despite discovery of the genetic basis for many inherited and certain acquired cardiac arrhythmias during the last decade, the connection between identified mutations and consequent arrhythmias remains unclear in many cases. For some, the mechanisms for arrhythmogenesis are well understood. Loss-of-function mutations in ether-a-go-go-related gene (HERG), the pore-forming subunit of inwardly rectifying K+ current (I_K1), decrease the “repolarization reserve” and render patients susceptible to reentry-induced arrhythmias during the late phase of the action potential, thus forming the basis for Long QT Syndrome 2 (LQT2) and certain acquired (drug-induced) Long QT Syndromes (17). Certain mutations in SCN5A, the gene for the cardiac sodium channel, affect how the channel inactivates; the mutant channels thereby generate a persistent inward depolarizing Na+ current during the action potential plateau phase, especially at slow heart rates, which forms the substrate for arrhythmia-triggering early afterdepolarizations in LQT3 (8). For some arrhythmogenic disorders resulting from haploinsufficiency of the sodium channel, the age-related slowing of cardiac conduction that leads to atrioventricular block, which defines progressive cardiac conduction defect (PCCD) or a subset of the autosomal dominantly inherited Brugada syndrome (BrS), for example, the molecular basis has been more difficult to understand.

There are at least two puzzling features about the connection between loss-of-function mutations in one SCN5A allele and the resultant arrhythmias. First, despite the presence of mutations that reduce the number of sodium channels from birth, patients with these disorders do not generally become symptomatic before the third or fourth decade of life. PCCD is clearly age related. Arrhythmogenic sudden death from BrS, the most common cause of death for men in Southeast Asia other than accidents (1), is rare in children; in a study of the natural history of BrS, the mean age at the time of the index cardiac event was 33 ± 13 y (16). Second, modeling of the cardiac action potential suggests a large safety factor for the sodium current; reducing the sodium current even by one-half should not, in itself, lead to conduction slowing or block (9). What additional factor(s) contribute and why symptoms occur primarily in older patients are now becoming clear from a number of recent studies.

Analysis of mice with a knockout of the SCN5A gene suggested that the development of fibrosis may be a major contributor to these arrhythmias (18). Homozygous Scn5a−/− mice died before birth, but heterozygous (Scn5a+/−) mice (viable and fertile) showed slowing of cardiac conduction and various degrees of block as they aged, similar to patients with PCCD (12). Correlating with the appearance of conduction slowing was extensive heterogeneous fibrosis within the ventricular myocardium and the bundle branches, as well as abnormal distribution of connexin 43, the gap junction responsible for propagation of electrical activity in ventricular myocytes (18, 21). Fibrosis may affect the conduction disturbances in BrS, too. A histopathological study of an explanted heart from a BrS patient showed extensive fibroelastosis and fatty infiltration within the right ventricle (6). Together, these suggest that a reduction in sodium channels might activate gene expression cascades that result in fibrosis. Indeed, the early growth response-1 transcription factor (Egr-1), a master regulator that influences the expression of many other genes, was found to be upregulated in the Scn5a+/− mice. Nevertheless, there are several missing links in these signaling pathways, and their identification could open the possibility of pharmacological intervention. In this context, a report in this issue offers new insight and perhaps therapeutic promise.

Measuring sodium channel currents in cultured mouse ventricular myocytes, Boixel et al. (5) in a study in this issue of the American Journal of Physiology-Heart and Circulatory Physiology found that incubation with aldosterone for 24 h increased current density in a dose-dependent manner and lengthened the action potential duration. This effect appeared dependent on the mineralocorticoid receptor (MR) because it was blocked with the MR antagonist spironolactone but not with the glucocorticoid receptor antagonist RU-38486. Confirming previous results from Bénitah and colleagues, this report also demonstrated that aldosterone, acting through the MR, increased Ca2+ channel current density (13) and fits well with a growing literature that shows how aldosterone influences the electrical properties of cardiac myocytes and increases action potential duration.

These results are compelling for at least two reasons. First, aldosterone has been shown to activate a number of mediators that can lead to myocardial fibrosis (15). One only has to implicate a homeostatic process whereby decreased sodium channel current density triggers a feedback loop that increases aldosterone to appreciate how haploinsufficiency for SCN5A could lead to fibrosis. Indeed, Egr-1, the transcription factor upregulated in Scn5a+/− mice, is activated specifically in the hearts of transgenic mice overexpressing the mineralocorticoid receptor but not in other aldosterone target tissues (10). Thus PCCD, the most common cause worldwide for pacemaker implantation, is ripe for testing whether aldosterone antagonism prevents or delays the development of conduction block. Second, we may now be seeing part of the molecular basis for the striking clinical finding that a significant portion of the mortality benefit of aldosterone antagonism in heart failure derives from a reduction in sudden death (14). Blockade of a mechanism that increases sodium channel density (this report) or increases calcium channel density and then decreases the transient outward current (I_to) (4) would ameliorate QT prolongation, a common finding and an independent risk factor for sudden death in heart failure (3, 19, 20, 22).

Address for reprint requests and other correspondence: G. S. Pitt, Columbia Univ., Dept. of Pharmacology, 630 W. 168th St., PH 7W 318, New York, NY 10032 (email: gp2004@columbia.edu).
A recent report (11) showing that loss-of-function mutations in SCN5A also underlie some forms of inherited dilated cardiomyopathy (DCM) makes it tempting to speculate even more broadly. Loss-of-function sodium channelopathies may represent different manifestations of a common starting point in which a reduction in sodium channel increases aldosterone. The distinct consequences inherent to specific syndromes could reflect the interactions of unique contributing factors that may derive, at least in part, from specific differences in effects of the mutations. “Loss-of-function” mutations (which implies that mutant channels, expressed in heterologous systems, fail to display the full complement of wild-type sodium channel functions) may produce channels that lack any inward current, channels that support a reduced inward current, or may instead affect channel trafficking, targeting, or interaction with other regulatory proteins. These defects may differentially alter the net sodium current or its kinetics, changing electrical activation and thereby the cardiac load within the complex milieu of the cardiac cycle so that over time the effects are mainly right-sided effects in some cases (BrS) or more global in others (DCM). The data in Boixel et al. (5) hint at this complexity: aldosterone increased sodium channel current density without changing channel protein or mRNA levels, but inhibitors of protein synthesis or trafficking blocked the increase, suggesting that aldosterone affected the expression and trafficking of a sodium channel regulatory protein.

Under certain circumstances, aldosterone may also have other effects that could contribute to sudden death, including stimulation of central sympathetic drive (7), release of norepinephrine from peripheral sympathetic nerves (2), and a decrease in heart rate variability and baroreceptor function (23). Regardless, the new information reported by Boixel et al. (5) suggests that MR blockade may have an important role in reducing sudden death in a far broader spectrum of circumstances than hitherto thought possible.

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