Published in final edited form as:
Circ Res. 2008 August 15; 103(4): 325–327. doi:10.1161/CIRCRESAHA.108.182055.

Increased Sensitivity to Local Anesthetic Drugs - Bedside to Bench

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Keywords

Brugada syndrome; local anesthetics; NA channels

This issue contains the surprising report of a middle-aged African-American with Brugada syndrome associated with two widely separated missense mutations in the Na channel gene and with dramatically increased lidocaine sensitivity[1]. Following a seizure in the Emergency Room he developed an episode of monomorphic ventricular tachycardia terminated by electric shock. After IV lidocaine was started he quickly developed the ECG characteristics of Brugada phenomenon. Although local anesthetics (LA) with slow off-rates typically induce such ECG changes, this has not been reported for lidocaine. After identifying the two mutations in this individual's Na channel α-subunit gene, Barajas-Martinez et al[1]. exposed the mutated channel to lidocaine and found markedly increased sensitivity to block.

The finding of two unrelated mutations in the same Na channel gene is unusual. Ackerman and colleagues[2] reported that one of these mutations, L1308F, is a rare polymorphism (seen once in 319) in an African-American population, but not in Caucasian, Asian, or Hispanic populations. Barajas-Martinez and colleagues[1] indicated that they have seen this polymorphism in 1% of their Caucasian population. No previous studies of lidocaine sensitivity has been reported for this polymorphism, but it now seems possible that individuals with the L1308F polymorphism are at risk of local anesthetic toxicity. This question deserves follow-up.

Why should we care much about rare syndromes such as Brugada, when they are a mere drop in the bucket of total cardiac arrhythmic death? Because they are a window into mechanisms of lethal arrhythmia and their study can lead to preventive or corrective therapy. Although these monogenetic diseases are rare, the conditions can be reproduced in the laboratory, an invaluable tool that is very difficult to achieve with such multifactorial diseases such as regional ischemia. Indeed, excellent progress has been made in understanding the way in which Brugada-related reduced membrane expression of Na channels in the background of nonuniform distribution of the repolarizing K channels can lead to localized early repolarization and initiation of reentry arrhythmia[3]. By all means, we still have much to learn about these monogenic diseases. In Brugada syndrome, for example, only a minority of patients have had a gene abnormality identified in the Na channel α-subunit. Regulation of expression of the Na channel gene itself is as yet poorly understood, much less the expression and roles of the several β-subunits. Several modulatory factors could alter gating of the Na channel in a regional way, thereby changing

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Disclosures: None

the delicate balance between Na currents and repolarizing ones. There are likely to be many players in that process that can result in a Na current that is defective, leading to a common arrhythmic mechanism.

Enthusiasm of cardiologists and pharmaceutical research companies for use of drugs in the prevention of arrhythmias was severely dampened as a result of the harmful outcome of antiarrhythmic drugs in the CAST trial. This has led to flourishing of alternative methods, most dramatically in use of implanted defibrillators or of ablative catheter procedures. For particularly high risk groups, these approaches have been lifesaving[4]. But as we consider expanding them into the overwhelming majority of those at risk, we find that they are only partially effective and/or are associated with serious medical and economic side-effects. Without disparaging the achievements of the device-intervention approach for the appropriate population, we can recognize their limitations for management of the larger population at risk for lethal arrhythmia. It remains crucial that we develop effective and safe drugs. Such development requires that we understand how drugs affect their targets, typically ion channels or their modifiers. For this effort we should not restrict the possible drug targets excessively, while recognizing that ion channels represent the final pathway for antiarrhythmic action [5]

Drugs do not intrinsically have good or bad effects; the good or harm depends on their actions and the desired therapeutic goal. A recent example of this is as follows[6]. Drugs that prolong repolarization are harmful for those with intrinsic normal repolarization (acquired long QT syndrome), but potentially therapeutic for those with abbreviated repolarization (short QT syndrome). The therapeutic goal requires that we match the pathological process with the drug action. Consequently, understanding their mechanisms of action is crucial. Modern ion channel biophysical methods now make that goal achievable.

The finding that the two mutations found by Barajas-Martinez and colleagues[1] increase lidocaine sensitivity raises the question of how LA drugs act. With some exceptions, the LA drugs access their binding site from inside. We know a great deal about their binding site; it is in the inner pore of the channel, a few Å below the selectivity filter[7,8]. For use-dependent block (UDB) the key residue is Phe-1759 of DIV-S6[9,11]. This site is unavailable for high affinity binding during the resting conformation of the pore, either because Phe-1759 does not face the pore in that state or because it is stearically blocked. With conformational changes in the S6 segments upon channel opening, and particularly upon binding of the inactivation particle, the site is fully available and high affinity binding occurs. It is these conformational changes that lead to the important use-dependence of LA action.

Most mutations in the binding site reduce LA affinity. Several nearby residues on DIV-S6 and DIII-S6, when mutated to Ala, do enhance resting LA block, but not USB[9,12]. But the mutations reported by Barajas-Martinez[1] to increase affinity are far from this binding site. How can these mutations affect LA block? The key to answering this question is recognizing the difference between binding and block. Drug binding initiates a series of allosteric conformational changes that alter channel gating. In addition, local drug concentrations in the pore are affected by the access/egress path(s) for the drug. Although the main path for LA drug access to its binding site is from the inside, the cardiac isoform normally has an accessory outside path for entry and exit of charged LA drugs, resulting in less accumulation of block between depolarizations and less UDB[13,14]. These isoform differences probably explain the most of the difference in LA block between the cardiac channel and nerve and skeletal isoforms.

Gating currents reflect the movement of the positively charged S4 helices in response to changes in the membrane electric field [15]. It has long been known that Na channel gating currents are reduced by LA drugs[16]. This effects have been recently confirmed for the cardiac channel by Sheets and Hanck [17], and they further showed that lidocaine immobilized the DIII-

S4 in its outward position, delayed recovery of DIV-S4, and and shifted its voltage-dependence. Prepositioning of these S4 segments to their more external locations by outside biotin-MTS interaction with Cys mutants caused a markedly increased lidocaine affinity for resting block[18].This result argues that DIII-S4 and lidocaine high affinity binding reciprocally influence each other. It is plausible to think that the L1308F polymorphism in DIII-S4 also results in a resting position of S4 different from normal, favoring exposure of the high affinity LA site and interfering with normal recovery of DIII-S4. Mutations in the S4 of the Shaker K channel have been shown to alter the rates of conformational changes during the final steps into and out of pore opening[19]. Such an idea can be tested by measuring gating currents in the L1308F mutant.

The increase in lidocaine affinity by V232I in DI-S4 is less understandable. However, Chanda and colleagues[20] have found striking effects of a mutation in DI-S4 of Nav1.4 on the movement of DIV-S4, which is linked to inactivation. We can make a suggestion as to the mechanism, by inference from the K channel crystal structures. It has been clearly shown that the S1–S4 "voltage-sensing" unit is functionally separate from the S5-P-S6 "pore" unit, with connection by the S4–S5 intracellular linker and variable contact between the inner part of S4 and S5 helices[21]. In the four domain assembly the S1–S4 unit lies behind the S5–S6 pore unit of the clockwise-located subunit. If the 3-dimensional structure of the Na channel is similar to that of the K channel, then the domain IV voltage-sensing unit lies behind the pore unit of domain 1. This provides a possible way that destabilization of conformational changes in domain 1 could affect the voltage-sensor of domain IV. It has long been puzzling that widely distributed mutations affect channel functions at a distance, but as we learn how these amazing ion channel machines work, the mutational effects are becoming more understandable.

In summary, an astute bedside observation of an individual with Brugada phenomenon has revealed important information about how the Na channel interacts with local anesthetics, and points to a polymorphism that may put these individuals at risk for local anesthetic toxicity. Continued clinical-laboratory cooperation, combined with the rapid progress in the molecular physiology of ion channels promises to enhance our search for effective antiarrhythmic drugs.

Acknowledgments

Sources of Funding: The author is supported by HL-065661.

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