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Inherited sodium channelopathies: models for acquired arrhythmias?

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VOLTAGE-GATED Na channels, transmembrane proteins that produce the ionic current responsible for the rapid upstroke of the cardiac action potential, are key elements required for rapid conduction through the myocardium and maintenance of the cardiac rhythm. As such, inherited mutations in SCN5A, the gene encoding the human cardiac Na channel (hH1; Fig. 1), are associated with a range of life-threatening disorders of cardiac rhythm. Moreover, the subset of mutations that decrease hH1 function in some cases provoke tachyarrhythmias (14) and in other cases bradyarrhythmias (37), highlighting the complex relationship between the Na channel and cardiac rhythm. It is also notable that inherited mutations that reduce Na channel function seem to sensitize patients to the proarrhythmic effects of antiarrhythmic drugs with Na channel-blocking properties (34). Studies are now examining the potential link between acquired proarrhythmic complications of drug therapy in patients experiencing myocardial ischemia [i.e., the Cardiac Arrhythmia Suppression Trial (CAST) trial (15)] and the functional defects seen in the inherited Na channel syndromes. Hence, the Na channelopathies are expanding our understanding of the proarrhythmic mechanisms caused by loss of Na channel function and may shed light on the common acquired rhythm disorders associated with coronary occlusion and structural heart disease.

INHERITED LOSS OF FUNCTION: THE “BRUGADA SYNDROME”

When the myocardium is depolarized, hH1 normally opens only transiently (~1 ms) and then rapidly closes, or “fast inactivates,” as the cardiac action potential ensues. Mutations in SCN5A linked to an autosomal dominant form of the long QT syndrome (LQT3; Fig. 1) result in partial failure of fast inactivation, allowing a small fraction of Na channels to continually open and thereby increase the Na current (evoking a gain of function; Ref. 6). This persistent Na current during the action potential plateau delays myocyte repolarization, evokes electrocardiographic (ECG) QT interval prolongation, and predisposes patients to a life-threatening polymorphic ventricular tachycardia (torsades de pointes). More recently, SCN5A mutations that reduce or eliminate Na current (a loss of function) have been shown to elicit idiopathic ventricular fibrillation (VF) (10). In these cases, QT interval prolongation is absent, but ECG ST segments are elevated (mimicking ischemic ECG manifestations) in patients who are free of structural heart disease or coronary blockages (8). Although some of these “Brugada syndrome” mutations render the hH1 channel entirely nonfunctional (10, 13), many of the mutations (R1512W, A1924T, T1620M; Fig. 1, Refs. 3, 14, 35) reduce Na current by facilitating fast inactivation. Although these mutations have functional effects directionally opposite to LQT3, their locus adjacent to LQT3 mutations throughout the hH1 primary sequence (Fig. 1) is intriguing (2).

Additional understanding of how loss of function may provoke diverse tachyarrhythmia syndromes has emerged from the analysis of a COOH-terminal amino acid insertion (1795insD; Fig. 1) that causes affected individuals to exhibit both LQT3 and Brugada syndrome: the QT interval is prolonged at slow heart rates, and “Brugada-like” ST segment elevations occur with exercise (7, 42). Like other LQT3 mutations, 1795insD disrupts fast inactivation to elicit a sustained Na current and thereby has the potential to prolong the QT interval. At the same time, 1795insD causes depolarized Na channels to occupy a more stable inactivated state, one that develops gradually over the period of the cardiac action potential (τ ≈ 50–100 ms) and has been termed “intermediate” inactivation (17) to distinguish it from fast inactivation (τ ≈ 1 ms).
and slow inactivation (time constant, $\tau \approx$ seconds; Ref. 36). Intermediate inactivation delays the recovery of Na channels between stimuli: at rapid heart rates where the diastolic recovery interval is brief, this may lead to a cumulative loss of function that reduces the available Na current (42). At slower heart rates, the Na channels have sufficient time to recover from inactivation between beats (despite the delay) and Na channel availability remains constant. Hence, the gain of function arising from LQT3-mediated disruption of fast inactivation predominates and the QT interval is prolonged (42). The Brugada T1620M hH1 mutant also exhibits, among other loss of function gating defects (10, 14), enhancement of intermediate inactivation (44), raising the possibility that this gating defect is a general proarrhythmic mechanism.

**“BALANCED” LOSS OF FUNCTION EVOES BRADYCARDIA**

Other SCN5A mutations produce loss of function but, unlike the Brugada syndrome tachyarrhythmias, elicit conduction slowing and bradycardia. A Dutch family carrying a mutation in the hH1 I-II linker (G514C; Fig. 1) exhibited isolated cardiac conduction disease requiring pacemaker therapy in two children, with slowed conduction throughout the myocardium (atria, ventricles, conduction system) (41). All family members had structurally normal hearts and exhibited no tendency toward ventricular tachyarrhythmias. Patch-clamp studies of heterologously expressed human cardiac Na channels (hH1) mutated to include G514C revealed changes in the voltage dependence of Na channel activation (stronger depolarizations required to open channels) that mirrored the loss of function defects associated with other Brugada mutations (14). However, a parallel depolarizing shift in the voltage dependence of inactivation (a gain of function defect) “balanced” the primary activation defect, causing the overall reduction in hH1 function to be small. In a computational model of cardiac action potential conduction (25), this mild loss-of-function hH1 defect was not sufficient to induce the marked action potential repolarization abnormalities associated with Brugada syndrome (Ref. 14; Fig. 2A; see below) but did predict myocardial conduction slowing of nearly 15%, which could contribute to the bradyarrhythmia phenotype (41).

Although the net G514C-imposed loss of function was minimized by the opposing gating defects, other balancing mechanisms may be operative in this and other inherited conduction disease syndromes. SCN5A mutations identified in two other families with isolated conduction disease would, on the basis of large deleted segments, produce entirely nonfunctional Na channels (37). Hence, modulating gene products, allele penetrance, and/or developmental factors may influence the relationship between conduction disease and Na channel function. Nonetheless, the 1795insD and G514C mutations illustrate that pairing of Na channel gating defects arising from a single mutation can evoke combinations of distinct arrhythmia phenotypes (i.e., Brugada and long QT syndromes) or may combine to evoke a single defect (isolated conduction disease).
INHERITED MUTATIONS AS MODELS FOR ACQUIRED ARRHYTMIA MECHANISMS

Whereas the inherited SCN5A mutations provide valuable molecular insights into Na channel gating mechanisms in rare syndromes, these mutant channels may be useful models for understanding the molecular mechanisms whereby pharmacological interventions or disease states provoke cardiac arrhythmias. Studies in canine myocardium suggest that loss of Na channel function may provoke VF by enhancing the normal transmural

**Fig. 2.** A: G514C elicits isolated conduction disease through “balanced” effects on Na channel gating. Shown are simulated endocardial and epicardial action potentials (adapted from Ref. 41). Left, wild-type action potentials, with the arrow indicating the epicardial “notch” due to transient outward potassium current (I_to) in the epicardial cell. Center, simulated effect of T1620M Brugada syndrome channels, with gating lesions that cause an unopposed reduction in Na channel function (14). These effects elicit early epicardial repolarization consistent with the Brugada syndrome electrocardiographic (ECG) ST segment elevation and risk for ventricular fibrillation. Right, G514C, with activation and inactivation modified in a balanced manner, yielding a small net reduction in Na channel function on the wild-type (WT) and G514C action potentials are shown on an expanded time base to illustrate the reduced rate of the action potential upstroke, which determines the rate of impulse propagation through the myocardium and explains the clinical phenotype of conduction slowing. B: a conceptual model of pore motion and methanesulfonate (MTS) accessibility during slow inactivation and use-dependent lidocaine (L) block (adapted from Ref. 27). The engineered F1236C side chain is relatively inaccessible in the rested, closed state (left), but on depolarization (center) the domain III outer pore-lining segment (P loop) changes position to increase the accessibility of the cysteinyI to sulfhydryl modification by a MTS reagent. Hence, the rate of sulfhydryl modification (k_a) increases because of reduced steric interference. When the channel inactivates during sustained depolarization (intermediate inactivation), the accessibility of the cysteine side chain is once again compromised (right) and the rate of sulfhydryl modification is also reduced (k_b < k_a). Lidocaine is bound to site(s) in the aqueous pore on the cytoplasmic (inner) side of the selectivity filter (31, 32) but in very close proximity to the selectivity filter P segment residues (40). The model suggests that the P segment structural rearrangements associated with intermediate inactivation may move the deepest P segment domains into positions that stabilize lidocaine binding (right).
The duration of the myocardial cell action potential in the epicardium is more sensitive to a reduction in Na current than the action potentials in the inner layers (midmyocardium, endocardium) because of the presence of a transient outward potassium current ($I_{to}$) that counterbalances Na current during the earliest phases of the action potential (Fig. 2A). By analogy, conditions that suppress Na current (ischemia (24), Na channel blockers (1, 34), or inherited mutations (1)) may similarly produce a proarrhythmic component of inactivation (20, 21). The depolarization gradient, causing reentry (20, 21).

These in vitro linkages between the proarrhythmic manifestations of ischemia and Na channel pharmacological blockade may underlie the increase in sudden death noted when patients at risk for ischemia are treated with Na channel blockers [CAST trial (15)]. Although studies have detected ischemia-related functional changes in a number of cardiac ion channels and transporters (9), it is likely that Na channel dysfunction plays a key role in reentrant arrhythmias under these conditions (19). Ischemia-induced arrhythmias can evolve from a site of slowed conduction near the ischemic border zone (28), consistent with a loss of Na channel function. Moreover, studies have identified proarrhythmic effects (rate-dependent slowing and facilitated reentry) due to Na channel blockade in fibers from the epicardial border zone of the infarcted heart (33, 45). Corroborating these findings are studies of Na channel function in cells isolated from the epicardial border zone of the 5-day infarcted canine heart that reveal a delay in recovery from inactivation after sustained depolarization (30), consistent with the postdepolarization refractoriness seen in that model (23). This slowed Na channel recovery (see Fig. 5 in Ref. 30) strongly suggests an enhancement of the intermediate component of inactivation. In addition, Pu et al. (30) found enhanced use-dependent lidocaine block in the border zone cells at a relatively low (20 μM) concentration, suggesting that enhanced intermediate inactivation may provoke a proarrhythmic pharmacological effect (see below).

Detailed biophysical studies of mutant Na channels have shed new light on how particular gating defects may elicit proarrhythmic sensitivity to Na channel blockade. Na channel-blocking agents exacerbate the ECG pattern in known cases of Brugada syndrome (26) and unmask the syndrome in patients who have SCN5A mutations and transiently exhibit Brugada-like ECG changes. Whereas intuition might suggest that this could result from a simple additive suppression of Na channel function (mutation + drug), recent studies indicate that the gating defects elicited by certain mutations actually sensitize the channel to drug action, causing a synergistic effect (18, 43). This theme has been highlighted in recent studies examining Na channel blockade in LQT3 patients. Although lidocaine or mexilitine may be useful in managing patients with LQT3 disorders (by counteracting the LQT3 gain of function with Na current suppression; Refs. 5, 38, 39), it was recently observed that flecainide, a potent Na channel blocker, elicits Brugada-like ECG ST elevation in a number of LQT3 patients (29).

This surprising pharmacological effect suggests that the inherited functional gating defects of LQT3 may somehow facilitate Na channel blockade. This possibility was first examined in studies of lidocaine action on the R1623Q LQT3 mutant (18). Although Na current recordings showed that lidocaine potently suppressed the sustained (pathological) R1623Q current, it was also noted that the rapid early component of R1623Q Na current (normally entirely resistant to therapeutic concentrations of lidocaine) was unusually drug sensitive. Further studies under drug-free conditions revealed a strong tendency for R1623Q channels, on depolarization, to inactivate without ever opening through a process known as “closed-state” inactivation (16). In additional studies, it was found that closed-state inactivation was enhanced in a number of LQT3 mutants in addition to R1623Q (including ΔKPQ and 1795insD) (43). This gating change markedly increased the channel sensitivity to flecainide and explained the clinical observation of flecainide-induced ECG ST changes in patients carrying these mutations (43).

Just as enhanced closed-state inactivation may potentiate Na channel blockade in LQT3 mutants, recent studies suggest that the intermediate inactivation gating enhancement seen in particular Brugada syndrome mutations (1795insD and T1620M as discussed above) may sensitize these channels to Na channel blockade. In addition to the rapid drug block that develops immediately on depolarization (potentiated by closed-state inactivation), many drugs exhibit additional blockade of Na channels during a sustained depolarization period (as elicited by the cardiac action potential). This stable block component persists long after the channel is repolarized (during diastole), causing a cumulative reduction in Na current at rapid heart rates (so-called “use-dependent” block; Ref. 12). Although this phenomenon was originally attributed to slow drug unbinding from the fast-inactivated channel, studies in both K channels (4) and Na channels (11, 27) suggest an alternative allosteric model that postulates that slow recovery from use-dependent block results from drug-induced formation of a more stable, long-lived inactivated conformational state that involves closure of the outer pore.

Recent studies in Na channels aimed at testing this hypothesis used an engineered cysteine residue strategically located at a site in the outer pore with restricted access to covalent (sulfhydryl) modification (27). The rate of covalent modification of this cysteinyll served as a sentinel for motion of the outer pore segments during intermediate inactivation gating (Fig. 2B). The studies found that longer pulses sufficient to induce intermediate (and slow) inactivation limited the rate of sulphydryl modification of the sentinel cysteine in the outer pore, whereas brief pulses that elicit fast inactivation did not, consistent with the notion of outer pore constriction during intermediate inactivation, analogous to C-type inactivation in K channels (22). Moreover, sulphydryl modification in the Na channel outer pore...
was further reduced by use-dependent lidocaine block from inside the membrane, an effect that could not be explained by direct drug shielding of the engineered cysteine. It was proposed that intermediate (and slower) kinetic components of inactivation and the use-dependent action of Na channel blockers both involve similar rearrangements in the outer pore structure and that intermediate inactivation may stabilize the interaction between lidocaine and the pore (Fig. 2B; Ref. 27).

Complementary studies in channels carrying disease-linked mutations support this proposal. In channels carrying the Brugada syndrome mutation 1795insD, use-dependent block by flecainide is nearly absent in the wild-type channel but appears to increase significantly in the mutant as a direct consequence of the mutation-induced increase in intermediate inactivation (43). These findings raise the possibility that the analogous changes in Na channel inactivation gating noted in ischemic border zone cells may explain the enhanced sensitivity to Na channel blockade in that model (30) and may also suggest a candidate molecular mechanism for the proarrhythmic clinical features of potent Na channel blockers in patients experiencing cardiac ischemia [i.e., the CAST trial (15)]. Ongoing studies are examining the detailed mechanisms whereby Na channels and other ion channels are functionally altered by myocardial cell pathology (ischemia, Ca\(^{2+}\) overload, hypertyrophy, etc.) and may facilitate the future development of targeted antiarrhythmic therapies aimed at correcting or preventing deranged Na channel function.

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REFERENCES


