Familial inappropriate sinus tachycardia: a new chapter in the story of HCN4 channelopathies

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This editorial refers to ‘A gain-of-function mutation in the cardiac pacemaker HCN4 channel increasing cAMP sensitivity is associated with familial Inappropriate Sinus Tachycardia’, by M. Baruscotti et al., on page 280.

Funny current and regulation of heart rhythm

The sinoatrial node (SAN) contains a small number of pacemaker cells (PCs), specialized cardiomyocytes whose automatic firing triggers each heart beat. Autonomic and endocrine modulation of PC automaticity enables precise neurohormonal regulation of heart rate (HR) in accordance with physiological demand. While the cellular mechanisms that underlie HR regulation are complex and still actively debated, several critical molecular players have been identified and cloned over the past few decades.1 Among the most important are the hyperpolarization-activated, cyclic nucleotide-gated (Hcn) ion channels, which conduct an inward current that is activated by hyperpolarization and modulated by cAMP binding. Hcn current, also known as funny current, contributes to early diastolic depolarization in PCs, and hence to firing rate.

Of the Hcn channel isoforms, Hcn4 is the most important for regulation of mammalian heart rhythm. Hcn4 is expressed in a steep gradient that parallels the gradient of automaticity among different types of cardiomyocyte: SAN PCs exhibit high level Hcn4 expression, atrioventricular nodal myocytes exhibit moderate expression, the His–Purkinje system exhibits lower expression, and there is minimal expression in working atrial and ventricular cardiomyocytes.2 Heart-specific Hcn4 deletion in adult mice causes severe bradycardia and death,3 and loss-of-function mutations in human Hcn4 cause familial sinus bradycardia, a rare genetic arrhythmia syndrome marked by early-onset sinus node dysfunction and bradycardia.4

Since the original description of familial sinus bradycardia,5 several other Hcn4-associated cardiac syndromes have emerged, including atrioventricular block,6 early-onset atrial fibrillation,7 Brugada syndrome,8 prolonged QT,9 and left ventricular non-compaction.10,11 Of note, each of these syndromes is associated with Hcn4 loss of function. The study by Baruscotti et al. in this issue of the journal adds a new piece to this puzzle by identifying the first gain-of-function mutation in Hcn4 associated with a clinical syndrome, inappropriate sinus tachycardia (IST).12 In doing so, the authors also make a contribution to the ongoing debate about the roles of Hcn4 in setting basal HR and in regulating chronotropic response, and provide a plausible mechanistic explanation for a unique form of IST that may also be relevant to patients with non-familial IST.

Inappropriate sinus tachycardia

Inappropriate sinus tachycardia is an uncommon disease in which the average daytime HR is elevated and the chronotropic response to activity is exaggerated in the absence of structural heart disease.13 The most common symptoms of IST are palpitations and activity intolerance, but chest pain, lightheadedness, syncope, gastrointestinal distress, and anxiety often occur as well. Although the long-term prognosis of IST is generally favourable, it produces a great deal of morbidity and functional incapacity and can be extremely difficult to treat. Various causes have been proposed for IST, including primary dysautonomia,14 activating antiadrenergic antibodies,15 intrinsic sinus node hyper-responsiveness,16 and anxiety disorder (Figure 1).

The standard pharmacological treatments for IST are negative chronotropic agents including beta-blockers and calcium channel blockers, which have limited efficacy and often cause extra-cardiac side effects.17 Catheter ablation of the sinus node was effective in the short term, but had a high rate of recurrence, as well as potential need for permanent pacing with extensive ablation. More recently, the negative chronotropic agent ivabradine has been used with success in IST.18 Because ivabradine selectively inhibits funny current, its efficacy raised the possibility that excessive activation of Hcn channels, either through autonomic input, increased surface expression, or genetic mutation, was part of the pathophysiology of IST.
Role of Hcn4 in the pathophysiology of inappropriate sinus tachycardia, SAN and pregnancy.

Figure 1 Role of Hcn4 in the pathophysiology of inappropriate sinus tachycardia (IST). This diagram illustrates the role of increased funny current in the context of proposed causes of IST, including increased pacemaker cell automaticity, increased sympathetic activity, activating anti-beta-adrenergic antibodies, anxiety, and the R524Q mutation in the Hcn4 C-linker, which increases the sensitivity of Hcn4 to cAMP. In theory, these mechanisms are not mutually exclusive and could be synergistic. β-AR, beta-adrenergic receptor.

Molecular basis of familial inappropriate sinus tachycardia, a novel genetic arrhythmia syndrome

Following this line of reasoning, Baruscotti et al. tested the hypothesis that gain-of-function mutations in Hcn4 can cause IST. Forty-eight IST patients with symptomatic mean daytime HR > 95 b.p.m. underwent targeted sequencing of the coding region of Hcn4. One of these patients had the missense mutation R524Q, which results in neutralization of a positive charge in the C-linker of Hcn4, a region known to couple cAMP binding to channel activation. This mutation was not observed in normal controls. When the family of the proband was characterized in more detail, several members with the mutation were found to have periods of unexplained tachycardia on Holter monitoring, along with symptoms of IST, whereas all of the family members without the mutation had normal heart rate variation.

Of note, while all affected family members exhibit periods of unexplained sinus tachycardia, not all family members with the mutation met the formal criteria for IST as defined by resting HR > 100 b.p.m. and average HR on a 24-h monitor > 95 b.p.m. (indeed, one member had periods of bradycardia). However, as the authors point out, incomplete penetrance and variable expressivity are commonly seen in other channelopathies, reflecting complex polygenic and environmental contributions to cardiac electrophysiology, so the phenotypic variation in this family is neither surprising nor without precedent in genetic arrhythmia syndromes.

To define the mechanistic basis for the clinical association of tachycardia with the mutation, the authors expressed the mutated ion channels in a heterologous system for detailed electrophysiological characterization. Activation of Hcn channels is coupled to two gating mechanisms: transmembrane voltage sensors that open the channel in response to hyperpolarization, and a cyclic nucleotide-binding domain (CNBD) that is coupled to the activation gate through a ‘C-linker region’. When cAMP binds the CNBD, a conformational change in the C-linker shifts the voltage dependence of activation such that the channels activate at less hyperpolarized voltages, leading to increased Hcn current at a given membrane potential. Because cAMP levels are affected by signalling through adrenergic receptors, this mechanism allows for autonomic regulation of Hcn current and firing rate.

The authors found that the voltage dependence of activation gating in R524Q mutant and R524Q/WT heteromeric channels was shifted to more depolarized potentials. In theory, such a shift could result from a change in the coupling of the voltage sensors to the activation gating mechanisms or from an alteration in the channel’s sensitivity to cAMP binding. In light of the location of the mutation in the C-linker, the authors hypothesized the latter mechanism, which was tested by reassessing the voltage dependence of activation with different cAMP concentrations. Consistent with the underlying hypothesis, there was no difference in the voltage dependence of activation between wild-type, mutant, and heteromeric channels under saturating concentrations of cAMP. The apparent difference in the voltage dependence of activation under limiting cAMP conditions was a result of heightened sensitivity in mutant channels to cAMP binding. Thus, based on these functional experiments, R524Q carriers would be predicted to exhibit higher resting HR with heightened sensitivity to sympathetic stimulation, exactly what is observed in IST.

Implications and questions for future research

The study of Baruscotti et al. is notable because it presents the first description of a genetic arrhythmia syndrome caused by gain of function of Hcn4, and it describes a novel heritable form of IST. Although only 1 of the 48 patients initially screened had a mutation in Hcn4, the fact that an Hcn4 mutation can produce the IST phenotype, together with the general effectiveness of ivabradine in IST, suggests that funny current may be an important part of the pathophysiology of this disease. Because Hcn channels couple adrenergic stimulation to HR, increased funny current may constitute a final common physiological pathway in IST regardless of whether the pathophysiology involves excessive adrenergic activation, SAN hyper-responsiveness, or a combination of the two. In this context, it is noteworthy that increased surface expression of Hcn channels occurs in other types of sinus tachycardia, including hyperthyroidism and pregnancy. Thus, it may be that patients with IST have transient elevations in Hcn surface expression and/or heightened cAMP sensitivity. Such changes could synergize with other causes of increased adrenergic input to the SAN (e.g., autoantibodies, chronic anxiety) to create the disease phenotype (Figure 1). Clearly, further research will be required to understand how the

Figure 1

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pathophysiology of non-familial IST relates to altered funny current, and to test whether mutations in other genes relevant to automaticity can cause familial forms of IST.

Finally, the specific contribution of funny current to basal HR and chronotropic response remains a matter of some controversy, as other mechanisms are also important determinants of HR. In defining a gain-of-function mutation in HCN4, the present study demonstrates that while funny current may be one of many factors that contribute to HR regulation under normal conditions, modulation of funny current can produce clinically significant tachycardia and may be a relevant player in other types of tachyarrhythmia. Understanding the dynamic regulation of HCN4 function and expression, both within and outside the SAN, may therefore be a fruitful avenue for further research on the molecular basis of selected tachyarrhythmias.

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