Tachycardia-bradycardia syndrome: Electrophysiological mechanisms and future therapeutic approaches (Review)

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Abstract. Sick sinus syndrome (SSS) encompasses a group of disorders whereby the heart is unable to perform its pacemaker function, due to genetic and acquired causes. Tachycardia-bradycardia syndrome (TBS) is a complication of SSS characterized by alternating tachycardia and brady-cardia. Techniques such as genetic screening and molecular diagnostics together with the use of pre-clinical models have elucidated the electrophysiological mechanisms of this condition. Dysfunction of ion channels responsible for initiation or conduction of cardiac action potentials may underlie both bradycardia and tachycardia; bradycardia can also increase the risk of tachycardia, and vice versa. The mainstay treatment option for SSS is pacemaker implantation, an effective approach, but has disadvantages such as infection, limited battery life, dislodgement of leads and catheters to be permanently implanted *in situ*. Alternatives to electronic pacemakers are gene-based bio-artificial sinoatrial node and cell-based bio-artificial pacemakers, which are promising techniques whose long-term safety and efficacy need to be established. The aim of this article is to review the different ion channels involved in TBS, examine the three-way relationship between ion channel dysfunction, tachycardia and bradycardia in TBS and to consider its current and future therapies.

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1. Introduction

The association between sick sinus syndrome (SSS) and atrial fibrillation (AF) has been recognized for more than 5 decades since 1968 (1) with the first description of tachycardia-bradycardia syndrome (TBS) reported 5 years later (2). Tachycardia complicates approximately 50% of SSS cases (2-4). A related condition, Bayes syndrome, involves inter-atrial block associated with AF (5-15). Our understanding of cardiac electrophysiology has significantly advanced with the use of pre-clinical animal models, which are amenable to

pharmacological, physical or genetic manipulation for studying the consequences of ion channel abnormalities (16-19), and have provided insight for translational application (14,20-25). These studies have identified the roles of different ion channels, such as hyperpolarization-activated, cyclic nucleotide-gated (HCN), Na$^+$ and transient receptor potential (TRP) channels, ryanodine receptors (RyR) and gap junctions (26-28), as well as tissue-level mechanisms, in the pathogenesis of TBS. To understand the molecular basis of how ion channel dysfunction leads to bradycardia or tachycardia, and the causal relationship between bradycardia and tachycardia, the mechanisms responsible for automaticity in the sinoatrial node (SAN) and mediating action potential conduction need to be considered.

2. Ion channels underlying SAN function

Automaticity of SAN is dependent on two closely coupled clocks, voltage- and calcium-dependent mechanisms (Fig. 1) (29). The voltage-dependent mechanism involves the funny current (I_f) mediated by HCN channels located at the plasma membrane (30). I_f has several unusual properties for a transmembrane current, including activation by a hyperpolarized voltage, permeability to both Na$^+$ and K$^+$ ions, regulation by intracellular cAMP, and small single channel conductance (31). There are four recognized HCN channel isoforms (1 to 4) (32). HCN4 is the predominant subtype found in the SAN (33,34). By contrast, the Ca^{2+}-mediated mechanism involves rhythmic release of Ca^{2+} from the sarcoplasmic reticulum (SR), subsequent reuptake by the SR Ca^{2+}-ATPase and extrusion via the Na$^+$-Ca^{2+} exchanger (35). Together, the complex interplay of ion channels and pumps gives rise to the pacemaker action potential (AP), which is uniquely characterized by spontaneous depolarization during phase 4 (Fig. 2).

Na$^+$ channels are found in high numbers in the periphery of the SAN, where they are thought to play a role in exit conduction of APs to the atrium (36,37). Each Na$^+$ channel is formed by a pore-forming α-subunit, a modulatory β-subunit and additional regulatory proteins. The NaV1.5 α-subunit, encoded by *SCN5A* (38), has four domains (I to IV), each of which contain six transmembrane segments (S1 to S6). The positive-charged S4 segments undergo outward movement upon membrane depolarization, opening the central pore to allow Na$^+$ entry (39,40). The resulting I_{Na} therefore partly determines myocardial excitability and conduction velocity of the APs. Late I_{Na} results in membrane depolarization in the atrial myocardium, which produces fast inactivation, by moving the linker region between domains III and IV to occlude the central pore (41-47). This is followed by slow inactivation, where the P-segment linker sequence between S5 and S6 bends back into the plasma membrane lining the outer region of the pore (48,49). The precision of sodium channel function is vital for the maintenance of transmembrane electrochemical gradient and therefore cardiac function.

Other ion channels are also involved in SAN function, such as HCN channels, predominantly HCN4, carry the I_f current which is a combination of both sodium and potassium currents. Alterations in the highly regulated activation and inactivation of the highly regulated cycle of ion channels, such as an increase in late I_{Na} can lead to arrhythmias (47). A
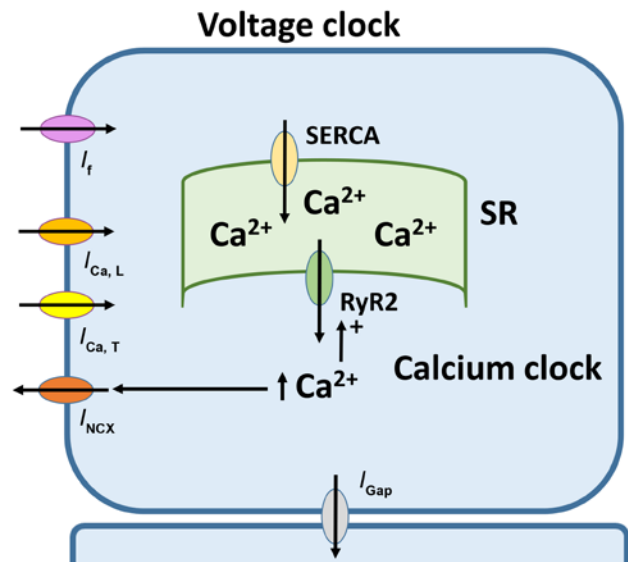

Figure 1. Sinoatrial node automaticity depends on both voltage- and calcium-dependent mechanisms. SR, sarcoplasmic reticulum.
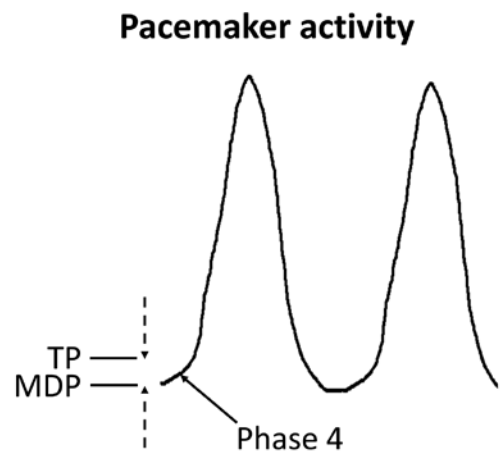

Figure 2. Pacemaker activity: from the maximum diastolic potential (MDP), spontaneous phase 4 depolarization brings the membrane to the threshold potential (TP), thereby initiating an action potential. Adapted from ref. 153 with permission.

genetic mutation in any part of this complex pathway results in SAN dysfunction leading to arrhythmias (50).

Conduction of APs from one myocyte to the next occurs via gap junctions, each of which consists of two hexamers of connexin (Cx) subunits (51-53). Cx 30.2, 40, 43 and 45 are found in cardiac tissues (54). Cx40 is expressed only in the atria and His-Purkinje system (55,56). Cx43 is expressed throughout the atria and ventricles (57). Cx45 is the predominant isoform found in the core of SAN (58), whereas Cx43, Cx40 and Cx45 are expressed in the periphery (50). However, few gap junctions are found in the SAN core, suggesting that intercellular coupling is not required for synchronization of electrical activity within the node (59,60). The conventional membrane voltage-dependent gating, transjunctional voltage-dependent gating (61), phosphorylation (62-64), intracellular Ca^{2+} (65-68) and pH (69,70) as well as the surrounding lipid environment (71-74) all regulate gap junctional conductance.
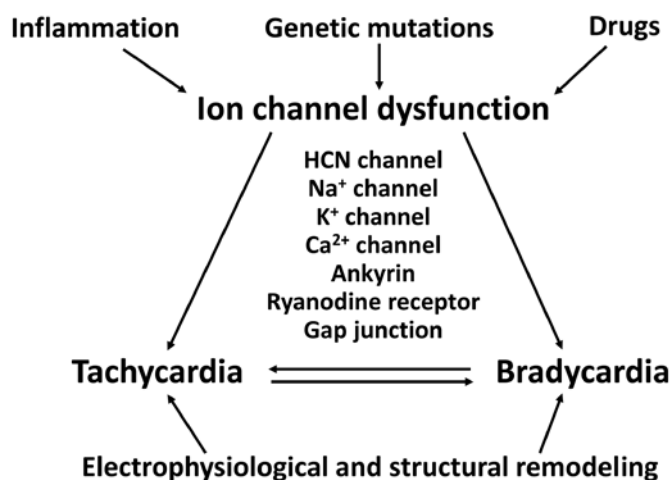
Figure 3. Molecular and electrophysiological mechanisms underlying tachycardia-bradycardia syndrome. HCN, hyperpolarization-activated, cyclic nucleotide-gated.

3. Tachycardia-bradycardia syndrome results from structural and electrophysiological remodeling

SSS can affect newborns and younger individuals, as well as elderly individuals over 65 years of age (36,75). TBS can be caused by genetic mutations, inflammation, ischaemia or drugs, involving both structural and electrophysiological remodeling (Fig. 3). Broadly, TBS can involve abnormal ion channel function, altered intercellular coupling or tissue level mechanisms.

4. Altered ionic currents

HCN4 is involved in mammalian cardiac pacemaking and is predominantly expressed in the SAN (28). Loss-of-function HCN4 mutations are known to cause atrioventricular (AV) block, long QT syndrome (LQTS), AF, familial TBS and non-compaction cardiomyopathy in addition to sinus bradycardia (76-80). The G1097W HCN4 mutation, which is a loss-of-function mutation resulting in a hyperpolarizing shift of the activation curve and reduced expression levels, demonstrates 4:1 AV block and reflex sinus tachycardia (81). A missense HCN4 mutation was found to lead to impaired trafficking of the channel to the surface membrane, resulting in SSS, long QT and *torsade de pointes* (82). Some of these phenotypes have been recapitulated in genetically modified mice, making them particularly useful for modeling TBS. For example, HCN4-knockout mice show severe sinus bradycardia complicated by AV block (83), whereas I_f-deficient mice generated by expression of a dominant-negative, non-conductive HCN4-channel subunit exhibit bradycardia, AV block and ventricular tachycardia (84). In this model, delayed afterdepolarizations in SAN, AV node and Purkinje fibres were observed, attributed to increased SR Ca^{2+} load and increased frequency of Ca^{2+} release from the SR (84).

Mutations in the SCN5A encoding for the Na^+ channels can lead to a range of clinical phenotypes, including SSS, Brugada syndrome, LQTS type 3, AVN block, dilated cardiomyopathy, AF and overlap syndromes (85-91). In a newborn patient, a gain-of-function SCN5A mutation producing a persistent inward Na^+ current was found to cause LQTS type 3, and alternating tachycardia-bradycardia of 2:1 AV block and ventricular tachycardia have been observed (92). Individuals with loss-of-function SCN5A mutations can suffer from SSS and Brugada syndrome, which are responsible for bradycardic and tachycardic complications, respectively (93).

Upregulation of the inward rectifier current (I_{K1}) results from reduced levels of microRNA-1, observed in heart failure. This causes membrane hyperpolarization, bradycardia and shortening of APs that predisposes to atrial reentry (94). Ankyrin-B, a member of the ankyrin family, is expressed at high levels in the SAN and has functions such as cell signaling and assembly of ion channels in the plasma membrane (95,96). Humans with ANK2 gene variants suffer from SND, AF and prolonged QT intervals (96-98). Mice heterozygous for a null mutation in ankyrin-B have been generated. Cardiomyocytes isolated from these mice showed altered Ca^{2+} handling and extrasystoles that presumably arise from delayed afterdepolarizations (98,99). Ankyrin-B normally forms a complex with Na^+-K^+ ATPase, the Na^+-Ca^{2+} exchanger and the IP_3 receptor. Loss of ankyrin-B therefore leads to impaired Ca^{2+} transport across the SR and plasma membranes.

Finally, a loss-of-function mutation in the Ca^{2+} channel gene has also been shown to cause TBS (100). Normally, Ca^{2+} entry through L-type Ca^{2+} channels plays a role in pacemaker activity by contributing to diastolic depolarization. Reduction in this current can reduce the degree of spontaneous depolarization, slow pacemaker activity and increase the likelihood of spontaneous arrhythmias in SAN cells

5. Abnormal calcium handling

Ca^{2+} in myocardial cells originates from two sources: the extracellular space and intracellular store, the SR. Increased Ca^{2+} levels can arise from a number of mechanisms, such as entry via voltage-gated ion channels, receptor-operated Ca^{2+} entry (ROCE), store-operated Ca^{2+} entry (SOCE) and SR release (101,102). Alterations in any of these processes can promote the development of TBS. Ca^{2+} overload can promote apoptosis of SAN cells and stimulate fibrosis and reduce conduction velocity of APs by a calmodulin kinase II-dependent pathway (103). It is also a feature in heart failure, in which persistent activation of angiotensin II and calmodulin kinase II, higher incidence of tachyarrhythmias are also observed (103,104). Sinus node dysfunction (SND) is frequently found in heart failure patients, and it is estimated that bradycardic complications account for approximately half of the cases of sudden death (105,106).

Increased SR Ca^{2+} release, observed in catecholaminergic polymorphic ventricular tachycardia (CPVT), can arise from defective SR Ca^{2+} sensing, increased sensitivity to cytoplasmic Ca^{2+} or abnormal activation by calmodulin (107). Patients with CPVT demonstrate SND, inducible atrial arrhythmias as well as the bidirectional ventricular tachycardia traditionally observed in this condition (107,108). Experiments in mouse models indicate that SND and atrial arrhythmias are both due to abnormal Ca^{2+} handling in CPVT (109,110). In calsequestrin 2-null mice, spontaneous Ca^{2+} release led to delayed afterdepolarizations and atrial-triggered activity (109). Loss of calsequestrin 2 also produced selective interstitial fibrosis

in the atrial pacemaker complex, which disrupted SAN pacemaker activity and created conduction abnormalities that increased the tendency of atrial arrhythmias, likely by a reentrant mechanism (110).

6. Altered intercellular coupling

In the SAN, gap junctions contribute to automaticity and exit conduction of APs to the myocardium surrounding nodal tissue (111). Cx43 haploinsufficiency resulted in reduced CV in the ventricles, with tachyarrhythmias preceding bradyarrhythmias, but little effect on SAN function (112). Cx40$^{-/-}$ mice showed intra-atrial block, ectopic rhythms and abnormal conduction in the right atrium (113), inducible atrial tachycardia (114), AVN and infra-Hisian conduction delays (115).

7. Tissue level mechanisms through remodeling

If arrhythmia persists untreated, the structure of the SAN can be modified and this remodeling can lead to fibrosis and disturbance of the electrophysiology and even apoptosis of cardiac cells. This in turn increases the risk of AF and paroxysmal AF developing into permanent AF (28). The electrophysiological and structure remodeling of the SAN not only lead to arrhythmias, as discussed, but also are responsible for arrhythmias refractory to medication and recurrence following cardioversion (28).

8. Bradycardia and tachycardia in TBS: Which is the cause?

The causal relationship between bradycardia and tachycardia is bidirectional. It is unclear which precipitates which (28). Tachyarrhythmias can promote SND, resulting in sinus bradycardia (1,2). Patients with AF demonstrate structural abnormalities in the form of fibrosis in their SAN (116). Atrial tachycardia in dogs was found to lead to downregulation of HCN2, HCN4 and KCNE1 (which modulates the α-subunit of the K$^+$ channel), which underlies the SND observed (27). In an atrial tachycardia pacing model of TBS in rabbits, SND was associated with reduced HCN4 expression, both of which were reversible upon cessation of tachycardia pacing (26). In humans, HCN4 has been identified as a gene candidate associated with AF from a meta-analysis of genome-wide association studies (117). Adenosine is elevated in the plasma of patients, and the consequent activation of adenosine A1 receptors in the SAN is likely responsible for heart rate reduction (118). In a canine tachycardia-pacing model, A1 receptors were upregulated, which was associated with prolonged SAN conduction time, conduction block within the SAN, post-pacing pauses, shortening of atrial repolarization durations leading to a higher propensity to AF (119).

Conversely, SND can lead to the development of tachycardia (120). Genetically modified mice with an inducible deletion of cells specifically in the cardiac pacemaking and conduction system presented with degenerative fibrosis of nodal tissue, progressive bradycardia, sinus pauses, supraventricular and ventricular tachycardia and chronotropic incompetence (121). Fibrosis of the atrium was found to lead to conduction abnormalities, increased dispersion of refractoriness, thereby predisposing to the development of circus-type or spiral-wave reentry (122). Fibrosis in the setting of reduced repolarization reserve can promote early afterdepolarizations and in turn atrial and ventricular tachycardia (123,124).

9. Current and future therapeutic options for TBS

The current treatment options for TBS involve removal or correction of extrinsic causes. In acute situations where heart block is observed, the parasympathomimetic agent atropine or beta agonist isoproterenol, or temporary pacing can be used to overcome the conduction abnormalities. Tachyarrhythmias can be managed by digoxin, quinidine or propranolol. Permanent pacing using an electronic pacemaker is, at present, the only curative option however battery life and electromagnetic interference are often problematic.

Animal models have been extensively used for exploring the electrophysiological basis of complex rhythm disorders in an attempt to develop a biological pacemaker which would be free of complications such as limited battery life (125-129). These systems provide a platform for elucidating the mechanisms of arrhythmogenesis in different medical conditions (17,130-133), determining the efficacy of novel therapeutic approaches and providing insights for translational application (134-136). Generally, there are two engineering biological alternatives to electronic pacemakers. The first is a gene-based bio-artificial SAN. Ventricular cardiomyocytes normally do not possess pacemaker activity, but they can be induced to exhibit pacemaker function by genetic suppression of the inward-rectifier K$^+$ channels (137) or expression of HCN channels by adenoviral transfer (135-145). A second approach is cell-based bio-artificial pacemakers. This involves differentiation of human embryonic stem cells or induced pluripotent stem cells into cardiomyocytes (146,147). For example, human mesenchymal stem cells pre-transfected with HCN2 channels can be used to introduce I_f into surrounding cardiomyocytes that subsequently possess pacemaker activity (148,149). Cardiomyocytes can be converted into pacemaker cells by a cell fusion technique, where fibroblasts engineered to express HCN1 are chemically fused to the cardiomyocytes using chemicals such as polyethylene-glycol 1500 (150). Human embryonic stem cells have also been differentiated into cardiomyocytes that demonstrated intrinsic pacemaker activity, capable of pacing the ventricular myocardium *in vivo* (135,151). Experimental data do not always produce the same results when applied to animal models (152) and it would therefore be sensible not to assume that animal models will produce the same results in a human heart. Future research is needed to establish the safety of these bio-artificial pacemakers, and little is known regarding their long-term efficacy. They may provide better treatment options for debilitating complex arrhythmias such as TBS.

10. Conclusion

In this review we summarized current literature to understand the molecular and electrophysiological mechanisms and discussed the current treatment and the exciting future possibility of superior biological pacemakers which are hopefully not a too distant possibility.

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