



## FUNNY CURRENT IN CARDIAC PACEMAKER CELLS AND ITS SPECIFIC INHIBITOR IVABRADINE

Sunny C\*, Brijesh Mukherjee, Durgabati Patel, Manjushree Mohanty

Department of Pharmacology & Department of Biochemistry, Kalinga Institute of Medical Sciences, KIIT University

**Received for publication:** December 19, 2012; **Revised:** January 12, 2013; **Accepted:** February 21, 2013

**Abstract:** Out of all the electrical discharges occurring in the cardio myocytes, the funny current ( $I_f$ ) or the pacemaker current ( $I_r$ ) is rather unusual. The existence of such an electrical activity in the sinoatrial node was established in 1970's. Because of their relevance to generation of pacemaker activity and modulation of spontaneous frequency, f-channels are natural targets of drugs aimed to pharmacologically control heart rate. Ivabradine is the most specific and selective  $I_f$  inhibitor and the only member of this family that is now marketed for pharmacological treatment of chronic stable angina in patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers. Recent studies have also indicated that funny channel inhibition can be used to reduce the incidence of coronary artery disease outcomes.

**Keywords:** Funny Current ( $I_f$ ), Pacemaker Current ( $I_r$ ), Ivabradine

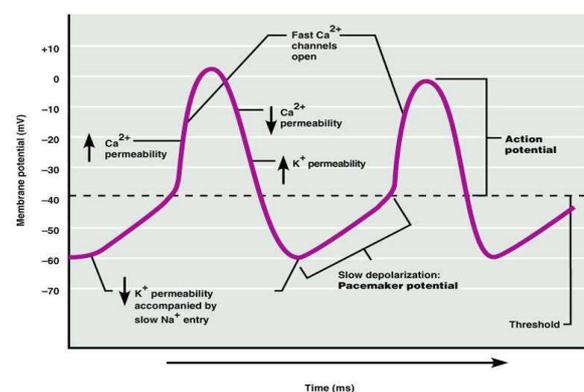
### INTRODUCTION

The different phases in the electrophysiology of cardiac impulse generation and transmission had been well established from quite a long time. But the most intriguing was the pacemaker current because any theories and any ion channel put forward to explain it stood weak. From then on an extensive research has been carried out to figure out the exact nature of the current. The cardiac pacemaker ( $I_f$ ) current has now been extensively characterized and its role in cardiac peacemaking has been investigated.<sup>[1][2][3]</sup>

The funny current as it is called, is highly expressed in spontaneously active cardiac regions, such as the sinoatrial node (SAN, the natural pacemaker region), the atrio-ventricular node (AVN) and the Purkinje fibres. Particularly unusual, the funny current is a mixed sodium-potassium current, inward and slowly activating on hyperpolarization at voltages in the diastolic range (normally from -60/-70 mV to -40 mV). When at the end of a sinoatrial action potential the membrane repolarises below the  $I_f$  threshold (about -40/-50 mV), the funny current is activated and supplies inward current, which is responsible for starting the diastolic depolarization phase (DD); by this mechanism, the funny current controls the rate of spontaneous activity of sinoatrial myocytes, hence the cardiac rate.

Another unusual feature of  $I_f$  is its dual activation by voltage and by cyclic nucleotides. Cyclic adenosine monophosphate (cAMP) molecules bind directly to f-channels and increase their open probability.<sup>[4]</sup> cAMP dependence is a particularly relevant physiological property, since it underlies the  $I_f$ -dependent

autonomic regulation of heart rate. Sympathetic stimulation raises the level of cAMP molecules which bind to f-channels and shift the  $I_f$  activation range to more positive voltages; this mechanism leads to an increase of the current at diastolic voltages and therefore to an increase of the steepness of DD and heart rate acceleration. Parasympathetic stimulation (which acts to increase probability of potassium channels opening but decreases the probability of calcium channel opening) decreases the heart rate by the opposite action, that is by shifting the  $I_f$  activation curve towards more negative voltages.



A similar current, termed  $I_h$ , has also been described in different types of neurons where it has a variety of functions, including the contribution to control of rhythmic firing, regulation of neuronal excitability, sensory transduction, synaptic plasticity and more. The molecular determinants of the pacemaker current belong to the Hyperpolarization-activated Cyclic Nucleotide-gated channels family (HCN), of which 4 isoforms (HCN1-4) are known. Based on their sequence, HCN channels are classified as

#### \*Corresponding Author:

Dr. Sunny C,

Department of Pharmacology

Kalinga Institute of Medical Sciences,

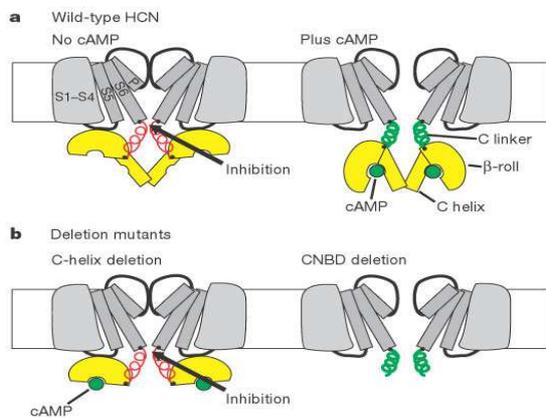
KIT University, Bhubaneswar - 751024, Odisha, India



members of the super family of voltage-gated K<sup>+</sup> (Kv) and CNG channels.<sup>[3][5]</sup>

### Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels:

These are proteins that serve as ion channels across the plasma membrane of heart and brain cells<sup>[8]</sup>. HCN channels are sometimes referred to as “pacemaker channels” because they help to generate rhythmic activity within groups of heart and brain cells. HCN channels are encoded by four genes (HCN1, 2, 3, 4) and are widely expressed throughout the heart and the central nervous system.<sup>[9][10]</sup> HCN4 is the main isoform expressed in the sinoatrial node, but low levels of HCN1 and HCN2 have also been reported. The current flowing through HCN channels, called the funny current or pacemaker current (I<sub>f</sub>), plays a key role in the generation and modulation of cardiac rhythmicity.<sup>[11]</sup>



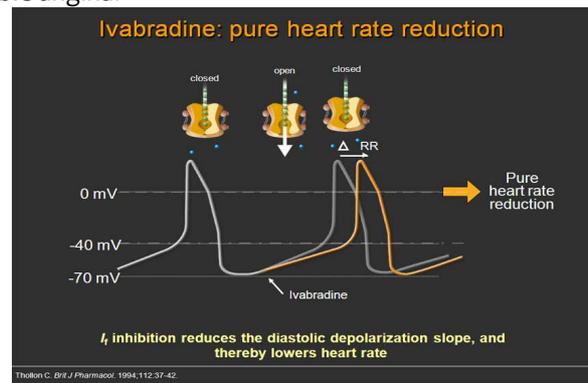
Cardiovascular diseases represent a major cause of worldwide mortality, and the relevance of the genetic component in these diseases has recently become more apparent. Genetic alterations of HCN4 channels (the molecular correlate of sinoatrial f-channels) coupled to rhythm disturbances have been reported in humans. For example an inherited mutation of a highly conserved residue in the CNBD of the HCN4 protein (S672R) is associated with inherited sinus bradycardia.<sup>[8]</sup> In vitro studies indicate that the S672R mutation causes a hyperpolarizing shift of the HCN4 channel open probability curve of about 5 mV in heterozygosis, an effect similar to the hyperpolarizing shift caused by parasympathetic stimulation and able to explain a reduction of inward current during diastole and the resulting slower spontaneous rate.

Biological pacemakers, generally intended as cell substrates able to induce spontaneous activity in silent tissue, represent a potential tool to overcome the limitations of electronic pacemakers. One of the strategies used to generate biological pacemakers involves the use of cells inherently expressing or

engineered to express funny channels. Different types of stem cells can be used for this purpose.<sup>[18]</sup>

### Mechanism of action:

Ivabradine acts on the I<sub>f</sub> and selectively inhibits the pacemaker current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing the heart rate and allowing more time for blood to flow to the myocardium.<sup>[16][17]</sup> It is selective for the I<sub>f</sub> current, lowering heart rate at concentrations that do not affect other cardiac ionic currents. Specific heart-rate lowering with ivabradine reduces myocardial oxygen demand, simultaneously improving oxygen supply. Ivabradine has no negative inotropic or lusitropic effects, preserving ventricular contractility, and does not change any major electrophysiological parameters unrelated to heart rate. Randomised clinical studies in patients with stable angina show that ivabradine effectively reduces heart rate, improves exercise capacity and reduces the number of angina attacks. It has superior anti-anginal and anti-ischaemic activity to placebo and is non-inferior to atenolol and amlodipine. Ivabradine therefore offers a valuable approach to lowering heart rate exclusively and provides an attractive alternative to conventional treatment for a wide range of patients with confirmed stable angina.



### Clinical significance:

Several agents called "heart rate reducing agents" act by specifically inhibiting f-channel function.<sup>[3]</sup> Ivabradine is the most specific and selective I<sub>f</sub> inhibitor and the only member of this family that is now marketed for pharmacological treatment of chronic stable angina in patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers. Recent studies have also indicated that funny channel inhibition can be used to reduce the incidence of coronary artery disease outcomes in a subgroup of patients with heart rate  $\geq 70$  bpm.<sup>[6]</sup> Ivabradine acts by reducing the heart rate in a mechanism different from beta blockers and calcium channel blockers, two commonly prescribed antianginal drugs. It is classified as a cardio tonic agent. Most neurological study of the heart illuminates Systole under Sympathetic influence. Funny

Current is likely an illumination of Parasympathetic electrical influence in Diastole.

It is also indicated in combination with beta-blockers in patients inadequately controlled by beta-blocker alone and whose heart rate exceeds 60 beats per minute. It has been shown to be as effective as the beta-blocker atenolol<sup>[12]</sup> and comparable with amlodipine<sup>[13]</sup> in the management of chronic stable angina. Apart from angina, it is also being used off-label in the treatment of inappropriate sinus tachycardia.<sup>[14]</sup> Adding ivabradine to heart-failure medication decreases both cardiovascular death rate and risk of hospitalization for heart-failure.<sup>[15]</sup>

#### Contraindications:

Ivabradine is contraindicated in sick sinus syndrome, and cannot be used concomitantly with inhibitors of CYP3A4 such as azole antifungals (such as ketoconazole), macrolide antibiotics, nefazodone and the anti-HIV drugs nelfinavir and ritonavir.<sup>[5]</sup>

#### Adverse effects:

14.5% of all patients taking ivabradine experience luminous phenomena (by patients described as sensations of enhanced brightness in a fully maintained visual field). This is probably due to blockage of I<sub>h</sub> ion channels in the retina which are very similar to cardiac I<sub>f</sub>. These symptoms are mild, transient, fully reversible and non-severe. In clinical studies about 1% of all patients had to discontinue the drug because of these sensations, which occurred on average 40 days after commencement of the drug.

Bradycardia (unusually slow heart rate) occurs at 2% and 5% for doses of 7.5 and 10 mg respectively (compared to 4.3% in atenolol). 2.6-4.8% reported headaches. Other common adverse drug reactions (1-10% of patients) include first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.<sup>[19]</sup>

#### Animal Studies With Ivabradine:

Several experimental studies in animals, including dogs and pigs, have clarified the different beneficial effects that may be associated with pure heart-rate lowering with Ivabradine<sup>[20] [21] [22] [23] [24] [25] [26] [27]</sup>. However, studies relating to the changes in biochemical profile have not yet been carried out and require a detailed deliberation.

#### Clinical trials:

Many clinical trials have been undertaken individually and in comparison for ivabradine and its effects. Following are some of the examples of such studies.

#### Coronary artery disease:

The Beautiful study<sup>[7]</sup> has shown that in coronary patients with a heart rate more than 70bpm, ivabradine significantly reduces the risk of

Coronary events by 22% (P=0.023)

Fatal and nonfatal myocardial infarction by 36% (P=0.001)

Coronary revascularization by 30% (P=0.016).

In the SHIFT study, ivabradine significantly reduced the risk of the primary composite endpoint of hospitalization for worsening heart failure or cardiovascular death by 18% (P<0.0001) compared with placebo on top of optimal therapy.<sup>[4]</sup> These benefits were observed after 3 months of treatment. SHIFT also showed that administration of ivabradine to heart failure patients significantly reduced the risk of death from heart failure by 26% (P=0.014) and hospitalization for heart failure by 26% (P<0.0001). The improvements in outcomes were observed throughout all prespecified subgroups: female and male, with or without beta-blockers at randomization, patients below and over 65 years of age, with heart failure of ischemic or non-ischemic etiology, NYHA class II or class III, IV, with or without diabetes, and with or without hypertension.

#### Ivabradine Monotherapy:

A randomised, placebo-controlled, double-blind, multicentre, multinational study in 360 patients with stable angina for at least 3 months and documented coronary artery disease evaluated ivabradine in a short dose-ranging phase and in longer-term use<sup>[28]</sup>.

After 2 weeks of treatment, resting heart rate was significantly slower with ivabradine compared with placebo at both peak and trough drug activities, and this reduction increased significantly with increasing dose

## CONCLUSION

'Pure' heart-rate lowering via I<sub>f</sub> inhibition is clinically feasible and can effectively prevent angina with acceptable tolerability. Ivabradine effectively prevents angina and concomitantly reduces ischemia. Ivabradine is currently the only agent shown to clinically lower heart rate with no negative inotropism or effects on conduction and contractility. Yet more studies need to be carried out for the effect of Ivabradine on various biochemical profiles, the effectiveness of monotherapy, the benefits of combined therapy, the best combinations that can be used and the complications.

## REFERENCES

1. Brown HF, DiFrancesco D, Noble SJ, (1979). How does adrenaline accelerate the heart? *Nature*, 280, 235-236.
2. DiFrancesco D, Ojeda C, (1980). Properties of the current  $I_f$  in the sino-atrial node of the rabbit compared with those of the current  $I_K$ , in Purkinje fibres. *Journal of Physiology*, 308, 353-367.
3. Baruscotti M, Bucchi A, DiFrancesco D, (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. *Pharmacology & Therapeutics*, 107, 59-79.
4. DiFrancesco D, Tortora P, (1991). Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. *Nature*, 351, 145-147.
5. Barbuti, A., Baruscotti, M., DiFrancesco, D. (2007). The pacemaker current: from basics to the clinics. *Journal of Cardiovascular Electrophysiology*, 18, 342-347.
6. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; BEAUTIFUL Investigators (2008) Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 372(9641):807-16.
7. Ferrari R, Ford I, Fox K, Steg PG, Tendera M, (2008), The Beautiful study: randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction – baseline characteristics of the study population. *Cardiology*.110 (4):271-82.
8. Milanese R, Baruscotti M, Gnechi-Ruscone T, DiFrancesco D, (2006). Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. *The New England Journal of Medicine*, 354, 151-157.
9. Luthi A, McCormick DA. 1998. Neuron. H-current: properties of a neuronal and network pacemaker. Vol. 21. pp 9-12.
10. Kaupp UB, Seifert R. Molecular diversity of pacemaker ion channels (2001) *Annu Rev Physiol*. 63:235-57. Review.
11. Notomi T, Shigemoto R (2004) Immunohistochemical localization of  $I_h$  channel subunits, HCN1-4, in the rat brain. *J Comp Neurol* 471: 241-276.
12. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K (2005). Efficacy of ivabradine, a new selective  $I_f$  inhibitor, compared with atenolol in patients with chronic stable angina. *Eur. Heart J*. 26 (23): 2529–36. doi:10.1093/eurheartj/ehi586. PMID 16214830.
13. Ruzyllo W, Tendera M, Ford I, Fox KM (2007). Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 67(3): 393–405. PMID 17335297.
14. Yusuf S, Camm AJ (2003). Sinus tachyarrhythmias and the specific bradycardic agents: a marriage made in heaven?. *J. Cardiovasc. Pharmacol. Ther.* 8 (2): 89–105. doi:10.1177/107424840300800202. PMID 12808482.
15. Stiles, Steve Shift: Adding HR-slowing agent ivabradine to HF meds cuts mortality, hospitalization. *TheHeart.org*. Retrieved 1 April 2011.
16. European Medicine Agency, Procoralan Summary of Product Characteristics. Retrieved 2010-09-13.
17. Anonymous (2006). New medicines: Procoralan. *Pharmaceutical Journal* 276 (7386): 131.
18. Kim Fox, Ian Ford, P Gabriel Steg, Michal Tendera, Prof Roberto Ferrari (2008). "Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction: a randomised, double-blind, placebo-controlled trial". *The Lancet* 372 (9641): 807–816.
19. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; on behalf of the SHIFT Investigators (2010). "Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study". *The Lancet* 376 (9744): 875–885.
20. Colin P, Ghaleh B, Monnet X, et al. Contributions of heart rate and contractility to myocardial oxygen balance during exercise. *Am J Physiol Heart Circ Physiol*. 2003; 284:H676–82.
21. Colin P, Ghaleh B, Monnet X, et al. Effect of graded heart rate reduction with ivabradine on myocardial oxygen consumption and diastolic time in exercising dogs. *J Pharmacol Exp Ther*. 2004; 308:236–40.
22. Vilaine JP, Bidouard JP, Lesage L, et al. Anti-ischemic effects of ivabradine, a selective heart rate-reducing agent, in exercise-induced myocardial ischemia in pigs. *J Cardiovasc Pharmacol*. 2003; 42:688–96.
23. Monnet X, Ghaleh B, Colin P, et al. Effect of heart rate reduction with ivabradine on exercise induced myocardial ischaemia and stunning. *J Pharmacol Exp Ther*. 2001; 299:1133–9.
24. Monnet X, Colin P, Ghaleh B, et al. Heart rate reduction during exercise-induced myocardial ischaemia and stunning. *Eur Heart J*. 2004; 25:579–86.
25. Colin P, Ghaleh B, Hittinger L, et al. Differential effects of heart rate reduction and beta-blockade on left ventricular relaxation during exercise. *Am J Physiol Heart Circ Physiol*. 2002; 282:H672–9.
26. Simon L, Ghaleh B, Puybasset L, et al. Coronary and haemodynamic effects of S 16257, a new bradycardic agent, in resting and exercising conscious dogs. *J Pharmacol Exp Ther*. 1995; 275:659–66.
27. Mulder P, Barbier S, Chagraoui A, et al. Long-term heart rate reduction induced by the selective  $I_f$  current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. *Circulation*. 2004; 109:1674–9.
28. Borer JS, Fox K, Jaillon P, et al. Anti-anginal and anti-ischemic effects of ivabradine, an  $I_f$  inhibitor, in stable angina: a randomized, double-blinded, multi centered, placebo-controlled trial. *Circulation*. 2003; 107:817–23.

Source of support: Nil

Conflict of interest: None Declared