ELSEVIER

Pharmacological Research 53 (2006) 399–406

Pharmacological research

www.elsevier.com/locate/yphrs

Review

Funny channels in the control of cardiac rhythm and mode of action of selective blockers

Dario DiFrancesco *

University of Milano, Department of Biomolecular Sciences and Biotechnology, Laboratory of Molecular Physiology and Neurobiology, via Celoria 26, 20133 Milano, Italy

Accepted 16 March 2006

Abstract

"Funny" (f) channels underlie the cardiac "pacemaker" I_f current, originally described as an inward current activated on hyperpolarization to the diastolic range of voltages in sino-atrial node myocytes [Brown, HF, DiFrancesco, D, Noble, SJ. How does adrenaline accelerate the heart? Nature 1979;280:235–236]. The involvement of funny channels in the generation and modulation of cardiac pacemaker activity has been amply demonstrated by thorough analysis since its discovery. The degree of funny current activation upon termination of an action potential determines the slope of diastolic depolarization, and hence pacemaker frequency; furthermore, I_f is under cAMP-mediated control by β-adrenergic and muscarinic stimulation and underlies the modulation of cardiac rate by the autonomous nervous system: it therefore represents a mechanism of fundamental physiological relevance.

Their function in pacemaking makes funny channels an obvious target for drugs aiming at regulation of spontaneous activity and cardiac rate. This explains the recent development of "heart rate-reducing" drugs which act as selective f-channel inhibitors, and as such are capable of specifically slow cardiac frequency by decreasing the rate of diastolic depolarization. These substances will be useful in treating diseases such as chronic angina and heart failure. Furthermore, in situ delivery of funny channels, or of a cellular source of funny channels, is a promising new technique for the development of biological pacemakers which may in a near future replace electronic devices. Finally, a channel mutation responsible for one type of a relatively common rhythm disturbance, sinus bradycardia, has been recently identified, highlighting the clinical relevance of funny channels in the pacemaker function.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Cardiac pacemaker; I_f current; Funny channels; Heart rate; Autonomic control

Contents

* Tel.: +39 02 5031 4931; fax: +39 02 5031 4932.
E-mail address: dario.difrancesco@unimi.it.

1043-6618/$ – see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phrs.2006.03.006

1. Introduction

Cardiac pacemaking is an electrical phenomenon, based on the function of ion channel proteins expressed on the membrane of specialized cardiac myocytes, the sino-atrial node (SAN) cells of mammalian heart. "Pacemaker" cells are endowed with the property of spontaneous activity, and generate repetitive action potentials at a constantly controlled rate, thus determining the cardiac frequency and consequently the overall cardiac performance. What gives pacemaker cells this ability? Several mechanisms contribute to provide the cellular and molecular elements necessary for pacemaking to occur, but among them, the I_f current has a major role in providing pacemaking competence.

SAN myocytes are characterized by the presence of a "slow diastolic" phase, which at the termination of an action potential slowly depolarizes the membrane until threshold is reached for a subsequent action potential, thus generating spontaneous, repetitive activity [2]. The origin of this phase has been thoroughly investigated [3,4], and it is now generally recognized that activation of I_f at the termination of an action potential is the process responsible for generation of the diastolic depolarization.

Originally described in the SAN [1], the funny current has been the object of intense investigation and its properties and function in cardiac pacemaker cells (and, in fact, in several other types of cells where funny channels are expresssed) have been described in detail [2,5–8].

In this short review I will summarize the properties of the funny current in cardiac cells and discuss therapeutic applications of the concept of pacemaker channels, specifically their potential use in the pharmacological control of heart rate. Review articles addressing more specifically the molecular correlates of native f-channels, the hyperpolarization-activated, cyclic-nucleotide gated (HCN) channels can be found elsewhere [7–9].

2. The funny current generates the diastolic depolarization phase of pacemaker potential

Diastolic depolarization, first recorded in Purkinje fibres, was originally proposed to originate from the decay of a K^+ conductance, based on conductance measurements during an action potential [10] or during voltage-clamp [11]. The mechanism proposed was analogous to that predicted by the squid axon Hodgkin–Huxley [12] model of electrical activity, where after termination of an action potential the membrane hyperpolarizes beyond the resting level, and then slowly depolarizes up to the resting membrane potential due to the decay of the previously activated delayed K^+ conductance.

This idea was subsequently strongly supported by the description in Purkinje fibres of the so called I_{K2} current, reported as a pure K^+ current activated upon depolarization in the diastolic range of voltages [13,14]. According to this description, the I_{K2} decay was the process underlying diastolic depolarization, and I_{K2} had the properties expected for the current predicted by Weidmann's and Vassalle's experiments. The relevance of I_{K2} to pacemaking was strengthened by evidence of the involvement of this component in rate acceleration caused by sympathetic stimulation [15]. The experimental evidence for a K^+-conductance decay hypothesis as the mechanism driving diastolic depolarization in Purkinje fibres was therefore firmly established to all accounts, and the mechanism was regarded as indisputable for over a decade. The I_{K2} current was considered as one of the best described cardiac components. Yet, the I_{K2} interpretation and consequently the K^+-conductance decay hypothesis, were deeply incorrect. In the late 1970s and early 1980s, a set of new experimental data appeared which paved the way to the demonstration that the Purkinje fibre pacemaker current was not an outward current activated on depolarization, but was no less than just the opposite, i.e., an inward current activated on hyperpolarization.

Among the findings that contributed to the re-interpretation of the Purkinje fibre's I_{K2}, an important one was the discovery of the funny (I_f) current in the sino-atrial node. The first detailed report of this current describing its elementary properties and role in the generation of spontaneous activity in the SAN, as well as the involvement in catecholamine-induced control of rate appeared in 1979 [1]. Records of the same current had appeared in previous publications in both mammalian and amphibian heart, but the component had not been considered physiologically relevant [16,17].

The "funny" current had atypical features, which justified its name: it was inward and activated on hyperpolarization within a voltage range comprising the range of diastolic depolarization and had unusually slow kinetics. These properties made I_f the most obvious candidate in the search for components involved in the initiation and control of pacemaking. Several features of the funny current in SAN cells were surprisingly similar to those of the I_{K2} current in Purkinje fibres [18]. The puzzle of having two nearly identical components of a totally different ionic nature was solved two years after the finding of I_f by the demonstration that I_{K2} was in fact, like I_f, an inward current activated on hyperpolarization and carried by Na^+ and K^+, rather than a pure K^+ current activated on depolarization [19,20]. How could an inward current, reversing close to −10/−20 mV, look like a pure K^+ current? The illusion had been caused by the presence, in Purkinje fibres, of a large K^+ inwardly-rectifying component, called I_{K1}, which decreases during the strong hyperpolarizing steps used to study I_{K2}: the superimposition of this component with I_f generates a "fake" reversal potential close to the K^+ equilibrium potential (E_K). Removal of I_{K1} (by Ba^{2+}-induced block) abolished reversal near E_K [19]; this latter result was particularly significant since it "unmasked" the real inward nature of the Purkinje fibre's pacemaker current and allowed for the first time to visualise the "conversion" of I_{K2} into an inward, hyperpolarization-activated current. These results established that I_{K2} was a "camouflaged" I_f, the two "pacemaker" currents in the two cardiac tissues being indeed of identical nature, and led to a rational, integrated interpretation of the origin of cardiac pacemaking in all different pacing regions of the heart.

Following the re-interpretation of I_{K2} and its identification with the nodal I_f, the funny current was systematically characterized in the SAN [5]. Importantly, the findings in cardiac pacemaker cells set the pace for the identification and description of ionic currents with similar properties in a large variety of neurons and other cell types, such as smooth muscle cells

Download English Version:

https://daneshyari.com/en/article/2562589

Download Persian Version:

https://daneshyari.com/article/2562589

Daneshyari.com