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What I_f the shoe doesn't fit?:

Rebuttal to DiFrancesco and Noble “The funny current has a major pacemaking role in the sinus node”

Edward G. Lakatta* and Victor A. Maltsev

Laboratory of Cardiovascular Science, NIA, IRP, NIH, 5600 Nathan Shock Drive, Baltimore, Maryland 21224

The concept that I_f is the most important pacemaker current has been widely promulgated since the late 1970s, and accordingly, has been widely accepted by a generation of pacemaker researchers and educators. Indeed, hyperpolarization-activated and cAMP-modulated- I_f manifests features apt to generate diastolic depolarization (DD) and mediate autonomic rate modulation. But sarcolemmal ion channels and proteins involved in intracellular Ca^{2+} balance/cycling operate together as a system. For example, inward I_{NCX} , is also activated by hyperpolarization, and is additionally regulated by intracellular $[\text{Ca}^{2+}]$ changes (triggered by the action potential and also occurring spontaneously via ryanodine receptors, RyRs, during DD). I_{NCX} is also larger in amplitude and activates much more rapidly than I_f . Autonomic stimulation enhances PKA- and CaMKII-dependent phosphorylation of sarcolemmal ion channels (e.g. I_{CaL} , I_{K}) and Ca^{2+} cycling proteins (e.g. phospholamban, RyRs) leading to changes in membrane potential and cell Ca^{2+} balance/cycling. The hypothesis that a coupled-clock system regulates basal automaticity and its response to neurotransmitters poses a formidable challenge to the concept that I_f is **the pacemaker mechanism**. “New evidence” (Himeno et al. *AJP*;2011;300:H251–H261) against the coupled-clock hypothesis, cited by DiFrancesco and Noble (*Heart Rhythm*; 2011), neither measured $[\text{Ca}^{2+}]$, nor addressed a role of I_f , and has been refuted on technical grounds (Maltsev et al. *AJP*;2011;300:H2323–H2324).

While DiFrancesco and Noble point out that I_f properties are “just right” for a specific role in pacemaker function, they fail to state exactly what this role is. The voltage- and cAMP-dependence of I_f does not prove that it is unique for pacemaker rate regulation, because the mechanisms mentioned above overlap I_f and are also “just right” for pacemaker rate regulation. A unique role of I_f in rate regulation certainly does not follow from the facts that funny-channels are: (i) specifically expressed in pacemaker cells; (ii) a marker of developing pacemaker tissue; (iii) exploited for “biological” pacemakers”. Additional “evidence” cited by DiFrancesco and Noble (Fig.A), like numerous prior studies in which I_f was genetically manipulated in mice (Fig.B–E), actually confirms that **I_f is not necessary for rate acceleration** in response to autonomic stimulation or exercise. In contrast, numerous studies demonstrate that when the coupled-clock system is impaired, either genetically or pharmacologically, with I_f intact, β -AR-mediated rate acceleration is markedly compromised

*Contact information: Edward G. Lakatta, M.D. Laboratory of Cardiovascular Science, NIA, IRP, NIH, 5600 Nathan Shock Drive, Baltimore, MD 21224-6825, USA, Telephone: 410-558-8202, Fax: 410-558-8150, LakattaE@grc.nia.nih.gov.

(cf. review Vinogradova-Lakatta;*JMCC*;2009;47:456–474) indicating that **I_f is also not sufficient for rate acceleration**. Mechanisms overlapping I_f function, however, appear to be both necessary and sufficient for rate acceleration (cf. review Lakatta et al.*Circ Res*; 2010;106:659–673).

Is there a specific role for I_f in rate regulation? Numerous studies in many species, including humans, have demonstrated that pharmacologic inhibition of I_f causes a modest bradycardia. Thus, the only documented **specific** role for I_f in pacemaking is to prevent modest bradycardia. (Deep bradycardia, conduction defects, and high mortality of the tamoxifen-induced HCN4 knockout in mice in Fig.A-study were not manifested in Fig.B-study which used much lower doses of tamoxifen).

We conclude that “the Cinderella pacemaking shoe” does not fit I_f! I_f, functioning together with its “team-mates” within a coupled-clock system, provides modest protection against bradycardia rather than regulates action potential firing rate acceleration.

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Figure.

Autonomic heart rate modulation is preserved in genetically manipulated mice with deficient I_f function