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Editorial

Novel regulation of the mammalian cardiac Na^+ channel by dipeptidyl peptidase 10 interactions: An editorial comment

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A number of distinct ion channel-mediated conductances are responsible for the mammalian cardiac action potential. Of these, a large inwardly directed transmembrane current which is carried almost entirely by Na^+ ions is perhaps the most well-known. This current, Nav1.5, is responsible for initiation of the action potential (excitability); regulation of the most prominent aspect of the refractory period; and modulation of conduction velocity and synchronous activation [1]. Nav1.5 has also been a focus for development of antiarrhythmic therapies focusing on abnormalities that arise from e.g., alterations produced by free radical challenges and/or genetic mutations in this channel protein [2,3]. In addition, a specific aspect of Nav1.5 kinetics – the fact that when this current is activated it turns off or inactivates incompletely, has been a focus for antiarrhythmic drug development [4,5]. These initiatives have targeted the slowly inactivating component or the so-called 'late Na^+ current ($I_{Na\text{-}L}$)' in mammalian hearts [6].

It is now well known that each Na^+ channel in mammalian hearts is a multicomponent protein complex, as opposed to consisting of only a Na^+-selective voltage-dependent pore [7,8]. Four components of this complex include: i) The alpha subunit, which is the Na^+-selective pore. ii) It is almost always expressed as a covalently bonded unit that also includes one or more transmembrane ß-subunits denoted $ß_{1-4}$ [9]. iii) Functional association of Na^+ channels with glycoproteins that localize to the immediate external face of the sarcolemma that can significantly regulate cardiac myocyte/extracellular matrix interactions [10]. iv) Important interactions of Na^+ channels with a number of different intracellular chaperones that can significantly change sarcolemma expression levels and therefore the density of Nav1.5 [8,11].

An interesting and forward looking paper in this Journal [12] provides a starting point for identification of another class of molecules that can selectively interact with Nav1.5. These entities appear to function as an additional class of ß-subunits. Specifically, Belau et al. [12] report that one particular member of the dipeptidyl peptidase family, DPP10 [c.f.13], can significantly change biophysical properties of Nav1.5 channels. These effects appear to be produced by site-specific interactions with the Nav1.5 alpha subunit. Their intriguing data, (although still preliminary) includes the first demonstration of detectable expression of DPP10 in both the atria and ventricles of human hearts, as well as somewhat augmented expression levels in a heart failure model. In addition, this study provides biochemical and molecular evidence illustrating co-immunoprecipitation of DPP10 and the Nav1.5 alpha subunit. In complementary investigations, heterologous expression maneuvers, combined with patch clamp electrophysiological recordings, reveal that adenovirus-mediated expression of DPP10 can: i) reduce the expression levels of I_{Na}, while also ii) displacing in the depolarizing direction (by approximately 10 mV) the gating parameters that regulate Nav1.5 activation and inactivation and iv) accelerating the recovery or reactivation time course of I_{Na}. These changed biophysical parameters are interpreted in terms of the possibility that, when binding DPP10, the slowly inactivating component of the I_{Na} could be increased somewhat and produce an increase in the duration of the action potential. Importantly, data from adult rat ventricular myocytes in which the expression of DPP10 has been increased reveal that the maximum rate (dV/dt) of the initial depolarization of the action potential is reduced and the recovery time course of I_{Na} becomes faster. Collectively, these changes in I_{Na} may be expected to reduce excitability, alter the refractory period of the action potential, and slow conduction velocity [c.f.29].

In an attempt to gain an initial semi quantitative impression of the electrophysiological consequences of the findings in the Belau et al. paper [12] we have introduced some of these changes into the biophysical parameters that regulate the I_{Na} in our mathematical models of adult human atrial [14,15] and ventricular [16] myocytes. Specifically, in each of these atrial and ventricular myocyte models the variables that regulate steady-state activation and inactivation of the I_{Na} were shifted 5 or 6 mV in the depolarizing direction and the maximum conductance variable for I_{Na} was decreased by 18% in accordance with the

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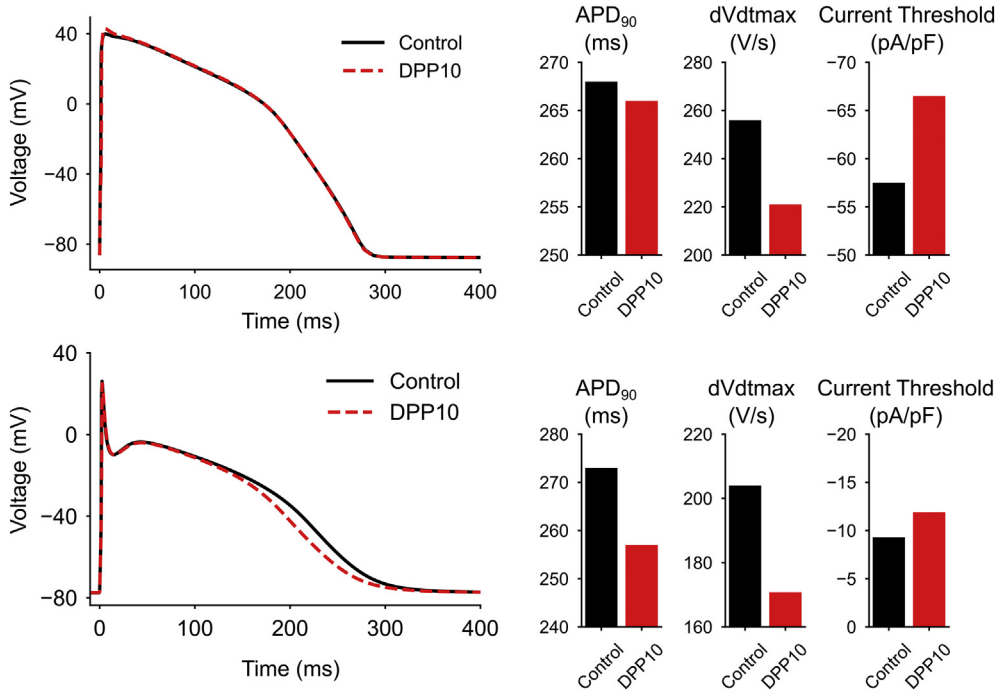

Fig. 1. Illustration of possible DPP10-induced effects on the human ventricular (top) and atrial (bottom) action potential based on mathematical modeling (see text). In each Panel the DPP10-induced change is shown as broken red lines. The three pairs of histograms to the right of each action potential pair illustrate DPP10-induced effects on APD90, dV/dt of the action potential upstroke, and the current needed to fire a regenerative action potential when each of the in silico myocytes was paced at 1 Hz.

published data in this paper. Our results are illustrated in Fig. 1 and summarized in the associated Fig. 1 Legend. In brief, when compared with control action potentials the membrane action potentials produced by our modified models that attempt to mimic DPPD10-induced effects show only small changes in action potential duration, but significant reductions in the upstroke dV/dt in both atrium and ventricle. We note that the decrease in the maximal Na^+ conductance was the most likely cause of the change in excitability and reduced dV/dt in both models.

It is of interest to consider the published experimental findings in more broad contexts that may be relevant to their physiological or pathophysiological importance [13]. Previous literature concerning the electrophysiological actions of DPP10 and/or two related family members (DPP6 and DPP4) has provided strong evidence that DPP10 and DPP6 can interact with selected K^+ channels. In the case of DPP10, electrophysiological data convincingly demonstrates significant interactions with very specific K^+ channel family members, Kv4.2 and Kv4.3 [17–19]. These currents regulate early repolarization of the action potential [15,20,21] and can also significantly alter action potential repolarization, post repolarization refractoriness, and spontaneous activity in neurons [17]. The question that arises therefore is: can one meaningfully assess the electrophysiological actions of DPP10 in mammalian atrial or ventricular myocytes by focusing only on the resulting modifications in Nav1.5? The data in Fig. 2 of the Supplemental section in [12] begin to address this possibility. Under their experimental conditions adenovirus-mediated expression of DPP10 does not alter the amplitude of K^+ currents generated by Kv4.3 and has little if any of the well-known actions of DPP10 on the time course of inactivation or reactivation of this current.

Going forward, it will be important to learn more about DPP10 expression in atrial and ventricular myocytes in healthy hearts and in pathophysiological settings. For example, are changes in this family of proteins restricted to DPP10, or do levels of DPP6 or perhaps even DPP4 also change? In other pathophysiological settings, e.g., diabetes, the disease-related changes in a number of different cell types appear to be in DPP4 only. Infact, this specific dipeptidyl peptidase is an actively pursued drug target [13]. It is also known that a number of splice variants of DPP10 may be expressed and that under these conditions Kv4.3 and/or 4.2 are selectively targeted and modified both in terms of the voltage-dependence of their gating and density of expression in the surface membrane [22,23]. Another function of the DPP family that deserves further consideration is the fact that these proteins show protease activity and therefore could function not only as a ß-subunit but also as a localized, perhaps tethered enzyme of metabolic significance. A recent paper [24] concerning DPP10 actions on transient outward currents in *Drosophila* preparations demonstrates that the DPP10 fly orthologue definitely is enzymatically active, but the authors also note that enzymatic activity of DPP10 has not been identified in studies of mammalian cells. Two final and more general questions concerning the molecular implications of this paper and its translational significance are the following: i) Given the recent demonstrations of functional interactions between Na^+ and K^+ channels in neurons and heart preparations [25–27] is the DPP10 interaction with the Na^+ channel amplified? ii) Based on the demonstrations in heart, skeletal muscle and neurons of highly nonlinear interactions [28–32] between the size of individual currents and their physiological properties can one be certain that DPP10-induced changes in I_{Na} would in fact alter action potential threshold, substrate excitability, or either micro or macro aspects of conduction velocity in cardiac syncytia, c.f. [28,33].

We acknowledge the novelty and potential significance of the primary data in this paper [12] and we look forward to the publication of additional data sets from this group and others.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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