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Stretch-activated channels in the heart: Contributions to length-dependence and to cardiomyopathy

Marie-Louise Ward[a,*], Iwan A. Williams[b], Yi Chu[b], Patricia J. Cooper[a], Yue-Kun Ju[b], David G. Allen[b]

[a]*Department of Physiology, Faculty of Medicine and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand*
[b]*Institute for Biomedical Sciences, School of Medical Sciences, University of Sydney F13, NSW 2006, Australia*

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Abstract

The stretch-induced increase in force production of ventricular muscle is biphasic. An abrupt increase in force coincides with the stretch, which is then followed by a slower response that develops over minutes (the slow force response or SFR). The SFR is accompanied by a slow increase in the magnitude of the intracellular Ca^{2+} transient, but the stretch-dependent mechanisms that give rise to this remain controversial. We characterized the SFR using right ventricular trabeculae from mouse hearts. Application of three different blockers of stretch-activated non-selective cation channels (SAC_{NSC}) reduced the magnitude of the SFR 60 s after stretch (400 μM streptomycin: from 86±25% to 38±14%, $P<0.01$, $n=9$; 10 μM $GdCl_3$: from 65±21%, to 12±7%, $P<0.01$, $n=7$; 10 μM GsMTx-4 from 122±40% to 15±8%, $P<0.05$, $n=6$). Streptomycin also decreased the increase in Ca^{2+} transient amplitude 60 s after the stretch from 43.5±12.7% to 5.7±3.5% ($P<0.05$, $n=4$), and reduced the stretch-dependent increase in intracellular Ca^{2+} in quiescent muscles when stretched. The transient receptor potential, canonical channels TRPC1 and TRPC6 are mechano-sensitive, non-selective cation channels. They are expressed in mouse ventricular muscle, and could therefore be responsible for stretch-dependent influx of Na^+ and/or Ca^{2+} during the SFR. Expression of TRPC1 was investigated in the *mdx* heart, a mouse model of Duchenne's muscular dystrophy. Resting Ca^{2+} was raised in isolated myocytes from old *mdx* animals, which was blocked by application of SAC blockers. Expression of TRPC1 was increased in the older *mdx* animals, which have developed a dilated cardiomyopathy, and might therefore contribute to the dilated cardiomyopathy.

Keywords: Stretch-activated ion channels; Trabeculae; Cardiac myocytes; Muscular dystrophy; Protein expression

Contents

*Corresponding author. Tel.: +64 9 3737599; fax: +64 9 3737499.
E-mail address: m.ward@auckland.ac.nz (M.-L. Ward).

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1. Introduction

The stretch-induced increase in force production of ventricular muscle has long been recognized and underlies the Frank–Starling relation (Frank, 1895; Patterson and Starling, 1914). It is thought that at least three different cellular mechanisms are involved (for review see, Allen and Kentish, 1985). (i) Increased overlap between the thick and thin filaments (Gordon et al., 1966; Fabiato and Fabiato, 1975). (ii) Increased Ca^{2+} sensitivity of the contractile machinery (Hibberd and Jewell, 1982; Fukuda and Granzier, 2005). (iii) Increased Ca^{2+} transients (the systolic rise in Ca^{2+} which activates the contractile proteins) which gradually become larger over some minutes after a stretch (Allen and Kurihara, 1982; Kentish and Wrzosek, 1998).

The last mechanism was first recognized by Parmley and Chuck (1973) who noted a slow increase in force following a stretch which took 5–10 min to reach completion. They argued that the increases in overlap of the thick and thin filaments should occur instantaneously with the stretch, and that the slow phenomenon was likely to be caused by changes in the degree of activation of the contractile proteins. These ideas were confirmed when it was shown that, following a stretch, there was a slow increase in the magnitude of the Ca^{2+} transients which caused the slow increase in force (Allen and Kurihara, 1982; Kentish and Wrzosek, 1998). Ca^{2+} transients could increase if there was additional Ca^{2+} entry into the muscle leading to an increase in resting $[Ca^{2+}]_i$ which would translate into greater SR Ca^{2+} load and greater release. The additional Ca^{2+} entry could possibly involve *L*-type Ca^{2+} currents during the action potential, or a Ca^{2+} entry pathway that was active throughout the cardiac cycle. Many studies of the action potential and *L*-type Ca^{2+} currents have shown that these are only marginally affected by stretch (Hongo et al., 1996); in contrast the enhancement of force and intracellular Ca^{2+} can occur even when the stretch is timed to occur only during diastole (Allen et al., 1988). These observations suggest that a Ca^{2+} entry pathway is invoked by stretch that is active during diastole.