Can T-type calcium channels make a change of heart after myocardial infarction? Fiction or fact, and for better or for worse?

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This editorial refers to ‘Role of T-type calcium channel subunits in post-myocardial infarction remodelling probed with genetically engineered mice’ by K. Le Quang et al., pp. 420–428, this issue.

The outcome of patients with myocardial infarction has improved dramatically over the last few decades. Evidence-based therapy comprises rapid recanalization with full restitution of flow by acute percutaneous coronary intervention, local and systemic antithrombotic therapy, the use of statins, β-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, and aldosterone receptor antagonists to protect the heart from subsequent adverse remodelling.1 The term ‘cardiac remodelling’ refers to a process involving changes in morphology and mechanical and electrical function that occur after injury such as myocardial infarction and pressure or volume overload. Remodelling allows for the maintenance of haemodynamic function but also results in cardiac hypertrophy, reactivation of a foetal gene programme, and arrhythmias, all relevant for prevention and treatment of heart failure and sudden death.2

Voltage-gated calcium channels play a fundamental role in nano-environmental networks of calcium-dependent effector systems, affecting mechanical and electrical function as well as gene expression of the heart. They appear to be involved in the cardiac remodelling process. Although the classical L (‘long-lasting’, ‘large’)-type calcium channel is essential for cardiac contraction, its ‘little brother’, the T (‘transient’, ‘tiny’)-type calcium channel, was proposed to be involved in cardiac pathophysiology3 soon after its discovery.4 Although known to be regulated by hormones,5 hypoxia,6 and development,7 its pathophysiological role in the ventricular myocardium is far from being clear (Table 1). Its subunits Cav3.1, 3.2, and 3.3 are also called α1G, α1H, and α1l, respectively. T-type calcium channels respond to more negative membrane potentials (low-voltage activated). When examined with barium ions as charge carriers, they can be discriminated from L-type channels by their lower single-channel conductance (‘tINY’), more rapid inactivation (‘transient’), and slower deactivation time course. In line with a suspected minor role in excitation–contraction coupling, T-type channels have been shown to reside at the surface sarcolemma rather than in T-tubules.8 T-type calcium channels play a role in initiating action potentials. In the heart, they contribute to the prepotential of the sinus node. Expression of T-type calcium channels depends on species, cardiac chamber, developmental stage, and pathology (Table 1).

Le Quang et al.9 report cardiac electrical and haemodynamic function after myocardial infarction in a genetic model lacking either of the two genes coding for the cardiac T-type calcium channel subunit, Cav3.1 or Cav3.2. Their aim was to study the contribution of T-type calcium channels in cardiac remodelling after myocardial infarction. Adult Cav3.1 or Cav3.2 knockout and littermate wild-type (WT) controls were examined before and after left anterior descending coronary artery (LAD) ligation and the resulting transmurral myocardial infarction by a range of elaborate in vivo and ex vivo techniques: echocardiography, telemetry Holter ECG, programmed electrical stimulation, invasive haemodynamics, and assessment of RNA expression of Cav3.1 and Cav3.2 subunits.

While at baseline the only detectable differences in the T-type calcium channel subunit Cav3.1 knockout mouse were sinus bradycardia and first-degree atrioventricular block, the adaptation to myocardial infarction revealed increased arrhythmia inducibility (in 9/11 knockout animals vs. 3/10 WT, induced by an invasive electrophysiological pacing study) and decreased contractility. Mortality, occurrence of spontaneous arrhythmias during telemetric observation, atrial arrhythmias, diastolic function, and infarction size were unchanged. Knockout of the Cav3.2 gene caused neither a difference at baseline nor after myocardial infarction. In summary, the study shows an unfavourable effect of the knockout of T-type calcium channel subunit Cav3.1 (but not of Cav3.2) on remodelling after myocardial infarction. The authors conclude that T-type calcium channel blockade targeting Cav3.1 subunits may not be beneficial. This is an important contribution to the understanding of the function of T-type calcium channels after myocardial infarction.

After enthusiastic reading of the paper by Le Quang et al.,9 we still do not know the mechanism of how the lack of the T-type calcium

REFERENCES

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channel Cav3.1 subunit leads to adverse cardiac remodelling. As RR and PR intervals were prolonged in Cav3.1 knockouts, changes in conduction or diastolic potential maintenance may be involved, e.g. in the border zone of myocardial infarction, but these parameters were not assessed. Although levels of T-type calcium channels are thought to be increased in remodelled hearts, there was no significant up-regulation in Cav3.1 or Cav3.2 mRNA expression. Comparing the concentration of target proteins in the heart was technically not feasible. Cellular electrophysiology should be used in future studies to assess the number of functional channels. Compensatory changes in other proteins may also have contributed to observed effects. Surprisingly, LAD ligation did not increase ventricular arrhythmias in WT mice to a significant degree in this study. Even if performing state-of-the-art experiments with strictly blinded procedures, one may overlook phenomena by working at the edge of statistical power due to ethical and spatial constraints. It is therefore reassuring that most but not all studies in mice carrying altered Cav3.1 and Cav3.2 genes point in the same direction as the present data set, showing an adverse effect of knockout and even a beneficial effect of specific expression.

The fact that this study in knockout mice generates results contrary to pharmacological studies (Table 1) makes it even more interesting. Non-specific action of pharmacological interventions may involve other voltage-dependent calcium channels, or even sodium and potassium channels. Therefore, an altered vascular resistance or sympathetic drive by target actions of mibefradil may have caused secondary effects on the heart. Accordingly, beneficial effects of T-type calcium channel blockers on cardiac remodelling have been advocated in some but not all pharmacological models (Table 1). The knockout model itself does not entirely exclude non-specific phenomena either, since compensatory changes may prevail. Furthermore, the global T-type calcium channel subunit knockout may have primary non-cardiac effects, given the physiological roles of T-type channels in the vascular and nervous system.

The experience with T-type calcium channel inhibitors in clinical cardiology is limited to a few months of mibefradil approval as an anti-anginal drug. It was taken from the market due to interactions with both P-glycoprotein and cytochrome P450 3A4, ensuing relevant drug–drug interactions. Additional experience may result from the use of the T- and L-type channel blocker efonidipine to treat hypertension in Japan. A scientific interest in subtype-specific substances targeting T-type calcium channels prevails. For example, blockade of T-type calcium channels with a novel type of pyridyl amide compound (TTA-A2) is supposed to inhibit high-fat diet-induced weight gain. Indirect effects on the heart should be taken into account when targeting T-type calcium channels for other purposes.

A major dilemma in heart failure therapy and sudden cardiac death prevention is the risk of ventricular arrhythmias with therapy increasing cardiac systolic function. If functional Cav3.1 T-type calcium channel subunits lead to better contractility at the expense of less calcium overload and reduced ventricular arrhythmia, then the T-type calcium channel subunit Cav3.1 acts exactly as we want, and we should dismiss the idea of blocking it. Relevance of these observations to human cardiac ventricular remodelling, however, is still unclear as T-type currents have not yet been detected in myocytes isolated from the diseased human ventricle, although Cav3.2 was originally cloned from human heart cDNA.

Future studies will reveal whether T-type calcium channel subunits are important for maintaining contractility and rhythm in remodelling after myocardial infarction, or whether this editorial addresses transient observations on a tiny channel.

### Conflict of interest

None declared.

### Table 1 Selected reports on the role of T-type calcium channels on remodelling

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease model</th>
<th>L-/T-type block, KO, OE</th>
<th>Observed effect of T-type calcium channels</th>
<th>+/- Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>LAD ligation MI remodelling</td>
<td>KO Cav 3.1, 3.2</td>
<td>KO enhances adverse cardiac remodelling</td>
<td>+</td>
</tr>
<tr>
<td>Mouse</td>
<td>—</td>
<td>OE Cav 3.1 vs. OE L-type-β</td>
<td>OE increases contractility without negative remodelling</td>
<td>+</td>
</tr>
<tr>
<td>Mouse</td>
<td>Overload, isoproterenol, exercise</td>
<td>KO Cav3.1 vs. OE Cav3.1</td>
<td>Hypertrophy enhanced in KO, abrogated in OE</td>
<td>+</td>
</tr>
<tr>
<td>Mouse</td>
<td>Pressure overload</td>
<td>KO Cav3.1, 3.2</td>
<td>KO 3.1 no effect, Cav3.2 hypertrophy calcineurin/NFAT signalling</td>
<td>–</td>
</tr>
<tr>
<td>Mouse</td>
<td>dnNRSF-TG DCM, WT MI heart failure</td>
<td>Mibefradil, efonidipine vs. nitrendipine</td>
<td>Mibefradil, efonidipine prevent sudden cardiac death better</td>
<td>–</td>
</tr>
<tr>
<td>Rat</td>
<td>Cardiac hypertrophy in spontaneously hypertensive rats</td>
<td>Increased expression, shift in alternative splicing of Cav3.2</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Rat</td>
<td>Post-infarction remodelling</td>
<td>Reexpression during remodelling</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Rat</td>
<td>Monocrotaline-induced hypertrophy in RV CM</td>
<td>Mibefradil</td>
<td>Block reduces contractile function in hypertrophied hearts</td>
<td>+</td>
</tr>
<tr>
<td>Hamster</td>
<td>Cardiomyopathic Syrian hamster</td>
<td>Increased current density</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Hamster</td>
<td>Cardiomyopathic Syrian hamster</td>
<td>Mibefradil</td>
<td>Block suppresses remodelling</td>
<td>–</td>
</tr>
<tr>
<td>Human</td>
<td>Terminal heart failure</td>
<td>Mibefradil</td>
<td>Search for T-type channel function yields no identifiable current</td>
<td>?</td>
</tr>
</tbody>
</table>

Studies make use of T-type/L-type calcium channel inhibitors, genetic knockout (KO) or specific expression (OE) in various cardiac disease models. See Le Quang et al. for further references, including those for cat and dog. ‘+’/+’ denotes a positive or negative postulated effect of the T-type calcium channel. LAD, left anterior descending coronary artery; MI, myocardial infarction; DCM, dilated cardiomyopathy; dnNRSF-TG, neuron-restrictive silencer factor transgenic mice; CM, cardiomyocyte.

The experience with T-type calcium channel inhibitors in clinical cardiology is limited to a few months of mibefradil approval as an anti-anginal drug. It was taken from the market due to interactions with both P-glycoprotein and cytochrome P450 3A4, ensuring relevant drug–drug interactions. Additional experience may result from the use of the T- and L-type channel blocker efonidipine to treat hypertension in Japan. A scientific interest in subtype-specific substances targeting T-type calcium channels prevails. For example, blockade of T-type calcium channels with a novel type of pyridyl amide compound (TTA-A2) is supposed to inhibit high-fat diet-induced weight gain. Indirect effects on the heart should be taken into account when targeting T-type calcium channels for other purposes.

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