**EDITORIAL**

Cx30 in the sinus node of murine heart: just one connexin more, or more? Evidence for a construction principle?

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This editorial refers to ‘Connexin 30 is expressed in the mouse sino-atrial node and modulates heart rate’ by Gros et al., doi:10.1093/cvr/cvp280.

One of the differences between a mere accumulation of cells and a tissue or even an organ is that in organized forms (tissue, organ) cells typically communicate with each other. They coordinate their function, growth, and differentiation. In addition to cell adhesion molecules, increted hormones and local mediators, direct intercellular communication via gap junction channels plays a key role in this process. In cardiac tissue, these channels also provide the basis for the propagation of the action potential from cell to cell.

Gap junction channels are dodecameric proteins consisting of connexin subunits of one (homomeric channels) or more isoforms (heteromeric channels). The connexins belong to an evolutionarily old protein family comprising 21 members in the mouse and 20 in man.1 In the mammalian heart typically three connexins are expressed: Cx43, encoded by the gene Gja1, is the most abundant; Cx40, encoded by Gja5, is confined to atria and the specific conduction system; Cx45, encoded by Gjc1, is found in early stages of development and in the specific conduction system, including sinus nodal cells.

In recent years, murine Cx30.2, encoded by Gjd3, (the murine orthologue of human Cx31.9, encoded by Gjd3 Ref here) and now Cx30, encoded by Gjb6, (see the report by Gros et al.2) have been found in the murine heart. Cx30 expression was limited to a narrow epicardial layer of the sinus node. Since Cx30-deficient mice exhibited—as the primary effect—a higher heart rate with lower standard deviation, the authors of this study assumed that Cx30 normally lowers sinus rate.

Is Cx30 just one cardiac connexin more? Or more? The unanswered question now is: why does the heart (and many other organs as well) express different connexins, although they all have similar functions? They all allow electrical current to pass, although with somewhat different single channel conductances (Table 1), and small molecules to be transferred from cell to cell. The conductance, however, may be different if several connexin isoforms together form a—heterotypic or possibly heteromeric—channel, as has been shown for Cx40/Cx43 channels.3 Thus, the first question is: are these Cx30 channels functional, and if so are they homomeric, heteromeric, or heterotypic channels? Or is it possible that they form functional hemichannels?

Mammalian species exhibit a wide range of body weight, lifespan, and heart rate and size, the heart rate being inversely related to body size.4 Interestingly, the number of heart beats in a lifetime seems to be limited to 1–2 billion,5 so that there is an inverse relationship between lifespan and heart rate. Moreover, small hearts in most cases beat at a higher rate.4 Nevertheless, the AV conduction delay does not proportionally decrease with increasing intrinsic heart rate and decreasing AV size.6 Sino-atrial node cells exhibit some variation regarding their size, which seems to be correlated with their intrinsic beating rate, maximum depolarization velocity, and connexin expression.7 An inner organization of the sino-atrial node seems to exist, with small, slower beating cells being located in the centre and larger, faster beating cells in the periphery.8

In order to adapt the beating rate of the sinus node to its size and to the mass of surrounding atrial tissue, it is necessary to adapt sino-atrial coupling to the local current source/sink ratio: the presence of connexins in sino-atrial cells means that these cells (as a small current source) can lose current to adjacent atrial cells (a large current sink). If coupling is too high, the current source may lose too much current to the sink (atrial mass). This current loss to adjacent cells would lower the slow diastolic depolarization and thereby could reduce heart rate. A decrease in connexins, e.g. by a deficiency in one isoform, would consequently reduce current loss to adjacent sites, which may increase depolarization rate.

However, what might be the physiological advantage of expressing a number of different isoforms with different local expression...
patterns (i.e. sinus node vs. atrium vs. working myocardium)? There is accumulating evidence that the expression of connexin isoforms can be regulated differentially. Thus, it can be imagined—but needs to be proven—that the variety of connexins is also necessary to ensure that via a certain stimulus gap junction intercellular coupling is altered only at a particular localization. This would enable the heart to control electrical communication locally. However, an important next step is to investigate whether different regulatory pathways for Cx30 and for the other cardiac connexins exist. In order to adapt coupling to a given situation, (i) various isoforms of connexins with different single channel properties (Table 1) may be expressed or (ii) the expression level, i.e. the number of channels, may be regulated. This might also contribute to establish a gradient of coupling between the centre and the periphery of the sino-atrial node.

Taken together, the expression of different isoforms with different single channel properties, the local distribution of the channels and the level of expression may resemble a construction principle to ensure upper and lower limits for a certain range of heart rate. It has been assumed, for example, that a coupling gradient may exist in sinus node or that the nodal cell strands might interwine with atrial strands. With the new findings of Gros et al., the number of murine sinus nodal connexins is increased to three: Cx45, Cx30.2, and Cx30. Interestingly, the human orthologue of murine sinus nodal connexins is increased to three: Cx45, Cx30.2, and Cx30.2. In the human cardiac conduction system, Cx30.2, Cx30.9, could not be detected in the human cardiac conduction system. Thus, the murine sino-atrial node probably exhibits specific characteristics to adapt coupling, size, and heart rate. It needs to be determined whether Cx30 might exist in the human sino-atrial node or that of other mammals, in order to understand whether Cx30, like Cx30.2, might also be a unique feature of the mouse heart. The present article by Gros et al. is an important step on the way to our understanding of the organization of the ‘electrical network heart’. In particular, this article contributes to a new understanding that gap junctions resemble a highly important construction principle and that the view ‘more coupling’ or ‘less coupling’ in terms of being ‘good’ or ‘bad’ is oversimplifying. Instead, the paper leads us to a differentiated view of coupling taking place in a complex surrounding of current sources and sinks, and that nature seems to use various isoforms of connexins to adapt the needs of coupling to this complex local situation. Impressively, the authors show how a change in sino-atrial coupling regarding only one out of the three sino-nodal connexin isoforms can affect heart rate and thereby, as a final consequence, ventricular morphology, thus demonstrating the complex interactions within the heart.

**Conflict of interest:** none declared.

### Table 1 Single channel conductance of gap junction channels formed by the various cardiac connexin isoforms

<table>
<thead>
<tr>
<th>Cx isoform</th>
<th>Single channel $\gamma(g)$ (pS)</th>
<th>Residual $\gamma(g)$ (pS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cx45</td>
<td>32$^a$</td>
<td>n.d.</td>
</tr>
<tr>
<td>Cx43</td>
<td>115$^b$</td>
<td>23$^b$</td>
</tr>
<tr>
<td>Cx40</td>
<td>180$^c$</td>
<td>36$^c$</td>
</tr>
<tr>
<td>Cx30.2</td>
<td>9$^d$</td>
<td>n.d.</td>
</tr>
<tr>
<td>Cx30</td>
<td>179$^d$</td>
<td>48$^d$</td>
</tr>
</tbody>
</table>

Data are dependent on intracellular pipette solution and may therefore vary among different observers. n.d., no data.

$^a$Data according to Kreuzberg et al.$^b$

$^b$Data according to Valiunas et al.$^c$

$^c$Data according to Bukauskas et al.$^d$

$^d$Data according to Valiunas et al.$^e$

### References


