Gap Junction Channel

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In most tissues, cells in contact with each other exchange cytosolic molecules of low molecular weight via channels aggregated at gap junctions. Gap junction mediated cell-to-cell communication allows neighboring cells to coordinate and regulate many functional activities in mature and developing organs. A gap junction channel is made of the interaction of two hemichannels (connexons/innexons) that form a hydrophilic pathway across the two apposed plasma membranes and the extracellular space (gap). Each connexon/innexon is an oligomer of six proteins (connexins/innexins) that span the plasma membrane and create a hydrophilic pore insulated from lipid bilayer and extracellular medium (Rev. in: Peracchia, C., Gap junction stucture and chemical regulation. Direct calmodulin role in cell-to-cell channel gating. Academic Press. An imprint of Elsevier: London, UK, 2019).

Gap junction channels have been thought to possess as many as four types of gates: fast transjunctional voltage (Vj) gate, slow Vj-gate, chemical gate and gate sensitive to membrane potential (Vm). However, since the behavior of the slow Vj-gate and the Vm-sensitive is the same as that of the chemical gate, most likely these gates are the same. We have named this gate “chemical/slow gate” (Peracchia, C. Calmodulin-mediated regulation of gap junction channels. Int. J. Mol. Sci. 2020, 21, 485). In 2000, we proposed a calmodulin (CaM)-mediated “cork-type” gating model. The model proposes two mechanisms. One, “Ca-CaM-Cork”, envisions physical blockage of the channel’s mouth by a CaM lobe (N-lobe?), likely to be combined with conformational connexin changes induced by Ca^{2+}-CaM binding to connexin sites. The other, “CaM-Cork”, also proposes a physical blockage of the channel’s mouth by a CaM lobe, but without calcium-ctivation. The first is only reversed by the return of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) to resting values. The latter is reversed by Vj positive at the gated side (Peracchia, C. Calmodulin-Cork model of gap junction channel gating. - One molecule, two mechanisms. Int. J. Mol. Sci. 2020, 21, 4938).

Evidence that gap junction mediated cell communication is finely regulated by nanomolar $[Ca^{2+}]_i$ via the direct action of Ca^{2+}-CaM indicates that gap junction channel gating is not just a safety mechanism for protecting cells from damaged/dead neighbors (healing-over). Rather, it is also a mechanism designed to finely modulate cell–cell exchange of small molecules.

In summary:

- At resting $[Ca^{2+}]_i$, (<50nM) some channels are spontaneously closed by the CaM-Cork gating mechanism.
- With moderate $[Ca^{2+}]_i$ rise (50–100 nM, the CaMKII cascade may be activated causing channels closed by the CaM-Cork mechanism to open.
- With greater $[Ca^{2+}]_i$ rise (>100 nM), the channels start closing by the Ca-CaM-Cork mechanism. CaM lobe channel mouth plugging is likely to include connexin conformational changes.
- CaM-Cork gated channels could be reopened by Vj positive at gated side, but since they would close at the negative side no Gj change would occur. This is not the case with heterotypic channels between wild-type connexins paired with more gating-sensitive mutants.
- Most Ca-CaM-Cork gated channels reopen with a drop in $[Ca^{2+}]_i$ to resting values (<50 nM). However, with prolonged exposure to high $[Ca^{2+}]_i$, channel gating may not be reversible.

Many questions still need to be answered in terms of molecular details, such as: Is CaM anchored to the NT or the CL2 domain? Is CaM anchored to connexins by the C-lobe or the N-lobe? Is the gating lobe the N-lobe or the C-lobe? Does the gating lobe bind to the CL2 or the NT CaM binding site? Are all of the CaMs anchored to a connexon Ca^{2+}-activated? If so, how many lobes gate the channel? Does CaM activation cause connexin conformational changes?

Keywords: gap junctions ; connexins ; channel gating ; calcium ; calmodulin ; cell communication ; cell-to-cell channels ; cell coupling ; cell uncoupling

1. Introduction

In most tissues, cells in contact with each other exchange cytosolic molecules of low molecular weight via channels aggregated at gap junctions. Gap junction mediated cell-to-cell communication allows neighboring cells to coordinate and regulate many functional activities in mature and developing organs [1][2][3]. A gap junction channel is made of the interaction of two hemichannels (connexons/innexons) that form a hydrophilic pathway across the two apposed plasma membranes and the extracellular space (gap). Each connexon/innexon is an oligomer of six proteins (connexins/innexins) that span the plasma membrane and create a hydrophilic pore insulated from lipid bilayer and extracellular medium.

Gap junction channels have been thought to possess as many as four types of gates: fast transjunctional voltage (Vj) gate, slow Vj-gate, chemical gate and gate sensitive to membrane potential (Vm). However, since the behavior of the slow Vj-gate and the Vm-sensitive is the same as that of the chemical gate, most likely these gates are the same. We have named this gate “chemical/slow gate” [1].

In 2000, we proposed a calmodulin (CaM)-mediated “cork-type” gating model [4] The model proposes two mechanisms. One, “Ca-CaM-Cork”, envisions physical blockage of the channel’s mouth by a CaM lobe (N-lobe?), likely to be combined with conformational connexin changes induced by Ca^{2+}-CaM binding to connexin sites. The other, “CaM-Cork”, also proposes a physical blockage of the channel’s mouth by a CaM lobe, but without Ca^{2+}-activation. The first is only reversed by the return of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) to resting values. The latter is reversed by Vj positive at the gated side.

2. Conclusion

Evidence that gap junction mediated cell communication is finely regulated by nanomolar $[Ca^{2+}]_i$ via the direct action of Ca^{2+}-CaM indicates that gap junction channel gating is not just a safety mechanism for protecting cells from damaged/dead neighbors (healing-over). Rather, it is also a mechanism designed to finely modulate cell–cell exchange of small molecules.

We have proposed a two-facet CaM-mediated gating mechanism: Ca-CaM-Cork and CaM-Cork. In summary:

- At resting $[Ca^{2+}]_i$, (<50nM) some channels are spontaneously closed by the CaM-Cork gating mechanism.
- With moderate $[Ca^{2+}]_i$ rise (50–100 nM, the CaMKII cascade may be activated causing channels closed by the CaM-Cork mechanism to open.
- With greater $[Ca^{2+}]_i$ rise (>100 nM), the channels start closing by the Ca-CaM-Cork mechanism. CaM lobe channel mouth plugging is likely to include connexin conformational changes.
- CaM-Cork gated channels could be reopened by Vj positive at gated side, but since they would close at the negative side no Gj change would occur. This is not the case with heterotypic channels between wild-type connexins paired with more gating-sensitive mutants.
- Most Ca-CaM-Cork gated channels reopen with a drop in $[Ca^{2+}]_i$ to resting values (<50 nM). However, with prolonged exposure to high $[Ca^{2+}]_i$, channel gating may not be reversible.

Many questions still need to be answered in terms of molecular details, such as: Is CaM anchored to the NT or the CL2 domain? Is CaM anchored to connexins by the C-lobe or the N-lobe? Is the gating lobe the N-lobe or the C-lobe? Does the gating lobe bind to the CL2 or the NT CaM binding site? Are all of the CaMs anchored to a connexon Ca^{2+}-activated? If so, how many lobes gate the channel? Does CaM activation cause connexin conformational changes?

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