

A superfamily of ion channels

SIR—Recent studies have revealed structural similarities among voltage-gated cation channels. It would be interesting to know whether some of the second-messenger-gated channels are similar in structure to voltage-gated channels. We report here that a second-messenger-gated channel, the bovine rod photoreceptor cyclic GMP-gated channel¹, belongs to the same superfamily as voltage-gated cation channels.

Like voltage-gated potassium channel polypeptides²⁻⁵, the cyclic GMP-gated channel polypeptide resembles one of the

four internally homologous domains of the alpha-subunit of voltage-gated sodium or calcium channels⁶⁻⁹. The six hydrophobic sequences (H1-H6) and an S4 sequence that is between H3 and H4 of the cyclic GMP-gated channel can be aligned with the corresponding sequences of potassium channels and each of the four domains of sodium and calcium channels (see figure). The probability of this occurring by chance is negligible, suggesting that cyclic GMP-gated and voltage-gated cation channels are related in structure.

The presence of an S4 sequence in the

cyclic GMP-gated channel polypeptide is interesting, as the S4 sequences in voltage-gated channels have been proposed to serve the function of voltage sensors. Unlike voltage-gated channels, the cyclic GMP-gated channel requires the binding of three or more molecules of cyclic GMP to become activated, though the gating shows weak voltage dependence (see ref. 1 for further references). The conservation of the S4 sequence in this second-messenger-gated channel could reflect a requirement for the close packing of the protein interior.

Ponder and Richards¹⁰ have proposed that the basic architecture of a globular protein is largely determined by the 'tertiary template', the core structure formed by buried residues that are inaccessible to solvent. Only a few particular combinations of amino acids fulfill the criteria for the tertiary template for a given globular protein^{10,11}. By analogy, the tertiary template of an ion channel could correspond to those residues that do not interact with water or lipids, or ions in the pore; these residues form the core structure and are important in establishing the basic architecture of the channel. Before the structure of a channel is determined, its tertiary template can not be identified. But on the basis of their conservation, it seems likely that some of the hydrophobic residues, and perhaps even some of the basic residues that are highly invariant among the cyclic GMP-gated and voltage-gated cation channels, correspond to part of this tertiary template. Thus, the S4 sequence probably arose in an ancestral channel. In addition to its postulated function as a voltage sensor for some of the descendant voltage-gated channels, it probably forms part of the core structure of both voltage-gated and cyclic GMP-gated channels.

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	S1/H1	S2/H2	S3/H3	S4
cGMP-gated channel	GNTYVNWLCFLLPVMHW	WLAFLVYLSDDVWVLLDNEVTRIT	FQKRLDVLVYIPDLDLILKIFGW	YFRLRLRLRLRISRMFFEQRTETRT
Shaker	RVAIVLSEVWVLLSIVIFCL	FFLEETLCLIMFTEELVRFLLA	WQVVDIIAIPVYITLATAVA	LAILRLVRLVRFVRFKLSRHSKGLQ
MK1/RCK1	RVAIVSWWVLLSIVIFCL	FFLEETLCLIMFSEFLVRRFA	TMFIDVAVIPYITLGTETA	LAILRLVRLVRFVRFKLSRHSKGLQ
BK2/RCK5	RVAIVSWWVLLSIVIFCL	FFLEETLCLIMFSEFLVRRFA	TMVLDVAVIPYITLGTETA	LAILRLVRLVRFVRFKLSRHSKGLQ
RCK3	RGAIIVSVLWVLLSIVIFCL	FFVVEYLCLIMFSEFLVRRFA	IMMLDVAIPYITLGTETA	LAILRLVRLVRFVRFKLSRHSKGLQ
RCK4	RGAIIVSVLWVLLSIVIFCL	FFVVEYLCLIMFSEFLVRRFA	IMMLDVAIPYITLGTETA	LAILRLVRLVRFVRFKLSRHSKGLQ
cxcl1	KLAIIEIMFVWVLLSIVIFCL	LAAGAVICIMFTEVLELRFES	P2MAIILVAVIPYITLGTETA	RQVQFVRLVRFVRFKLSRHSKGLQ
Shab	RVAIVSWVLLSIVIFCL	LAMVAVICIMFTEVLELRFES	GLMIDLAILVAVIPYITLGTETA	RRVQFVRLVRFVRFKLSRHSKGLQ
Shaw	KTIQVSVVFLICISLSFCL	ETVIEVCNMFTEVLELRFES	SVMLIDYIATVAVIPYITLGTETA	ADILEFFSIRIMVRLVRFVRFKLSRHSKGLQ
1st domain, Na ⁺ channel				
brain I	ILVHSLFSLMCLMCLITLNCV	TKNVEYTFGIVTFESLKIILA	PWMLDFVITVTFAYVEFVNLG	VSALRTERVRLAKTIVIPVGLKATIV
II	ILVHSLFSLMCLMCLITLNCV	TKNVEYTFGIVTFESLKIILA	TKNVEYTFGIVTFESLKIILA	VSALRTERVRLAKTIVIPVGLKATIV
III	ILVHSLFSLMCLMCLITLNCV	TKNVEYTFGIVTFESLKIILA	PWMLDFVITVTFAYVEFVNLG	VSALRTERVRLAKTIVIPVGLKATIV
muscle	ILVHSLFSLMCLMCLITLNCV	TKNVEYTFGIVTFESLKIILA	PWMLDFVITVTFAYVEFVNLG	VSALRTERVRLAKTIVIPVGLKATIV
eel	IVFNASNFIFIMFIFSNCL	SKIVEYTFGIVTFEIVKVL	PWMLDFVITVTFAYVEFVNLG	VSALRTERVRLAKTIVIPVGLKATIV
Ca ²⁺ channel				
heart	IVKSFESTIILLIFPANCV	LEKLEVFYVLSIAEAMKIIIA	GNWLDLIVLGVSTALLEGV	VNALRAFVRLVRLVRFVRFKLSRHSKGLQ
channel	IVKSFESTIILLIFPANCV	LEKLEVFYVLSIAEAMKIIIA	GNWLDLIVLGVSTALLEGV	VNALRAFVRLVRLVRFVRFKLSRHSKGLQ
2nd domain, Na ⁺ channel				
brain I	VMDFPVDLAIITICVNLTL	LTVGNLVTGIFTAEMFLKIIA	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
II	VMDFPVDLAIITICVNLTL	LTVGNLVTGIFTAEMFLKIIA	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
III	VMDFPVDLAIITICVNLTL	LTVGNLVTGIFTAEMFLKIIA	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
muscle	VMDFPVDLAIITICVNLTL	LTVGNLVTGIFTAEMFLKIIA	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
eel	VMDFPVDLAIITICVNLTL	LTVGNLVTGIFTAEMFLKIIA	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
Ca ²⁺ channel				
heart	LVKSRVYVWVILVILVNLTA	QDIANVLLSLETFIEMLLKMYG	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
channel	LVKSRVYVWVILVILVNLTA	QDIANVLLSLETFIEMLLKMYG	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
3rd domain, Na ⁺ channel				
brain I	IVHNKVFYVWVILVILVNLTA	LEVADKVFYVWVILVILVNLTA	ANWLDLIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
II	IVHNKVFYVWVILVILVNLTA	LEVADKVFYVWVILVILVNLTA	ANWLDLIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
III	IVHNKVFYVWVILVILVNLTA	LEVADKVFYVWVILVILVNLTA	ANWLDLIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
muscle	IVHNKVFYVWVILVILVNLTA	LEVADKVFYVWVILVILVNLTA	ANWLDLIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
eel	IVHNKVFYVWVILVILVNLTA	LEVADKVFYVWVILVILVNLTA	ANWLDLIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
Ca ²⁺ channel				
heart	IVNATVWVWVILVILVNLTA	LFYVDIAFTSVTVVIVLKMVT	YENILDLVWVILVILVNLTA	LSVLSFRLLRFLVRFKLSRHSKGLQ
channel	IVNATVWVWVILVILVNLTA	LFYVDIAFTSVTVVIVLKMVT	YENILDLVWVILVILVNLTA	LSVLSFRLLRFLVRFKLSRHSKGLQ
4th domain, Na ⁺ channel				
brain I	QVDFISIMILCLMVMWV	LSRNILVFLVGTGCVLKLIS	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
II	QVDFISIMILCLMVMWV	LSRNILVFLVGTGCVLKLIS	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
III	QVDFISIMILCLMVMWV	LSRNILVFLVGTGCVLKLIS	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
muscle	QVDFISIMILCLMVMWV	LSRNILVFLVGTGCVLKLIS	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
eel	QVDFISIMILCLMVMWV	LSRNILVFLVGTGCVLKLIS	GNMIFDGIIVLTVLSEVLEGLANV	LSVLSFRLLRFLVRFKLSRHSKGLQ
Ca ²⁺ channel				
heart	SYEYFVWVWVILVILVNLTA	SDILNVAFTIIFTEMLIKLIIA	PNWVDFLIVIGSITDVLISL	ESARISAPFRLVRFKLSRHSKGLQ
channel	SYEYFVWVWVILVILVNLTA	SDILNVAFTIIFTEMLIKLIIA	PNWVDFLIVIGSITDVLISL	ESARISAPFRLVRFKLSRHSKGLQ

S5/H4 H5 S6/H6

	S5/H4	H5	S6/H6
cGMP-gated channel	ISNLVWYIIIIHNAACVYFSI	EYFVAVDPLIGVLIPIATVGNIGS	IFADCAEAGVTLVLRKIQVQVYVS
Shaker	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
MK1/RCK1	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
BK2/RCK5	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
RCK3	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
RCK4	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
cxcl1	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
Shab	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
Shaw	LGLLIFPFLGVVFLSSAVYFA	DAFWAVVMTVYGVGDMPVFGWG	IUGSCLCAGVTLVLRKIQVQVYVS
1st domain, Na ⁺ channel			
brain I	VNLTVECLSVFALIGQLFNG	DTFVWVFLVFLRMTQDFNENLQGL	TYMIFVFLVFLGSPYLINLIIA
II	VNLTVECLSVFALIGQLFNG	DTFVWVFLVFLRMTQDFNENLQGL	TYMIFVFLVFLGSPYLINLIIA
III	VNLTVECLSVFALIGQLFNG	DTFVWVFLVFLRMTQDFNENLQGL	TYMIFVFLVFLGSPYLINLIIA
muscle	VNLTVECLSVFALIGQLFNG	DTFVWVFLVFLRMTQDFNENLQGL	TYMIFVFLVFLGSPYLINLIIA
eel	VNLTVECLSVFALIGQLFNG	DTFVWVFLVFLRMTQDFNENLQGL	TYMIFVFLVFLGSPYLINLIIA
Ca ²⁺ channel			
heart	IALLVEMVYIYAIIGLELFG	DNFQSMVTVYQCITMGEQTVLVY	WVYVFLVFLGSPYLINLIIA
channel	IALLVEMVYIYAIIGLELFG	DNFQSMVTVYQCITMGEQTVLVY	WVYVFLVFLGSPYLINLIIA
2nd domain, Na ⁺ channel			
brain I	GNLNLVLAIVFIFAVVGMQL	DFHSLVFLVFLRMTQDFNENLQGL	ANCLVFLVFLGSPYLINLIIA
II	GNLNLVLAIVFIFAVVGMQL	DFHSLVFLVFLRMTQDFNENLQGL	ANCLVFLVFLGSPYLINLIIA
III	GNLNLVLAIVFIFAVVGMQL	DFHSLVFLVFLRMTQDFNENLQGL	ANCLVFLVFLGSPYLINLIIA
muscle	GNLNLVLAIVFIFAVVGMQL	DFHSLVFLVFLRMTQDFNENLQGL	ANCLVFLVFLGSPYLINLIIA
eel	GNLNLVLAIVFIFAVVGMQL	DFHSLVFLVFLRMTQDFNENLQGL	ANCLVFLVFLGSPYLINLIIA
Ca ²⁺ channel			
heart	IASLILVFLVFLRMTQDFNENLQGL	NFQQLISVTVYQCITMGEQTVLVY	WVYVFLVFLGSPYLINLIIA
channel	IASLILVFLVFLRMTQDFNENLQGL	NFQQLISVTVYQCITMGEQTVLVY	WVYVFLVFLGSPYLINLIIA
3rd domain, Na ⁺ channel			
brain I	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
II	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
III	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
muscle	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
eel	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
Ca ²⁺ channel			
heart	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
channel	LVCLIFWVFLVFLRMTQDFNENLQGL	DNVGVVFLVFLRMTQDFNENLQGL	RYESVFLVFLGSPYLINLIIA
4th domain, Na ⁺ channel			
brain I	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
II	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
III	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
muscle	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
eel	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
Ca ²⁺ channel			
heart	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA
channel	LFLVWVFLVFLRMTQDFNENLQGL	ETFGNSMCLVFLRMTQDFNENLQGL	PSVGVFLVFLGSPYLINLIIA

Sequence alignment of the cyclic GMP-gated channel and voltage-gated potassium, sodium and calcium channels. Crosses, residues in the cyclic GMP-gated channels found in at least 8 of the 36 sequences of voltage-gated cation channels. Dots, residues found in less than 8, but at least one of these 36 sequences. Asterisks, residues in the cyclic GMP-gated channel that are identical to the corresponding residues in four or more of the nine groups of voltage-gated channel sequences (the group of Shaker and RCK1, 3, 4, 5, and each of the four domains of the sodium or calcium channel). The probability of finding the same level of sequence identity as observed for all 12 residues marked by asterisks is 2.3×10^{-56} . Details of the sequence alignment and statistical treatment are available from the authors on request.

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