Ion Channels

Structure comparison of K+ channels and characteristics of the Hyperpolarization-activated cation currents (HCN)

Presentation Out line

- Voltage gated ion channels
- Superfamily of voltage gated K+ channels
- Characteristics of HCN:
  - → **Function**
  - → **Structure**
- Comparison voltage gated K+ channels/HCN

Presentation Out line

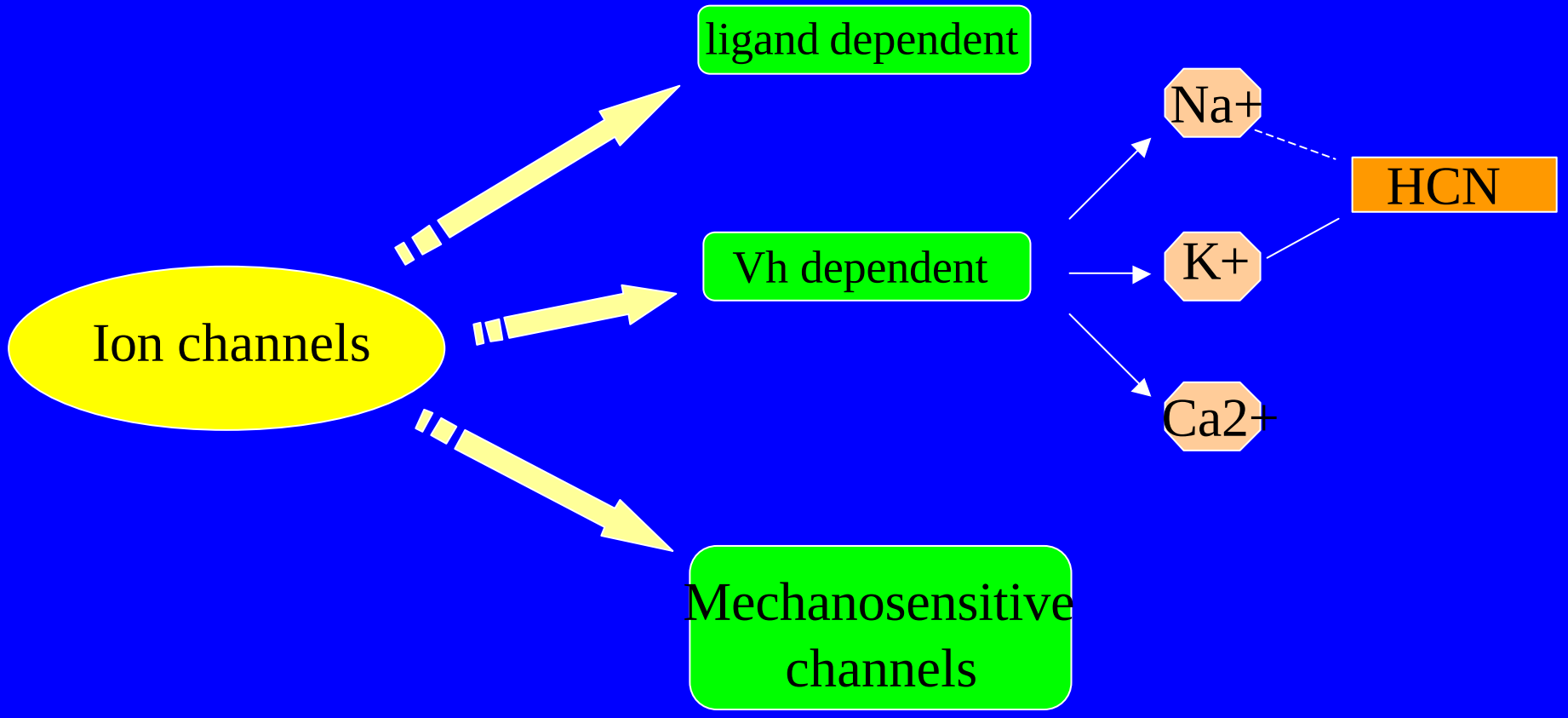
1. Voltage gated ion channels
2. Superfamily of voltage gated K+ channels
3. Characteristics of HCN:

   → **Function**

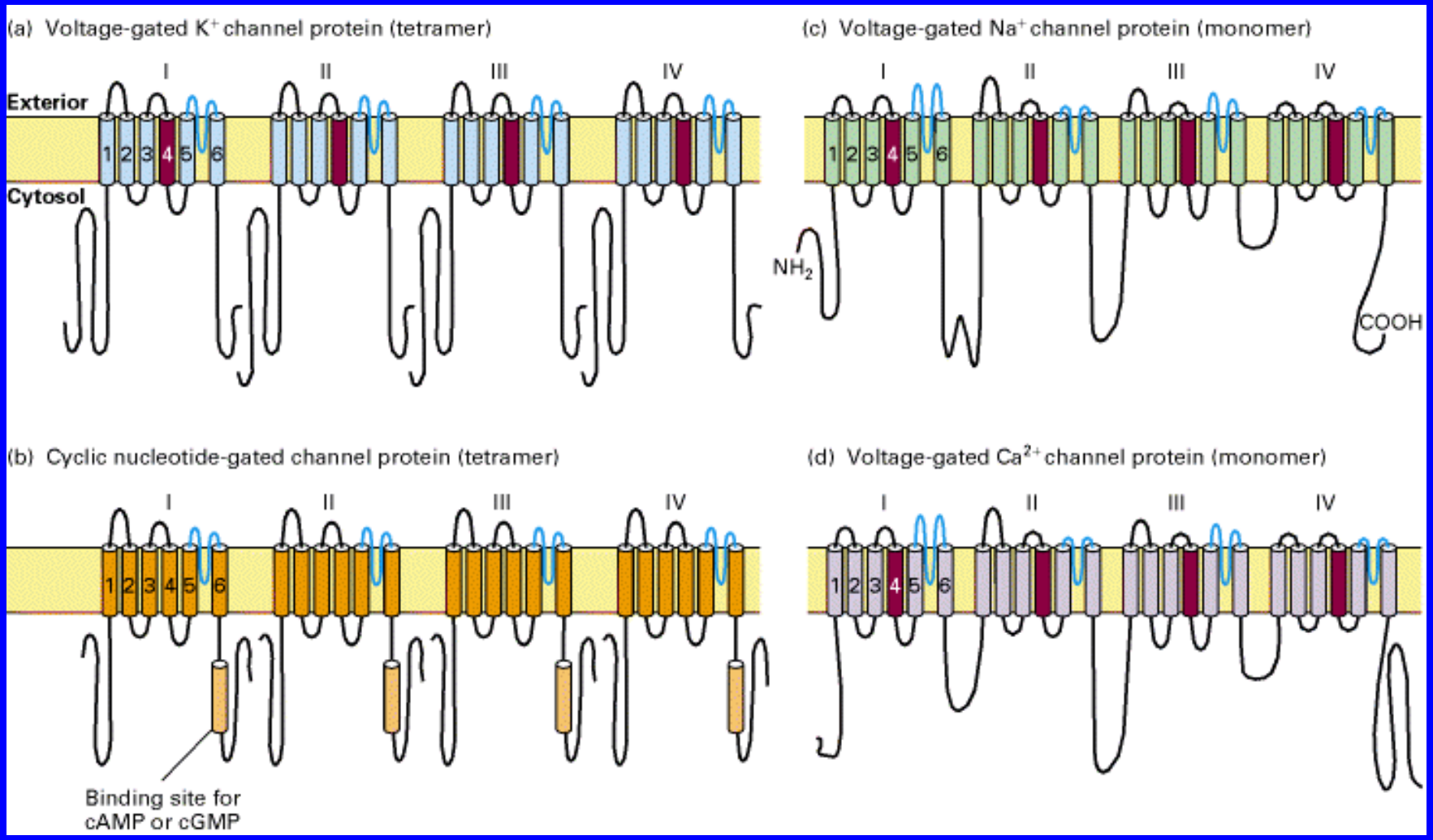
   → **Structure**

4. Comparison voltage gated K+ channels/HCN

1. Voltage gated ion channels



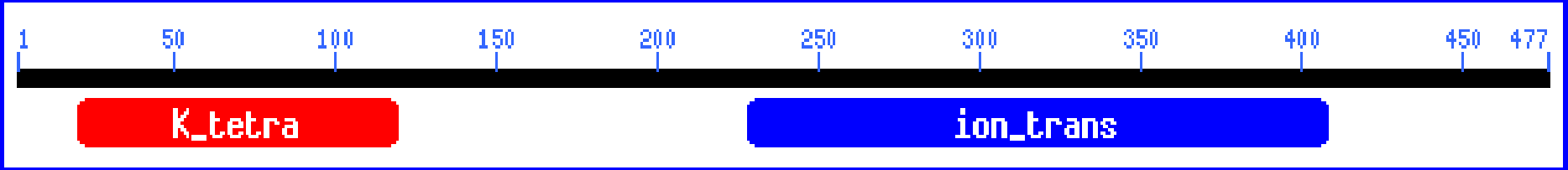
Voltage gated ion channels



- 6 Trans membran domains
- 1 pore domain
- 1 selectivity domain

2. Superfamily of voltage gated K+ channels

Exemple:

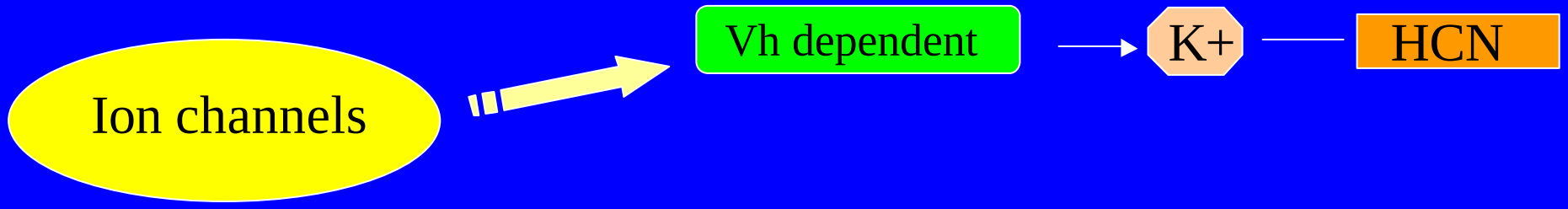


➔ 6 TM domains

➔1 Ion channel domain

3. Characteristics of HCN

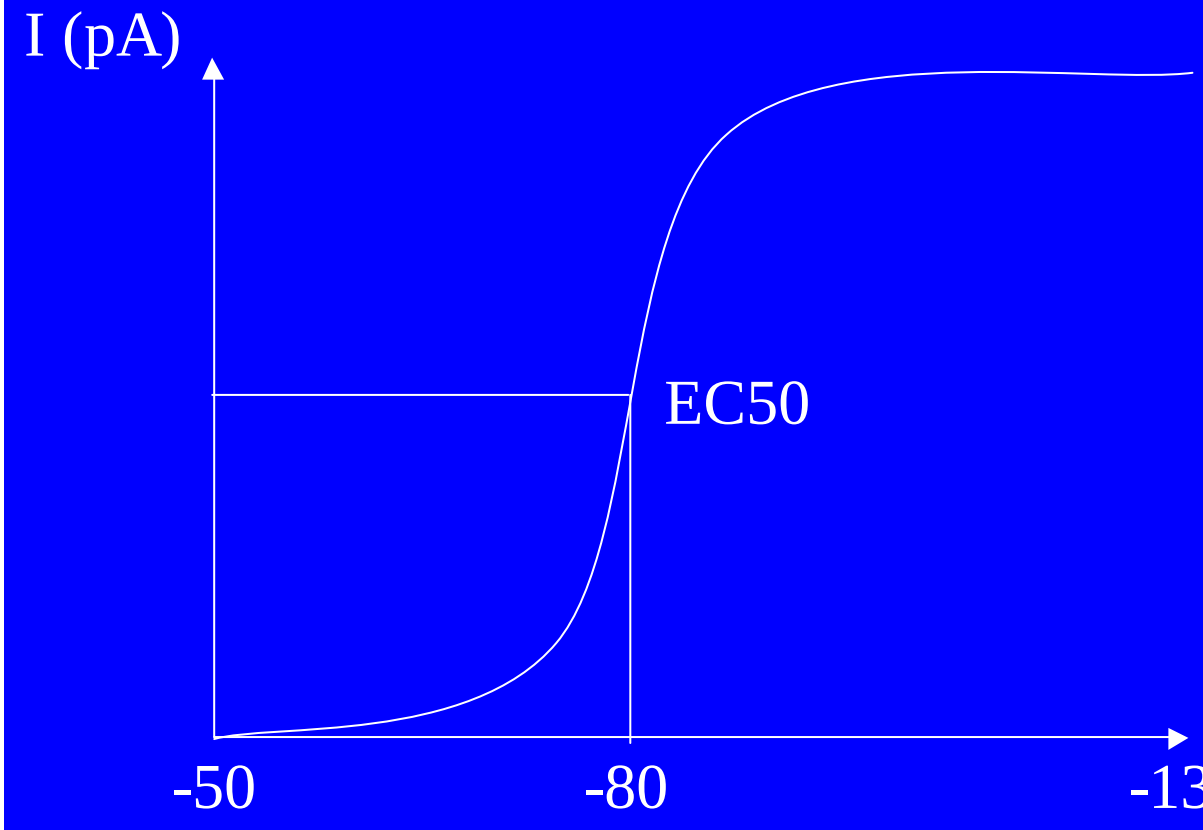
- Function:
  - ➔ Expressed in heart and nerve cells
  - ➔ Cardiac and neuronal pacemaker function
  - ➔ Setting of resting potentials

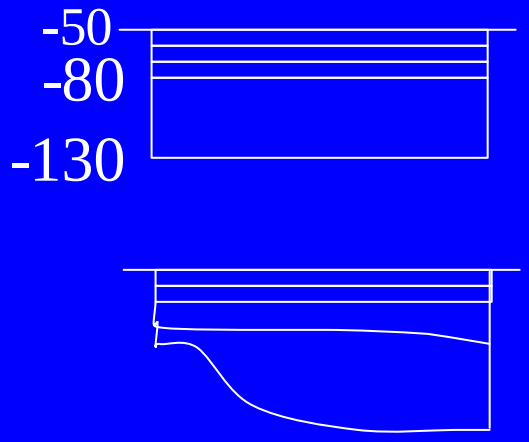


- Physiological characteristics and structure:

➔ 3 particular characteristics:

- Activated by hyperpolarization:

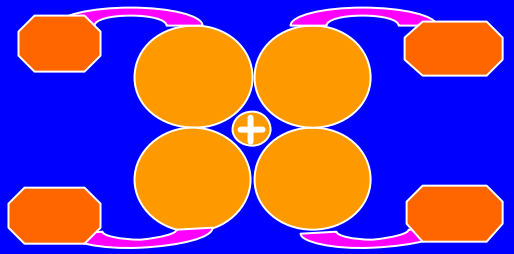




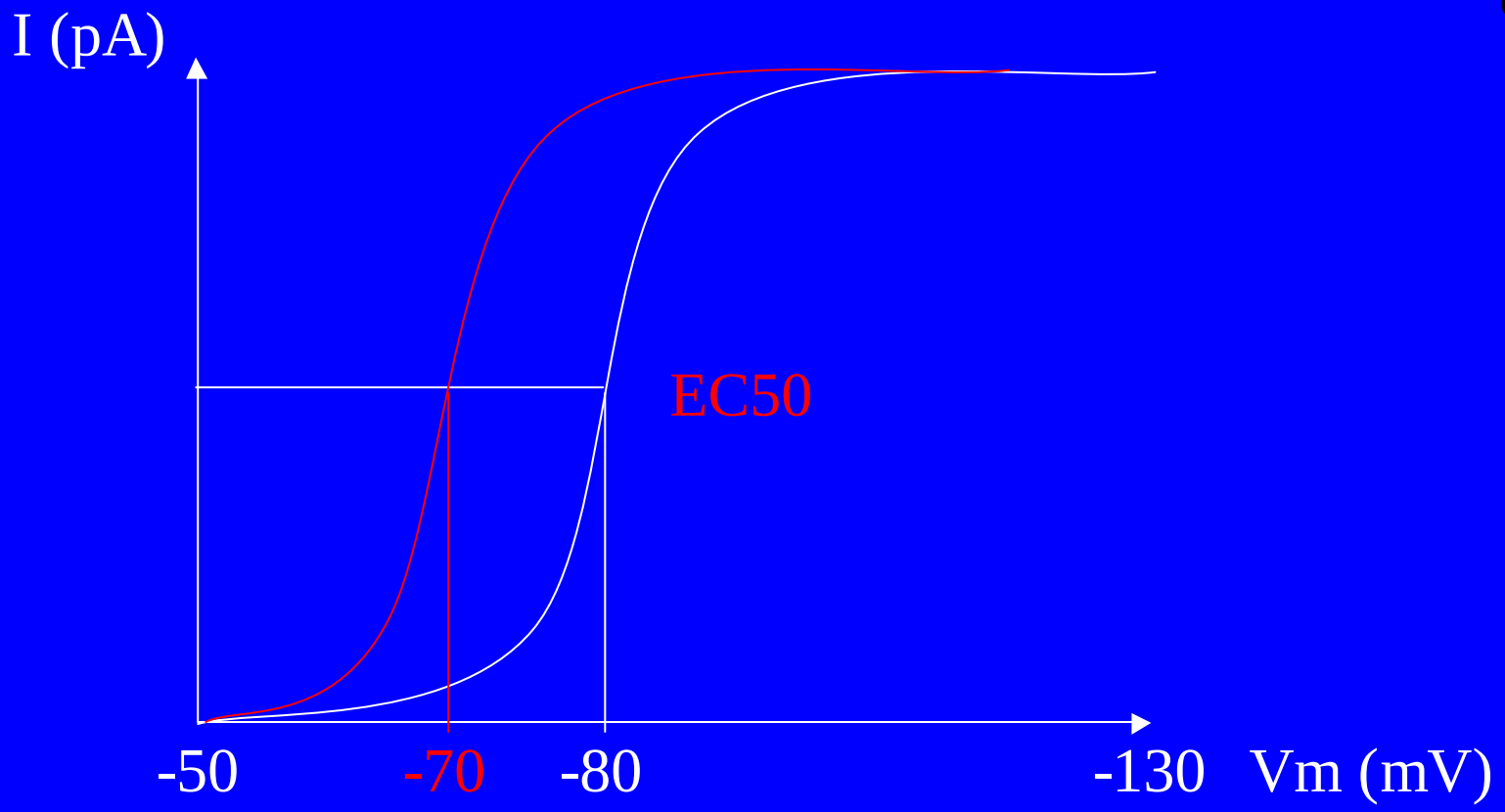
➔ Slow activation

- selectivity: Na+/K+

- Regulated by cAMP:

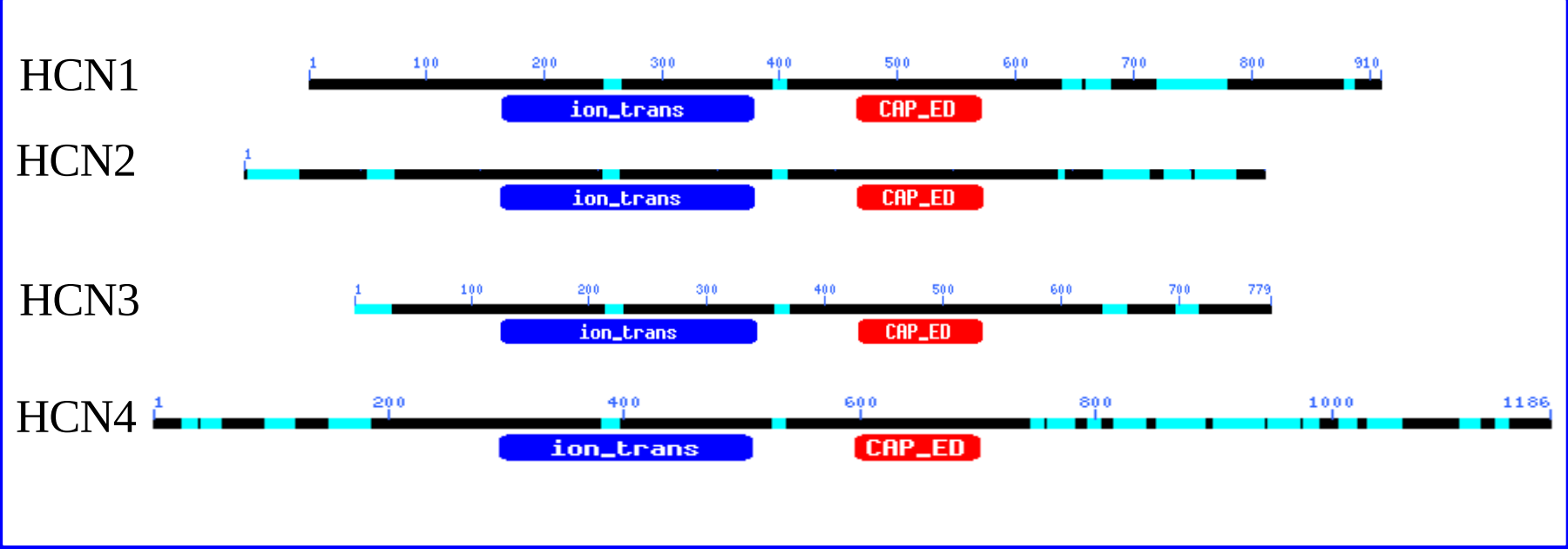


cAMP



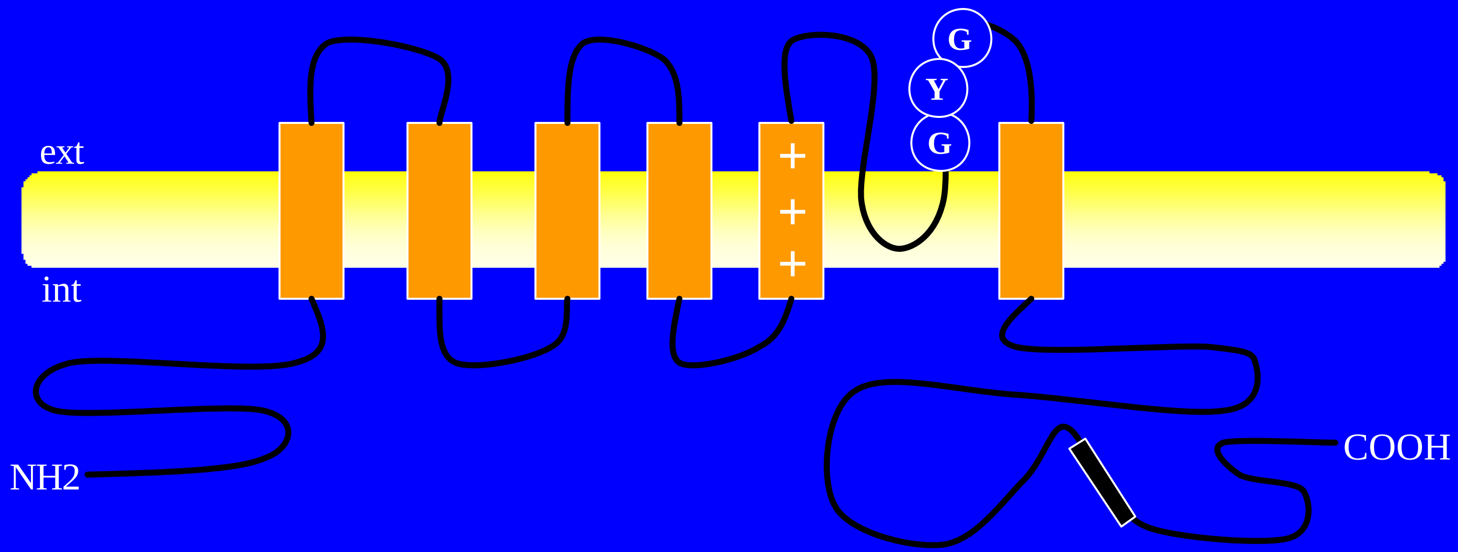
Structure

➔ 4 isoforms: HCN1-4:



Description of the domains

6 TM domains:



S1 S4

HCN1 L I M L I M MVGNL V I I PVGITFF . . . . KTARALRIVRFTKILSLLRLL

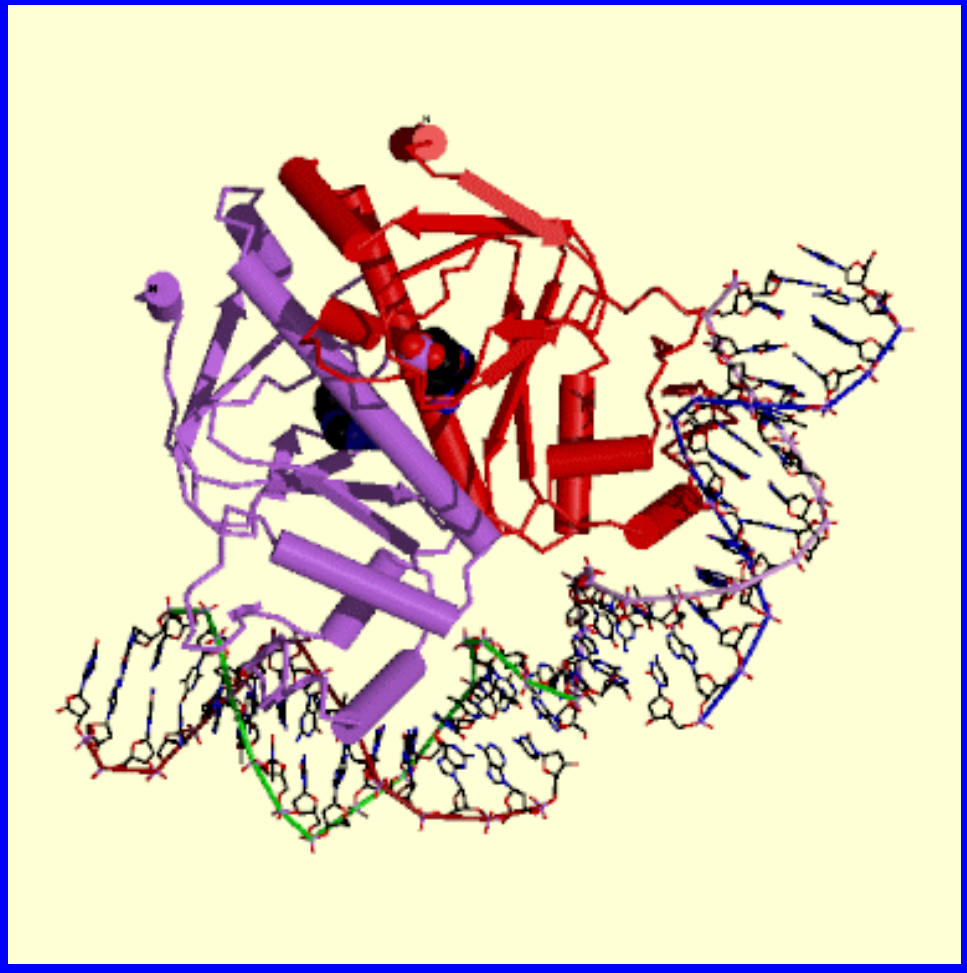
HCN2 FT M L L F MVGNL I I I PVGITFF . . . . KTARALRIVRFTKILSLLRLL

HCN3 L I M L L L MVGNL I V L PVGITFF . . . . KTARALRIVRFTKILSLLRLL

HCN4 LT M L L L MVGNL I I I PVGITFF . . . . KTARAVRIVRFTKILSLLRLL

cAMP binding domain:

```
HCN1 LFANADPFVTAMLSKLRFEVFQPGDYIIREGAVGKKMYFIQHGVAGVITKSSKEMKLTDGSYFGEICLLTKGRRTASVRADTYCRLYSLSVDNFNEVLEEYPMMRRAFETVAIDRLD
HCN2 LFANADPNFVTAMLTKLKFEVFQPGDYIIREGTIGKKMYFIQHGVVSVLTKGNKEMKLSDGSYFGEICLLTRGRRTASVRADTYCRLYSLSVDNFNEVLEEYPMMRRAFETVAIDRLD
HCN3 LFAHADPSFVTAVLTKLRFEVFQPGDLVVRGSVGRKMYFIQHGLLSVLARGARDTRLTDGSYFGEICLLTRGRRTASVRADTYCRLYSLSVDHFNAVLEEFPMMRRAFETVAMDRLR
HCN4 LFANADPNFVTSMLTKLRFEVFQPGDYIIREGTIGKKMYFIQHGVVSVLTKGNKETRLADGSYFGEICLLTRGRRTASVRADTYCRLYSLSVDNFNEVLEEYPMMRKKNSILLHKVQH
```



Question

Which sequence explain the different selectivity between K+ channel and HCN

4. Comparison between VGK+ channels and HCN

Potassium Channel

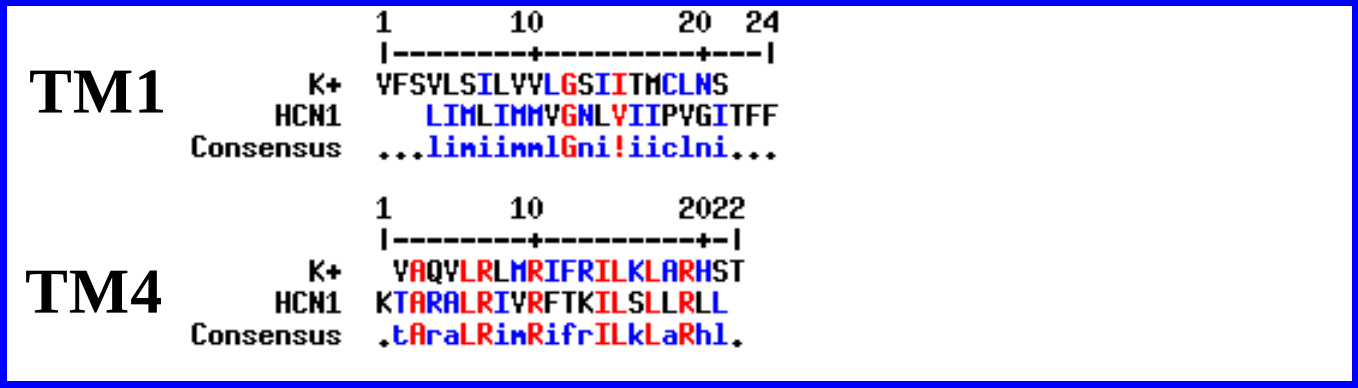
HCN1


```
                1       10        20        30        40        50        60        70        80        90       100       110       120       130
                |-------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
K+                                RFEIVEHFGIAWFTFELVARFAVAPDFLKF-FKNALNLIDLMSIVPF-YITLVVNLVVESSP-TLANLGRVAQVLRLMRIFRILKLARHSTGLRSLGATLKYSYKEVGLLL-LYLSV
HCN1  PWIIFNVASDTVFLLDLIMNFRTGTVN-EDSSEIILDPKVIKMNYLKSWFVVDFISSIPVDYIFLIVEKGMDSEVYKTARALRIVRFTKILSLLRLLRLSRLIRYIHQWEEIFHMTYDLASAVVRIFNLI
Consensus             .............rl#i!enFriatfn.EdsarialaPdfiKm.%lnalnl!DliSi!Pf.YIfL!V#lgm#Sep.klAragR!arflri$rilRiLrLaRhirgirqleailhmsYdeagall.i%nl!

                131     140       150       160       170       180       190       200       210       220   226
                |-------+---------+---------+---------+---------+---------+---------+---------+---------+-----|
K+    GISIFSVVAYTIEKEENEGLATIPACWWATVSMTTVGYGDVVPGTTAGKLTASACILAGILVVVLPITLI
HCN1  GMMLLLCHWDGCLQFLVPLLQDFPPDCWVSLNEMVNDSWGKQYSYALFKAMSHMLCIGYGAQAPVSMSDLWITMLSMIVGATCYAMFVGHATALIQ
Consensus GimillchadgceqeenegladipadcWwalneMtndgwGdqypgalaga$sanaCIgaGaqapVlmidLi.........................
```

<u>Conclusion</u>: Big differences in the sequences: link with function?

Sequence Alignment of Transmembran domains



Conclusion:

➔ Differences for TM1

➔ TM4 is more conserved its differences can not explain the selectivity difference of those two channels

Which difference is responsible of the selectivity?

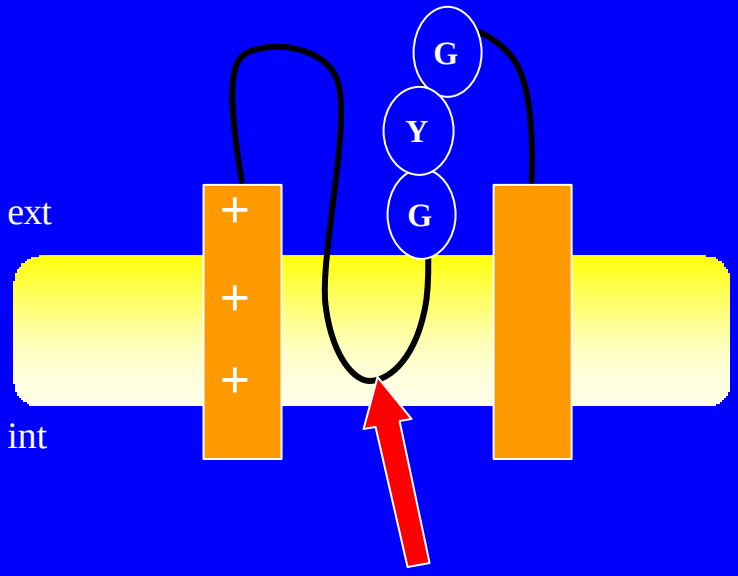
Sequence Alignment of Pore-Forming Domain

```
                1       10        20   25
                |-------+---------+----|
potassium          PACWWATVSMTTVGYGDVVP
     HCN1      GKQYSYALFKAMSHMLCIGYGAQAP
Consensus      ....paalfkAmshMlc!GYGaqaP
```

Conclusion:

➔ Both have signature sequence of K+ selective channels (GYG)

➔ Amino acids forming the pore before GYG are different, this difference could explain the special selectivity of HCN



Ion Channel Team

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