Ion Channel Diseases
'Channelopathies'

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A rapidly growing group of diseases caused by ion channel dysfunction is classified as “channelopathies”

Ion channels are involved in various cellular functions

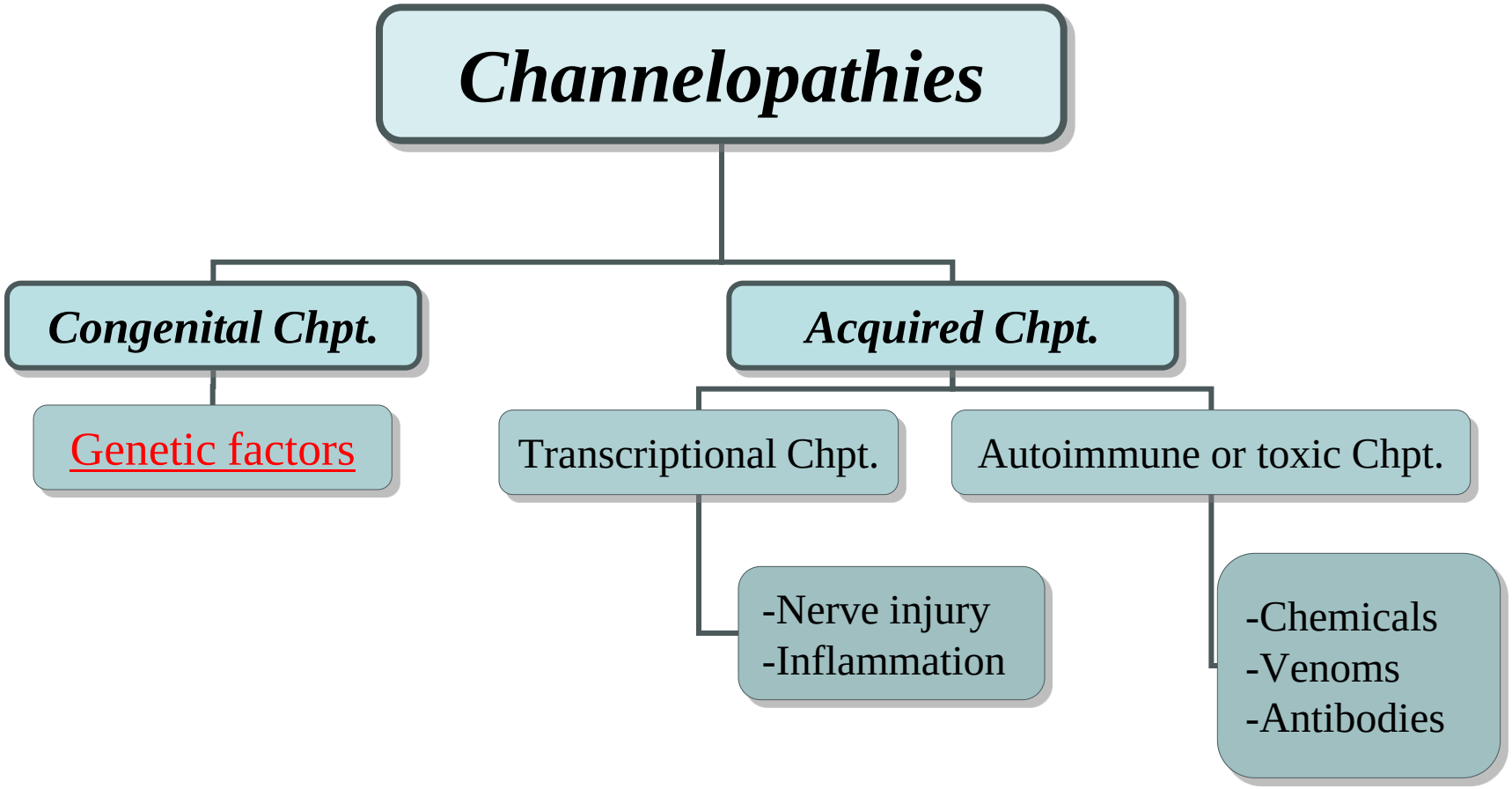
- Generation of electrical currents
- Transepithelial transport
- Regulation cellular volume and pH
- Acidification of intracellular organelles
- Chemical signalling

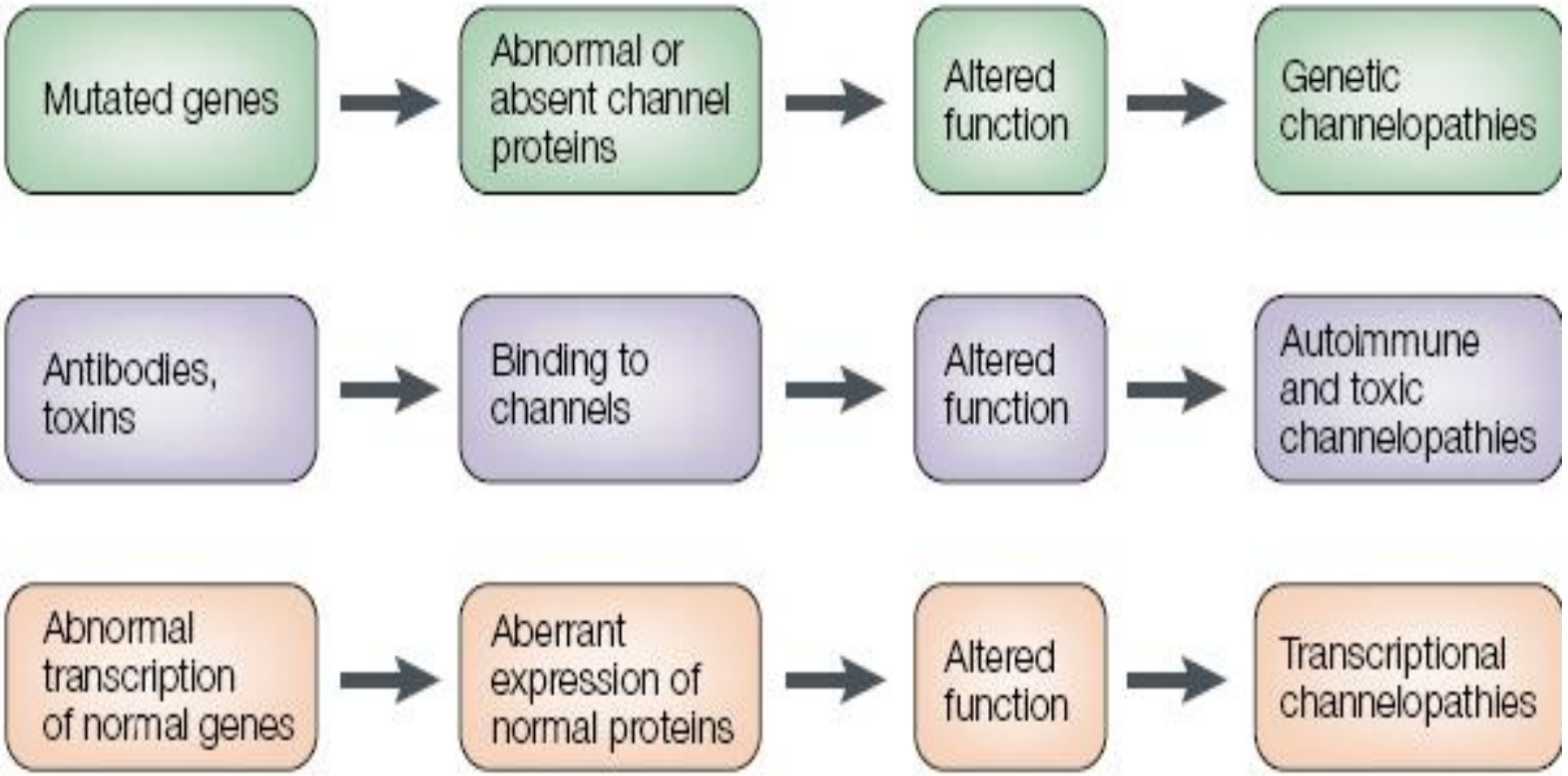
What kind of tissue, organ or cell is subjected to a channel disorder?

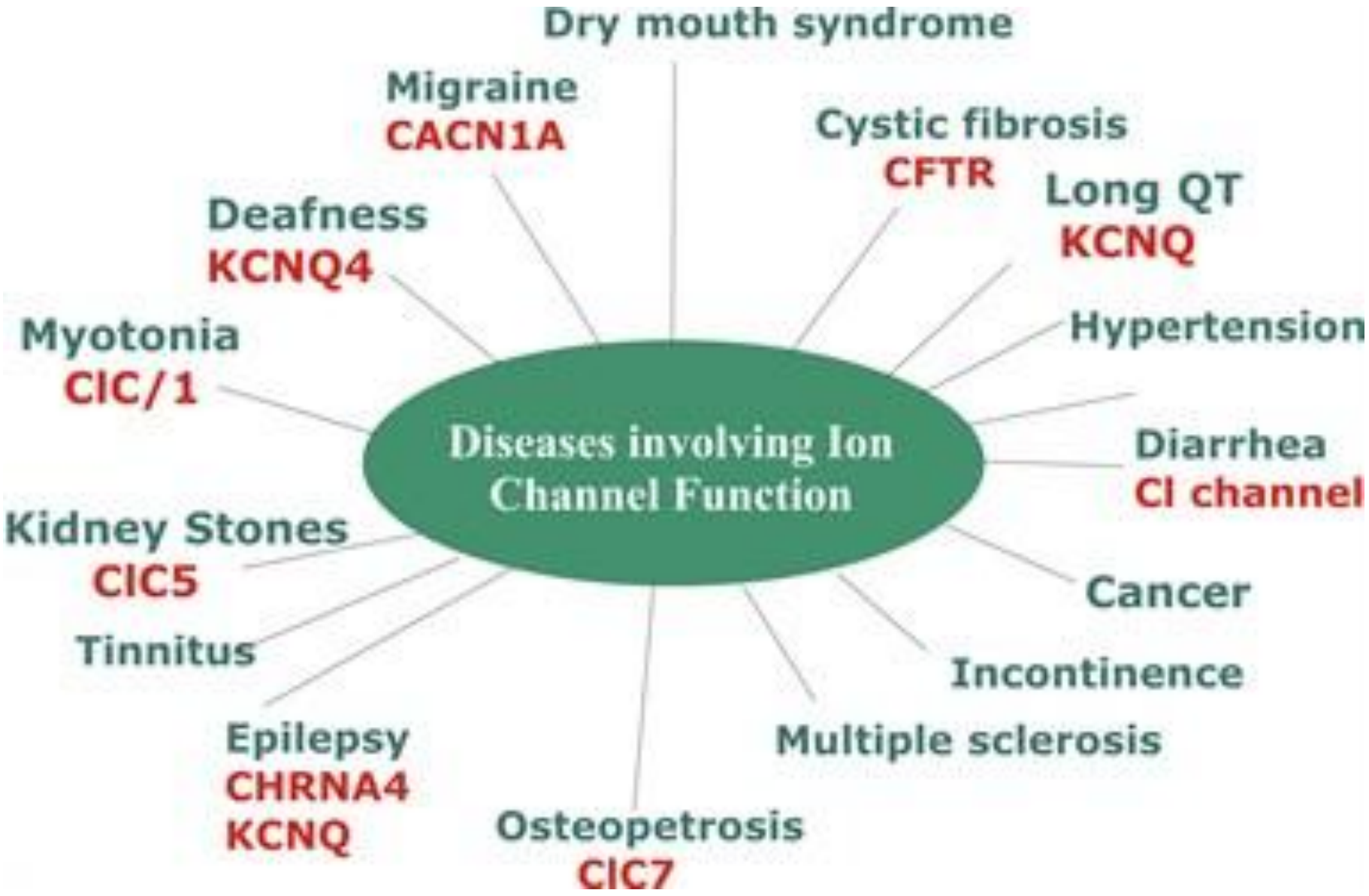
- Virtually every organ, tissue, cell and even subcellular organelles.

Table 1. Known ion channel diseases

Channel	Gene	Channel-forming unit/ligand	OMIM	Disease
Cation channels:				
CHRNA1/ACHRA	*CHRNA1*	α, ACh	100690	Myasthenia congenita
CHRNA4	*CHRNA4*	α, ACh	118504	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	*CHRNB2*	β, ACh	118507	Autosomal dominant nocturnal frontal lobe epilepsy
Polycystin-2	*PKD2*	α	173910	Autosomal dominant polycystic kidney disease (ADPKD)
CNGA3	*CNGA3*	α, cGMP	600053	Achromatopsia 2 (color blindness)
CNGB1	*CNGB1*	β, cGMP	600724	Autosomal recessive retinitis pigmentosa
CNGB3	*CNGB3*	β, cGMP	605080	Achromatopsia 3
Sodium channels:				
$Na_v1.1$	*SCN1A*	α	182389	Generalized epilepsy with febrile seizures (GEFS+)
$Na_v1.2$	*SCN2A*	α	182390	Generalized epilepsy with febrile and afebrile seizures
$Na_v1.4$	*SCN4A*	α	603967	Paramyotonia congenita, potassium aggressive myotonia, hyperkalemic periodic paralysis
$Na_v1.5$	*SCN5A*	α	600163	Long-QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)
SCN1B	*SCN1B*	β	600235	Generalized epilepsy with febrile seizures (GEFS+)
ENaCα	*SCNN1A*	α	600228	Pseudohypoaldosteronism type 1 (PHA1)
ENaCβ	*SCNN1B*	β	600760	PHA1, Liddle syndrome (dominant hypertension)
ENaCγ	*SCNN1G*	γ	600761	PHA1, Liddle syndrome
Potassium channels:				
$K_v1.1$	*KCNA1*	α	176260	Episodic ataxia with myokymia
KCNQ1/K_vLQT1	*KCNQ1*	α	192500	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNQ2	*KCNQ2*	α	602235	BFNC (epilepsy), also with myokymia
KCNQ3	*KCNQ3*	α	602232	BFNC (epilepsy)
KCNQ4	*KCNQ4*	α	603537	DFNA2 (dominant hearing loss)
HERG/ KCNH2	*KCNH2*	α	152427	Long-QT syndrome
Kir1.1/ROMK	*KCNJ1*	α	600359	Bartter syndrome (renal salt loss, hypokalemic alkalosis)
Kir2.1/IRK/KCNJ2	*KCNJ2*	α	600681	Long-QT syndrome with dysmorphic features (Andersen syndrome)
Kir6.2/K_{ATP}	*KCNJ11*	α	600937	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
SUR1	*SUR1*	β	600509	PHHI
KCNE1/MinK/ISK	*KCNE1*	β	176261	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNE2/MiRP1	*KCNE2*	β	603796	Long-QT syndrome
KCNE3/MiRP2	*KCNE3*	β	604433	Periodic paralysis
Calcium channels:				
$Ca_v1.1$	*CACNA1S*	α	114208	Hypokalemic periodic paralysis, malignant hyperthermia
$Ca_v1.4$	*CACNA1F*	α	300110	X-linked congenital stationary night blindness
$Ca_v2.1$	*CACNA1A*	α	601011	Familial hemiplegic migraine, episodic ataxia, spinocerebellar ataxia type 6
RyR1	*RYR1*	α	180901	Malignant hyperthermia, central core disease
RyR2	*RYR2*	α	180902	Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia type 2
Chloride channels:				
CFTR	*ABCC7*	α	602421	Cystic fibrosis, congenital bilateral aplasia of vas deferens
ClC-1	*CLCN1*	α	118425	Autosomal recessive (Becker) or dominant (Thomsen) myotonia
ClC-5	*CLCN5*	α	300008	Dent's disease (X-linked proteinuria and kidney stones)
ClC-7	*CLCN7*	α	602727	Osteopetrosis (recessive or dominant)
ClC-Kb	*CLCNKB*	α	602023	Bartter syndrome type III
Barttin	*BSND*	β	606412	Bartter syndrome type IV (associated with sensorineural deafness)
GLRA1	*GLRA1*	α, glycine	138491	Hyperekplexia (startle disease)
GABAα1	GABRA1	α, GABA	137160	Juvenile myoclonus epilepsy
GABAγ2	*GABRG2*	γ, GABA	137164	Epilepsy
Gap junction channels:				
Cx26	*GJB2*		121011	DFNA3 (autosomal dominant hearing loss) DFNB1 (autosomal recessive hearing loss)
Cx30	*GJB4*		605425	DFNA3
Cx31	*GJB3*		603324	DFNA2
Cx32	*GJB1*		304040	CMTX (X-linked Charcot–Marie–Tooth neuropathy)


Channelopathies
Congenital Chpt.
Acquired Chpt.
Genetic factors
Transcriptional Chpt.
Autoimmune or toxic Chpt.
-Nerve injury
-Inflammation
-Chemicals
-Venoms
-Antibodies


Mutated genes
Abnormal or absent channel proteins
Altered function
Genetic channelopathies
Antibodies, toxins
Binding to channels
Altered function
Autoimmune and toxic channelopathies
Abnormal transcription of normal genes
Aberrant expression of normal proteins
Altered function
Transcriptional channelopathies


Dry mouth syndrome
Migraine
CACN1A
Cystic fibrosis
CFTR
Long QT
KCNQ
Deafness
KCNQ4
Hypertension
Myotonia
ClC/1
Diseases involving Ion Channel Function
Diarrhea
Cl channel
Kidney Stones
ClC5
Cancer
Tinnitus
Incontinence
Epilepsy
CHRNA4
KCNQ
Multiple sclerosis
Osteopetrosis
ClC7

General properties of channelopathies

- A change in the channel
    - Structure
    - Expression
    - Localization

- A change in the function of the cell
    - “Gain off function”
    - “Loss of function”

Genetic channelopathies

- Mutation in ion channel genes is the cause.
- "Loss of function" mutations often lead to recessive inheritance of the disease.
  - CFTR mutation "Cyctic Fibrosis"
  - CLCNKB mutation "Bartter Syndrome"
- (homozygos) Patients with recessive mutations are worse than (heterozygous) patients with dominant mutations
- For example dominant-negative mutation of KCNQ1 K^+ channel leads to severe cardiac arrhythmia while homozygous recessive mutation leads to deafness in additon.

Genetic channelopathies

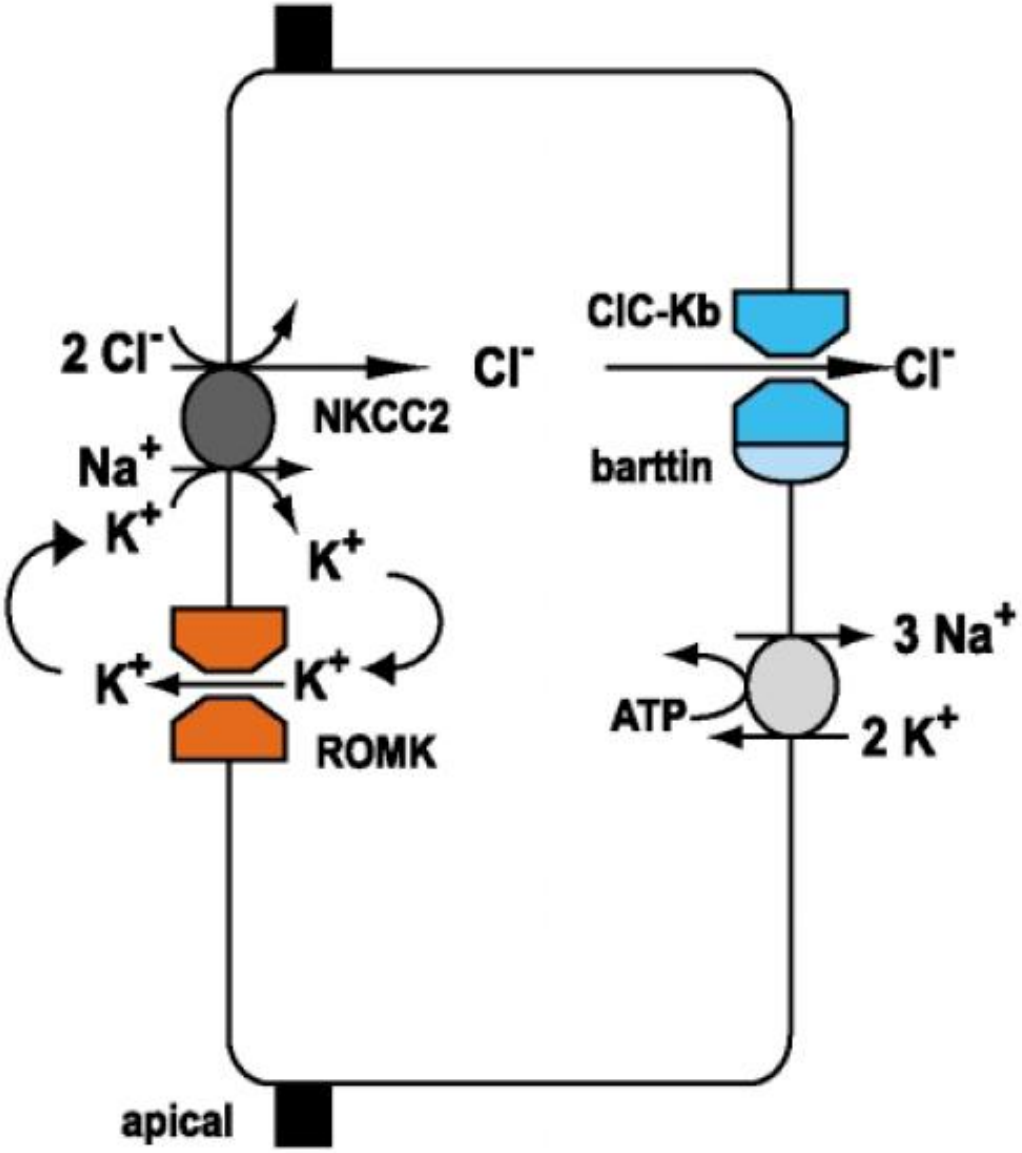
- Observation of the disease is also dependent on expression level of the current
- KCNQ2 and KCNQ3 mutation which is not dominant-negative, cause dominant neonatal convulsions since 20-30 % reduction of the current can not be tolerated
- “Gain of function” mutations are most often associated with dominant inheritance of the disease
- Mutations in various isoforms of sodium channels cause para-myotonia, cardiac arrhytmia and epilepsy as result of the additional late sodium current due to insufficient inactivation.

Genetic channelopathies

Bartter syndrome

- Bartter syndrome is a group of hereditary tubulopathies
  - Salt wasting
  - Hypokalemic metabolic alkolosis
  - Hypereninemic hyperaldesteronism
  - Normal blood pressure
- Autosomal recessive inheritance
- Occurs in infancy or early childhood
- Impaired transepithelial transport in the thick ascending limb of the loop of Henle is the cause

thick ascending limb

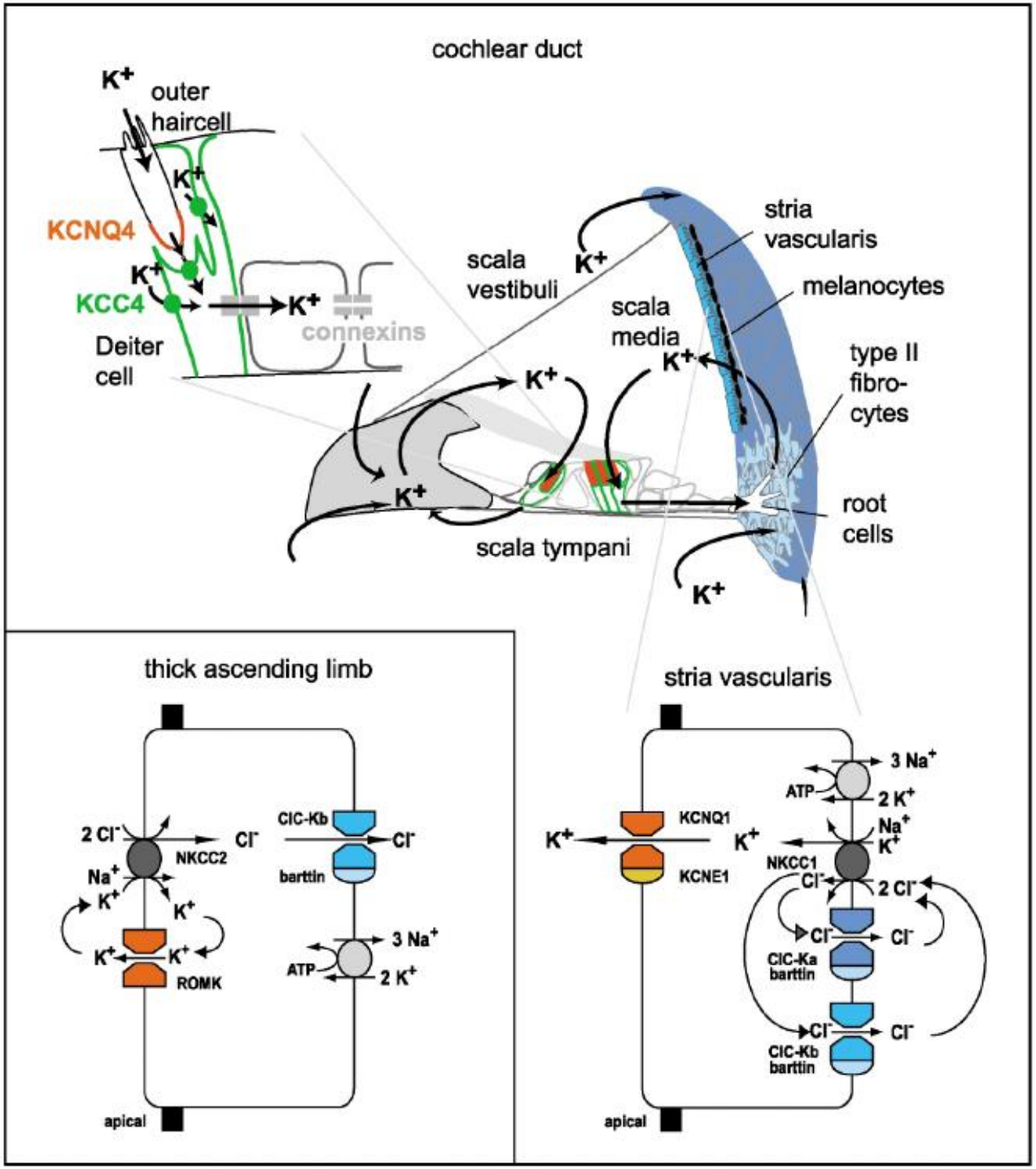


Genetic channelopathies
Deafness

- Fluid surrounding of the upper part of hair cells, endolymph, has elevated [K^+] and low [Na^+].
- K+ entering the cell through the mechanosensitive channel leaves the cell through the KCNQ4 channel at the basolateral side.
- Mutated KCNQ4 leads to autosomal dominant progressive hearing loss
- K^+ removed by the Deiter cells through a K-Cl co-transporter KCC4
- K^+ diffuses through the gap junctions to the adjacent cell.
- At least three connexin genes GJB2, GJB3, GJB6 are involved in deafness.

Genetic channelopathies
Deafness

- In stria vascularis Na-K/ATPase and Na-K-2Cl transporter NKCC1 is taken into the marginal cells.
- To increase the efficiency the Cl- has to recycle across the basolateral membrane.
- This is achieved by CIC-Ka/barttin and CIC-Kb/barttin Cl-channels
- Mutations in barttin leads to deafness in addition to renal symptoms in Bartter type 4.
- K is secreted into endolymph through KCNQ1 and KCNE1 potassium channels.
- Homozygous loss of both channel leads to Jervel-Lange-Nielsen syndrome chracterized by cardiac arrhytmia and congenital hearing loss.

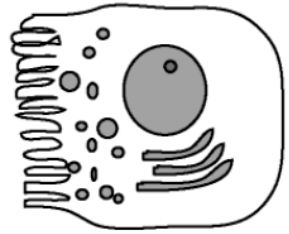

cochlear duct
K+
outer haircell
KCNQ4
KCC4
Deiter cell
connexins
scala vestibuli
stria vascularis
melanocytes
scala media
type II fibro-cytes
root cells
scala tympani
thick ascending limb
2 Cl-
NKCC2
Na+
ROMK
ClC-Kb
barttin
3 Na+
ATP
2 K+
apical
stria vascularis
KCNQ1
KCNE1
NKCC1
ClC-Ka barttin
ClC-Kb barttin

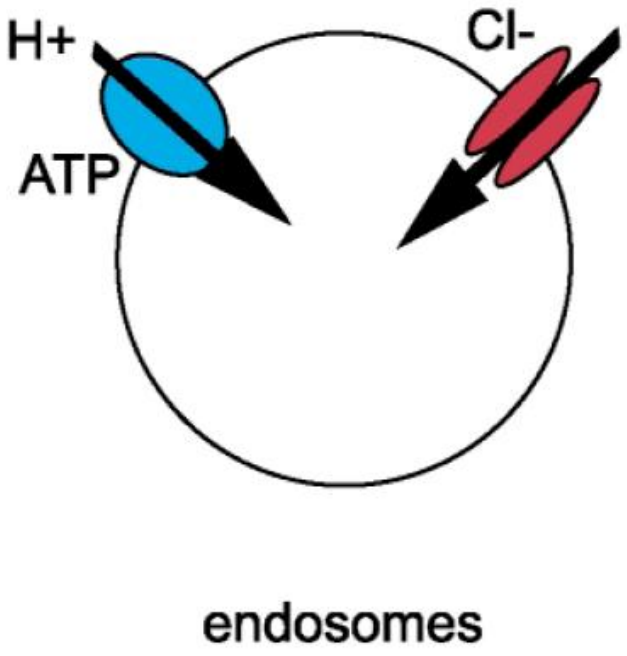
Genetic channelopathies
Liddle Syndrome

- In principle cells of distal collecting duct Na^+ enters the cell passively through the apical ENaC channels
- Na^+ accumulates in the body if ENaC channel is over expressed and decreases if ENaC channels are down regulated
- Na^+ absorption is accompanied by water retention
- Pathophysiological volume expansion leads to hypertension while the opposite induces hypotension
- In Liddle syndrome internalization of the ENaC channels are impaired “gain of function”, leads to a <u>salt sensitive hypertension</u>

Genetic channelopathies
Dent's Disease

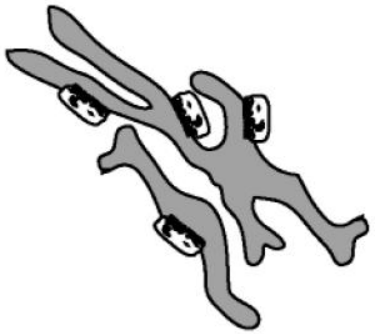
- X-linked Hypercalciuric nephrolithiasis
- CLCN5 encodes a chloride channel CIC-5
- Mutations leads to failure in acidification of renal endosome and internalization small proteins. Apical endocytosis of parathyroid hormone and vitamin-D impaired
- Disturbances of renal phosphate and calcium handling leads to Kidney stones

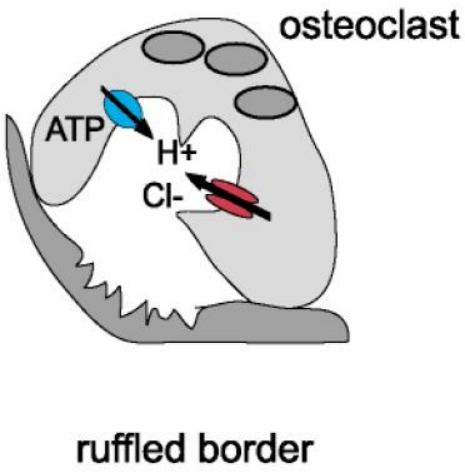




Genetic channelopathies
Bone Diseases

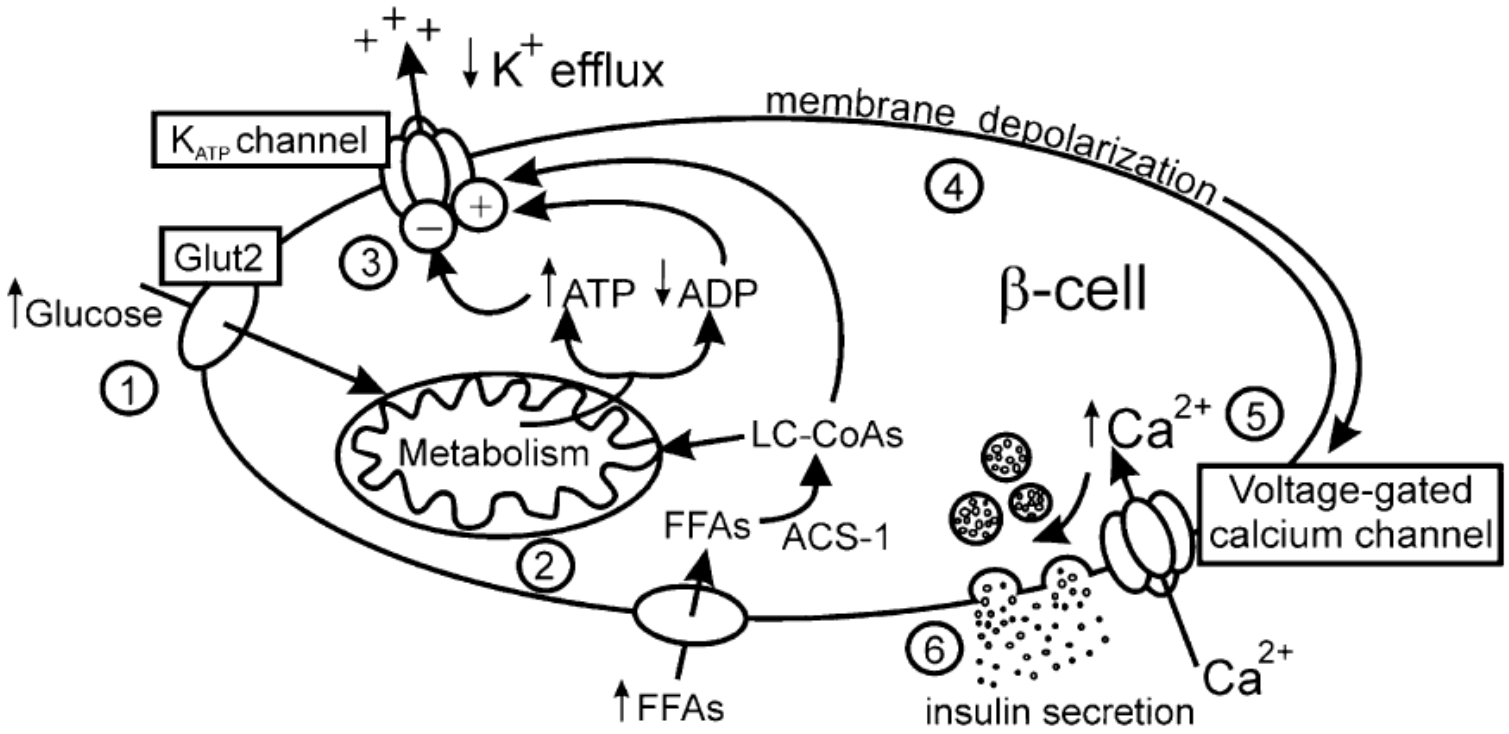
- Mutations in Cl^- channel gene CLCN/ are associated with severe autosomal recessive osteopetrozis
- CIC7 is colocalized with H^+-ATPase on part of osteoclastic membrane facing the bone resorption lacuna.
- In osteopetrozis number of osteoclasts are normal but they fail to acidify the lacuna





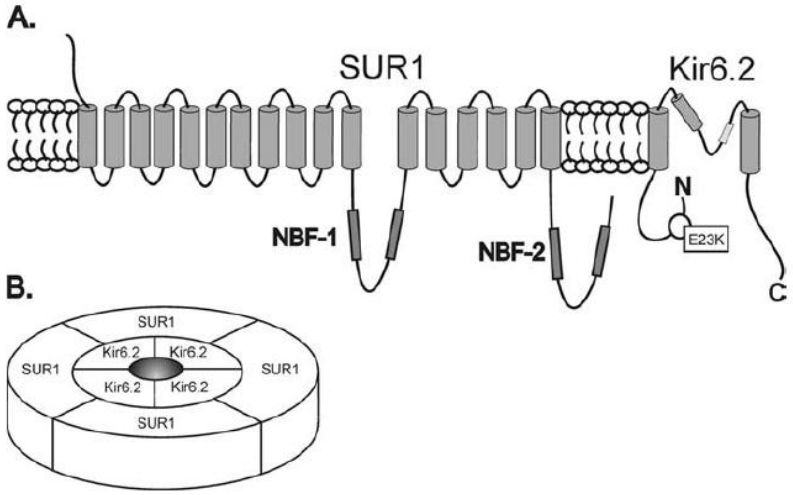
Genetic channelopathies

Persistent Hyperinsulinemic Hypoglycemia



Genetic channelopathies
Persistent Hyperinsulinemic Hypoglycemia

- K-ATP channel is consisted of 4 pore forming units, Kir6.2 (encoded by KCNJ11).
- SUR1 transmembrane protein is necessary for expression of the channel on surface membrane.
- Mutations in either part results in autosomal recessive disorder PHH manifests at birth or early in the first year of life.



Genetic channelopathies

Best Disease

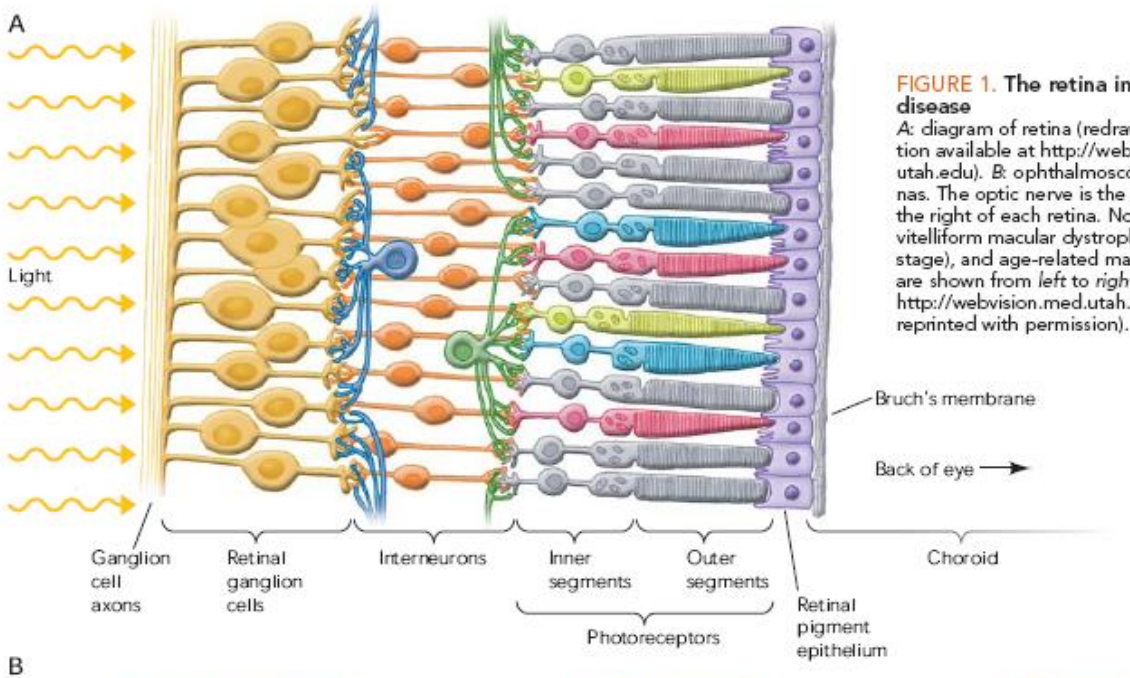
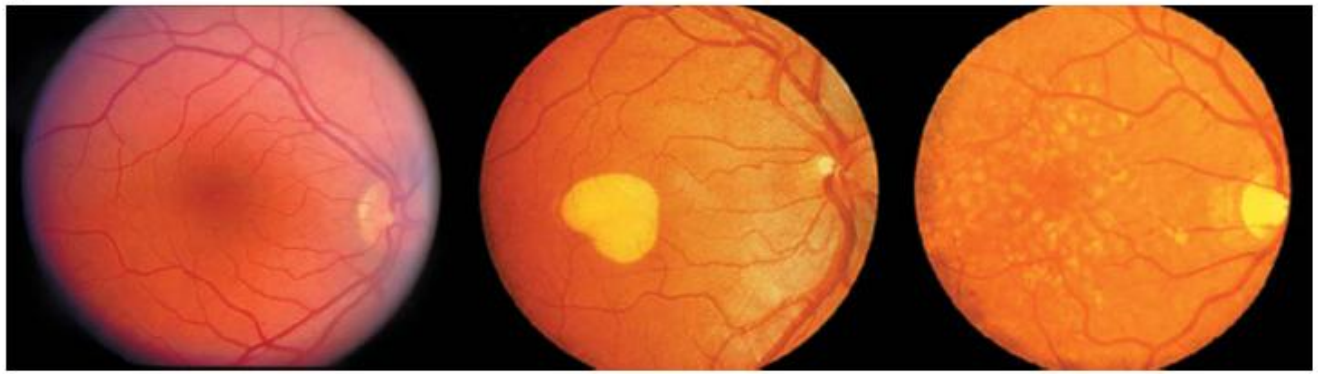


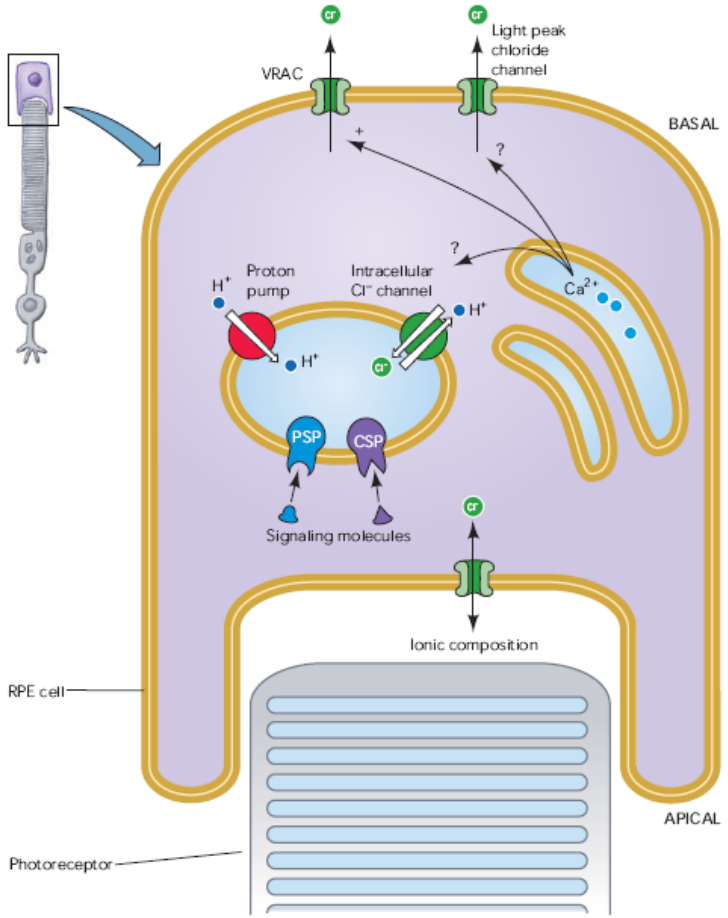
FIGURE 1. **The retina in health and disease**
A: diagram of retina (redrawn from an illustration available at http://webvision.med.utah.edu). *B*: ophthalmoscopic images of retinas. The optic nerve is the yellowish spot on the right of each retina. Normal retina, Best vitelliform macular dystrophy (vitelliform stage), and age-related macular degeneration are shown from *left* to *right*. (Images are from http://webvision.med.utah.edu/ and are reprinted with permission).

B



Genetic channelopathies
Best Disease

- Best disease is an age related macular degeneration
- Several bestropins have been identified. There are compelling evidences that bestropins are Cl- channels
- Cl- channels are involved in
  - Regulation of fluid environment
  - Cell volume regulation
  - Intracellular Cl channels
  - Calcium regulation

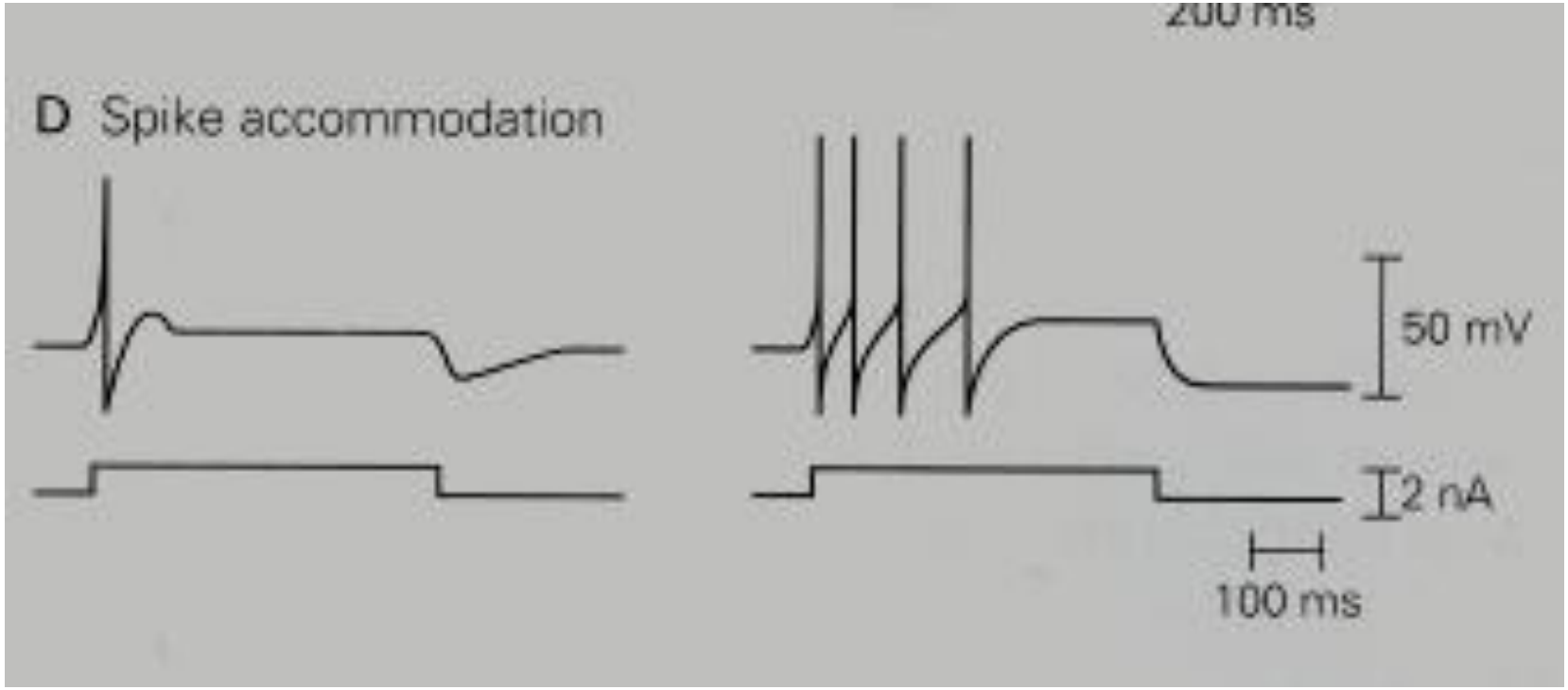


Genetic channelopathies
Neurological Disorders

- Ion channels have key function in nervous system.
  - Generation
  - Repression
  - Propagation of action potentials
- Na^+ channel depolarizes the neurons
- K^+ channels causes hyperpolarization
- Cl^- channel may induce hyperpolarization
- Ca^{++} channel depolarizes the neuron, however Ca^{++} is more important as second messenger.
- Thus, loss of function mutations in K^+ and Cl^- channel and gain of function mutations in Na^+ channels may induce hyperexcitability and perhaps epilepsia.

Genetic channelopathies
Epilepsy

- *KCNQ2 and KCNQ3 underlie benign familial neonatal convulsions (BNFC)*
- *M currents is a noninactivating potassium current involved in regulating the subthreshold excitability of neurons.*
- *In BNFC the M current reduced 25 %. This amount suffice to evoke convulsions since it has very important critical role in neuronal excitability.*
- *Homozygous knockout of KCNQ2 is lethal in mice*

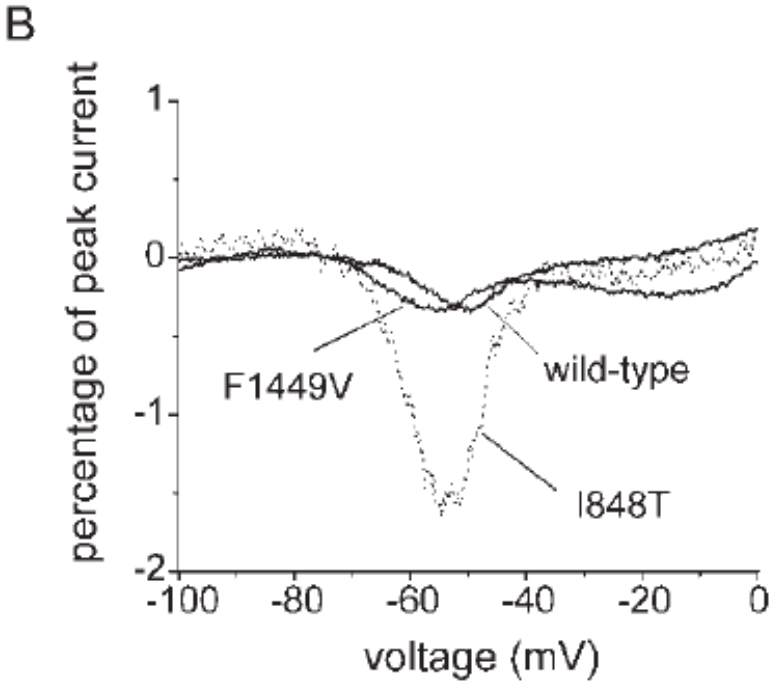

200 ms
D Spike accommodation
50 mV
2 nA
100 ms

Genetic channelopathies
Epilepsy

- Some mutations in sodium channel gene SCN1A and SCN2A leads to a sodium channel population with impaired inactivation properties
- Those causes generalized febrile and afebrile seizures respectively
- Mutation in calcium channel gene CACNA1A can cause ataxia
- Mutation in GABRA1 gene encoding GABAa receptor is associaed with autosomal dominant juvenile myoclonus epilepsia
- Mutation of glycine receptor cause startle disease
- There has been no reports indicating an association of epilepsy with the major excitatory neurotransmitter **glutamate** receptors.

Erythromelalgia

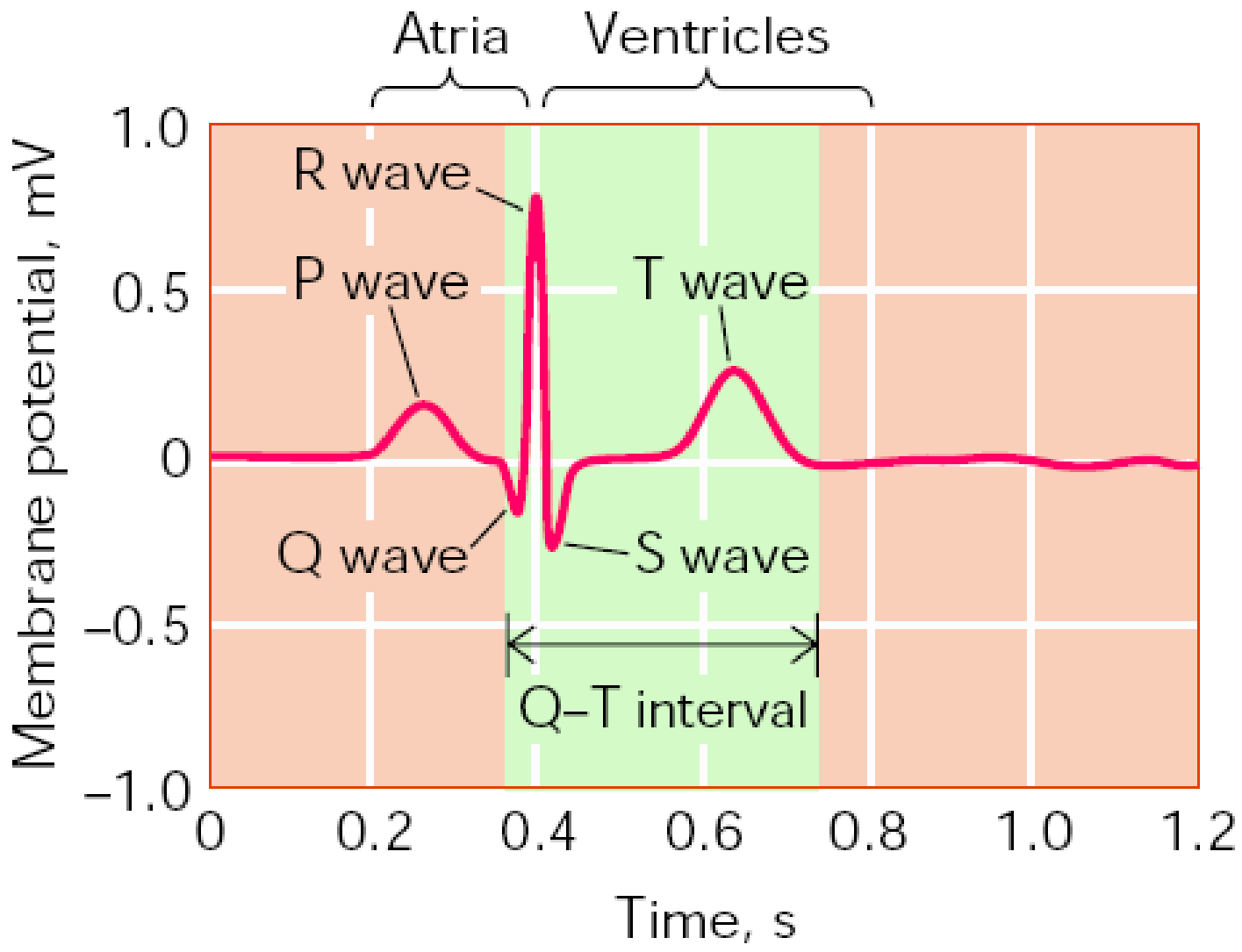
- Characterized by an severe burning pain in extremities in response to warm stimuli or moderate exercise.
- autosomal dominant inheritance.
- mutation in Nav1.7 sodium channels present in dorsal root ganglion neurons is the cause.
- This channel is not expressed in CNS



Genetic channelopathies

Cardiac Arrhytmias

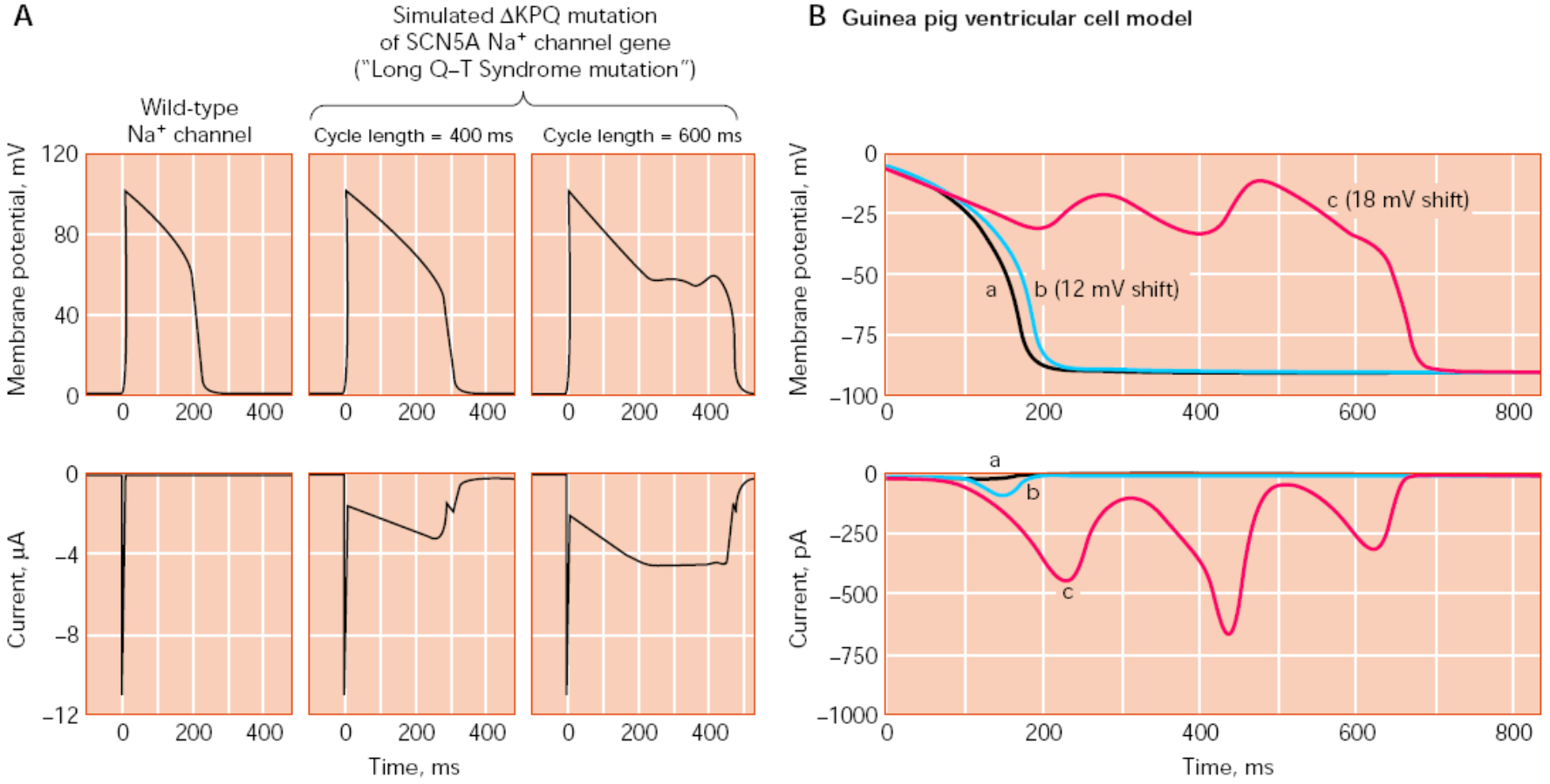
- Each heartbeat initiated by a depolarization in pacemaker cells spreads through the heart.
- Cardiac action potential is much longer than neuronal one due to long lasting opening of the calcium channels.


Atria
Ventricles
1.0
0.5
0
−0.5
−1.0
Membrane potential, mV
R wave
P wave
T wave
Q wave
S wave
Q–T interval
0
0.2
0.4
0.6
0.8
1.0
1.2
Time, s

Genetic channelopathies

Cardiac Arrhytmias

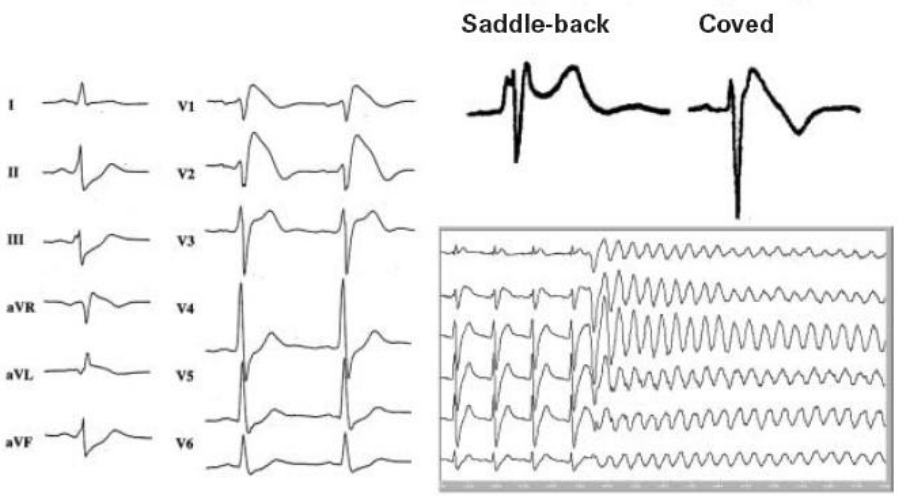
- The fast initial depolarization is achieved by Nav 1.5 sodium channel coded in SCN5A gene
- Mutations leads to sodium channel with incomplete inactivation.
- Several different types of potassium channels also contribute repolarization of the cardiac action potentials
- KCNQ1/KCNE1 mutation results in long-QT sendrome.


A
Simulated ΔKPQ mutation
of SCN5A Na+ channel gene
("Long Q–T Syndrome mutation")
Wild-type
Na+ channel
Cycle length = 400 ms
Cycle length = 600 ms
Membrane potential, mV
120
80
40
0
0
200
400
Current, μA
0
−4
−8
−12
Time, ms
B Guinea pig ventricular cell model
Membrane potential, mV
0
−25
−50
−75
−100
a
b (12 mV shift)
c (18 mV shift)
0
200
400
600
800
Current, pA
0
−250
−500
−750
−1000
a
b
c
Time, ms

Genetic channelopathies

Cardiac Arrhytmias Brugada Syndrome

- This is an idiopathic cardiac arrhythmia which can lead to a ventricular fibrillation and sudden death
- Typical ECG pattern helps diagnosis
- Biophysically sodium currents are smaller
- 20 different genetic mutations has been associated with Brugada syndrome
- Recently it was identified that ankyrin-G which anchors Nav1.5 sodium channel
- Mutations in ankyrin-G results of loss of binding to sodium channel and results in Brugada syndrome



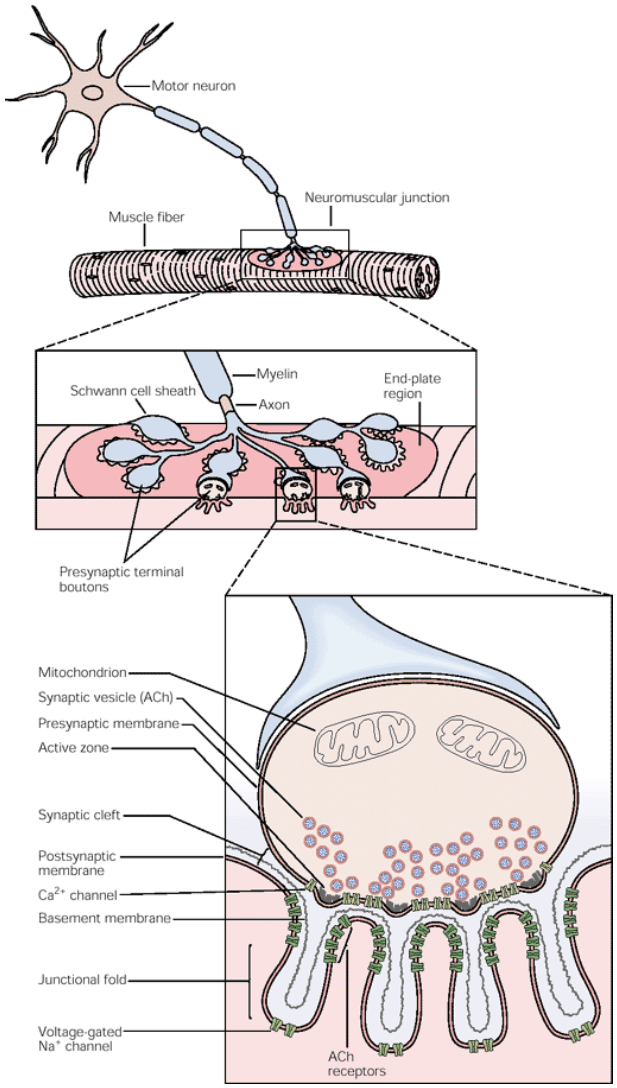
Genetic channelopathies
Disturbances of Skeletal Muscle

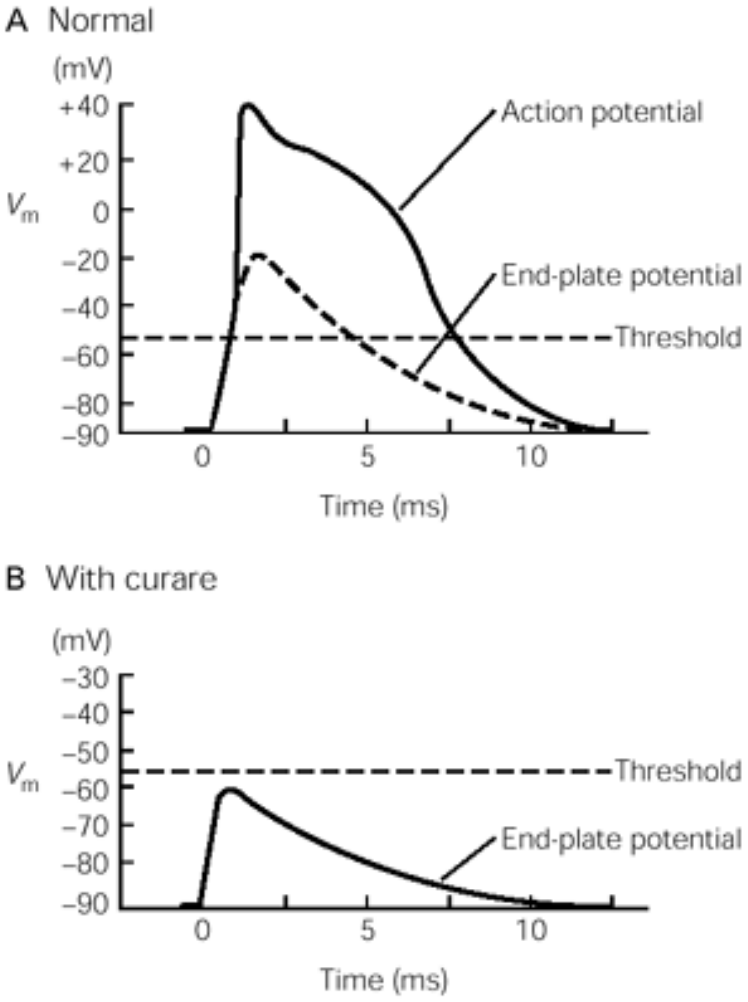
- Depolarization at the motor end plate activates extrasynaptic sodium channels, resulting in action potential and calcium release
- A defect in sodium channel inactivation may cause myotonia as in
  - Pramyotonia congenita
  - Hyperkalemic and hypokalemic paralyis
- Cl- conductance plays a major role in repolarizing part of the action potential. Mutations in CLCN1 gene encoding CIC-1 channel cause
  - Myotonia congenita
- Mutations in RYR1 gene which encodes intracellular calcium release channel cause
  - Malignant hyperthermia

Acquired Channelopathies

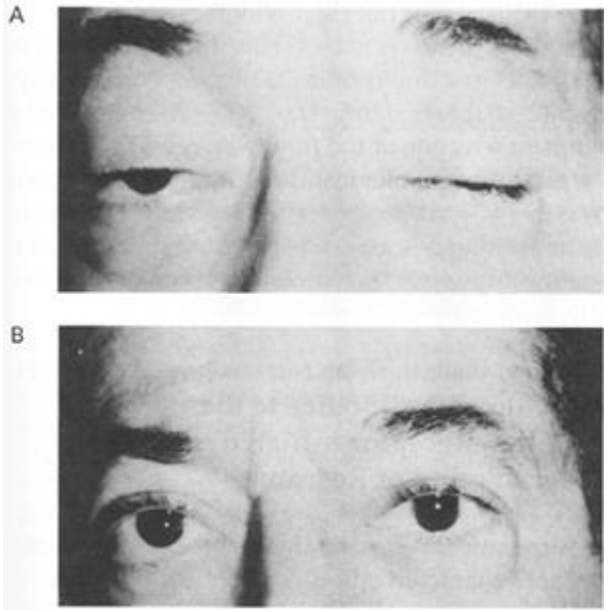
- When peripheral nerve is cut within some days a new family of sodium channel is expressed in the neuronal soma. Neuron becomes more excitable.
- Snake, scorpion, anemone, bee, frog, fish venom mediates the toxic effect by severely altering functional properties of various ionic channels.
- Inflammation is another factor affecting ion channels.

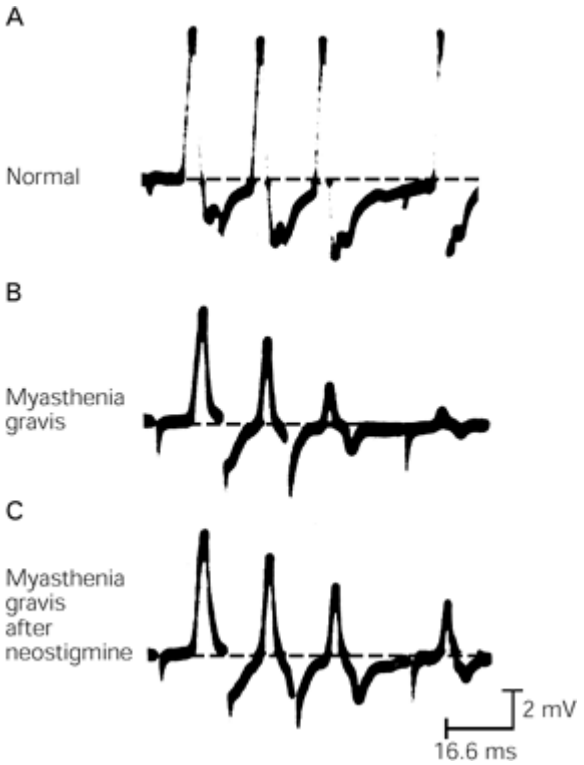
Neuromuscular Junction

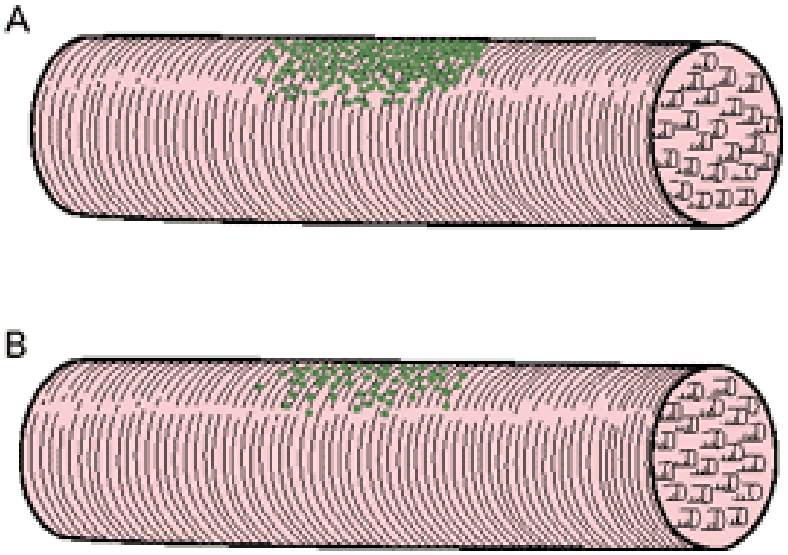


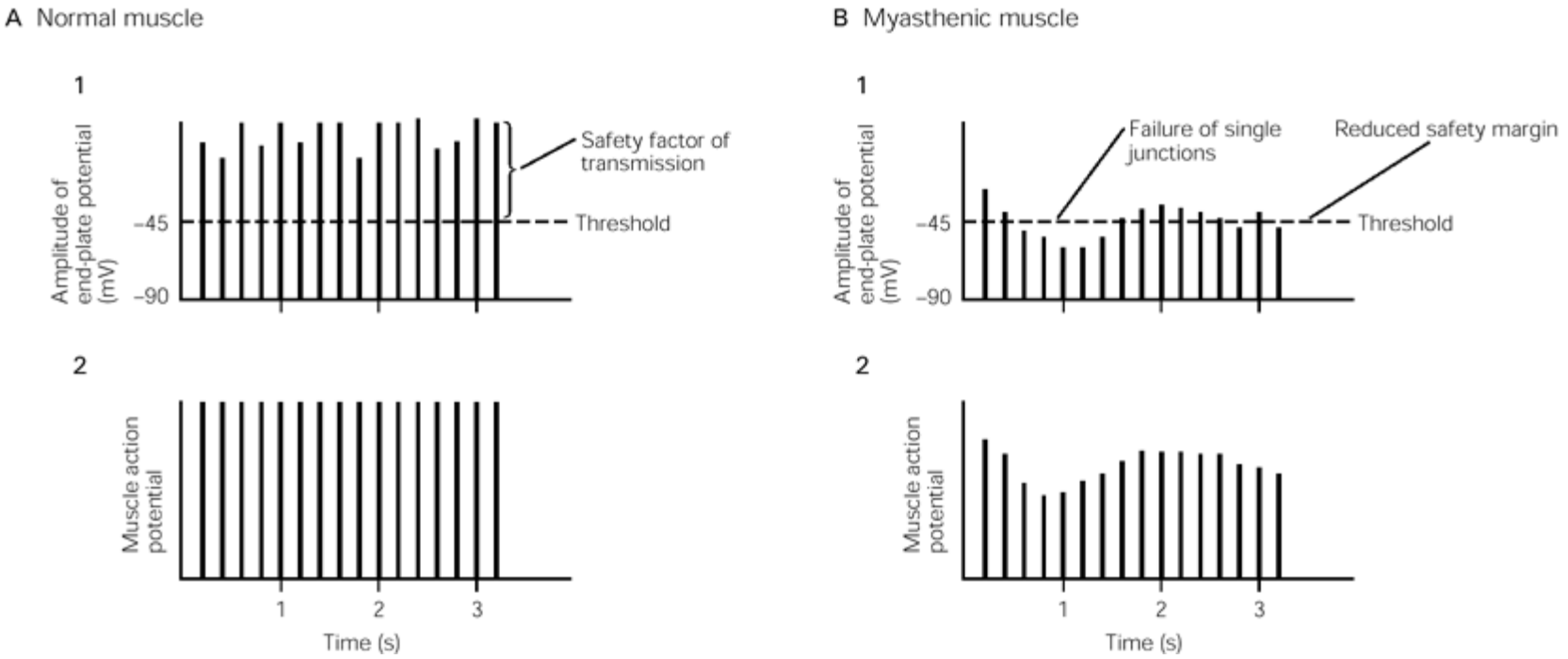


Myastenia gravis






A
B


A Normal muscle
1
Amplitude of end-plate potential (mV)
−45
−90
Safety factor of transmission
Threshold
2
Muscle action potential
1
2
3
Time (s)
B Myasthenic muscle
1
Amplitude of end-plate potential (mV)
Failure of single junctions
Reduced safety margin
−45
−90
Threshold
2
Muscle action potential
1
2
3
Time (s)

Lambert Eaton Syndrome

- Mostly observed in patients with Small cell lung cancer
- Progressive weakness is the major symptom
- Antibodies against to the presynaptic voltage gated calcium channels in the motor end plate is detected in the blood samples
- Morphology of the presynaptic site is altered regular alignment of the VGCC is lost

Rasmussen Encephalitis

- Rasmussen encephalitis is a rare disease observed in childeren under the age of 10
- Seizures, loss of motor functions, hemiparesis, inflammation of the brain are the are observed
- Autoantibodies bind to glutamate receptor are the cause of the disaese

Transcriptional Channelopathies

- Results from expression of nonmutated channels
- Dysregulated production of normal channel proteins as a result of changes in transcription may perturb the cellular function

Sodium channels are diverse

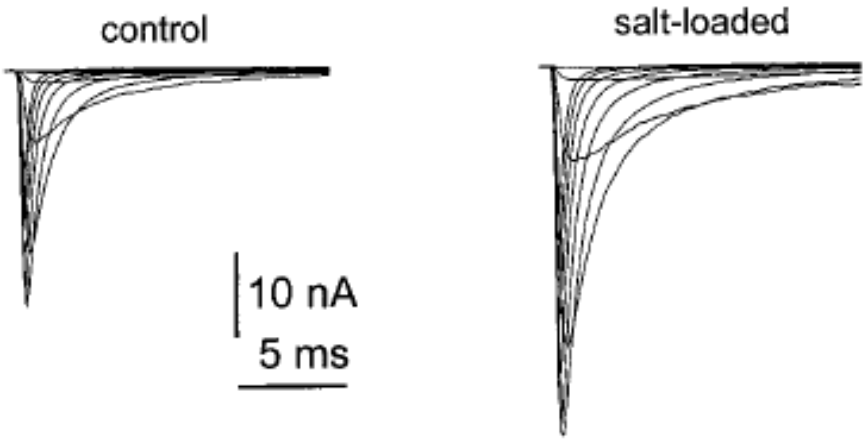
- 10 sodium channel genes has been identified in human genome and 9 has been shown to code distinct sodium channels.
- They have different voltage-dependence and kinetic properties.
- Selective expression of the channels endow the cells with different functional properties.

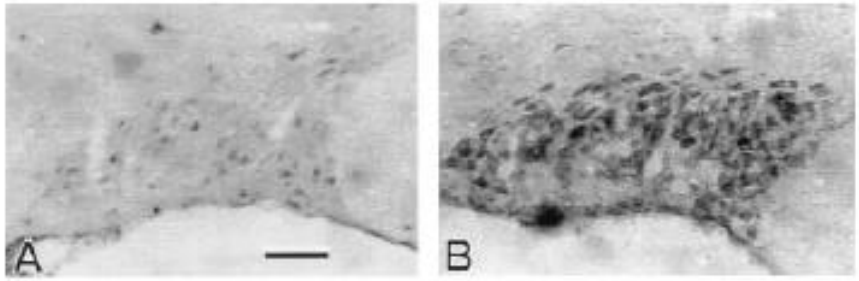
Sodium channels are diverse

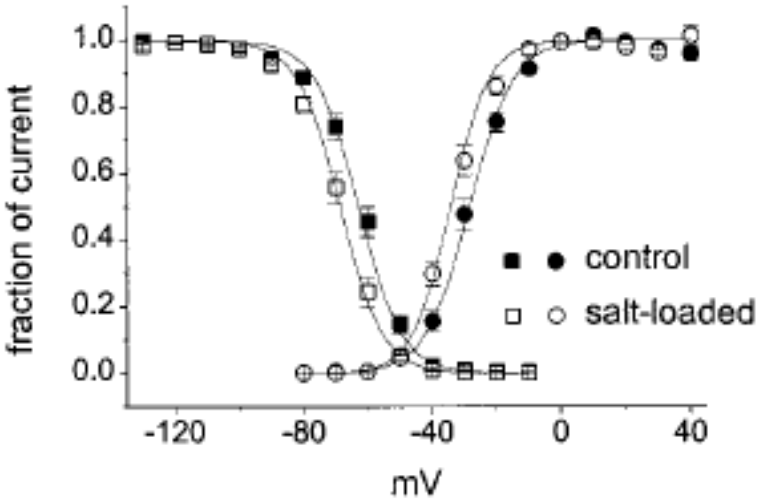
- Nav1.1, Nav1.2, Nav1.3 rise during the course of development
- NGF and GDNF upregulate Nav1.8 and Nav1.9 and downregulate Nav1.3 sodium channels
- Further, electrical activity may modulate expression of sodium channels

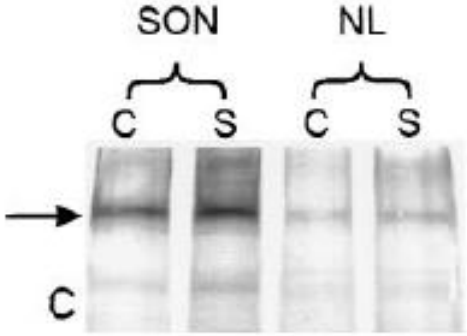
Sodium channels are diverse

- *Magnocellular neurosecretory neurons of hypothlamic supraoptic nucleus are slient at normal conditions.*
- *When osmotic pressure increases they fire at a high frequency bursts of action potentials and trigger release of vasopressin.*
- *It was shown that after salt loding conditions expression of Nav1.2 and Nav1.6 increased in association with the transition to bursting state*
- *Nav1.6 can be activated by small depolarizations*


control
salt-loaded
10 nA
5 ms


A
B

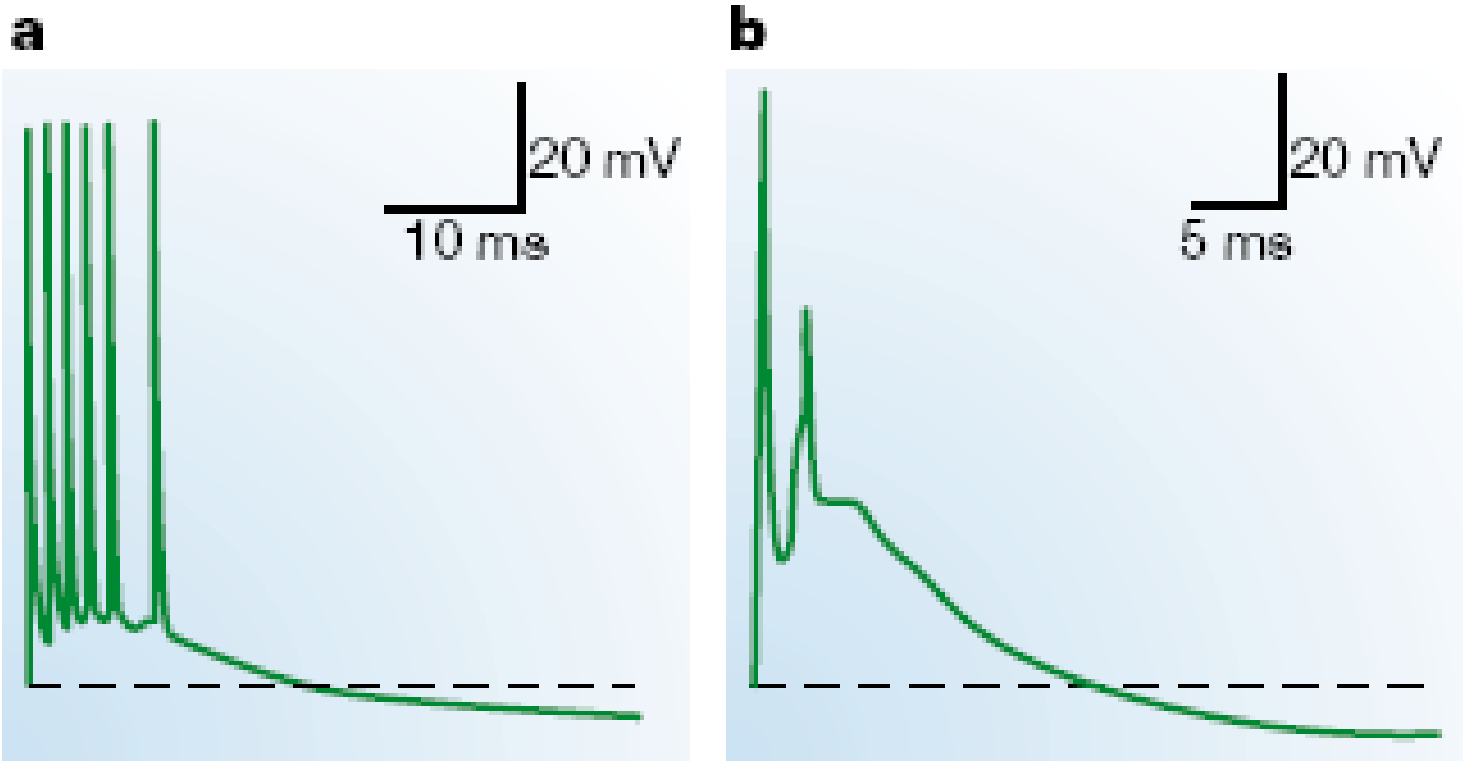

fraction of current
1.0
0.8
0.6
0.4
0.2
0.0
-120
-80
-40
0
40
mV
control
salt-loaded


SON
NL
C
S
C
S
C

Peripheral nerve injury
Neuropathic pain and paraesthesiae

- Neuropathic pain
- Burning or electrical type of pain developing in response to injury of a nerve
- Paraesthesiae
- Spontaneously developing pain described as pins or needles, probably due to demage to sensory fibres in spinal cord

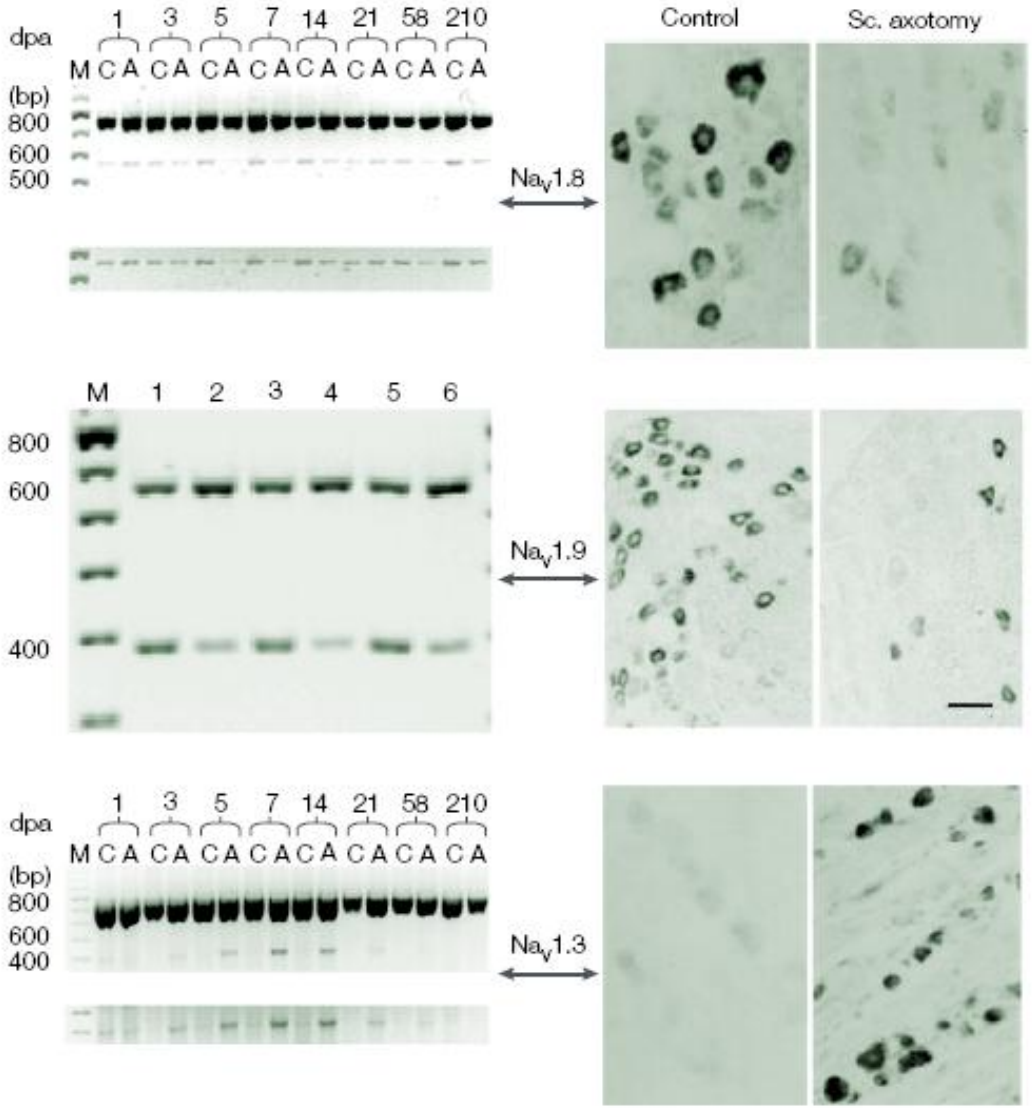
Neuropathic pain and paraesthesiae



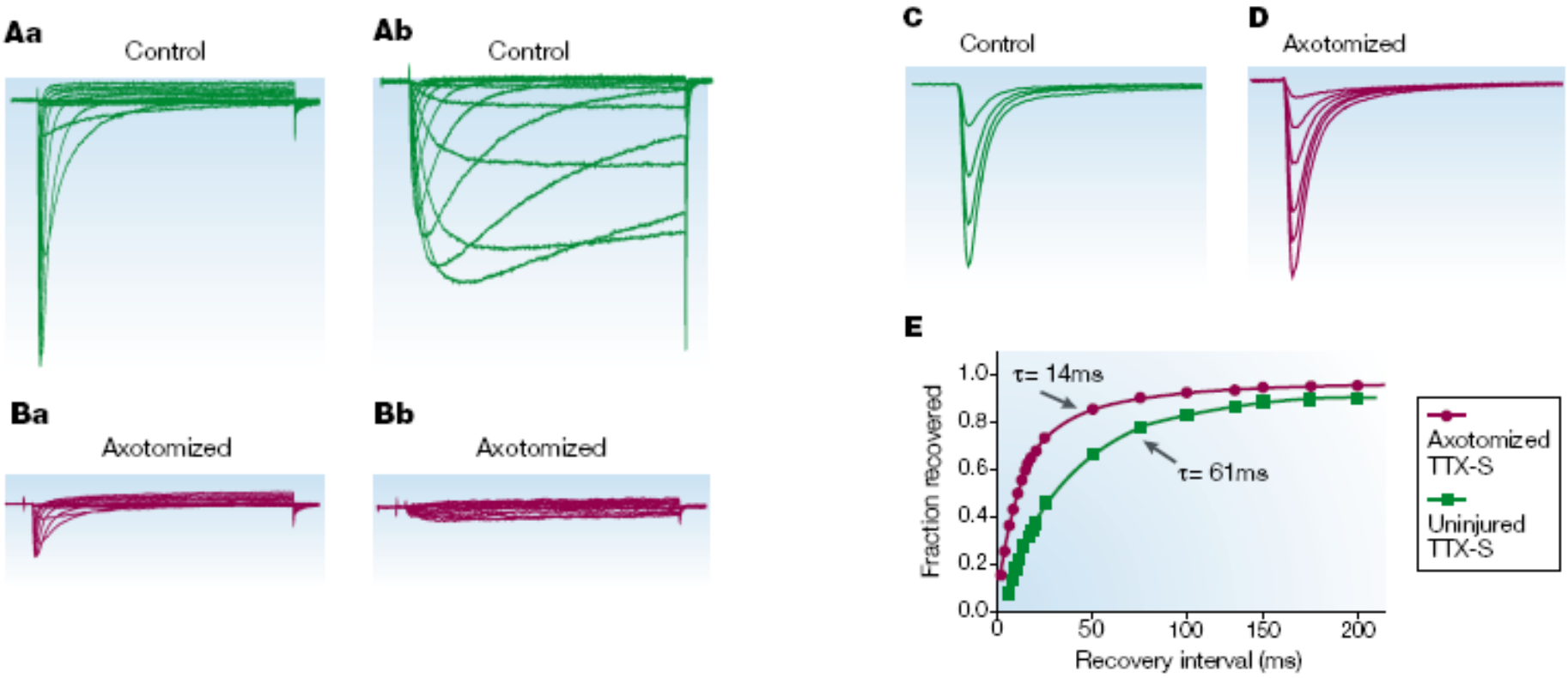
Peripheral nerve injury
Neuropathic pain and paraesthesiae

- Prolonged duration of opening opening indicates persistant activation of a sodium channel
- However, it was not possible to conclude if it is different mode of the same pre-existing channel or expression of a new type of channel

Neuropathic pain and paraesthesiae



Neuropathic pain and paraesthesiae



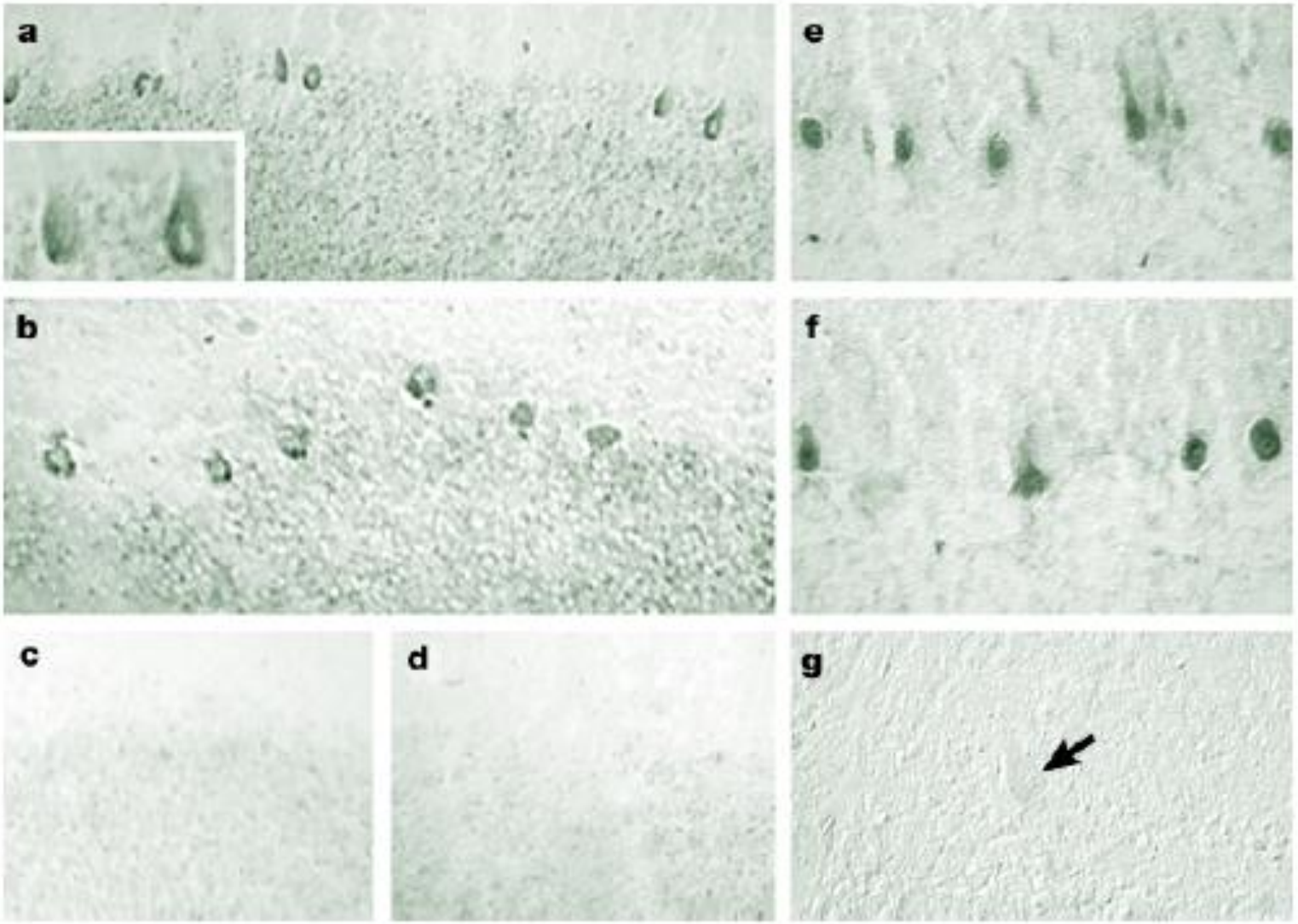
Peripheral nerve injury
Neuropathic pain and paraesthesiae

- The factors triggering changes in sodium channel expression are not fully understood
- NGF and GDNF are responsible for expression of Nav1.8 and Nav1.9
- Loss of access to peripheral sources of neurotrophic factors is the most probable cause

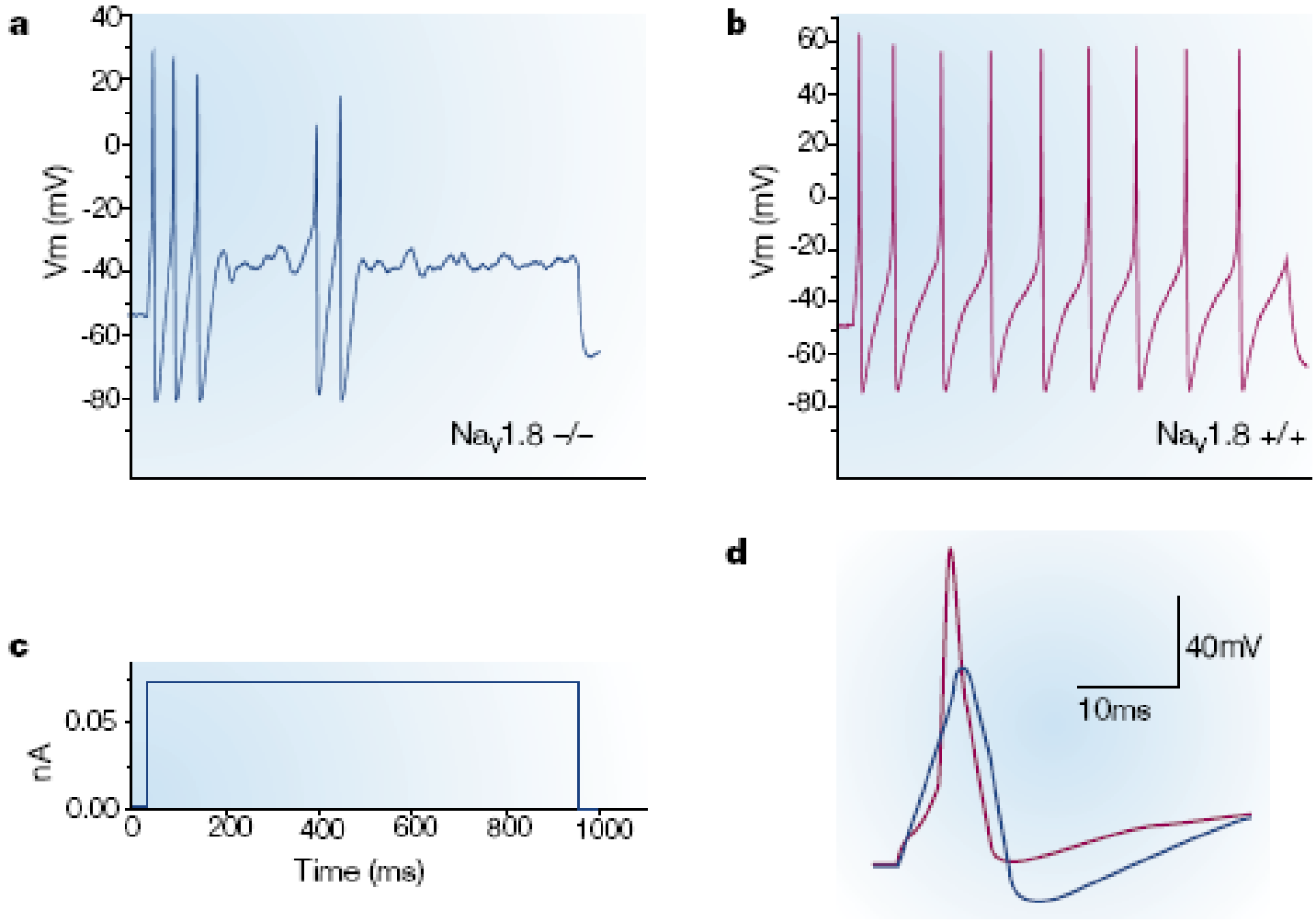
Multiple Sclerosis

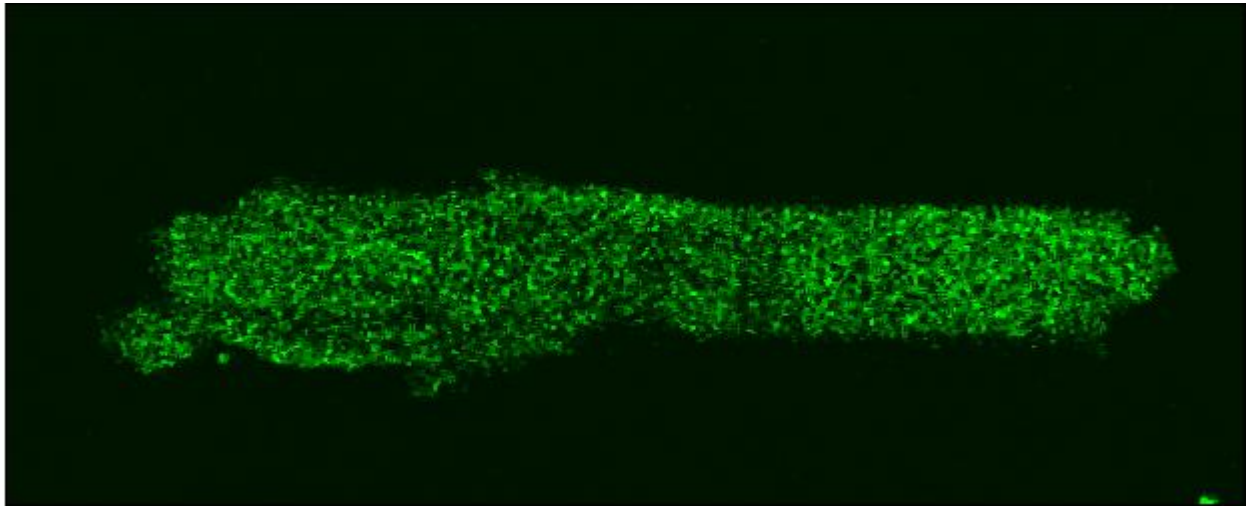
- Demyelination is the hallmark of MS
- Axonal degeneration is also present
- Recently a change in sodium channel expression is also observed
- In paranodal region sodium channels are present at a low density
- Following demylination Nav1.8 expression increases

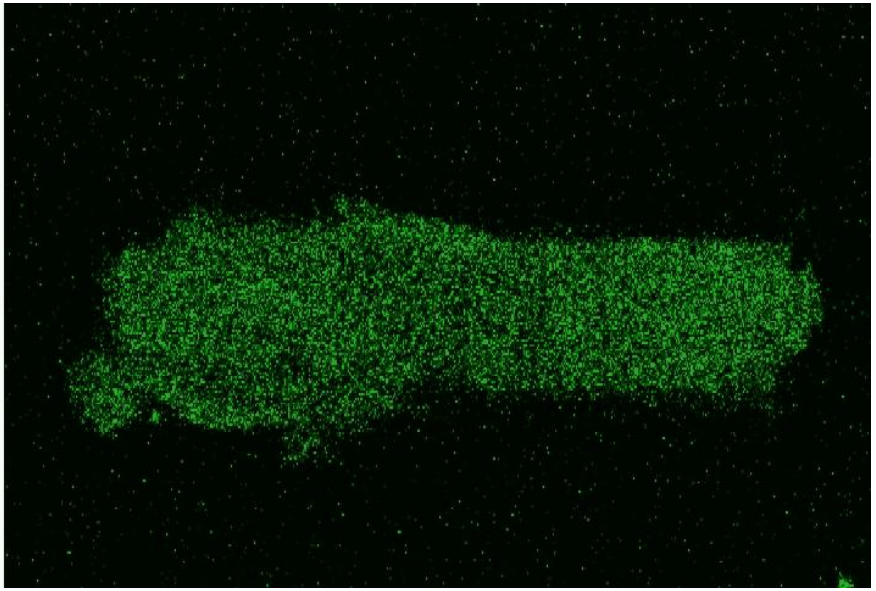
Multiple sclerosis



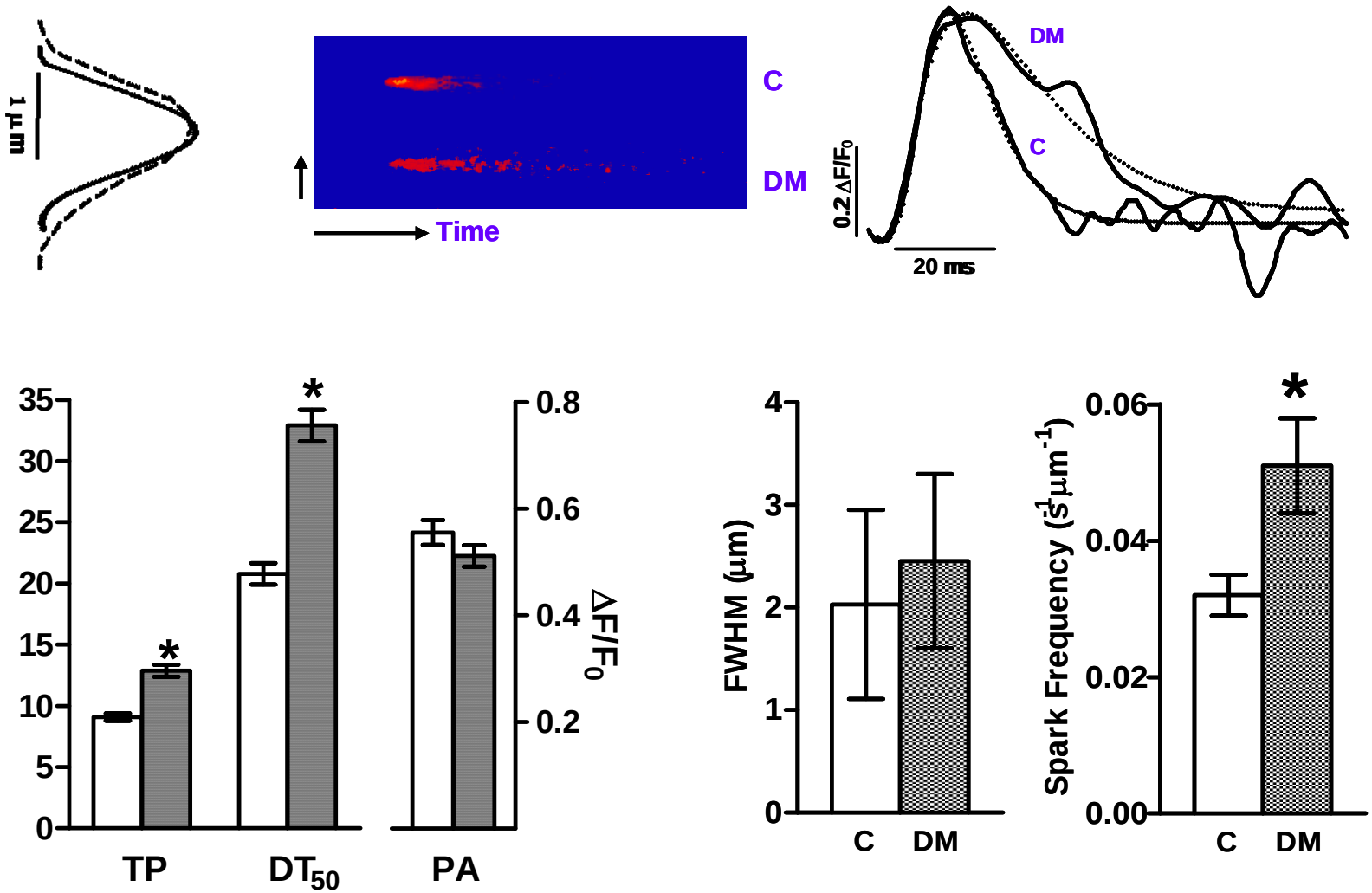
Multiple sclerosis







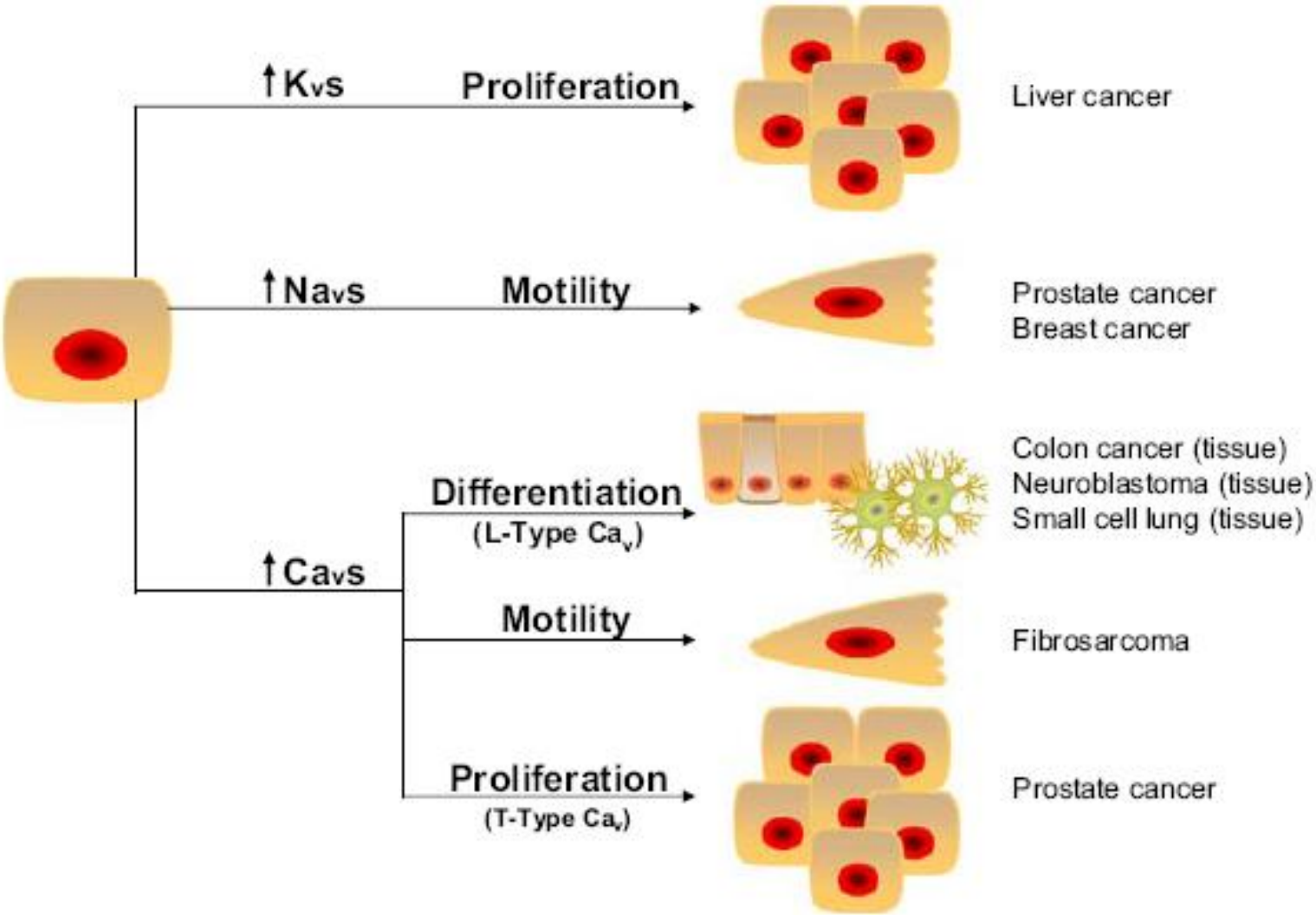
Ca^{2+} sparks parameters in diabetic cardiomyocytes



Yaras et al., Diabetes, 2005

Voltage Sensitive Ion Channels and Cancer

Voltage sensitive ion channels and cancer



Voltage sensitive ion channels and cancer

Channel group	Expression level associated with cancer	Evaluation parameter	Cancer
K_v	Up	Immunostaining	Colon
	Up	RT-PCR	Glioma
	Up	RT-PCR	Oral squamous cell
Na_v	Up	RT-PCR, IHC	Breast
	Up	Western	Prostate
	Up	RT-PCR	Prostate
Ca_v	Up	qPCR	Prostate
	Up	qPCR, confocal	Colon
	Up	Flow cytometry	Neuroblastoma, small cell
	Up	RT-PCR	Small cell
	Up	RT-PCR	Small cell
	Up	Electrophysiology	Fibrosarcoma
ENaC	Up	RT-PCR, Western	Leukemia
Na K-ATPase	Down	IHC	Prostate

Voltage sensitive ion channels and cancer

- Ion channels are involved in malignant progression of cancer
- There are evidences indicating control of cell proliferation and migration by ion channels
- Cell specific differentiation????
- Current efforts to create new drugs to ion channels is promising to halt the progression of cancer by either cytostatic or cytotoxic mechanisms

*Inflammation induced channelopathy in the **GIS***

- Inflammation markedly alters the motility of the GIS system.
- Orderly passage of food from osephagus to colon is achieved by the coordinated movement of the muscle layers under the influence of
  - Neuronal
  - Hormonal
  - Myogenic factors
- Each of those factors, which is dependent on ion channels, alters the excitability of the muscle cells.

Contractile Patterns

- Phasic contractions
  - APs superimposed on slow wave generated by ICC, involved in local mixing and distal propagation of luminal content.
- Tone
  - Basal level of tone in smooth muscle cells is maintained by intracellular calcium concentration.
- Migrating motor complexes
  - Cyclic contractions due to periodic firing of enteric neuronal network.
- Giant migrating contractions
  - Contraction with large amplitude, happening two or three times daily, involved in defecation and under neuronal control.

*Changes in contractile patterns in **inflammation***

- Phasic contractions
  - Suppressed due to a damage to the ICC cells.
- Tone
  - Suppressed.
- Migrating motor complexes
  - Frequency may not change but amplitude reduced.
- Giant migrating contractions
  - Increased in frequency DIARRHEA??.

*Changes in contractile patterns in **inflammation***

- Circular muscles
  - Suppression of contractions.
- Longitudinal muscles
  - Contractions either unchanged or enhanced.

Changes in electrical excitability of the smooth muscle cells

- Smooth muscle cells depolarized
- ICC damaged
- Calcium currents reduced 70 %
- At least in some models of inflammation calcium channel protein expression is not decreased.
- Steady state of activation shifted to more negative potentials.
- Responses to Ca^{++} channel agonist attenuated.

Changes in calcium channels in intestinal smooth muscle cells.

- In smooth muscle cells two isoforms of calcium channels are present (alternative splicing of Cav.12).
- Each isoform is regulated by different promoters.
- Loss of calcium current is restored by Nuclear factor (NF-kB) inhibitor.
- NF-kB is inactive complexed to inhibitor IkBalpha.
- NF-kB is increased in inflamatory bowel diseases.
- NFAT is another transcriptional factor expressed in intestine
- Activation of NFAT requires Ca/calmodulin dependent protein phosphatase “calcineurin”.
- Ca channels are substrate to non receptor tyrosine kinase c-src, which looses its affinity to the channel protein

Changes in ionic channels are selective.

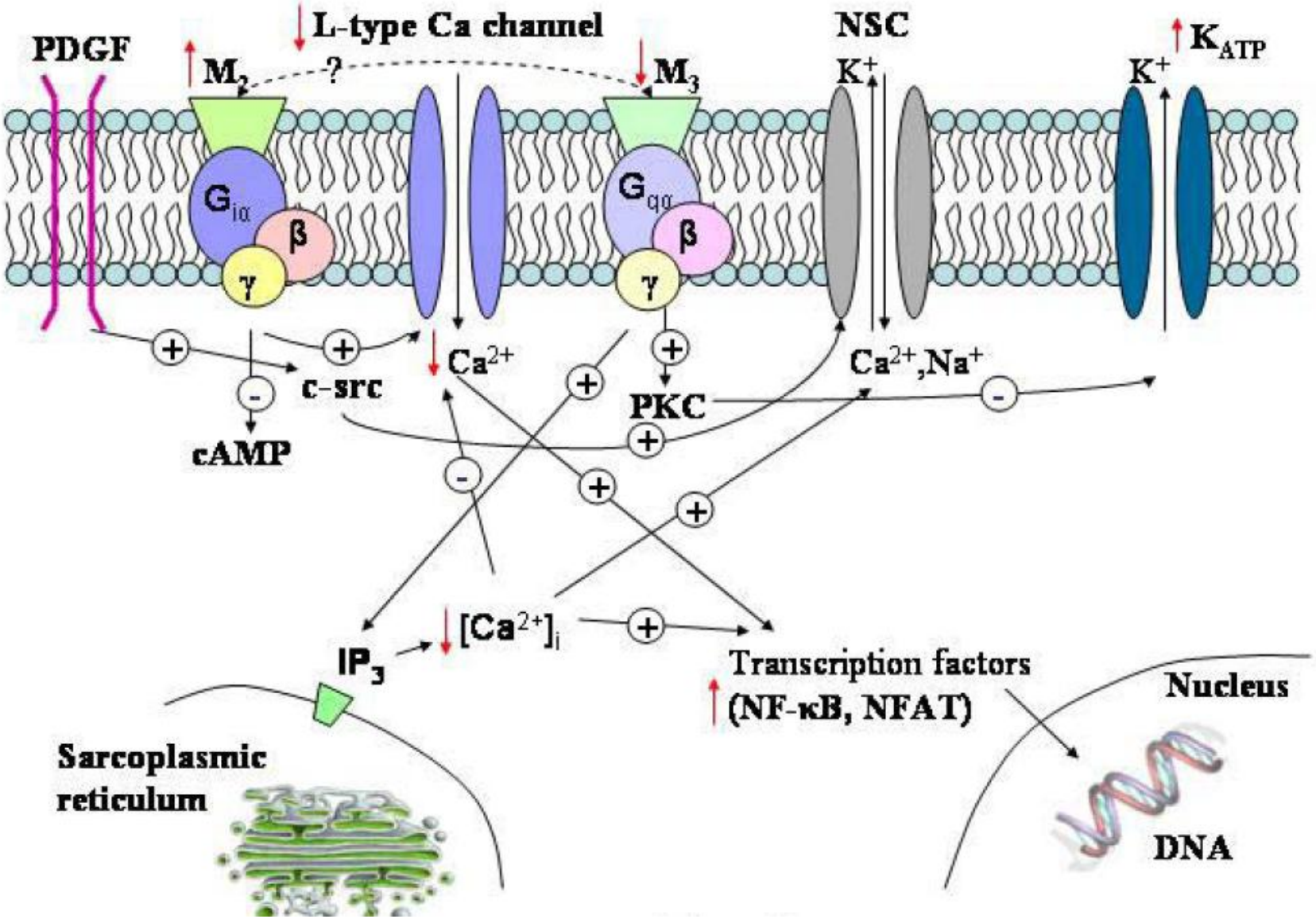
- Ca^{++} current decreases in inflammation
- Transient potassium channels do not change
- K-ATP channel, coupling cell metabolism to membrane excitability, increased 20 folds
- Thus, upregulation of some potassium channels together with the depression of the calcium channels may account for the decreased motility of smooth muscle after inflammation

Changes in muscarinic receptor coupling in inflammation

- Muscarinic agonists increase opening of a non selective cation channel by a combined action of M2 and M3 receptors.
- Inflammation results in 30 % reduction in muscarinic receptor density.
- This may account for the reduction in the GIS motility observed in inflammation.

Inflammation induced changes in GIS

- Are not releted to a defect in genes.
  - 1. Calcium current reduced
  - 2. Muscarinic activity (mediated via the cation channel) is reduced
  - 3. K-ATP channel is upregulated
- Changes are related to conditional modulation of the ionic channels and receptor signalling pathways.
- Thus, this is a typical example of **“transcriptional channelopathies”**


PDGF
M2
?
L-type Ca channel
M3
NSC
K+
K+
KATP
Gi
β
γ
Gq
β
γ
Ca2+
c-src
cAMP
PKC
Ca2+,Na+
IP3
[Ca2+]i
Transcription factors
(NF-κB, NFAT)
Nucleus
Sarcoplasmic
reticulum
DNA

CFTR Videomov.flv