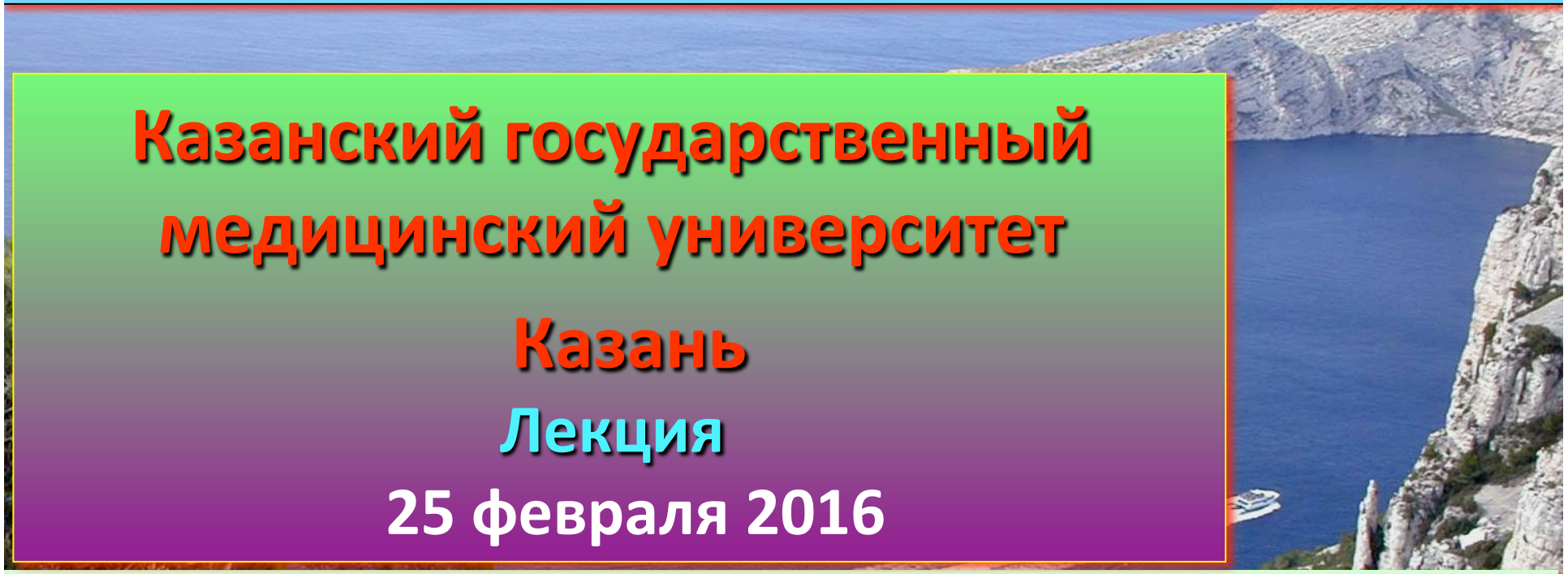
Молекулярная организация нервной системы

Лекция 3- 4-2(25):

Наследственные Каналопатии. Эпилепсия



Казанский государственный медицинский университет

Казань

Лекция

25 февраля 2016

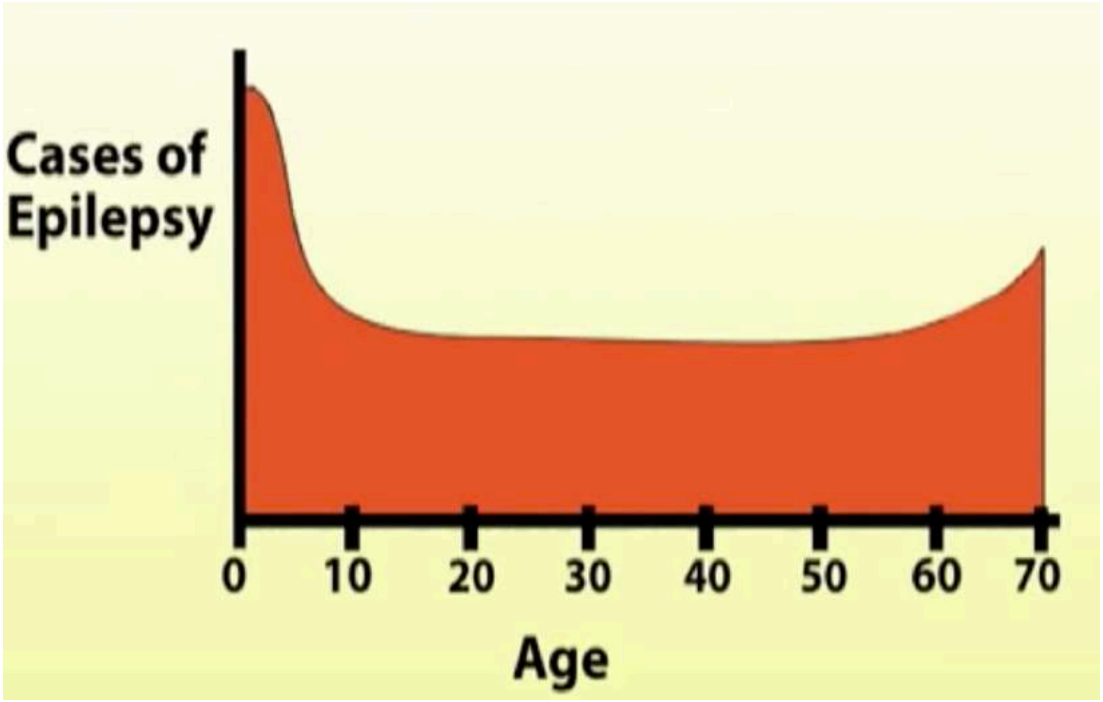
П.Д. Брежестовский

Институт динамики мозга
Факультет медицины
Университет Aix-Marseille
Марсель, Франция
pbreges@gmail.com

Эпилепсия

Эпилепсия – введение

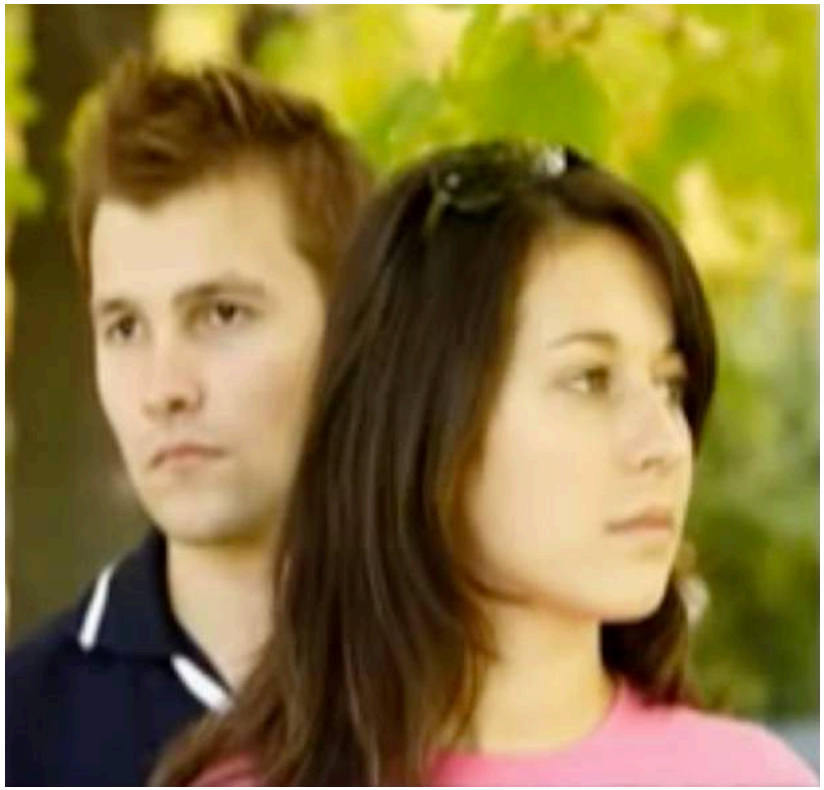
- Около 1% людей (более 60 млн на планете
- Почти 3 млн в США
- В детстве – до 10 лет и – после 60-ти



Эпилепсия у детей

- Травмы при рождении
- Инфекции
- Врожденные аномалии
- Высокая температура

Эпилепсия в среднем возрасте



- Травмы головы
- Инфекции
- Алкоголь
- Стимулирующие препараты
- Побочные эффекты лечения

Эпилепсия у пожилых людей

- Опухоль мозга
- Инсульт

Эпилепсия – нарушение химического баланса

Другие причины эпилепсии

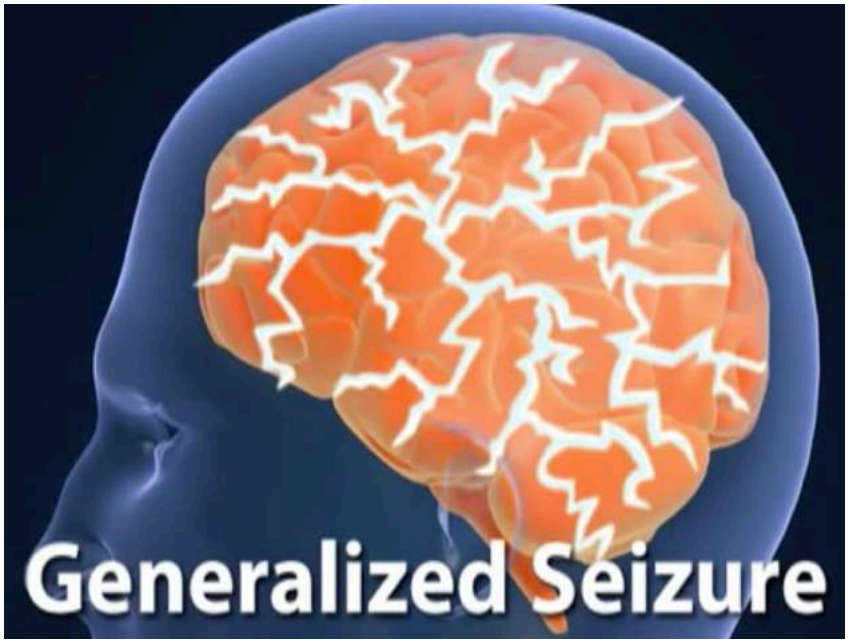
- Низкий уровень сахара в крови
- Низкий уровень кислорода
- Низкий уровень натрия
- Низкий уровень кальция
- Расстройства печени или почек

Эпилепсии генетической природы

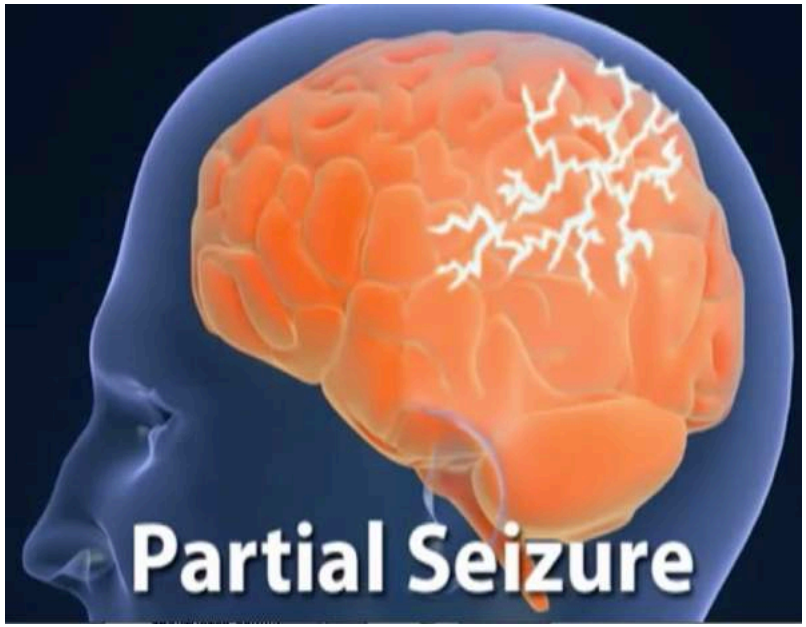
- Генетические дефекты ионных каналов приводят к нарушениям возбуждения мозга
- **Обобщенные припадки**:
  - приступы в обоих полушариях головного мозга
  - генерализованные тонические-клонические приступы
  - Эпилепсия отсутствия
  - Миоклоническая

Эпилепсия: основные виды

- Частичные эпилептические припадки
- Генерализованные эпилептические припадки



Генерализованные: оба полушария



Частичные: начало в ограниченной зоне мозга

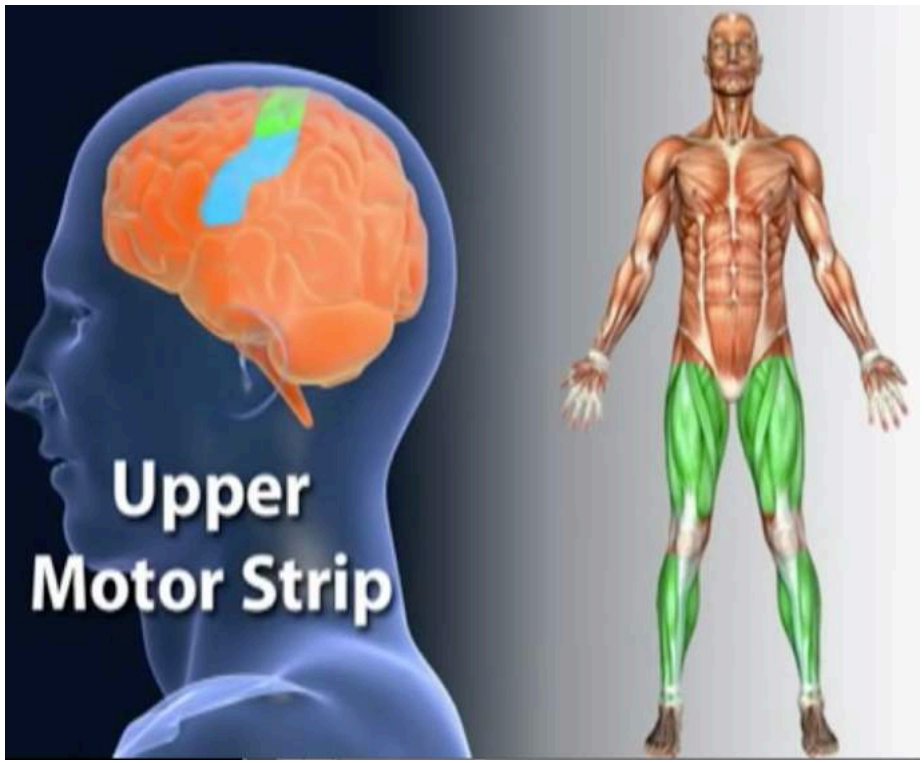
Генерализованные тонические-клонические приступы

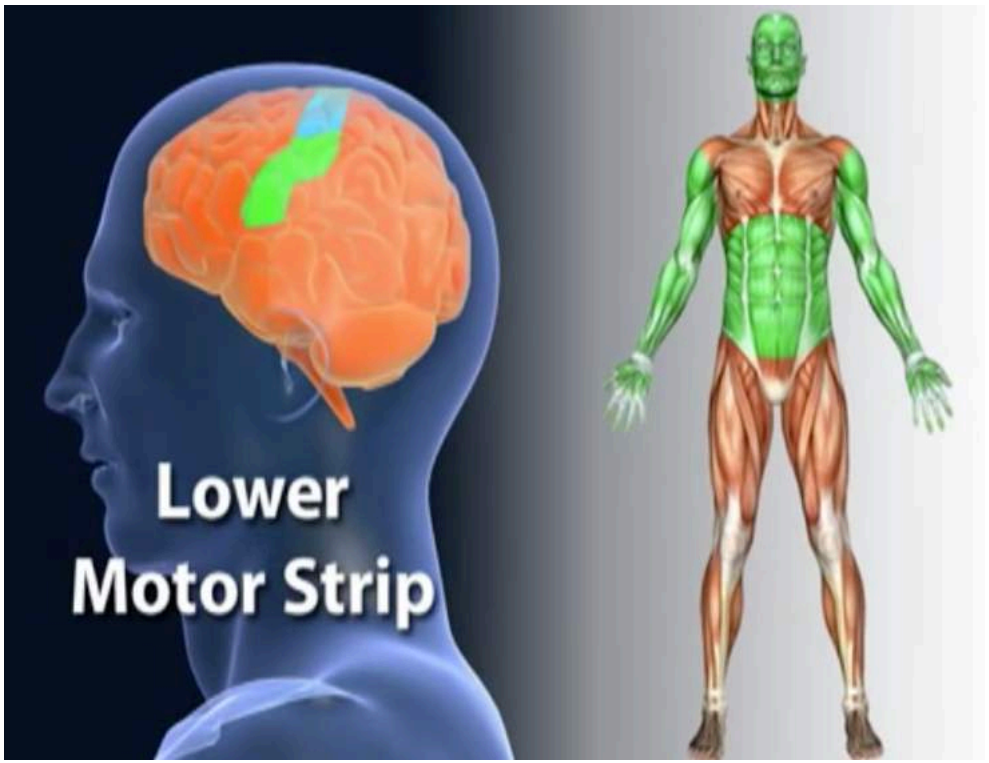
Генерализованная эпилепсия

Эпилепсия отсутствия
Petit Pal seizure

Эпилепсия отсутствия

Моторные зоны коры

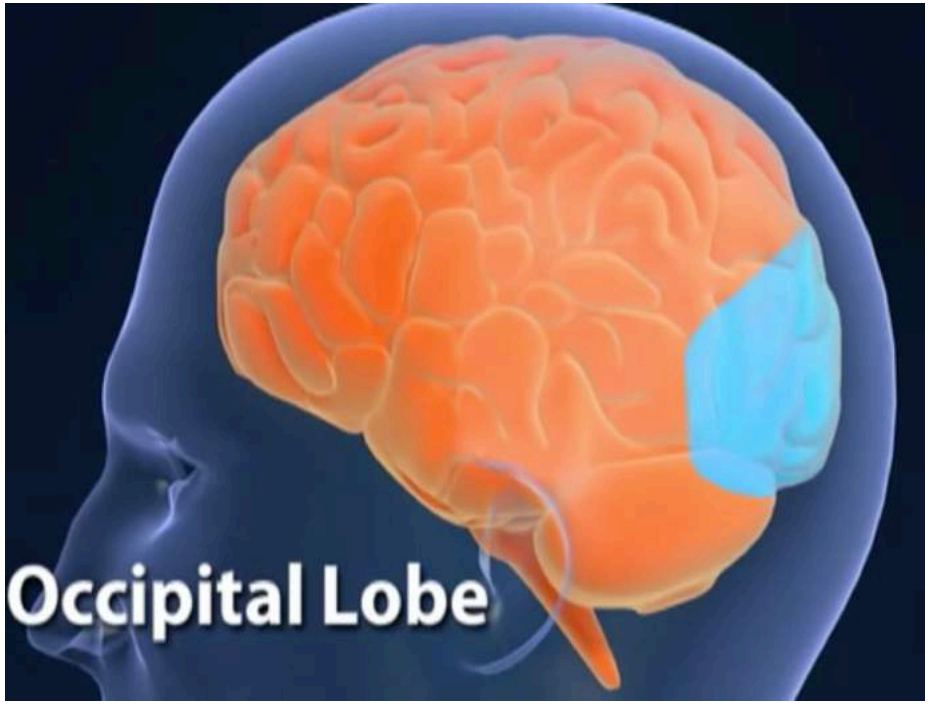


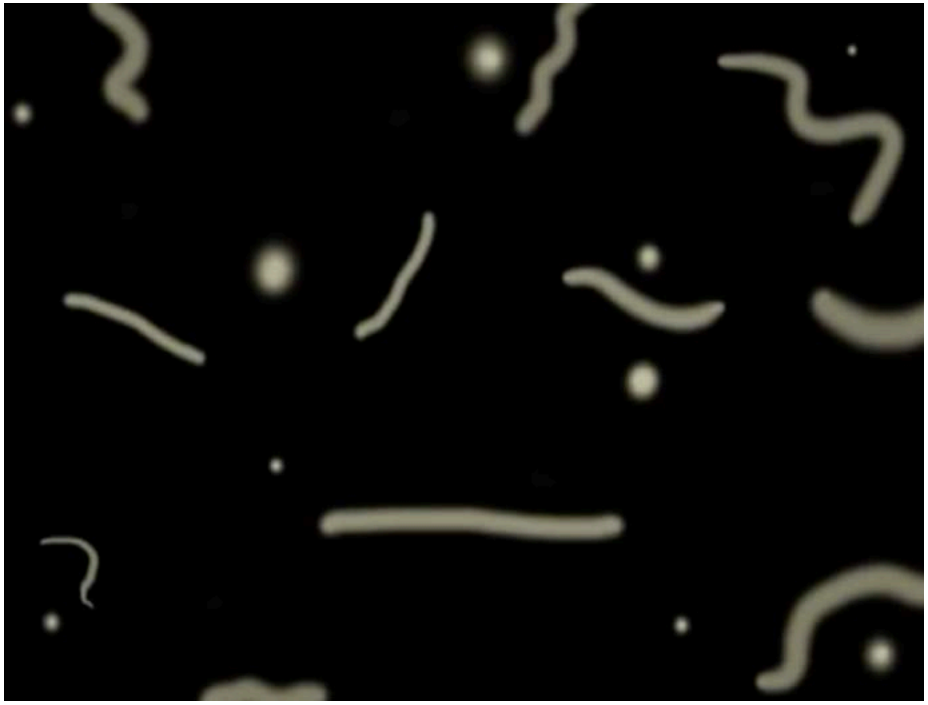


Верхняя моторная зона:
Контроль нижней части тела

Нижняя моторная зона:
Контроль корпуса и верхней части тела

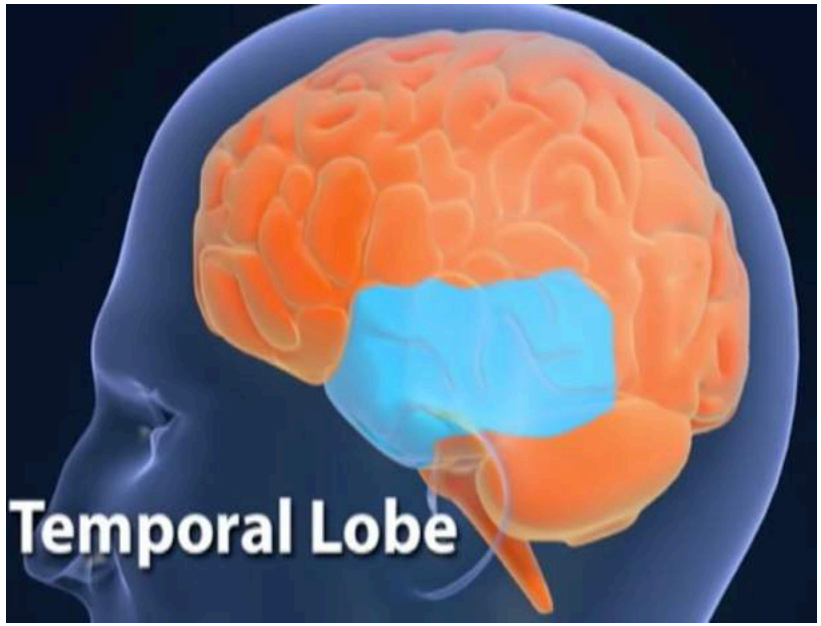
Затылочная доля – зрительная кора

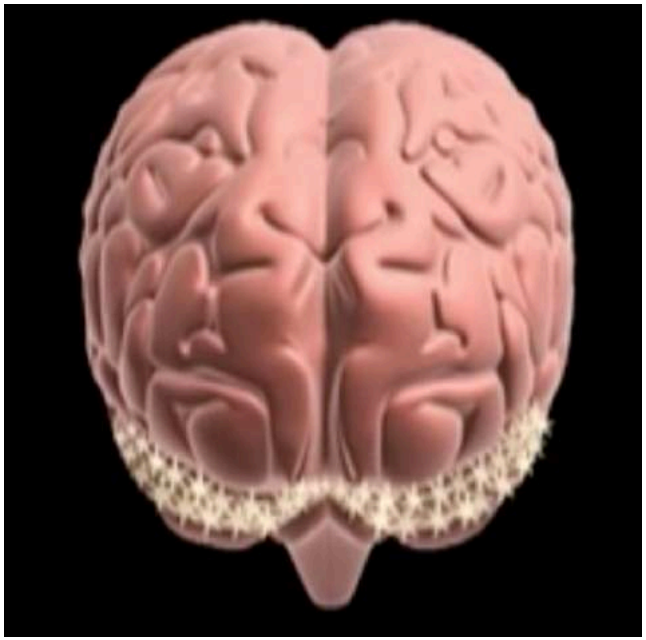




Зрительная зона коры:
Вспышки света, зрительные галюцинации

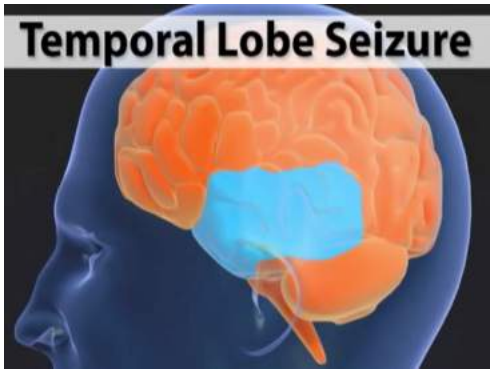
Височная доля – сложная или простая частичная эпилепсия





- Остановка активности
- Смятение
- Временная потеря памяти
- Отрывочные автоматические движения, не осознавая повторений

Частичная моторная эпилепсия

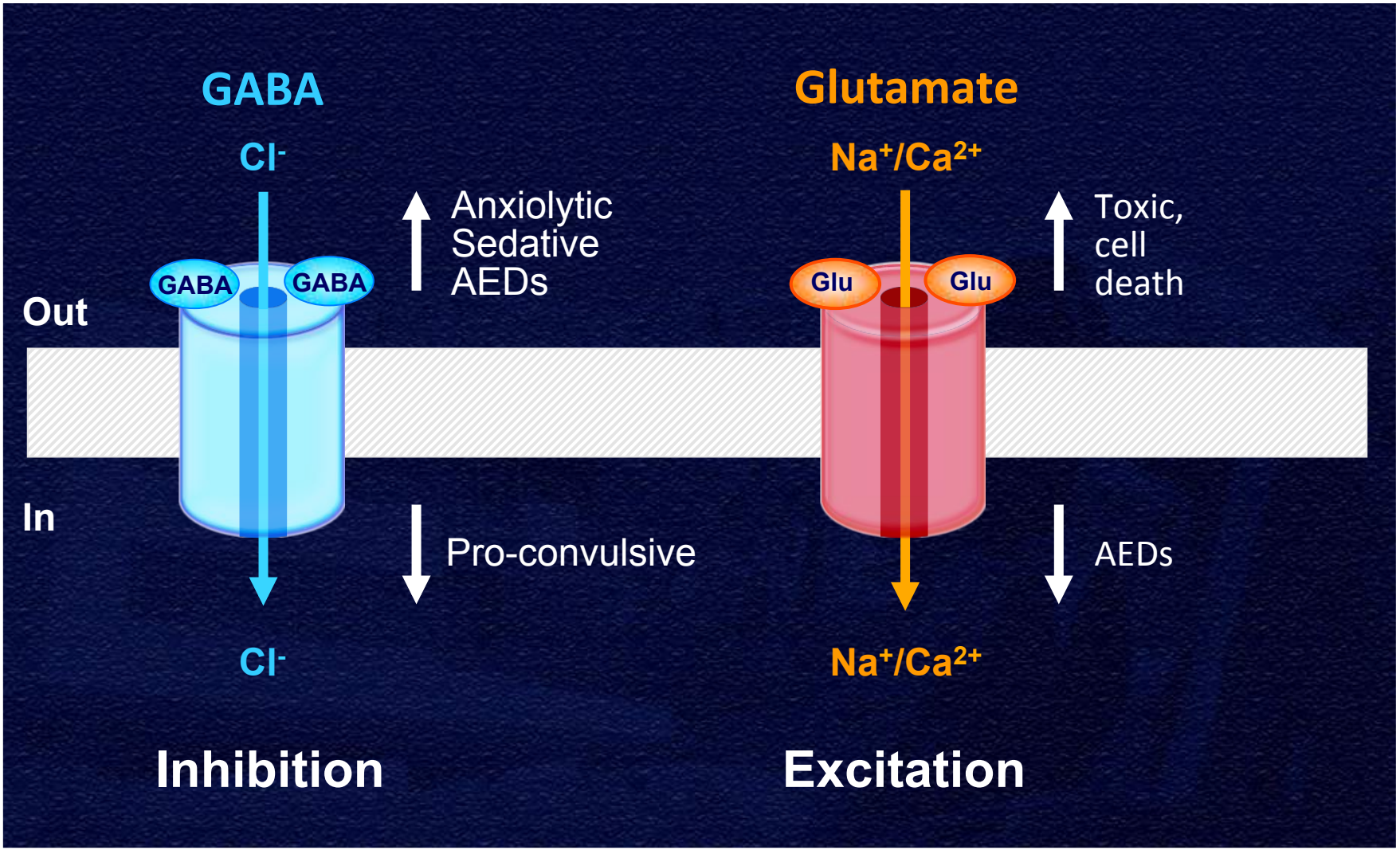


Начало в височной зоне: сложные частичные припадки

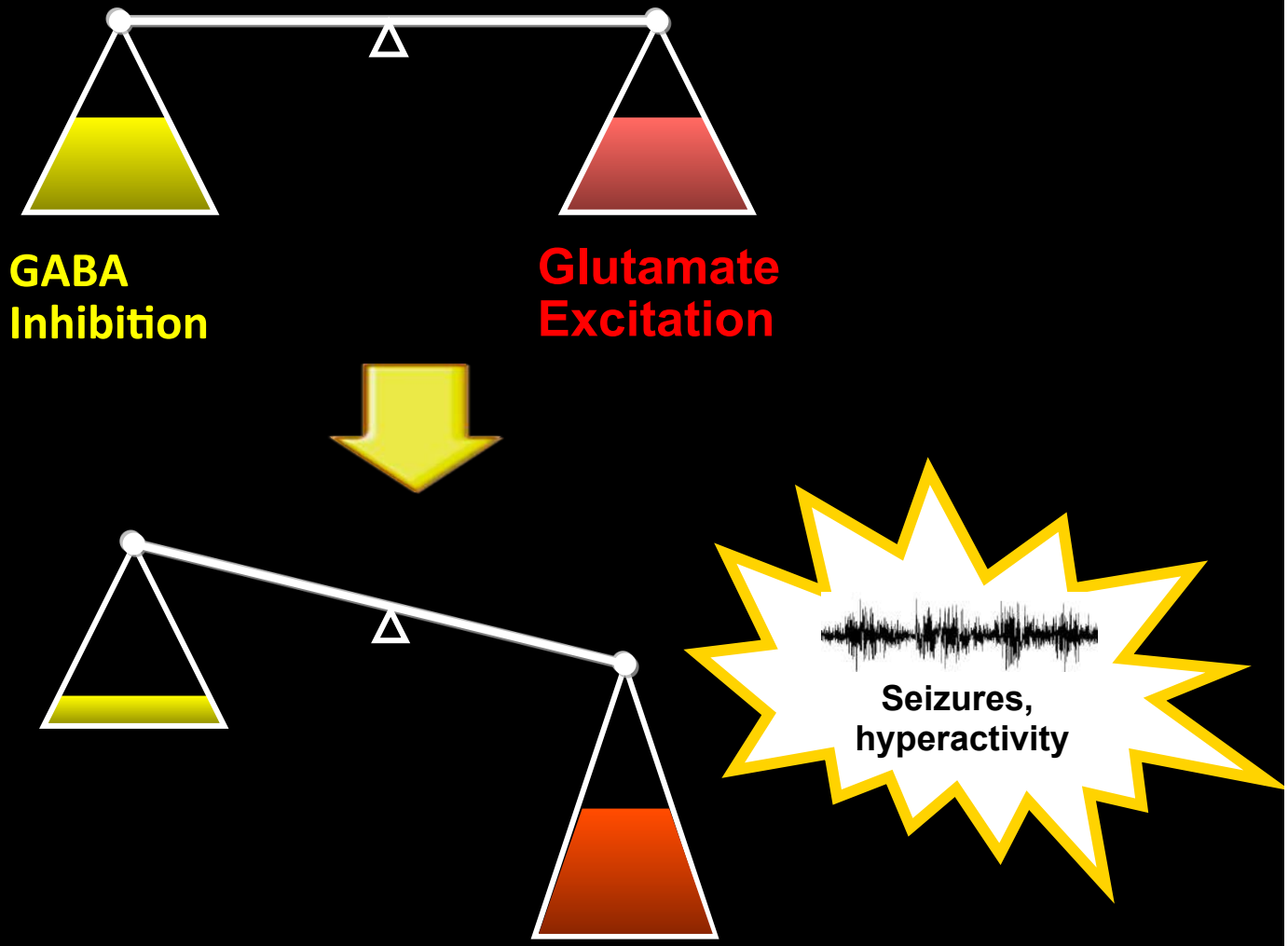
- Головокружение,
- головная боль,
- онемение конечностей
- легкомысленность
- Необычные ощущения:
  - тревога, паника
  - ДЕЖА ВЮ (уже видел), ЖАМЕ ВЮ (никогда)
  - ощущения вкуса, звука, расстройста зрения, странные запахи

Причина: нарушения возбуждения/торможения

Inhibition and Excitation



Баланс между возбуждением и торможением



- Мутации ГАМК рецепторов
- Снижение потенциала покоя (К+ каналы)
- Изменение свойств Na+ каналов
- Изменение свойств Ca^{2+} каналов
- Изменение св-в ц-нуклеотидных каналов
-

Epilepsy and Channelopathies

- Na^+ channels
- K^+ channels
- $GABA_A$ channels
- Ca^{2+} channels
- Acetylcholine receptor channels

Nervous system channelopathies -1

Disease	Channel protein
Achromatopsia type 2	Cyclic nucleotide-gated channel, α3 subunit
Achromatopsia type 3	Cyclic nucleotide-gated channel, β3 subunit
Aland Island eye disease	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit
Andersen-Tawil syndrome	Kir2.1: potassium channel, inwardly-rectifying, subfamily J, member 2
Benign familial infantile epilepsy	Nav2.1: sodium channel, voltage-gated, type II, α subunit
Benign familial neonatal epilepsy	Kv7.2: potassium channel, voltage-gated, KQT-like subfamily, member 2
	Kv7.3: potassium channel, voltage-gated, KQT-like subfamily, member 3
Bestrophinopathy, autosomal-recessive	Bestrophin 1
Central core disease	RyR1: ryanodine receptor 1
Charcot-Marie-Tooth disease type 2C	Transient receptor potential cation channel, subfamily V, member 4
Childhood absence epilepsy	γ-aminobutyric acid A receptor, α1 subunit
	γ-aminobutyric acid A receptor, α6 subunit
	γ-aminobutyric acid A receptor, β3 subunit
	γ-aminobutyric acid A receptor, γ2 subunit
	Cav3.2: calcium channel, voltage-gated, T type, α1H subunit
Cognitive impairment with or without cerebellar ataxia	Nav1.6: sodium channel, voltage-gated, type VIII, α subunit
Cone-rod dystropy, X-linked, type 3	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit
Congenital distal spinal muscular atrophy	Transient receptor potential cation channel, subfamily V, member 4
Congenital indifference to pain, autosomal-recessive	Nav1.7: Sodium channel, voltage-gated, type IX, α subunit
Congenital myasthenic syndrome	Cholinergic receptor, muscle nicotinic, α1 subunit
	Cholinergic receptor, muscle nicotinic, β1 subunit
	Cholinergic receptor, muscle nicotinic, δ subunit
	Cholinergic receptor, muscle nicotinic, ε subunit

Nervous system channelopathies -2

Congenital stationary night blindness type 1C	Transient receptor potential cation channel, subfamily M, member 1
Congenital stationary night blindness type 2A	Cav1.4: calcium channel, voltage-gated, L type, α1F subunit
Deafness, autosomal-dominant, type 2A	Kv7.4: potassium channel, voltage-gated, KQT-like subfamily, member 4
Deafness, autosomal-recessive, type 4, with enlarged vestibular aqueduct	Kir4.1: potassium channel, inwardly-rectifying, subfamily J, member 10
Dravet syndrome	Nav1.1: sodium channel, voltage-gated, type I, α subunit
	γ-aminobutyric acid A receptor, γ2 subunit
Early infantile epileptic encephalopathy type 7	Kv7.2: potassium channel, voltage-gated, KQT-like subfamily, member 2
Early infantile epileptic encephalopathy type 11	Nav2.1: sodium channel, voltage-gated, type II, α subunit
Early infantile epileptic encephalopathy type 13	Nav1.6: sodium channel, voltage-gated, type VIII, α subunit
Early infantile epileptic encephalopathy type 14	K_{Ca}4.1: potassium channel, subfamily T, member 1
EAST/SeSAME syndrome	Kir4.1: potassium channel, inwardly-rectifying, subfamily J, member 10
Episodic ataxia type 1	Kv1.1: potassium channel, voltage-gated, shaker-related subfamily, member 1
Episodic ataxia type 2	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit
Episodic ataxia type 5	Cavβ4: calcium channel, voltage-gated, β4 subunit
Familial episodic pain syndrome	Transient receptor potential cation channel, subfamily A, member 1
Familial hemiplegic migraine type 1	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit
Familial hemiplegic migraine type 3	Nav1.1: sodium channel, voltage-gated, type I, α subunit
Generalized epilepsy with febrile seizures plus (GEFS+)	Navβ1: sodium channel, voltage-gated, type I, β subunit
	Nav1.1: sodium channel, voltage-gated, type I, α subunit
	γ-aminobutyric acid A receptor, γ2 subunit

Nervous system channelopathies -3

Generalized epilepsy with paroxysmal dyskinesia	K_{Ca}1.1: potassium channel, calcium-activated, large conductance, subfamily M, α1 subunit
Hereditary hyperekplexia	Glycine receptor, α1 subunit
	Glycine receptor, β subunit
Hyperkalemic periodic paralysis	Nav1.4: sodium channel, voltage-gated, type IV, α subunit
Hypokalemic periodic paralysis type 1	Cav1.1: calcium channel, voltage-gated, L type, α1S subunit
Hypokalemic periodic paralysis type 2	Nav1.4: sodium channel, voltage-gated, type IV, α subunit
Juvenile macular degeneration	Cyclic nucleotide-gated channel, β3 subunit
Juvenile myoclonic epilepsy	γ-aminobutyric acid A receptor, α1 subunit
	Cavβ4: calcium channel, voltage-gated, β4 subunit
Malignant hyperthermia susceptibility	RyR1: ryanodine receptor 1
	Cav1.1: calcium channel, voltage-gated, L type, α1S subunit
Mucolipidosis type IV	TRPML1/mucolipin 1
Multiple pterygium syndrome, lethal type	Cholinergic receptor, muscle nicotinic, α1 subunit
	Cholinergic receptor, muscle nicotinic, δ subunit
	Cholinergic receptor, muscle nicotinic, γ subunit
Multiple pterygium syndrome, nonlethal type (Escobar variant)	Cholinergic receptor, muscle nicotinic, γ subunit
Myotonia congenita, autosomal-dominant (Thomsen disease)	CIC-1: chloride channel 1, voltage-gated
Myotonia congenita, autosomal-recessive (Becker disease)	CIC-1: chloride channel 1, voltage-gated

Nervous system channelopathies -4

Nocturnal frontal lobe epilepsy type 1	Cholinergic receptor, neuronal nicotinic, α4 subunit
Nocturnal frontal lobe epilepsy type 3	Cholinergic receptor, neuronal nicotinic, β2 subunit
Nocturnal frontal lobe epilepsy type 4	Cholinergic receptor, neuronal nicotinic, α2 subunit
Nocturnal frontal lobe epilepsy type 5	K_{Ca}4.1: potassium channel, subfamily T, member 1
Paramyotonia congenita	Nav1.4: sodium channel, voltage-gated, type IV, α subunit
Paroxysmal extreme pain disorder	Nav1.7: Sodium channel, voltage-gated, type IX, α subunit
Potassium-aggravated myotonia	Nav1.4: sodium channel, voltage-gated, type IV, α subunit
Primary erythermalgia	Nav1.7: sodium channel, voltage-gated, type IX, α subunit
Retinitis pigmentosa type 45, autosomal-recessive	Cyclic nucleotide-gated channel, β1 subunit
Retinitis pigmentosa type 49, autosomal-recessive	Cyclic nucleotide-gated channel, α1 subunit
Retinitis pigmentosa type 50, autosomal-dominant	Bestrophin 1
Scapuloperoneal spinal muscular atrophy	Transient receptor potential cation channel, subfamily V, member 4
Small fiber neuropathy	Nav1.7: sodium channel, voltage-gated, type IX, α subunit
Spinocerebellar ataxia type 6	Cav2.1: calcium channel, voltage-gated, P/Q type, α1A subunit
Spinocerebellar ataxia type 13	Kv3.3: potassium channel, voltage-gated, Shaw-related subfamily, member 3
Vitelliform macular dystrophy	Bestrophin 1
Vitreoretinochoroidopathy	Bestrophin 1

Some heritable epilepsies

- - generalized epilepsy with febrile seizures plus related disorders (GEFS+),
- - autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE),
- - benign febrile neonatal convulsions (BFNC)
- - generalized epilepsy with paroxysmal dyskinesia (GEPD).

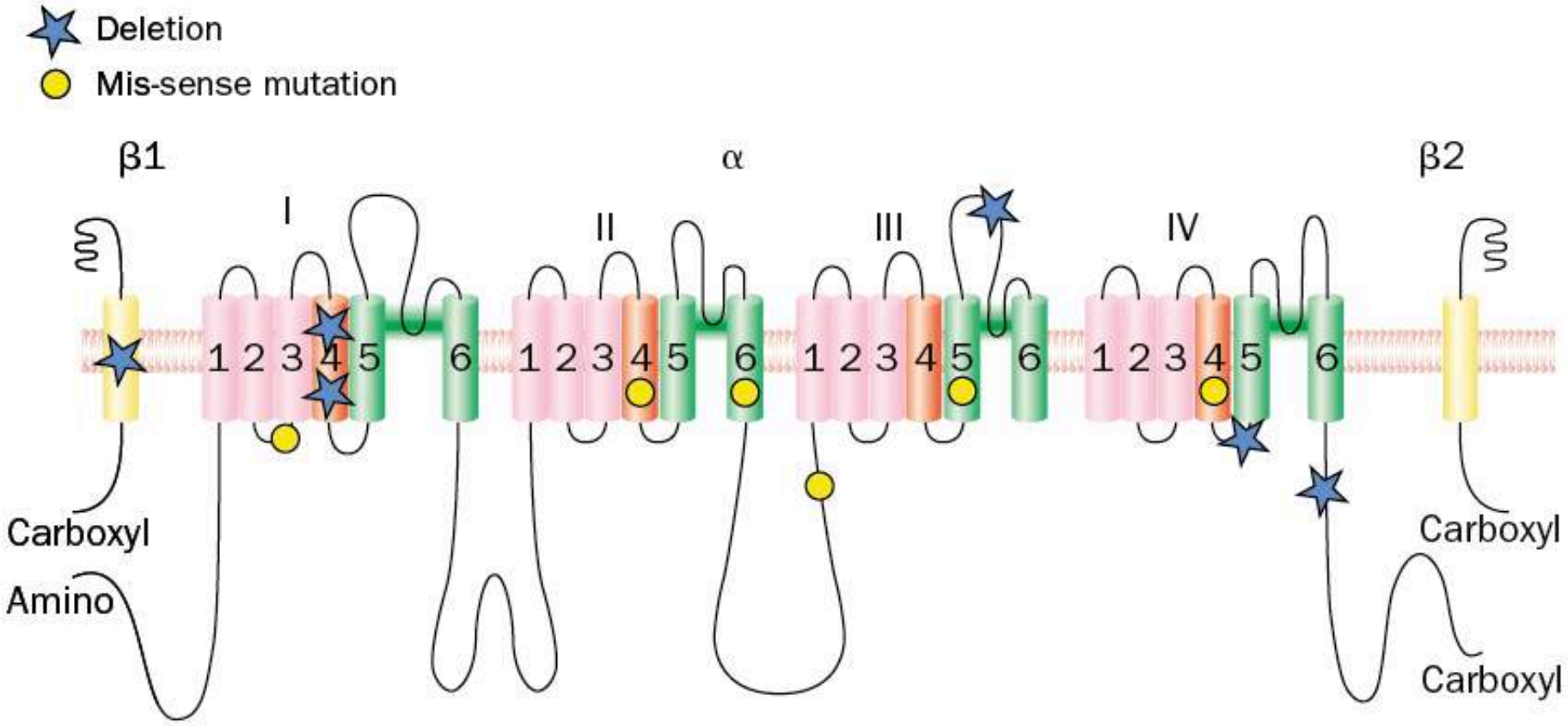
Generalized epilepsy with febrile seizures plus (GEFS+)

- beyond early childhood
- seizures with fever
- affect approximately 3% of all children under six year
- **<u>Main causes of dysfunction</u>**:
  - Na^+ channel α subunit SCN1A
  - Na^+ channel β subunit SCN1B
  - $GABA_A$ receptor

Генерализованная эпилепсия: фебрильные судороги (Синдром Дравела)

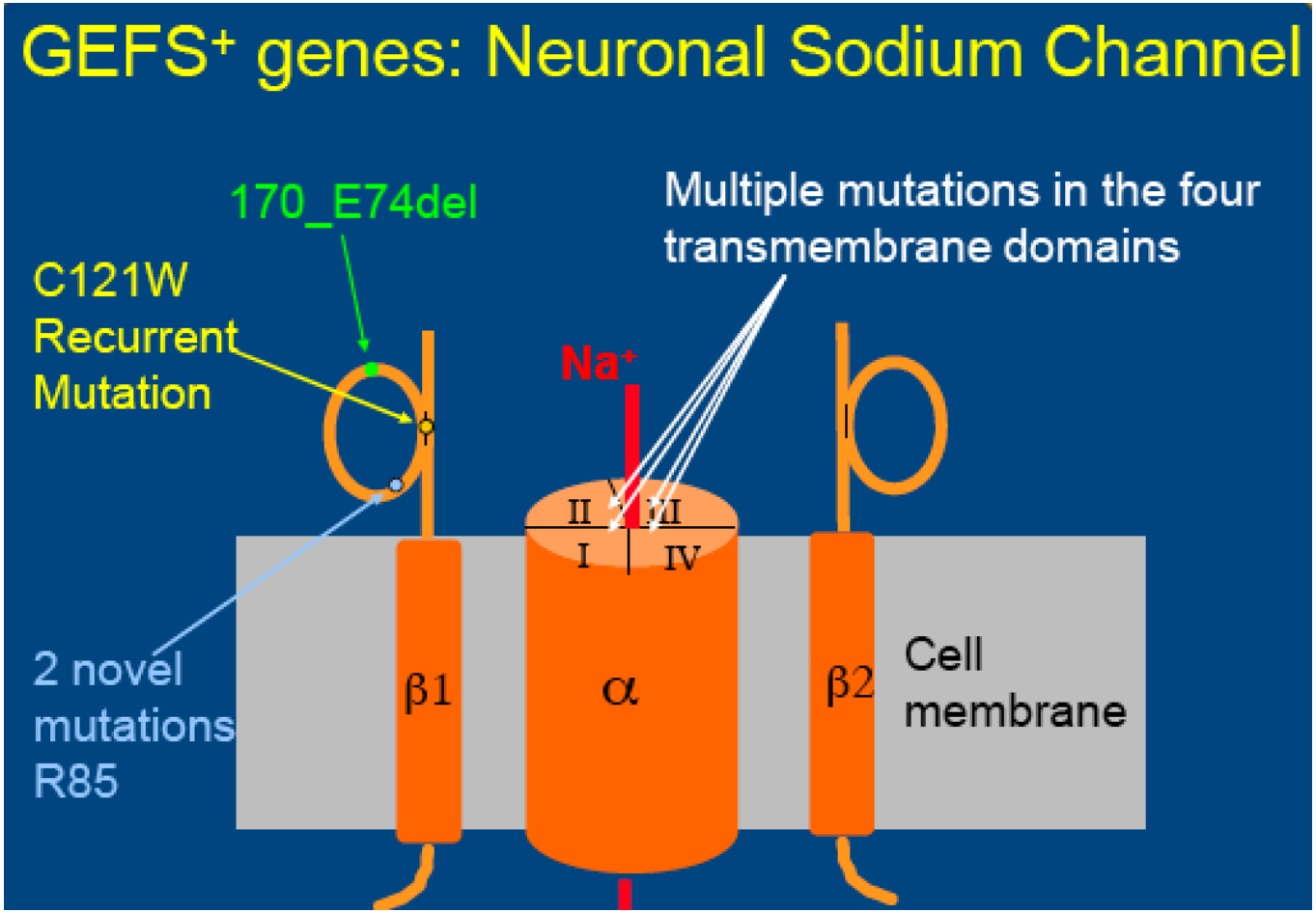
- детская эпилепсия
- приступы при высокой температуре
- примерно 3% детей до 6 лет
- **Основные причины**:
  - мутации α субъединицы Na^+ канала (SCN1A)
  - мутации β субъединицы Na^+ канала (SCN1B)
  - Мутации $GABA_A$ рецептора

Na^+ channel mutations in patients with epilepsy



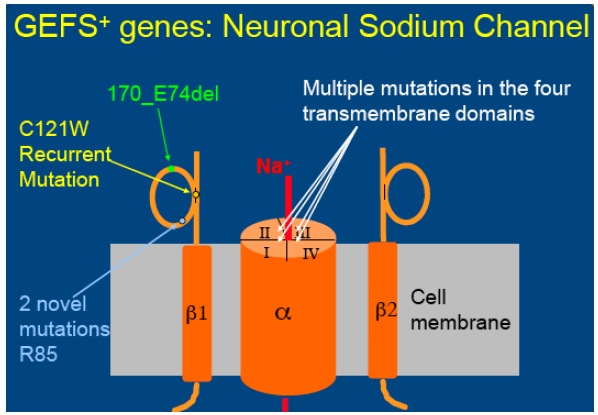
Avanzini and Franceschetti, 2003

Generalized epilepsy with febrile seizures plus (GEFS+)



-missing 5 amino acids in the N-terminus (I70_E74del)
-C121W mutant at the disulfide bond

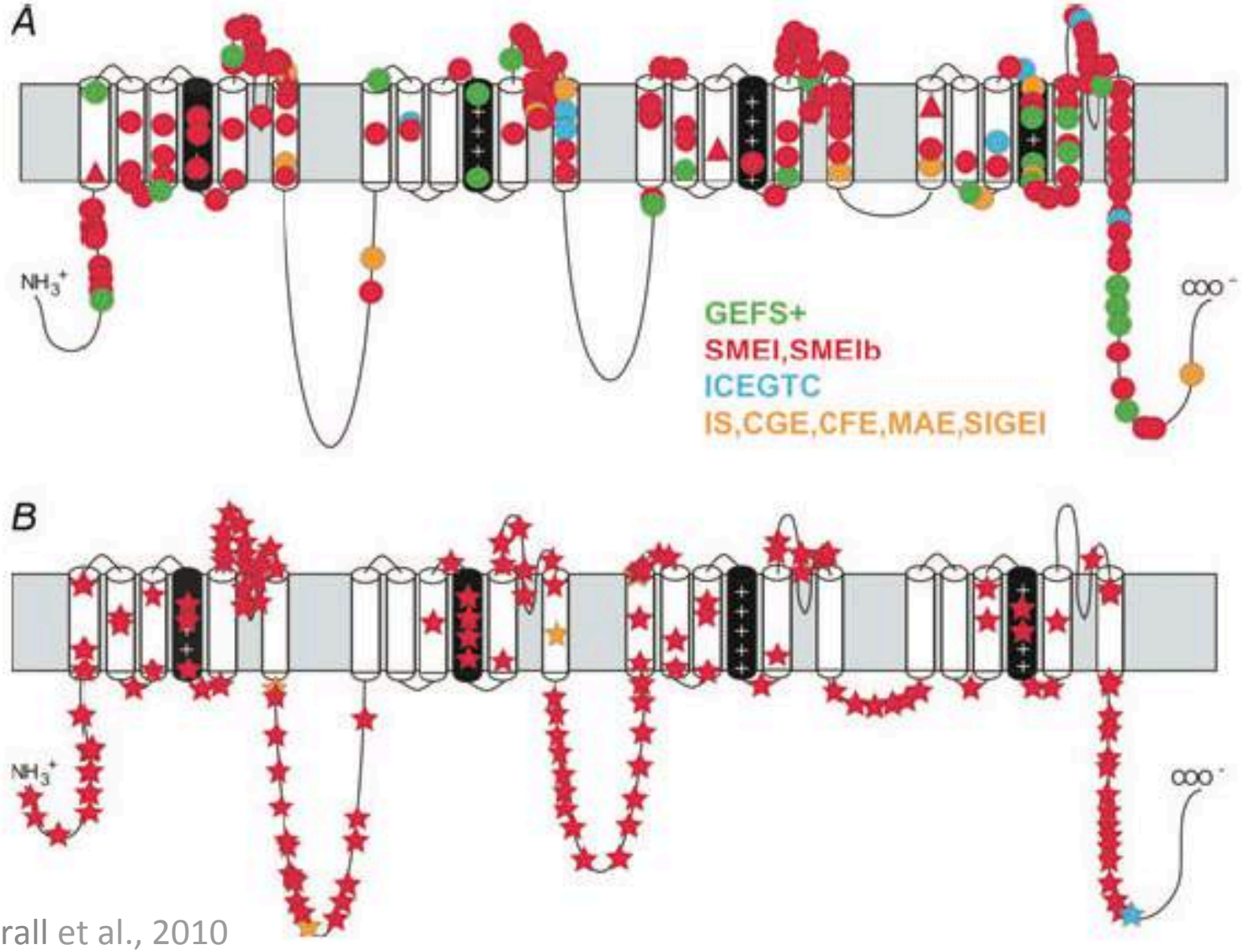
Generalized epilepsy with febrile seizures plus (GEFS+)



- Nav1.1 канал – один из 9 субъединиц
- Экспрессируется в ГАМК-ергических нейронах
- Мутации в β субъединице:
  - потеря 5 а.кислот
  - мутация C121W

-missing 5 amino acids in the N-terminus (I70_E74del)
-C121W mutant at the disulfide bond

Mutations in Na^+ channel patients with epilepsy

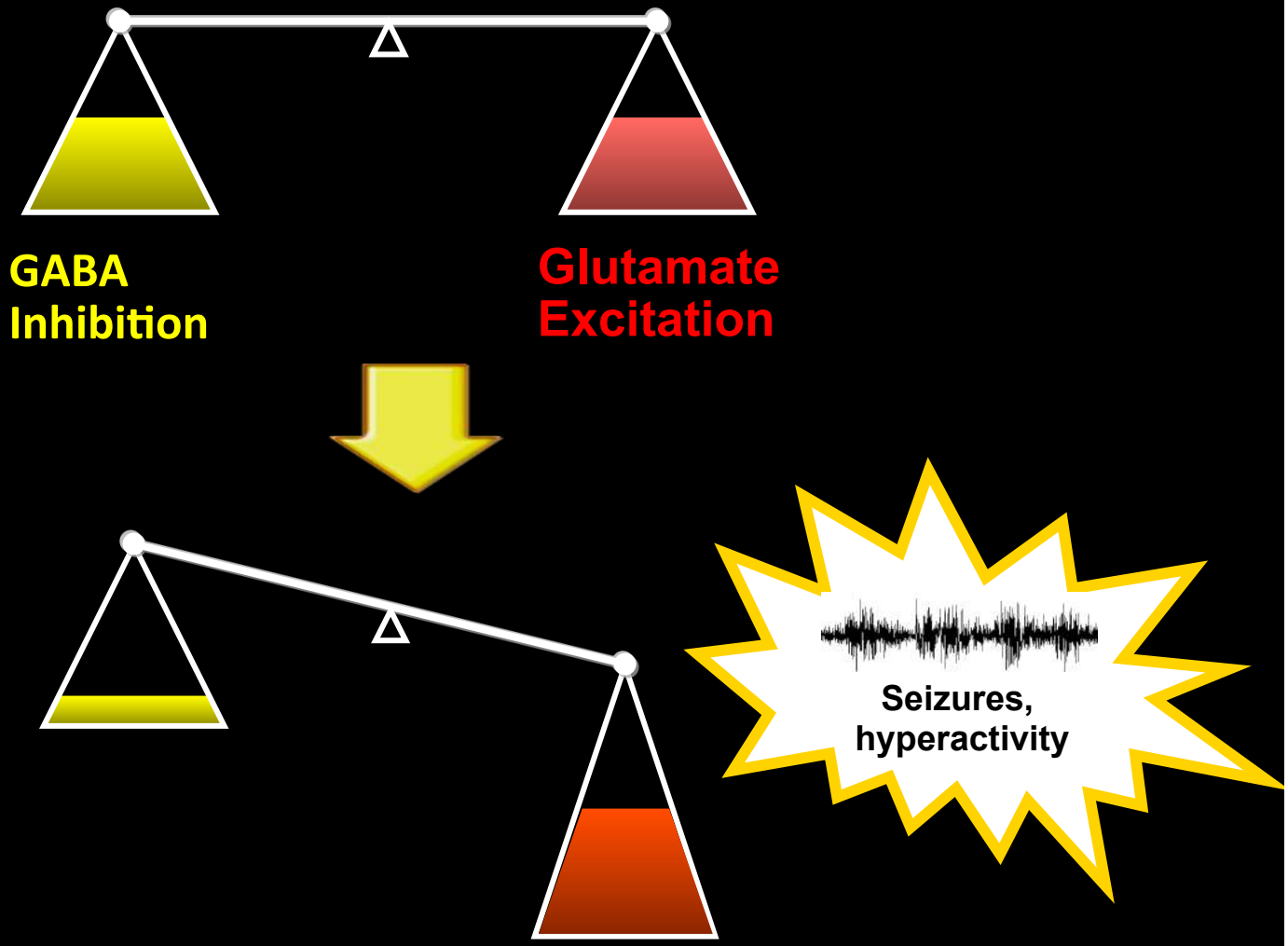


Catterall et al., 2010

Мутации Na каналов

- Нарушение "гомеостаза" возбуждения
- Лечение затруднено

Баланс между возбуждением и торможением



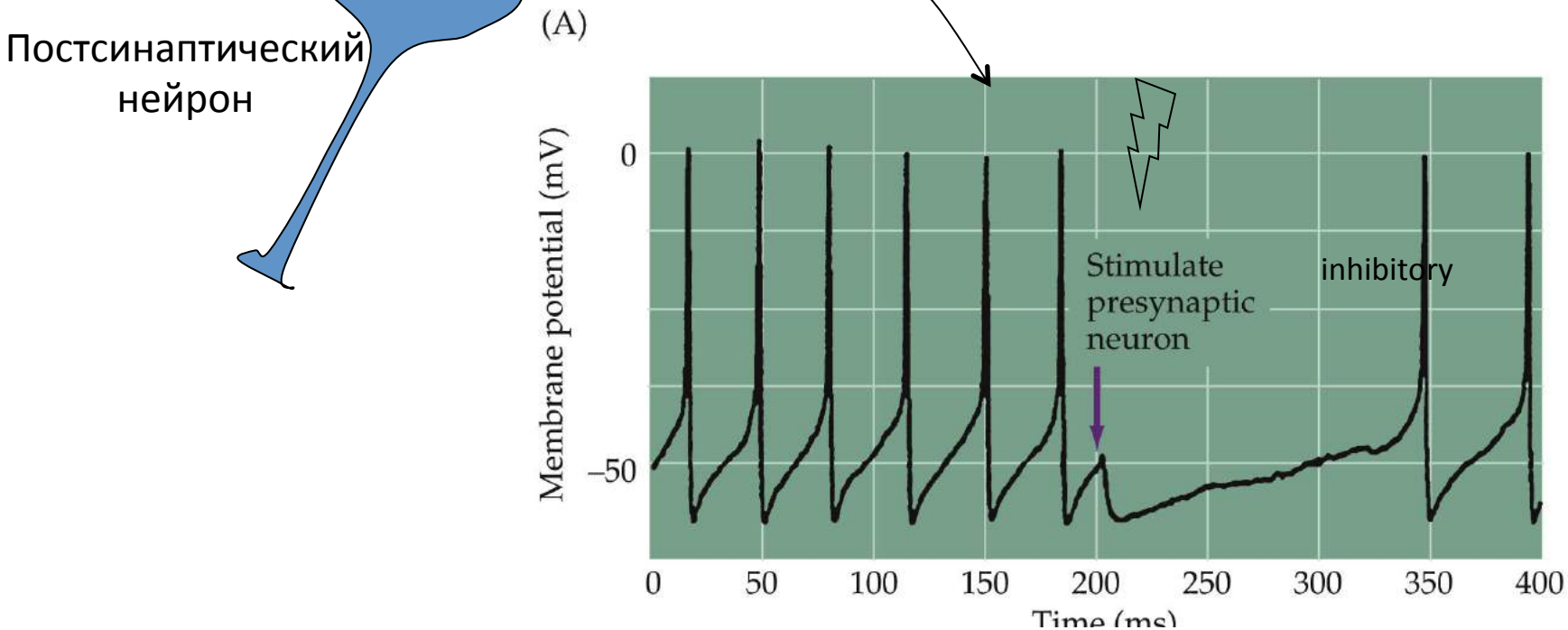
ГАМК – основной тормозной нейромедиатор в ЦНС

Тормозной нейромедиатор ингибирует возбуждение постсинаптического нейрона

Глутаматергичесий пресинаптический нейрон

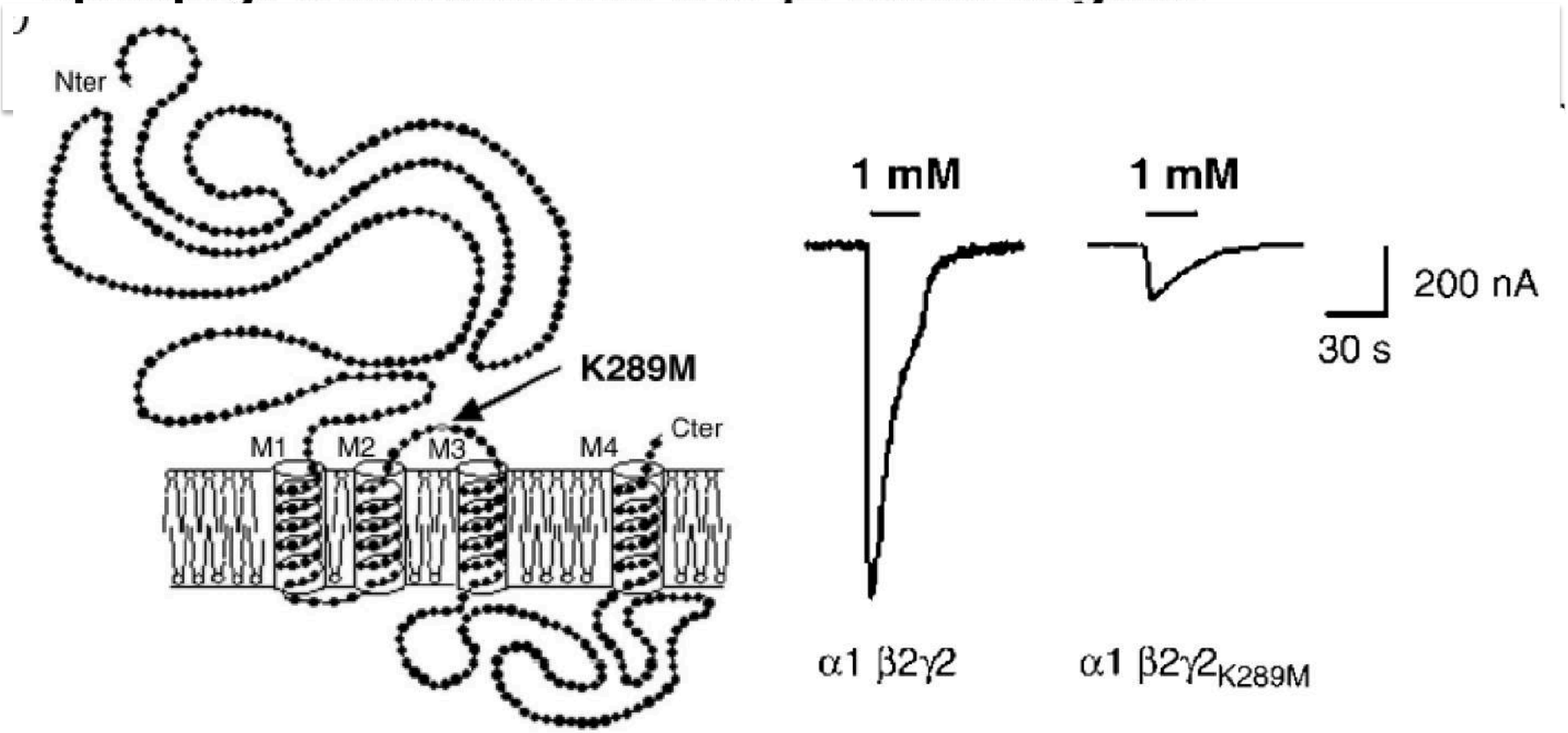
GABAергический пресинаптический нейрон

Постсинаптический нейрон



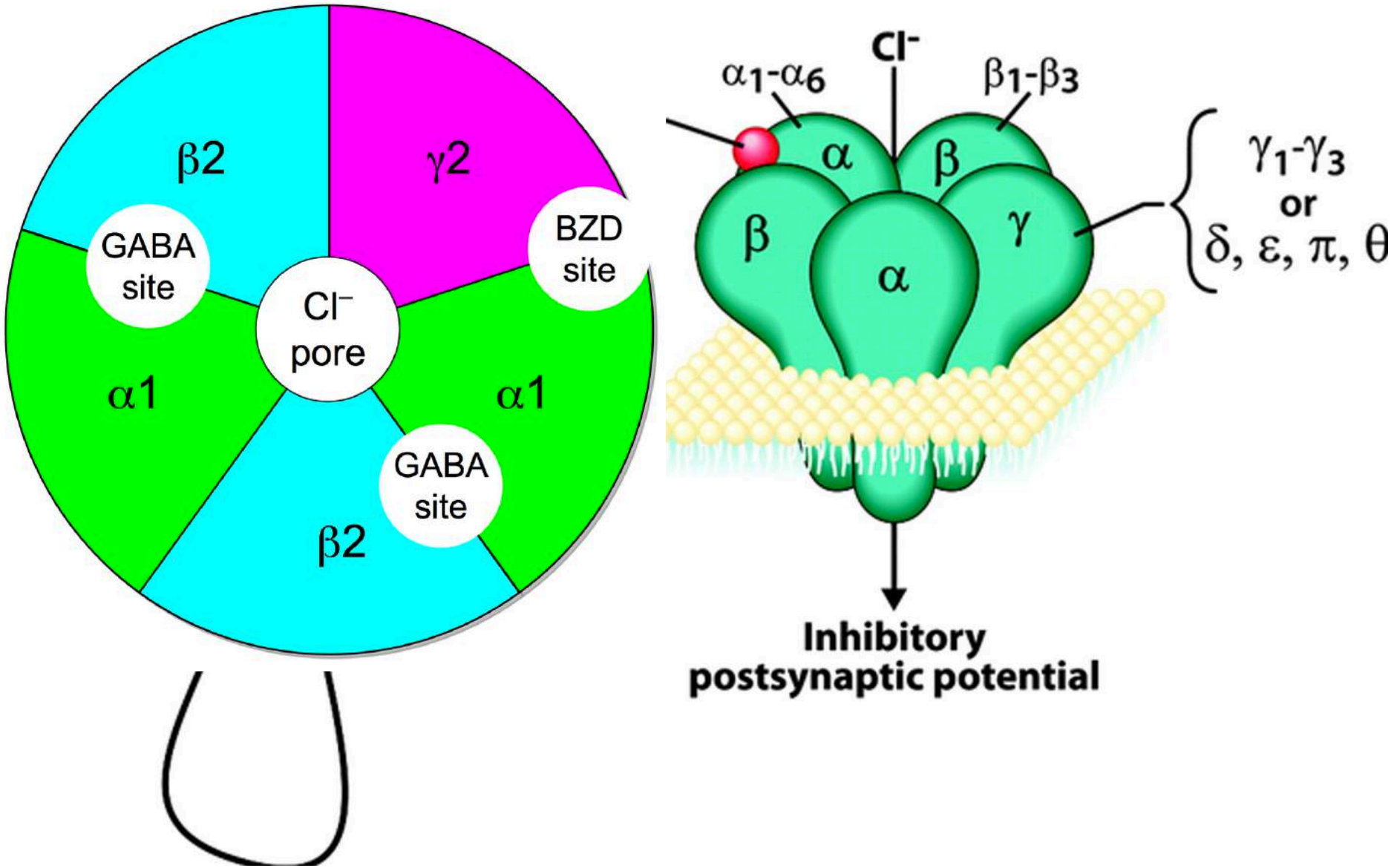
Generalized epilepsy with febrile seizures plus (GEFS+)

First genetic evidence of $GABA_A$ receptor dysfunction in epilepsy: a mutation in the γ2-subunit gene

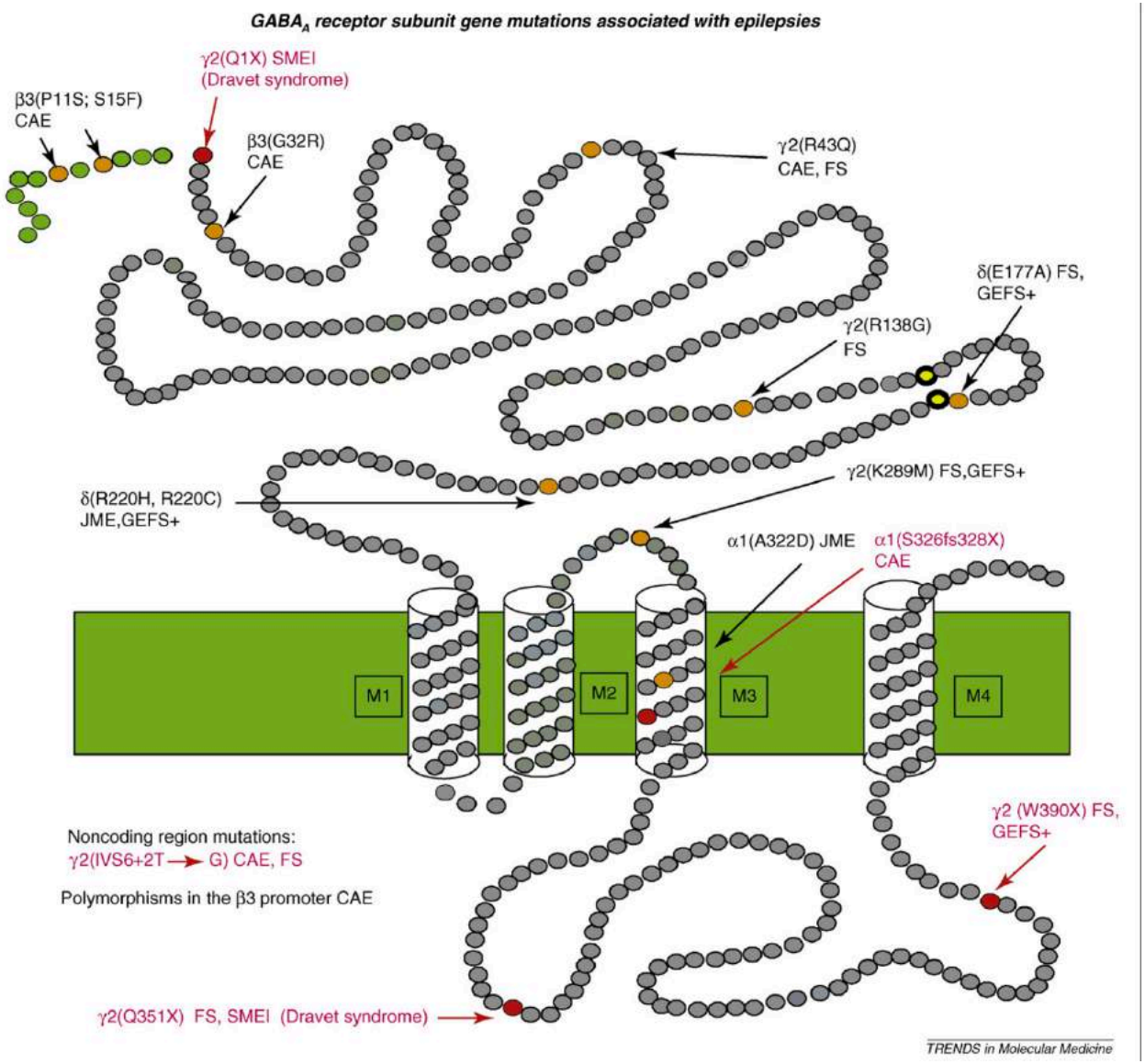


Baulac et al., Nature Genet., 2001

Структурная организация ГАМК рецепторов



Мутации ГАМК$_A$ рецептора приводящие к эпилепсии



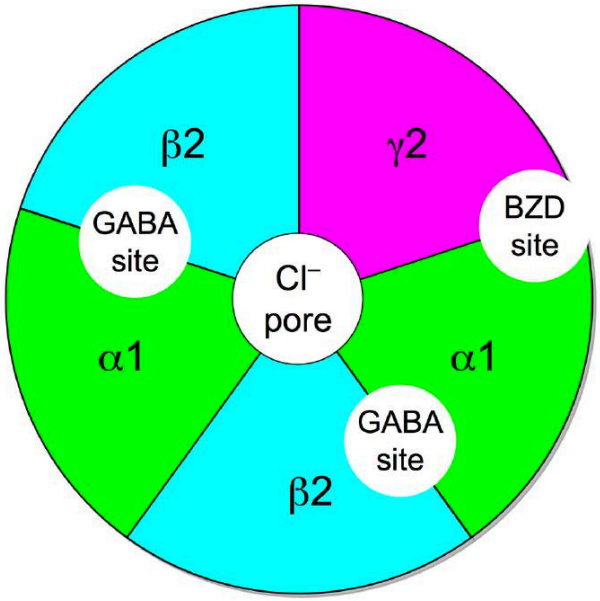
м

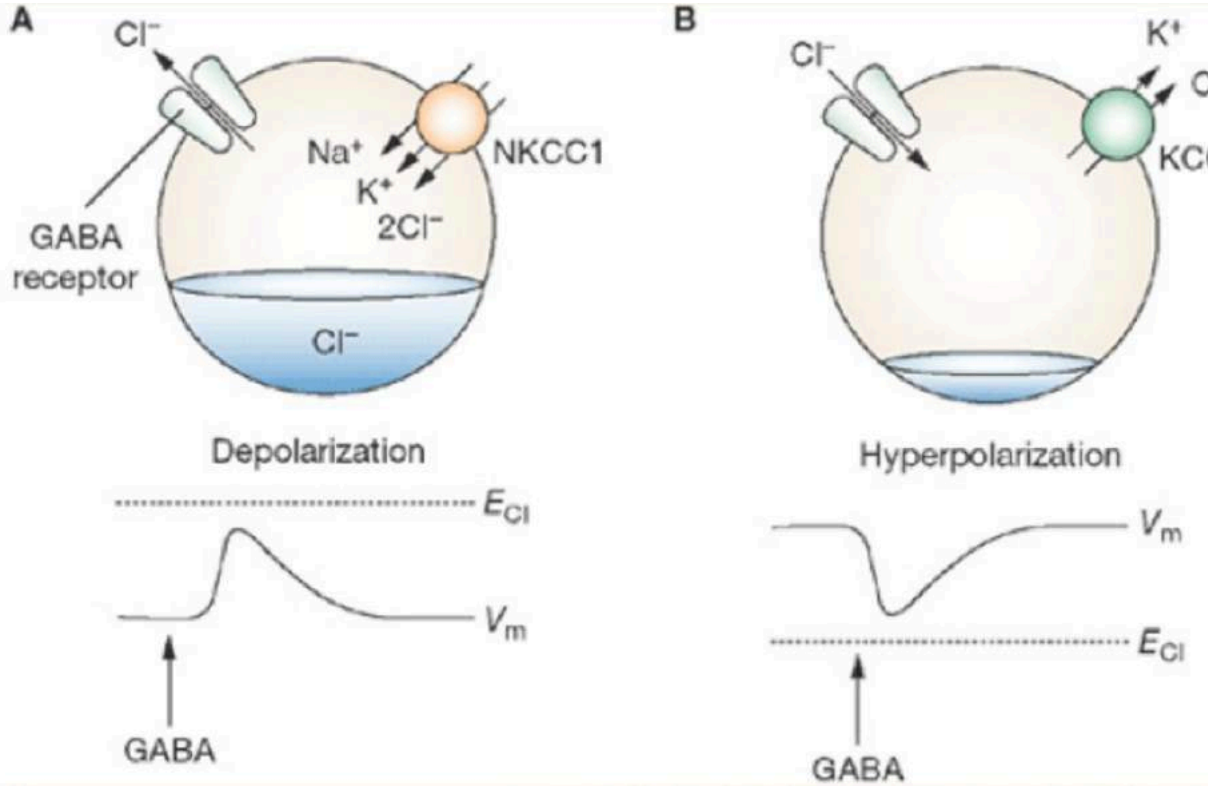
ия KCC2

$GABA_AR$ dysfunction in epilepsy

- **Childhood absence epilepsy:**
  - premature stop codon (S326fs328X) in a1 GABA subunits (Maljevic et al., 2006)
  - (R46W) in α6 GABA (Hernandez et al., 2011)
  - beta 3 GABA (Tanaka et al., 2008)
  - truncated γ2 subunit (Tian et al., 2012)

Лечение



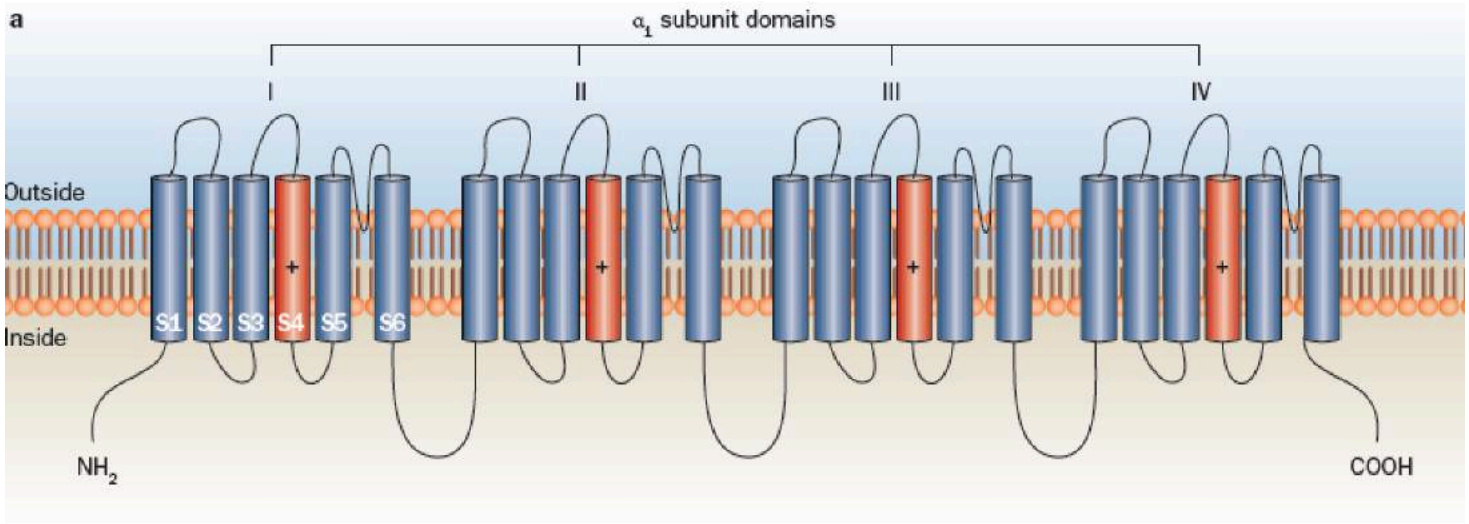


- Бензодиазепины:
  – диазепам, клоразепат, флуразепам
- ингибирование NKCC1 активация KCC2 транспортеров
- Хирургия

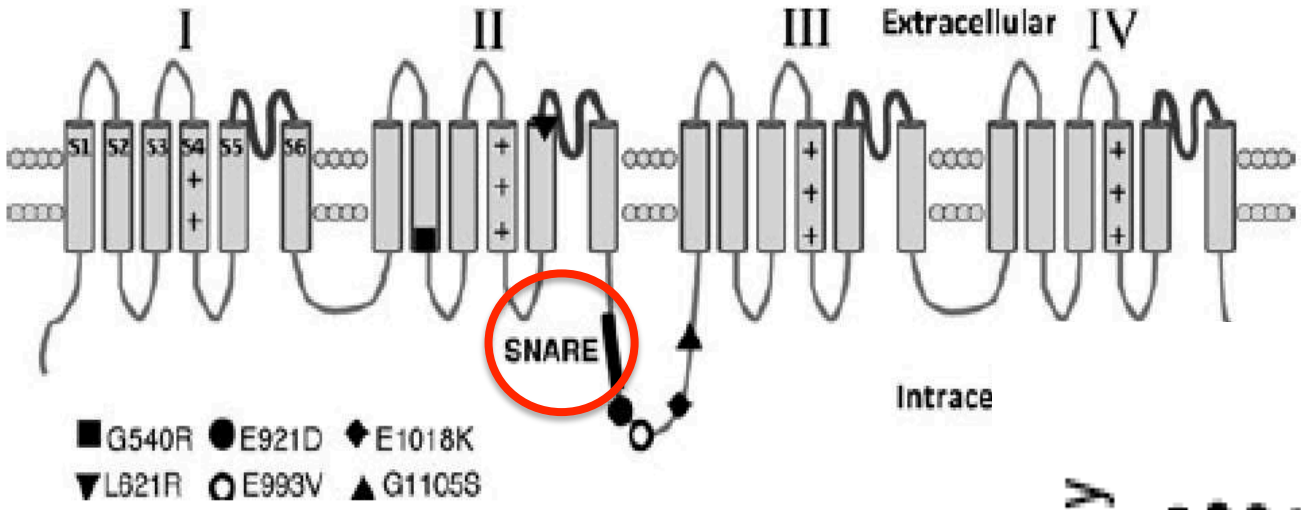
Absence epilepsy (“petite mal” seizure)

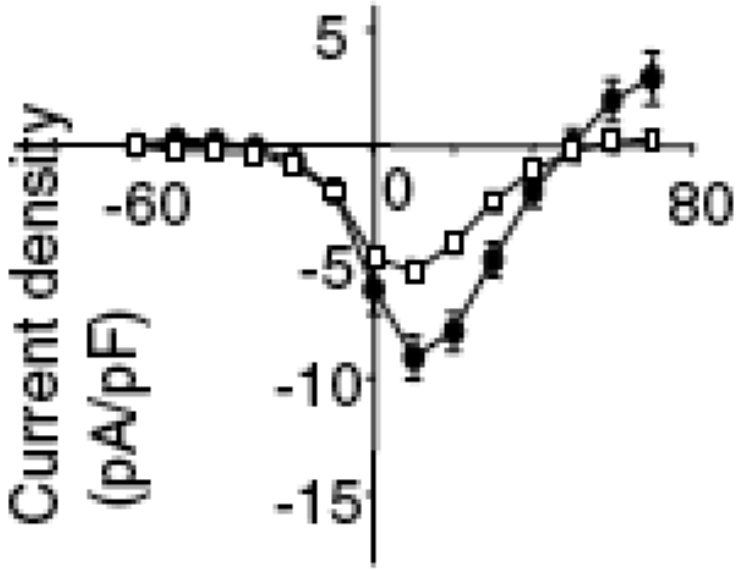
- two of every 1,000 people
- absence seizures are brief (< 20-30 sec)
- can occur 50-100 times a day
- results from an abnormal synchronization of the thalamocortical circuit

Эпилепсия отсутствия


a
α1 subunit domains
I
II
III
IV
Outside
Inside
S1
S2
S3
S4
S5
S6
+
NH2
COOH
b
α2
S–S
α1
Outside
Inside
I
II
III
IV
δ
β
c
S3
S2
S4
S6
S1
S5
Pore
I
II
III
IV

P/Q channel dysfunction may be linked to episodic ataxia and epilepsy



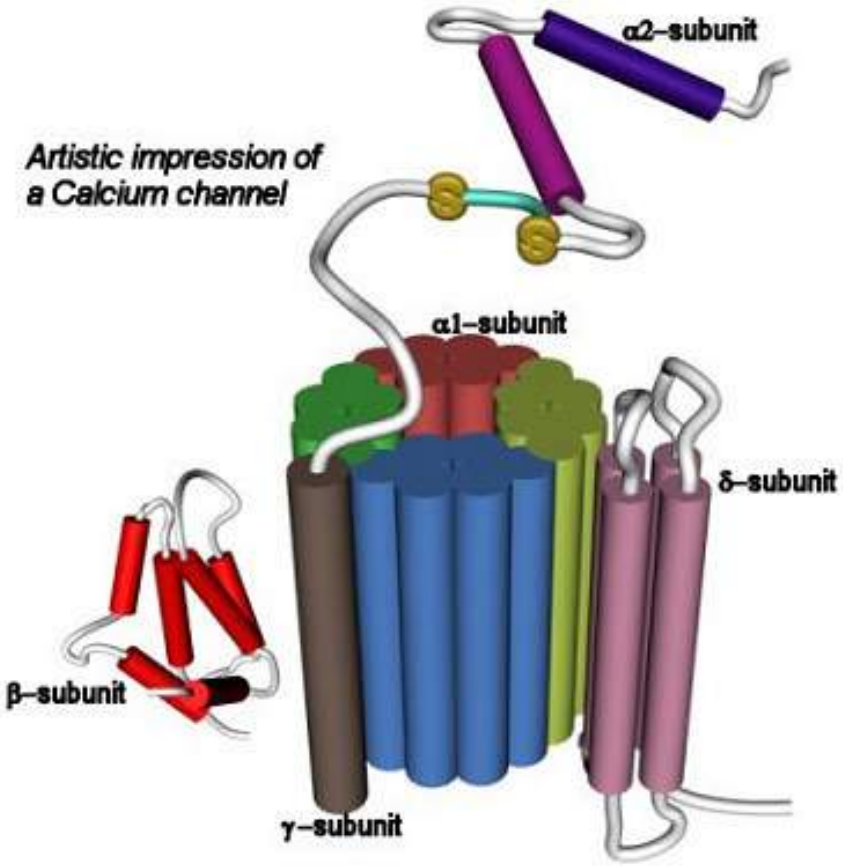


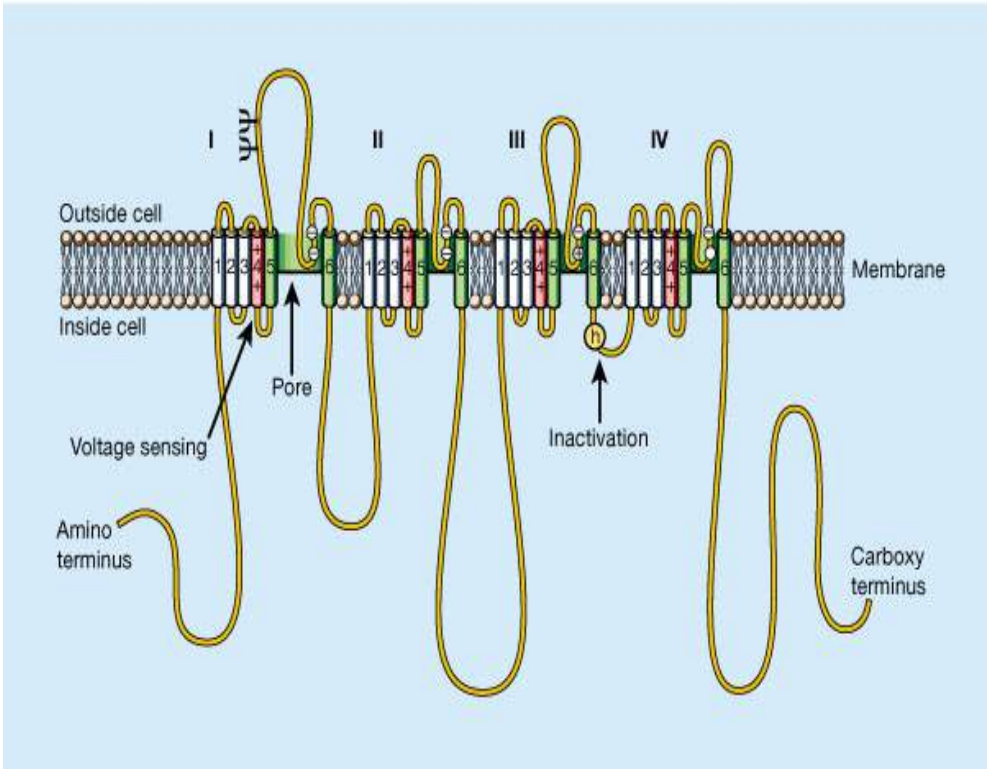
- 30% decrease of P/Q Ca^{2+} channels density

Treatment: pharlacologicald activators of Ca^{2+} channels

Rajakulendran et al., J.Physiol., 2010

VACC are heterologous multimers

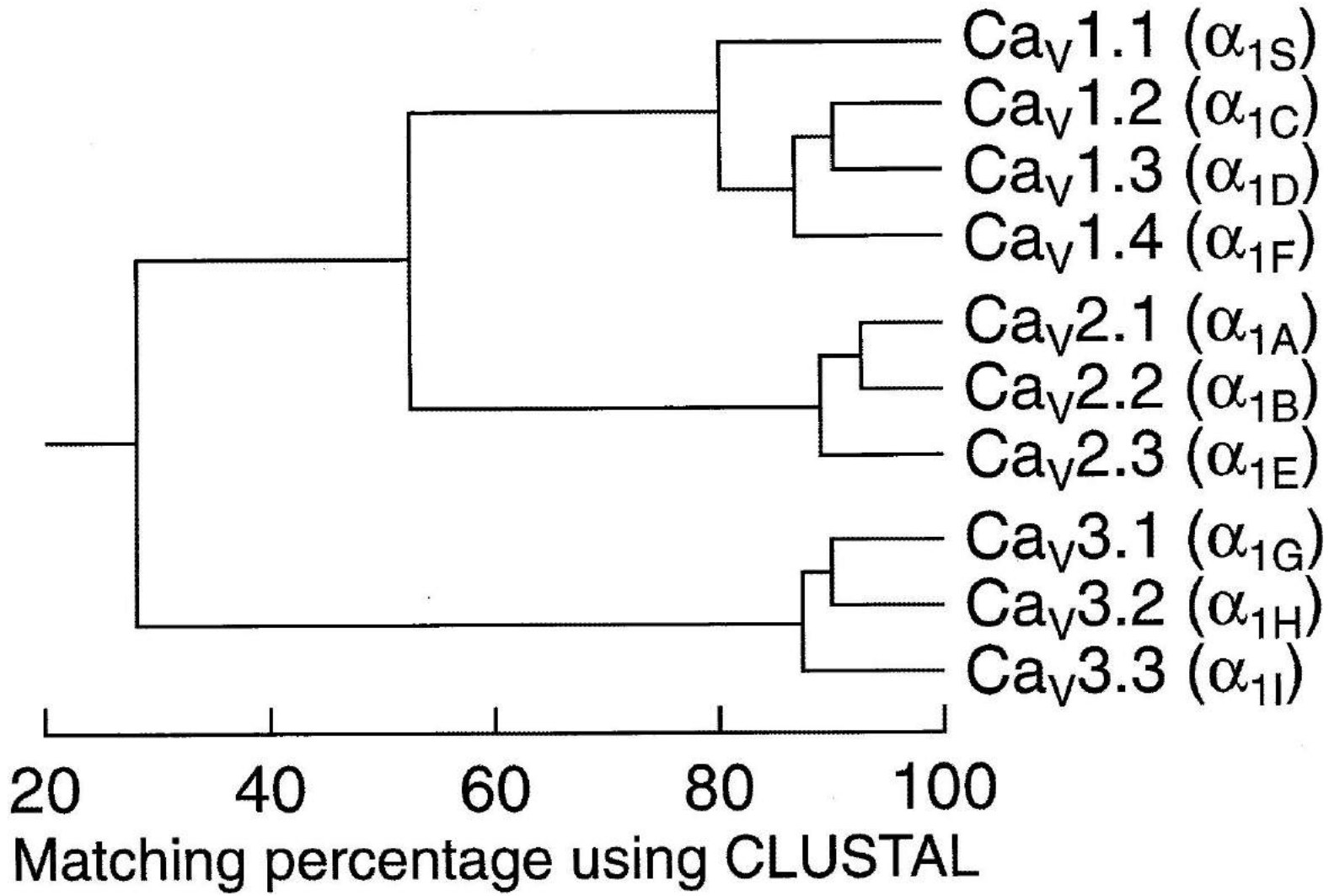




Each alpha1subunit has 4 homologous repeat domains, each comprised of 6 transmembrane segments

alpha1 modulated by other subunits

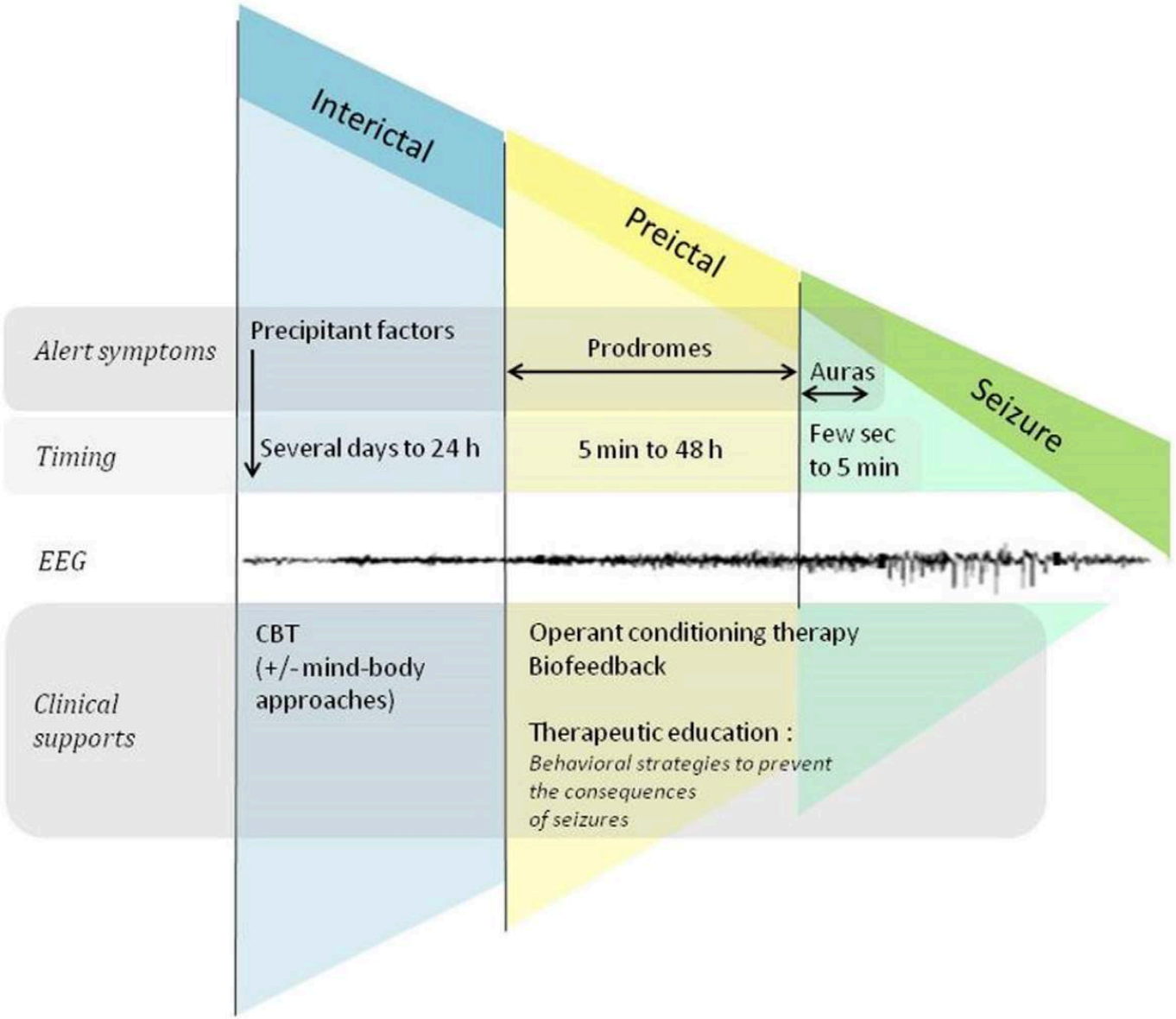
Channelopathies of Cav2.1



Three distinct diseases from distinct mutations of P/Q channel.

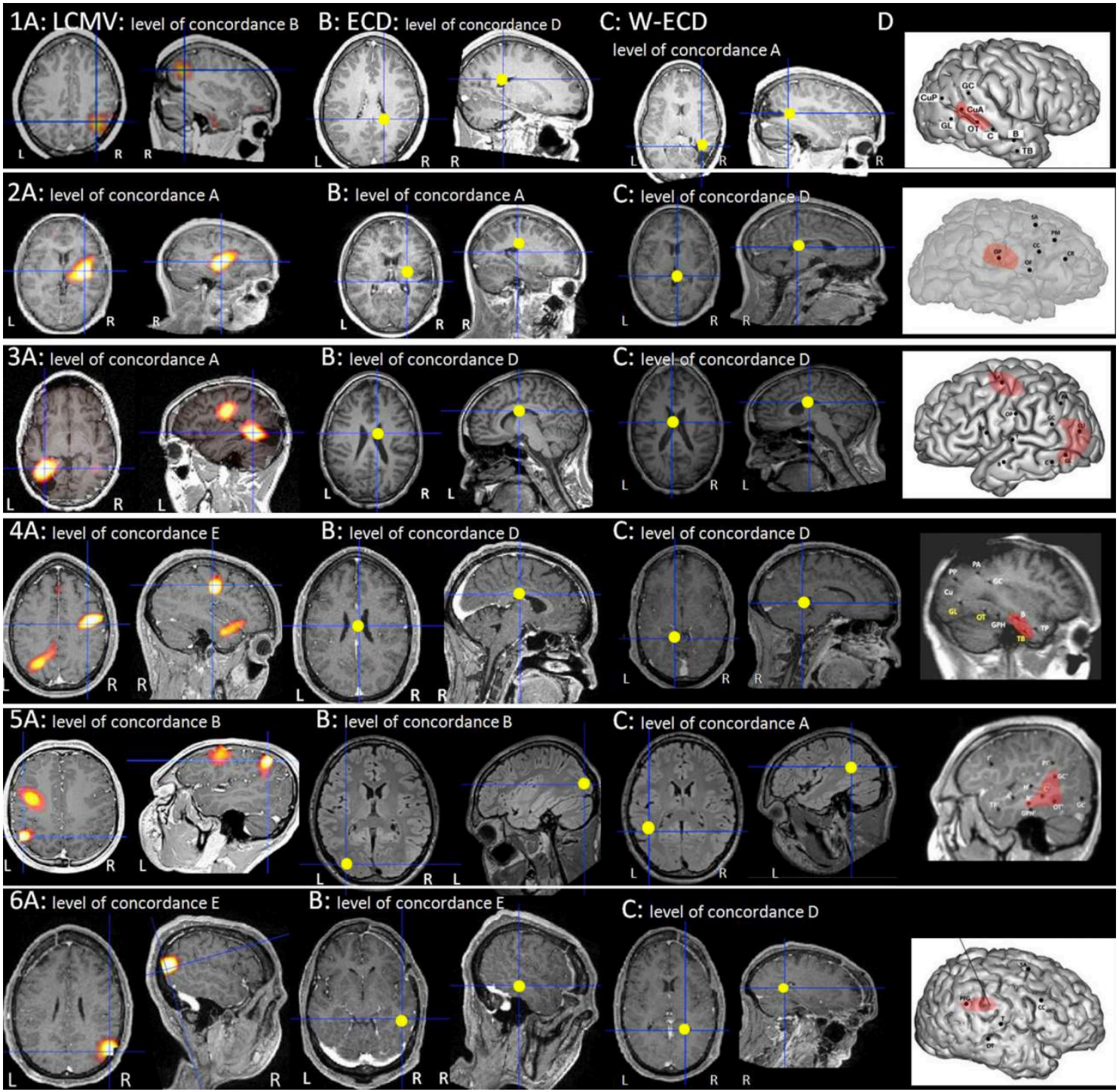
- **Familial Hemiplegic Migraine (FHM)** Intermittent headache with aura and paraesthesia, hemiplegia, hemianopia or dysphasia.
- **Episodic Ataxia type 2 (EA2)** Intermittent cerebellar disturbance incl, vertigo, diplopia and nystagmus. Mild progressive cerebellar atrophy. Rarely associated with absence seizures.
- **Spinocerebellar Ataxia type 6 (SCA6)** Progressive cerebellar degeneration.

Стадии больного эпилепсией



Поиск очагов воозбуждения

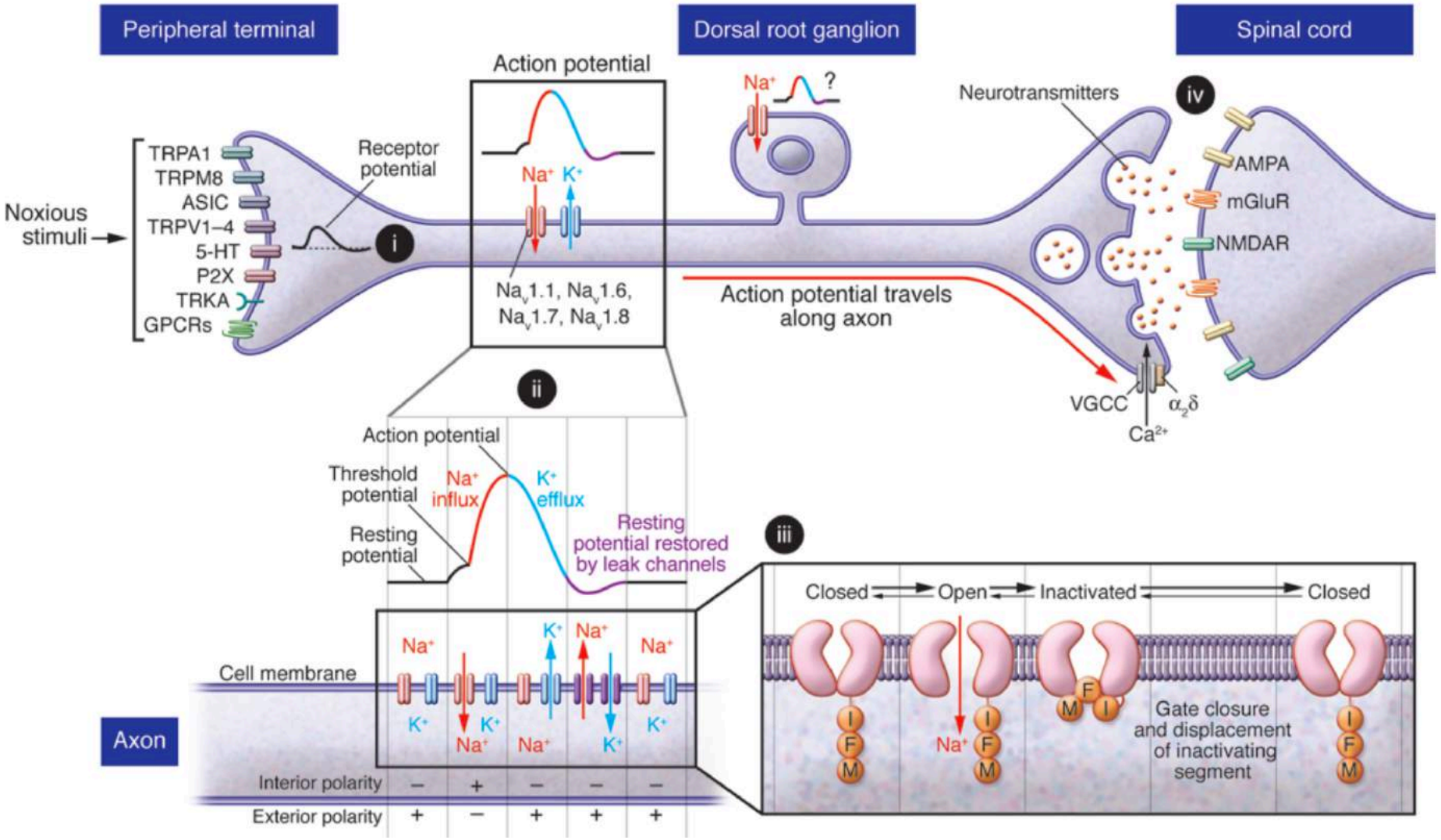
- МРТ
- ПЭТ
- ЕЕГ
- Микроэлектроды
- Модельный анализ


1A: LCMV: level of concordance B
B: ECD: level of concordance D
C: W-ECD
level of concordance A
D
2A: level of concordance A
B: level of concordance A
C: level of concordance D
3A: level of concordance A
B: level of concordance D
C: level of concordance D
4A: level of concordance E
B: level of concordance D
C: level of concordance D
5A: level of concordance B
B: level of concordance B
C: level of concordance A
6A: level of concordance E
B: level of concordance E
C: level of concordance D
L
R

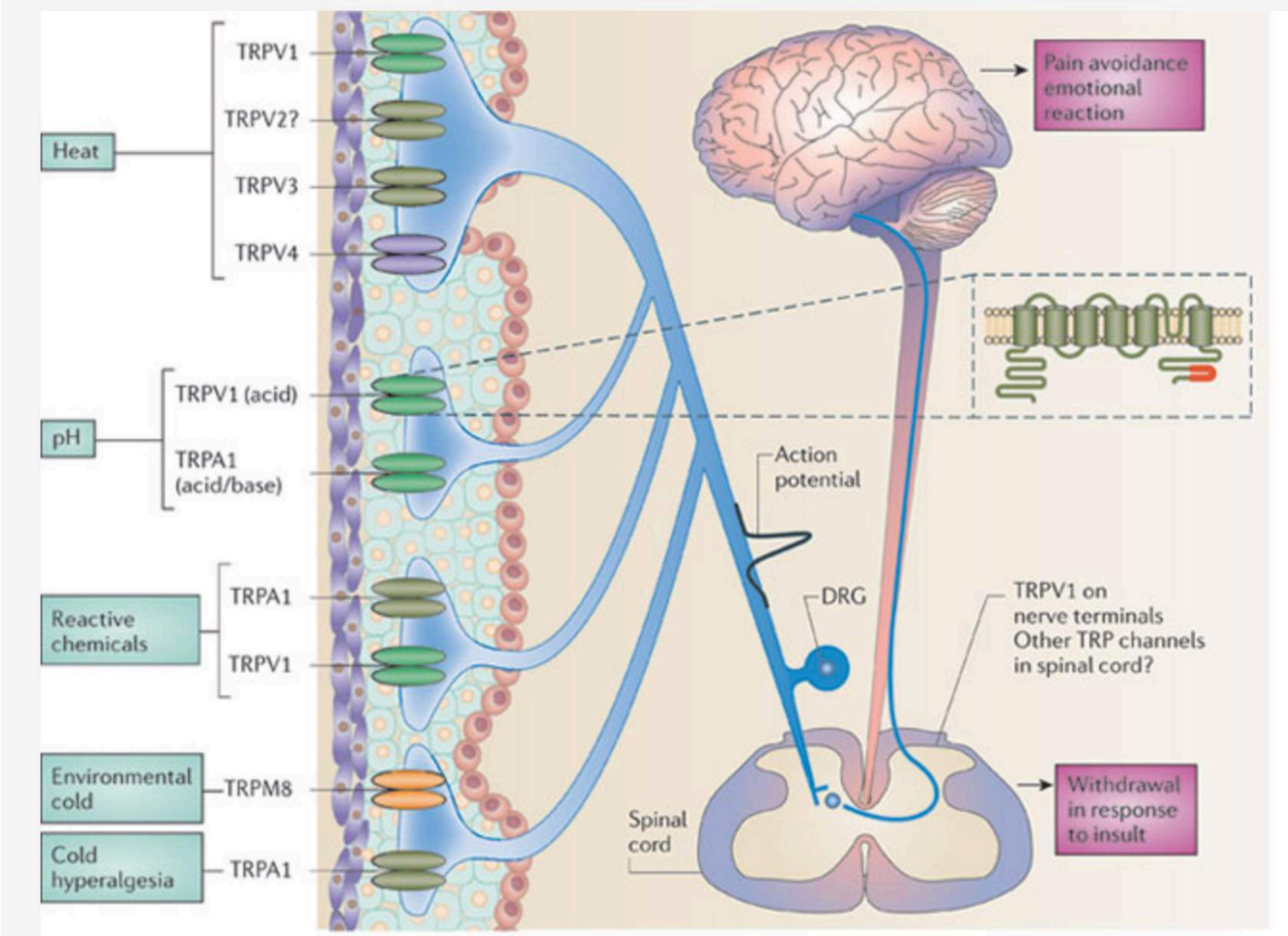
Лечение резистентных патологий

- Определение источника
- Хирургия

Боль и каналопатии



TRP каналы в нервной системе

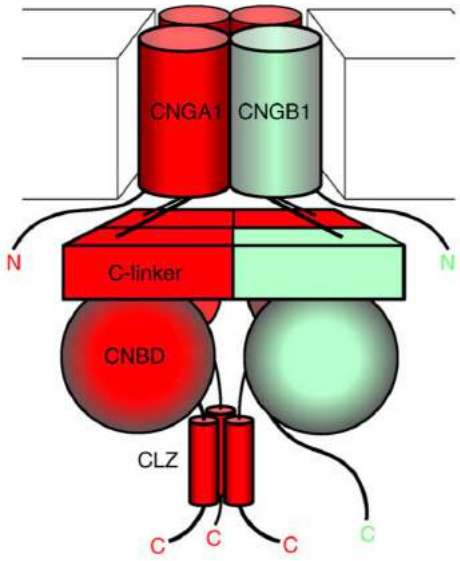


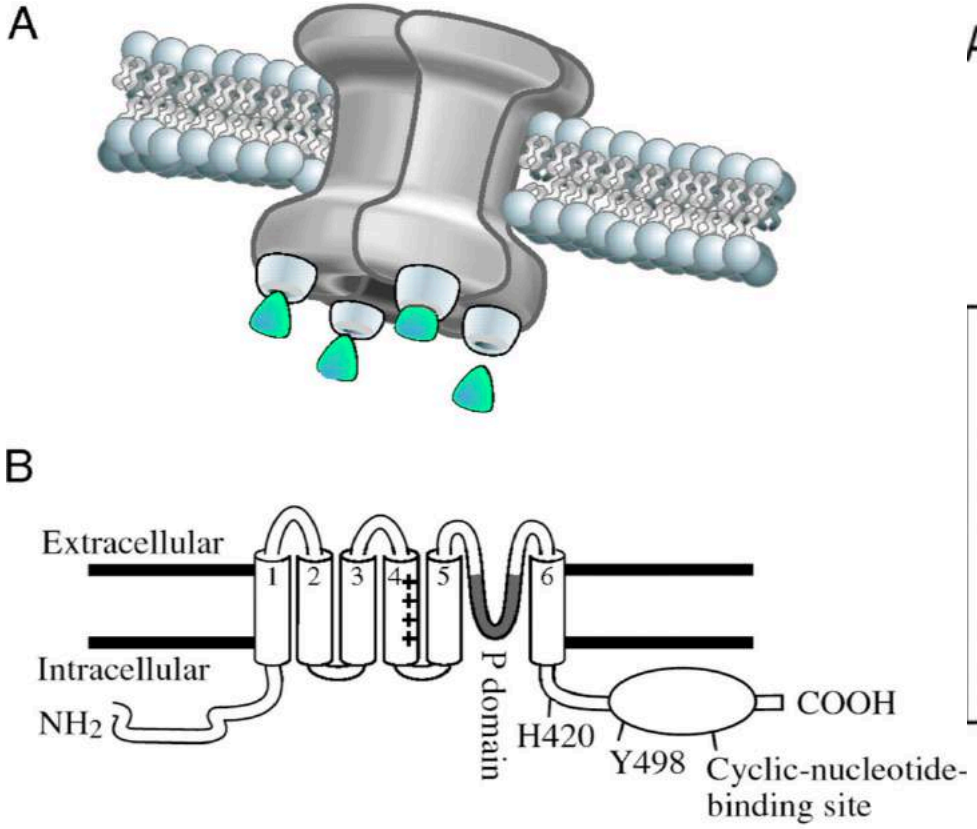
Боль и каналопатии

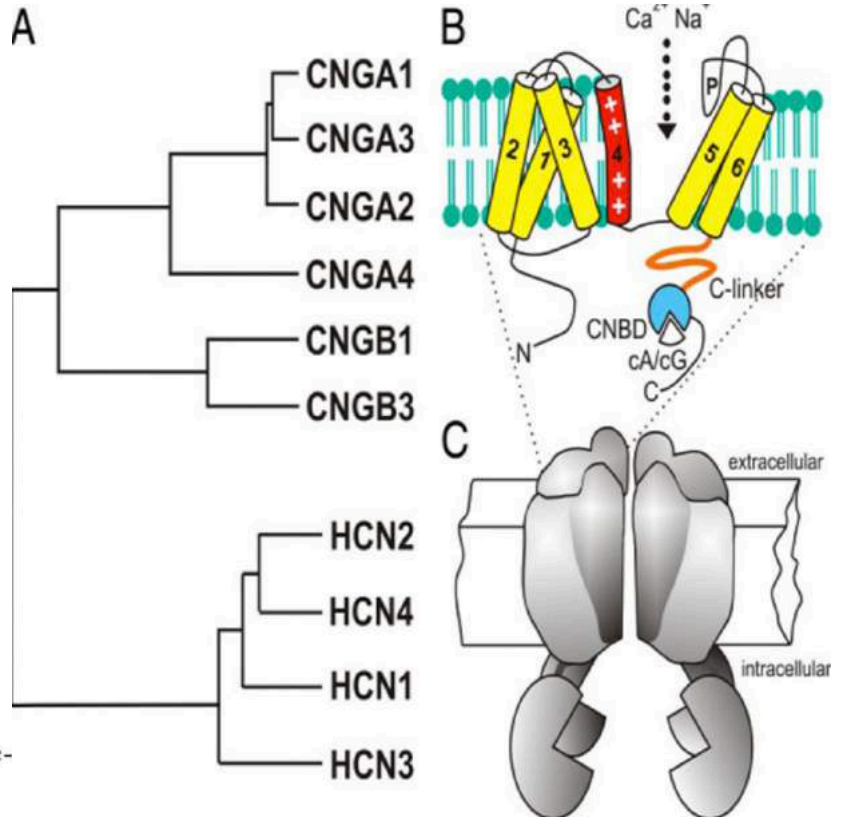
- G-белок активируемые каналы
- Агонист-активируемые каналы
- Потенциал-управляемые каналы
- TRP (transient receptor potential) - каналы

HCN каналы

- ионные каналы актируемые циклическими нуклеотидами (CNG1-4)
- активируемые гиперполяризацией нуклеотид-управляемые каналы (HCN1-4)

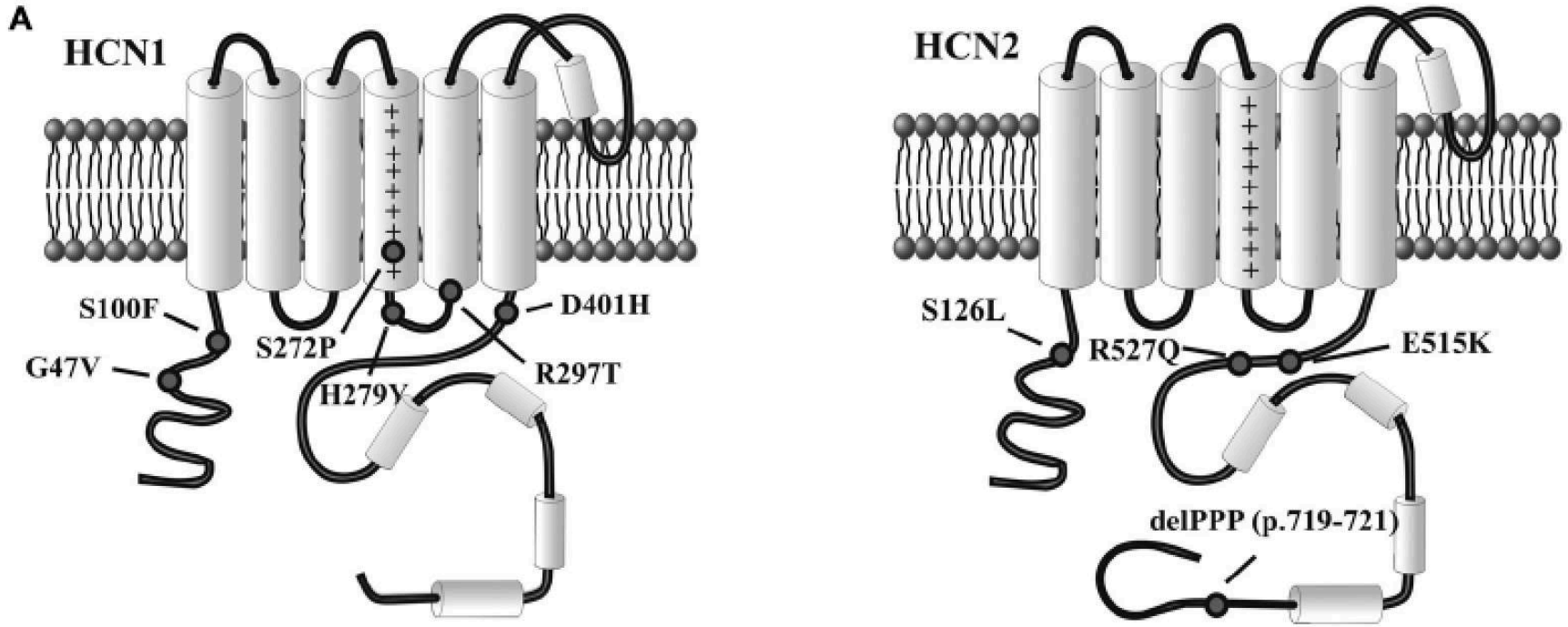






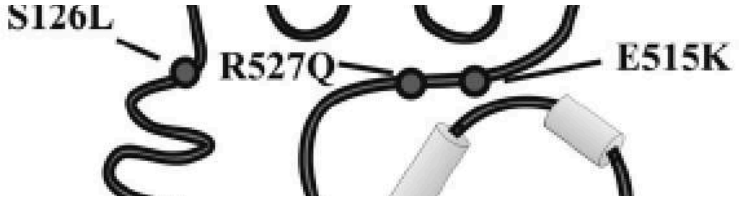
HCN каналопатии: эпилепсия

- HCN1: G47V S100F S272P H279Y R297T D401H
- HCN2: R527Q delPPP E515K S126L
- HCN2



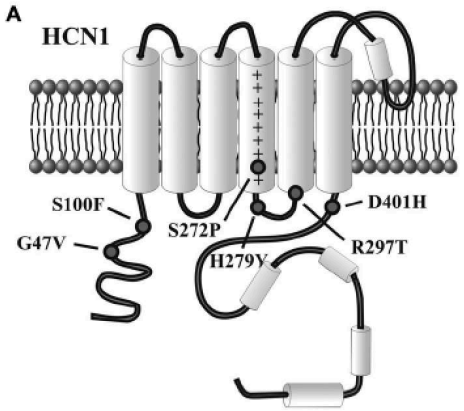
HCN каналопатии: эпилепсия

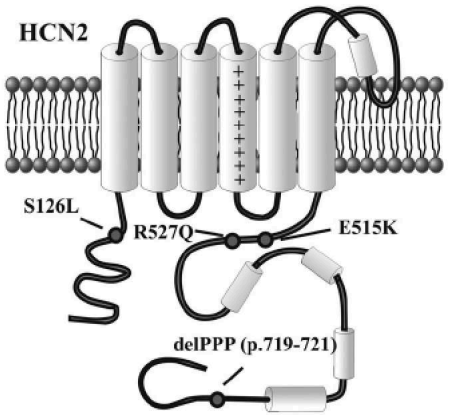
Gene	Mutations	Phenotype
HCN1	G47V S100F S272P H279Y R297T D401H	Early infantile epileptic encephalopathy (Dravet-like syndrome)
HCN2	R527Q	Idiopathic generalized epilepsy
	delPPP	Febrile seizures (FS); genetic epilepsy with FS plus (GEFS+)
	E515K	Idiopathic generalized epilepsy
	S126L	FS

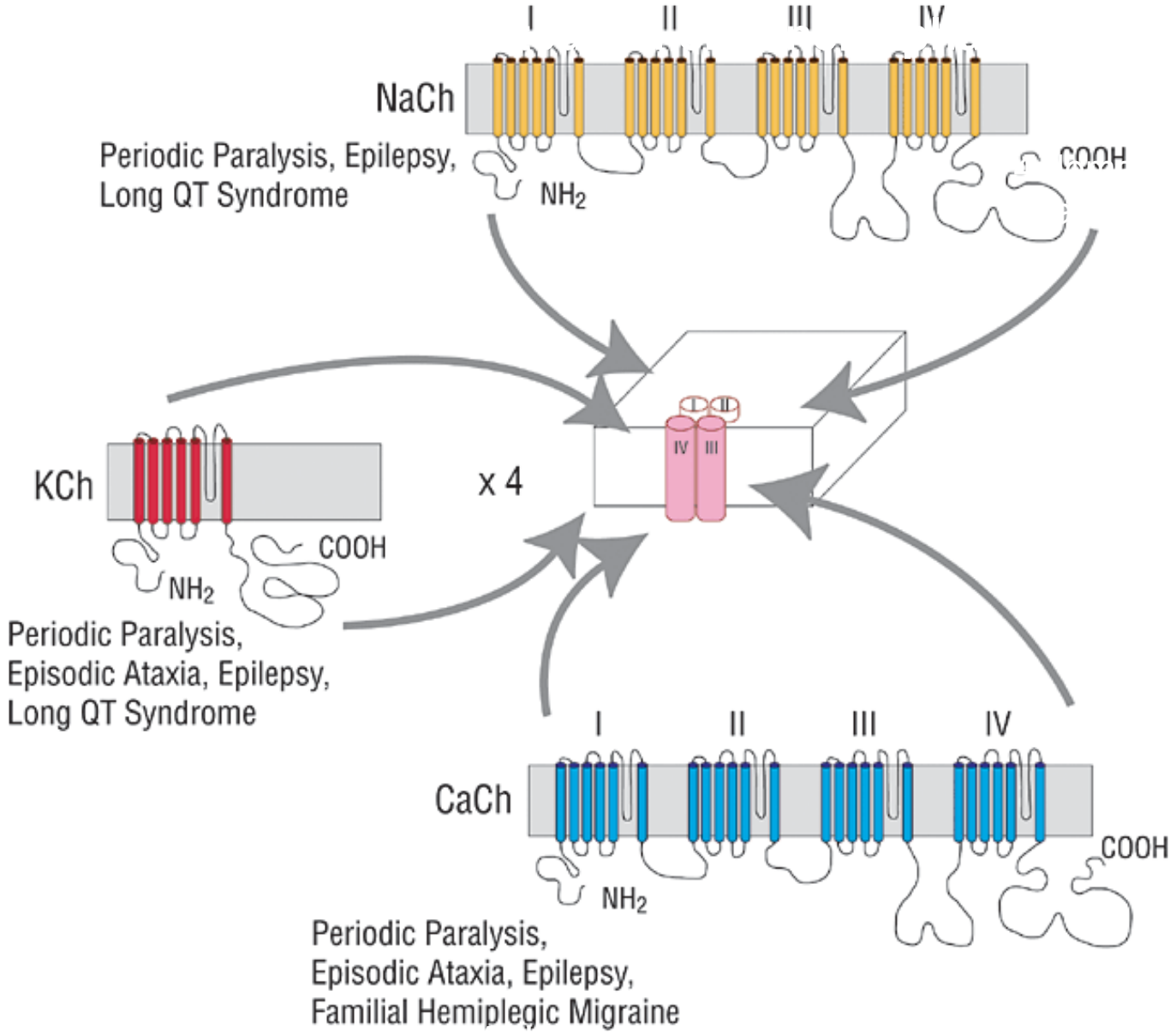


HCN каналопатии

- Эпилепсия:
  - **HCN1:** G47V S100F S272P H279Y R297T D401H
  - **HCN2:** R527Q delPPP E515K S126L
- Боль:
  - воспалительная (**HCN2)**
  - нейропатическая (**HCN1**)
- Болезнь Паркинсона
  - HCN2 и HCN4 в допам. нейронах среднего мозга







ARCHIVES OF
NEUROLOGY

На память

Каналопатии:

- Мутации многих классов ассоциируются с болезнями
- Разные мутации могут приводить к одним каналопатиям
- **Основные каналопатии эпилепсии:**
  - Na^+ channel α and β subunit
  - $GABA_A$ receptor
  - Ca^{2+} channels

Литература каналопатии

- Spillane, J., Kullmann, D. M., & Hanna, M. G. (2016). Genetic neurological channelopathies: molecular genetics and clinical phenotypes. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(1), 37-48.
- DiFrancesco, J. C., & DiFrancesco, D. (2015). Dysfunctional HCN ion channels in neurological diseases. *Frontiers in cellular neuroscience*, *6*.
- Moran, M. M., McAlexander, M. A., Bíró, T., & Szallasi, A. (2011). Transient receptor potential channels as therapeutic targets. *Nature Reviews Drug Discovery*, *10*(8), 601-620.

Table. Recognized Human Channelopathies

Disease	Gene	Ion Channel
Hyperkalemic periodic paralysis	*SCN4A*	Sodium channel
Paramyotonia congenital	*SCN4A*	Sodium channel
Potassium-aggravated myotonia	*SCN4A*	Sodium channel
Hypokalemic periodic paralysis type 1	*CACNLA3*	Calcium channel
Myotonia congenita	*CLCN1*	Chloride channel
Andersen-Tawil syndrome	*KCNJ2*	Potassium channel
Congenital myasthenic syndrome	*CHRNA*, *CHRNB*, *CHRNE*	Acetylcholine receptor
Episodic ataxia with myokymia (type 1)	*KCNA1*	Potassium channel
Episodic ataxia with nystagmus (type 2)	*CACNA1A*	Calcium channel
Familial hemiplegic migraine type 1	*CACNA1A*	Calcium channel
Familial hemiplegic migraine type 2	*ATP1A2*	Sodium-potassium transporter
Spinocerebellar ataxia type 6	*CACNA1A*	Calcium channel
Myasthenic syndromes	*CHRNA*, *CHRNB*, *CNRNE*	Acetylcholine receptor
Hereditary hyperekplexia	*GLRA1*	Glycine receptor
Long QT syndrome type 1	*KVLQT1*	Potassium channel
Long QT syndrome type 2	*HERG*	Potassium channel
Long QT syndrome type 3	*SCN5A*	Sodium channel
Long QT syndrome type 4	*ANK2*	Ankyrin B
Long QT syndrome type 5	*minK*	Potassium channel
Long QT syndrome type 7	*KCNJ2*	Potassium channel