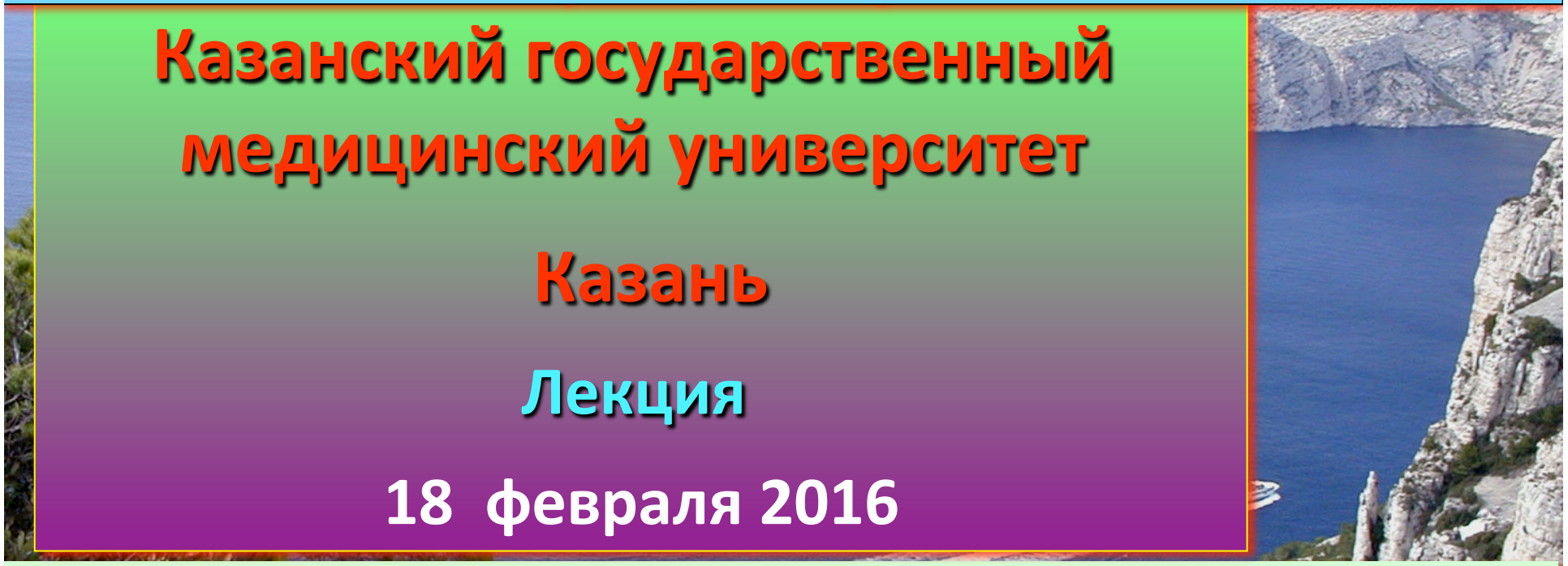
Молекулярная организация нервной системы

3-доп (21) Лекция: кластеризация рецепторов



Казанский государственный медицинский университет

Казань

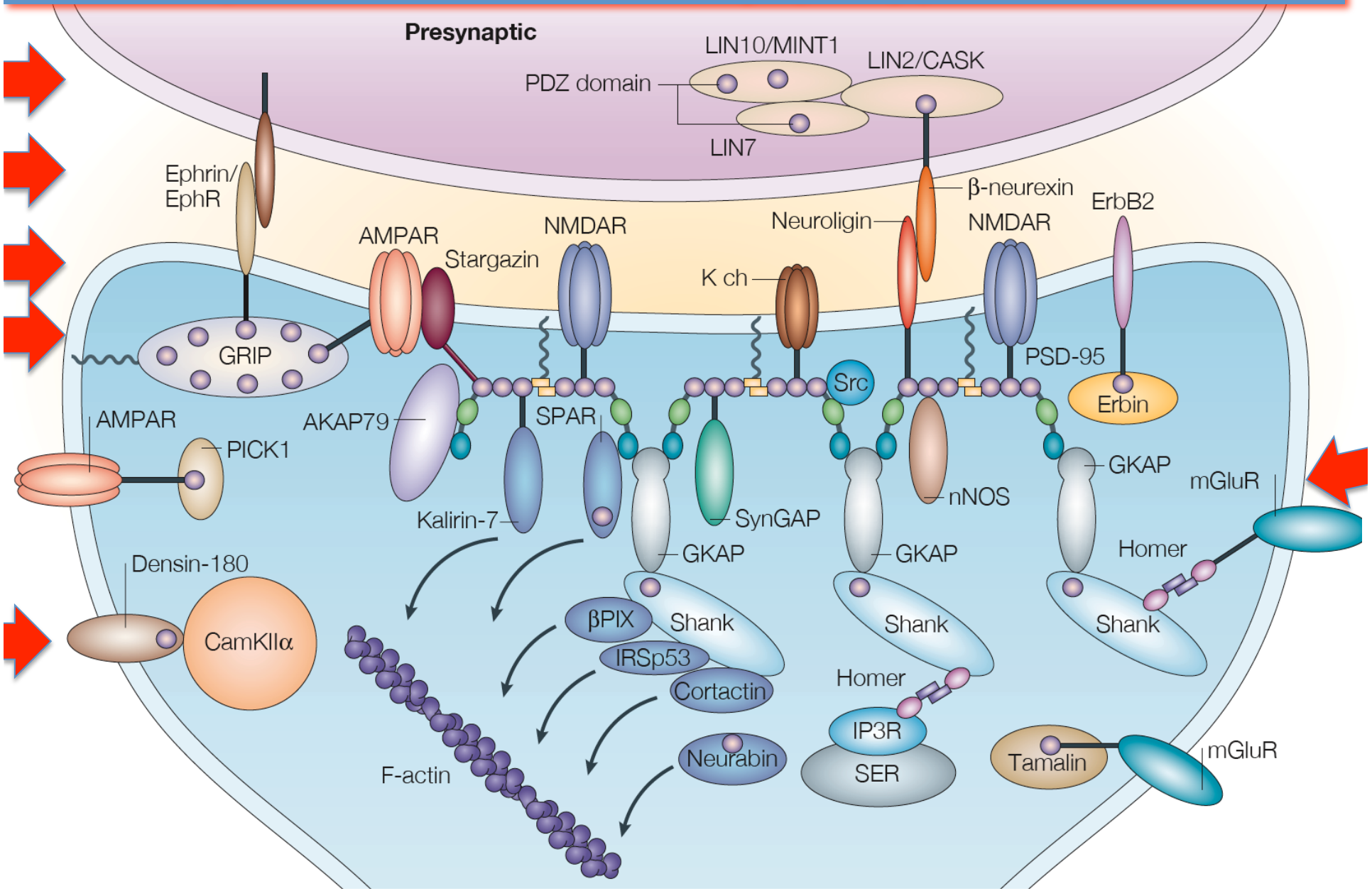
Лекция

18 февраля 2016

П.Д. Брежестовский

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

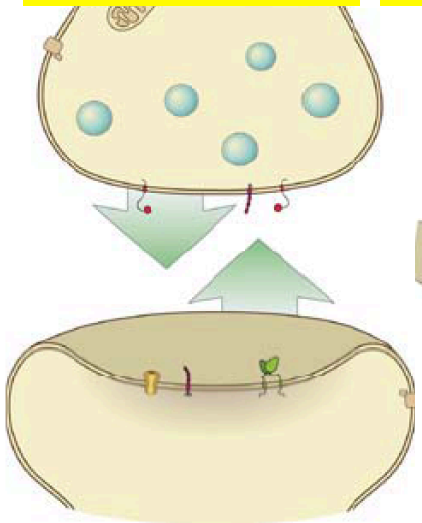
Схема белок-белковых взаимодействий между некоторыми компонентами формирующими синапс



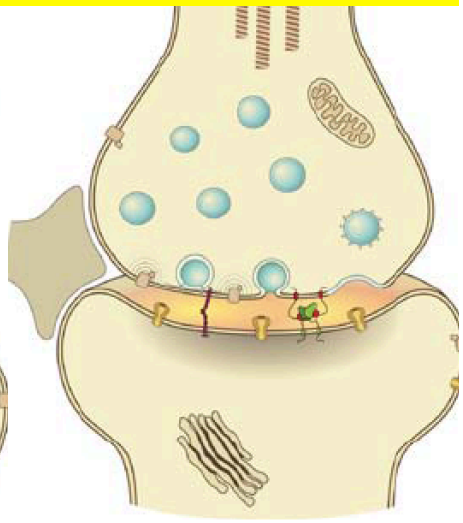
- формирование пре- и пост- синаптических контактов
- кластеризация рецепторов
- клеточная дифференцировка

Этапы установления и специализации синаптических контактов

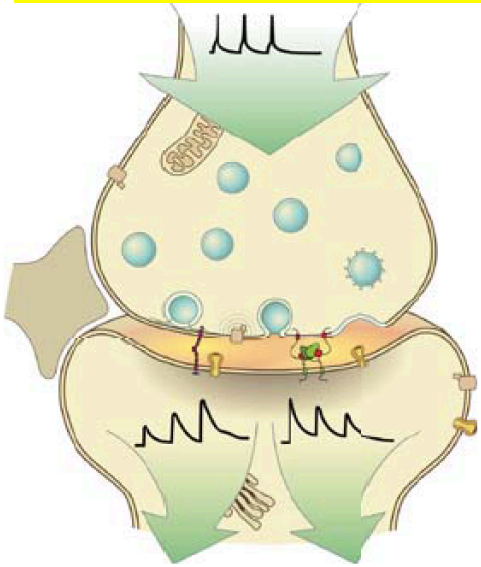
1. Поиск контакта



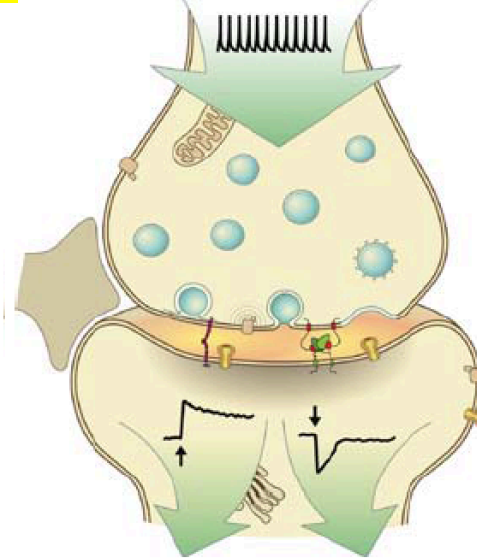
2. Установление контакта



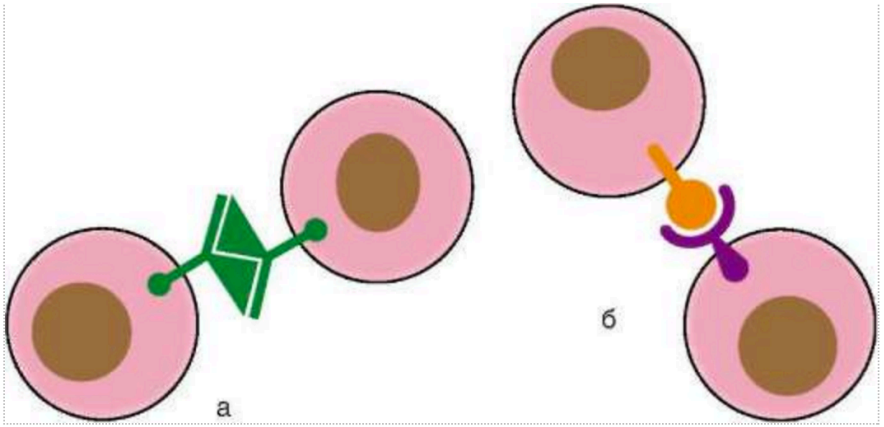
3. Специализация



4. Пластичность

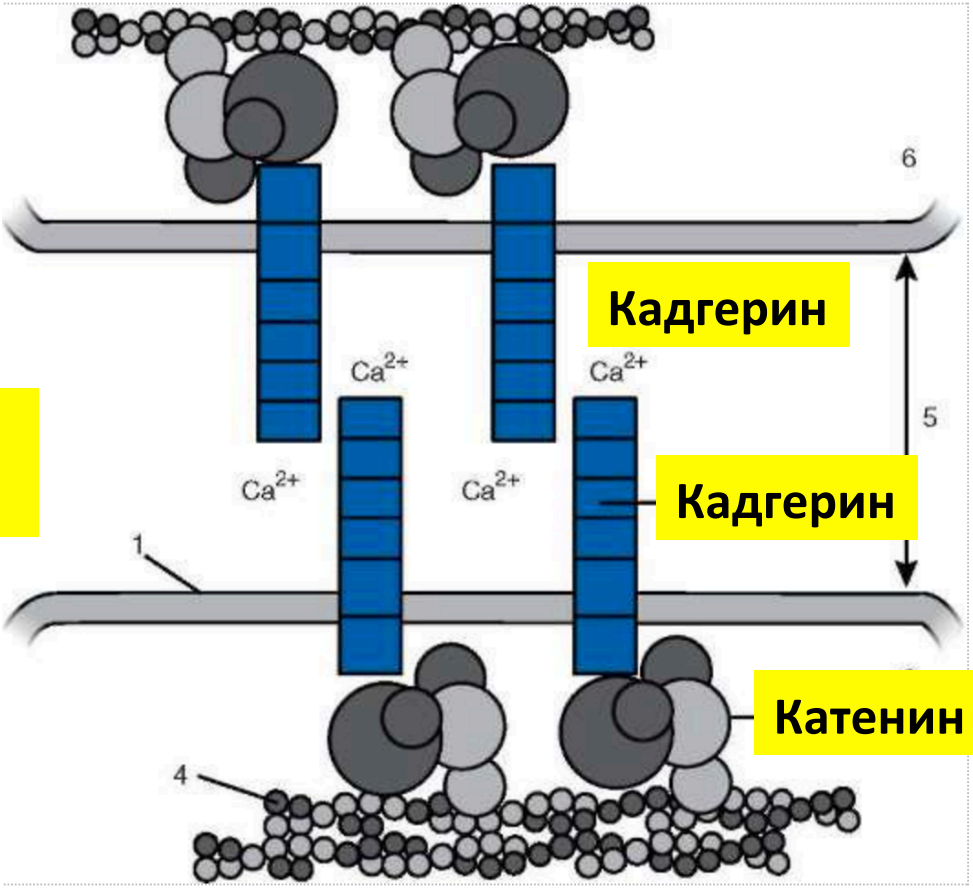


Гомофильные и гетерофильные механизмы адгезии белков

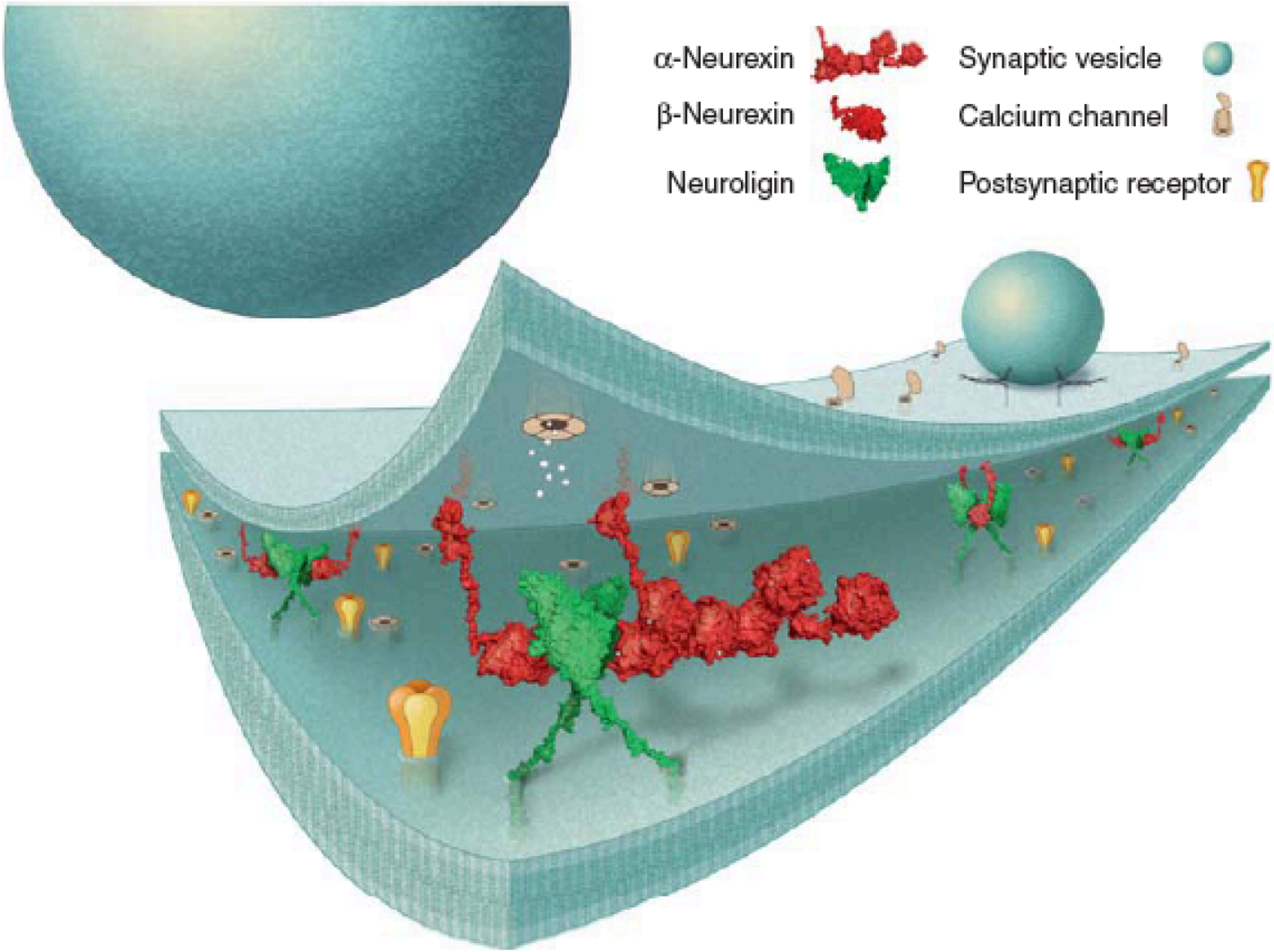


Гомофильные взаимодействия

Гетерофильные взаимодействия

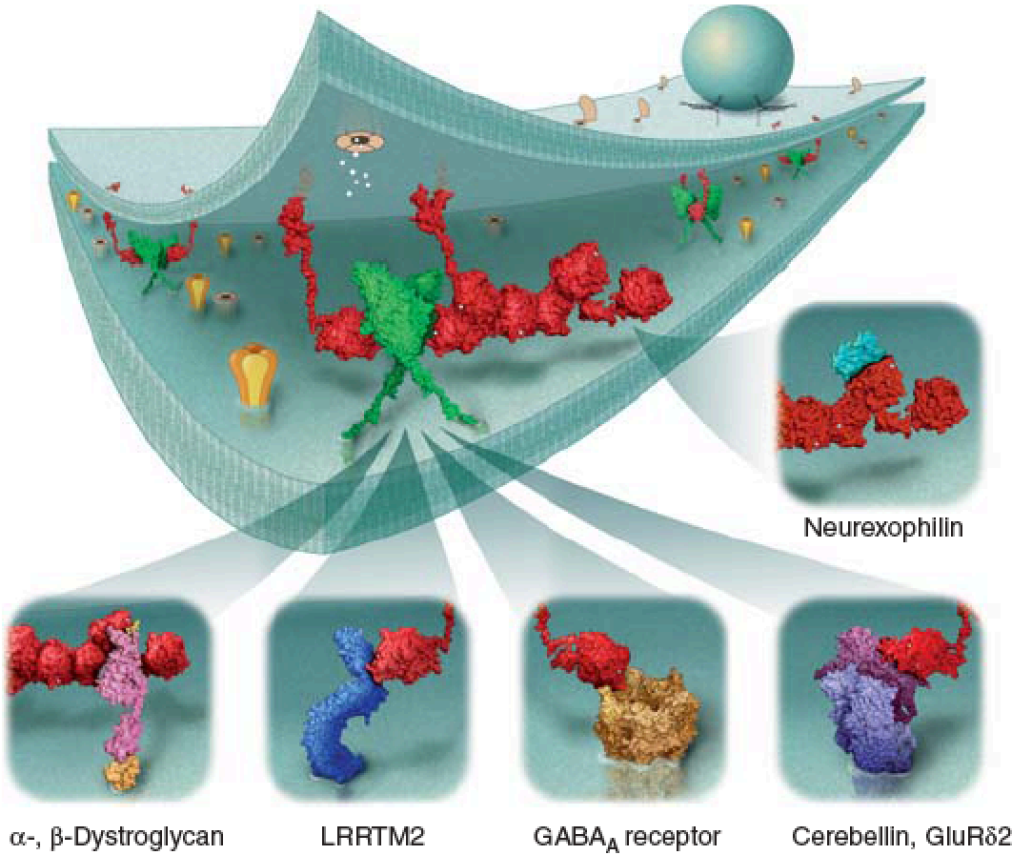


Нейрексины/нейролигины в формировании пре- пост-синаптических связей.



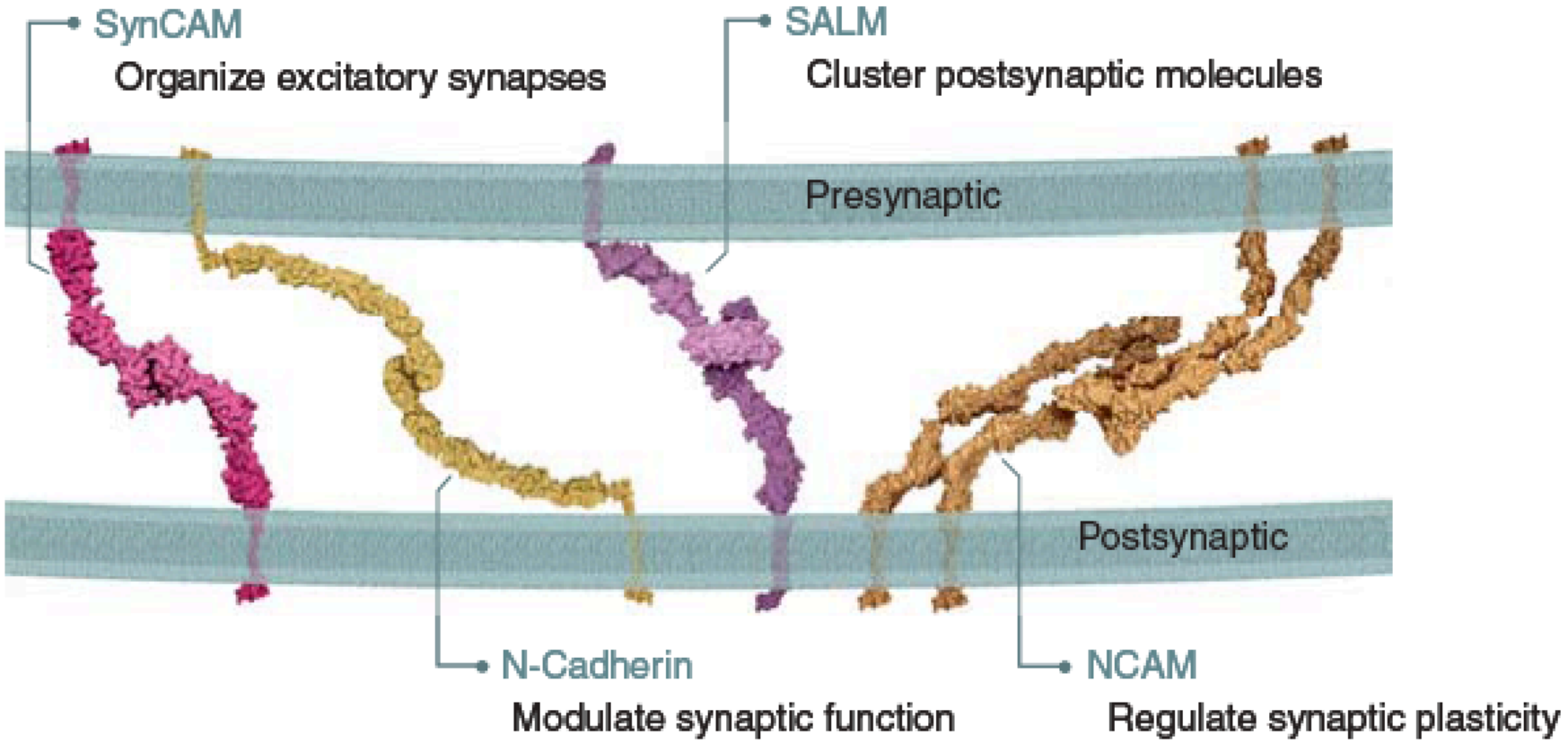
Missler et al., 2012

Нейрексины - синаптические якори

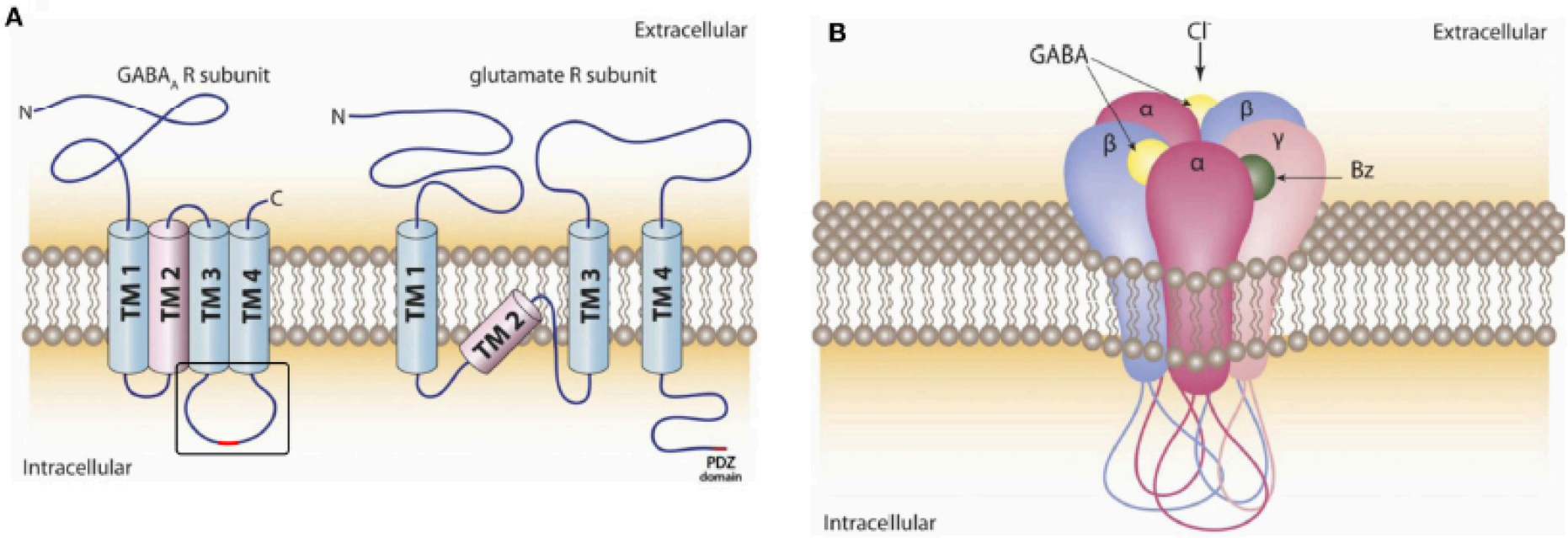


Missler et al., 2012

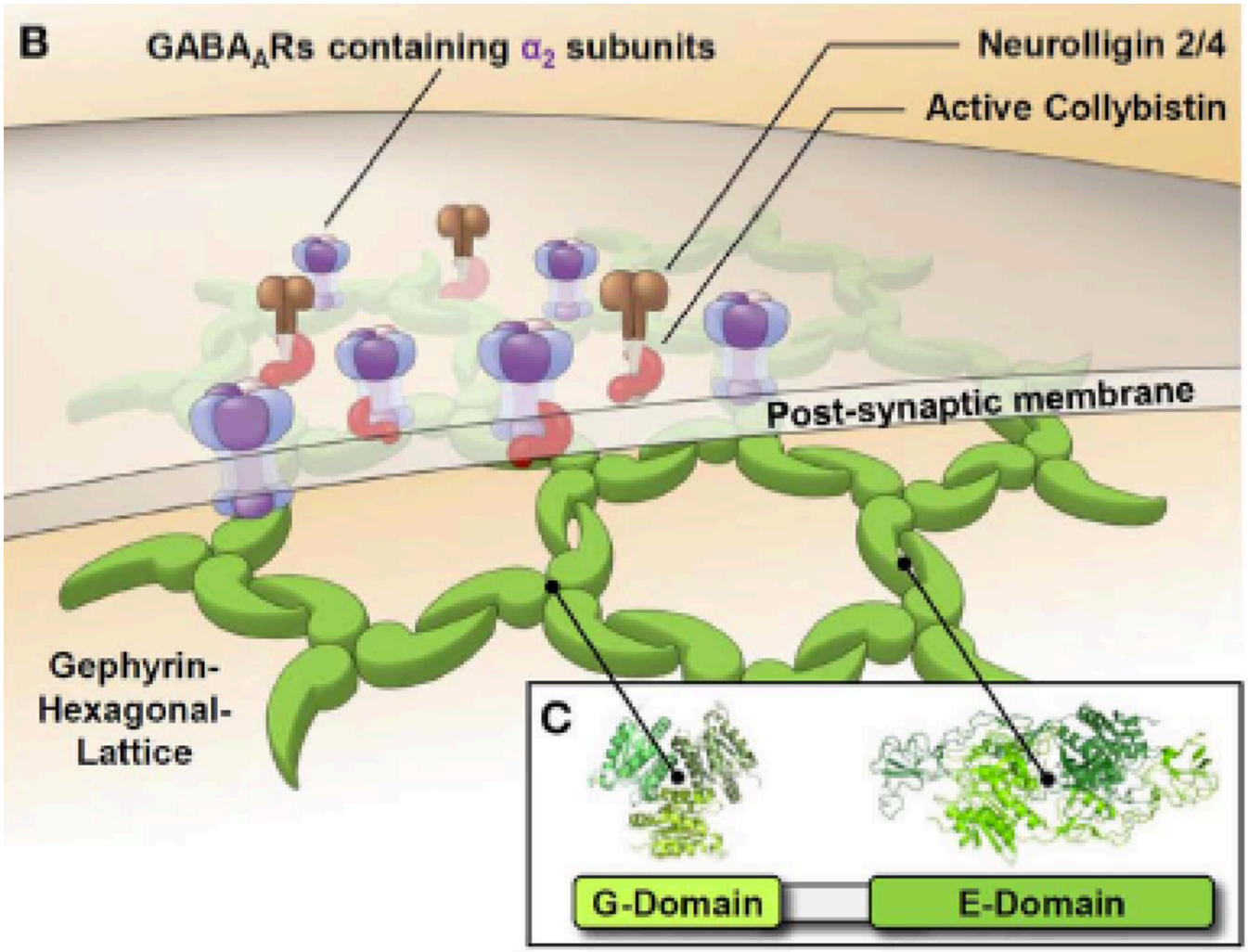
Белки синаптической адгензии



Missler et al., 2012


A
Extracellular
GABA$_A$ R subunit
glutamate R subunit
N
C
TM 1
TM 2
TM 3
TM 4
Intracellular
PDZ domain
B
Cl$^-$
GABA
α
β
γ
Bz
Extracellular
Intracellular

Формирование синаптических кластеров ГАМК рецепторов

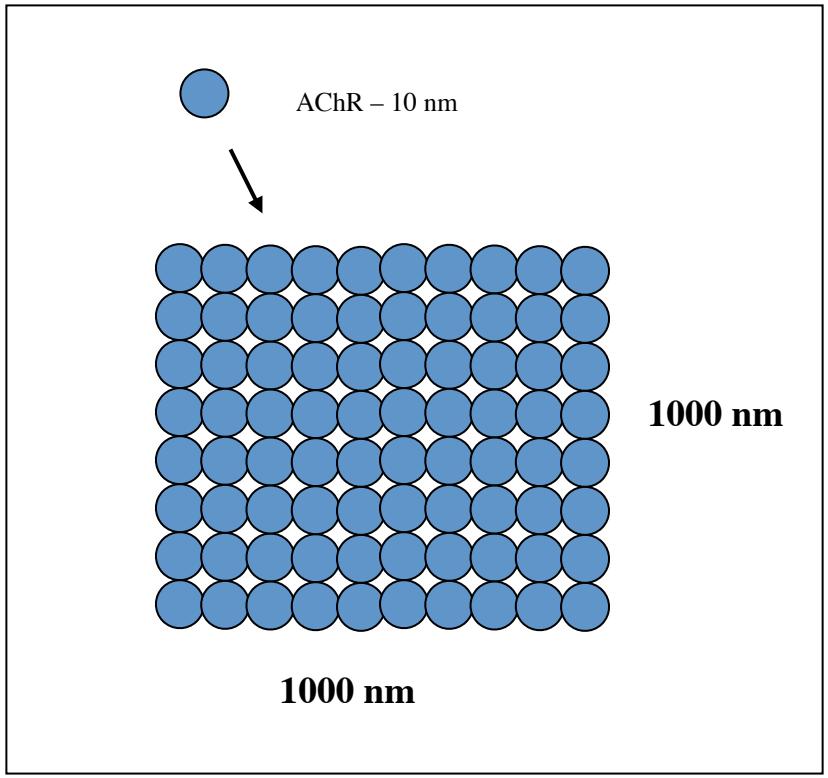


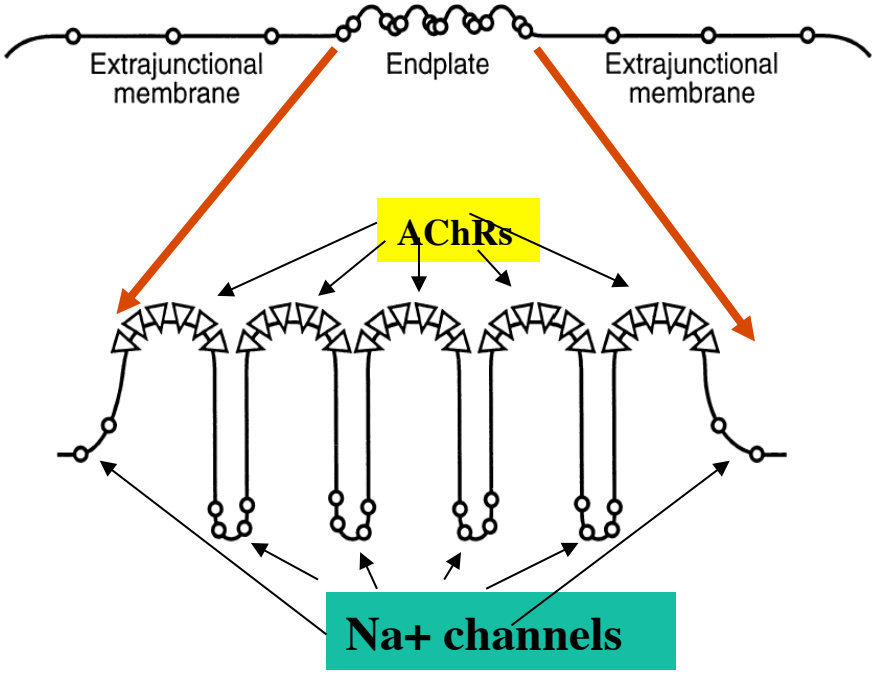
Tretter et al., 2012

Формирование АХ синапса

Density of AChRs on postsynaptic membrane:

10 000 AChRs/μm^2



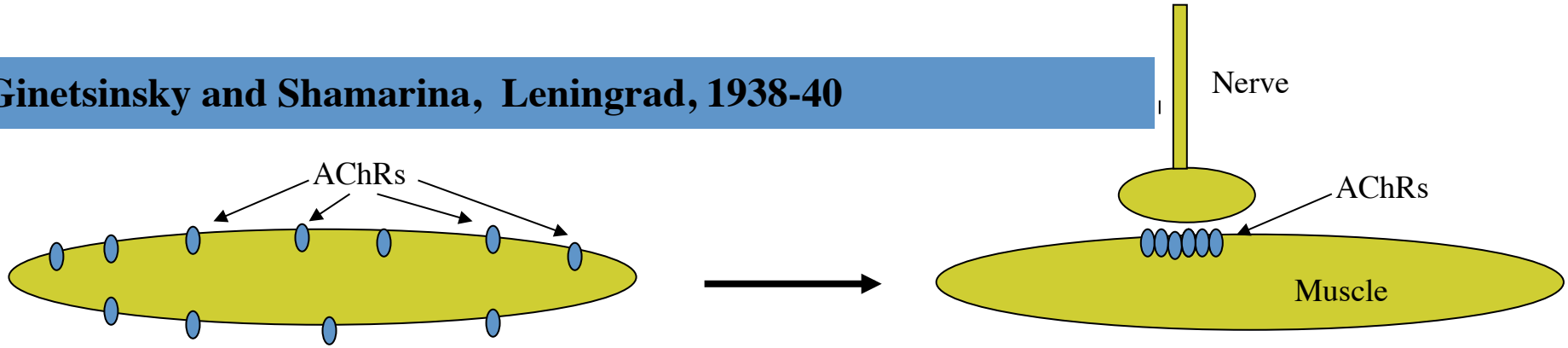


It should be a specific machinery

for clustering AChR channels on the postsynaptic membrane

Phenomenon of Embryonic and Denervated Muscle

Ginetsinsky and Shamarina, Leningrad, 1938-40



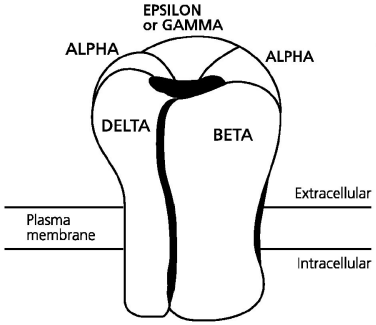
Embryonic and de-innervated muscle

-AChRs are diffused

-Kinetics is slow (10-100 ms)

-Single-channel condutance is small (40 pS)

-Subunit composition: αβγδ



Adult and innervated muscle

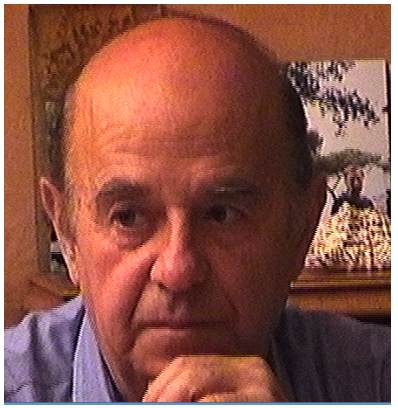
-AChRs are clustered

-Kinetics is rapid (1-5 ms)

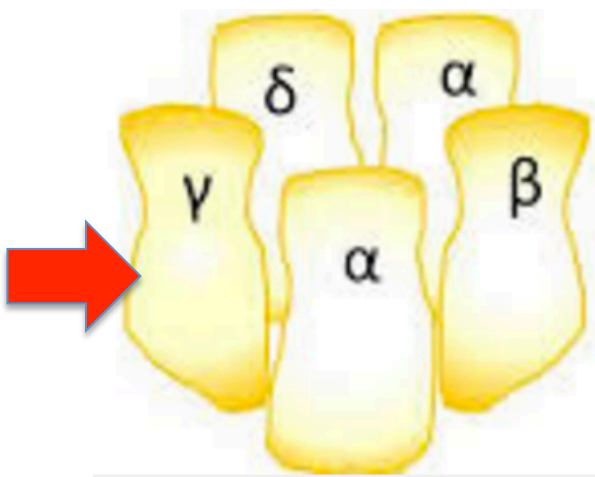
-Condutance is high (90 pS)

-Subunit composition:αβεδ

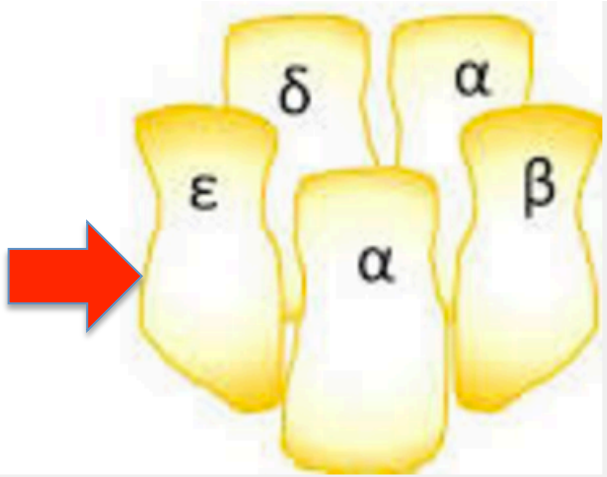
Ricardo MILEDI, London, 1960



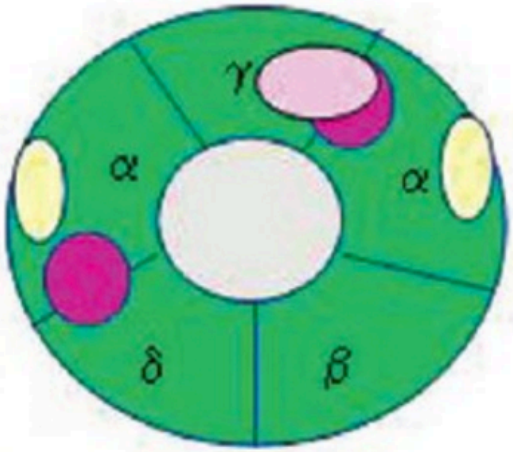
Эмбриональные клетки



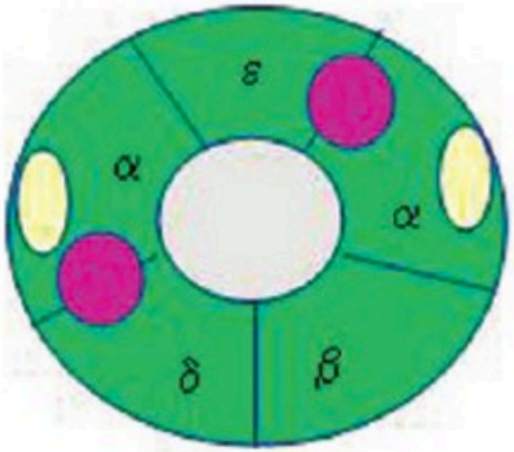
Взрослые клетки



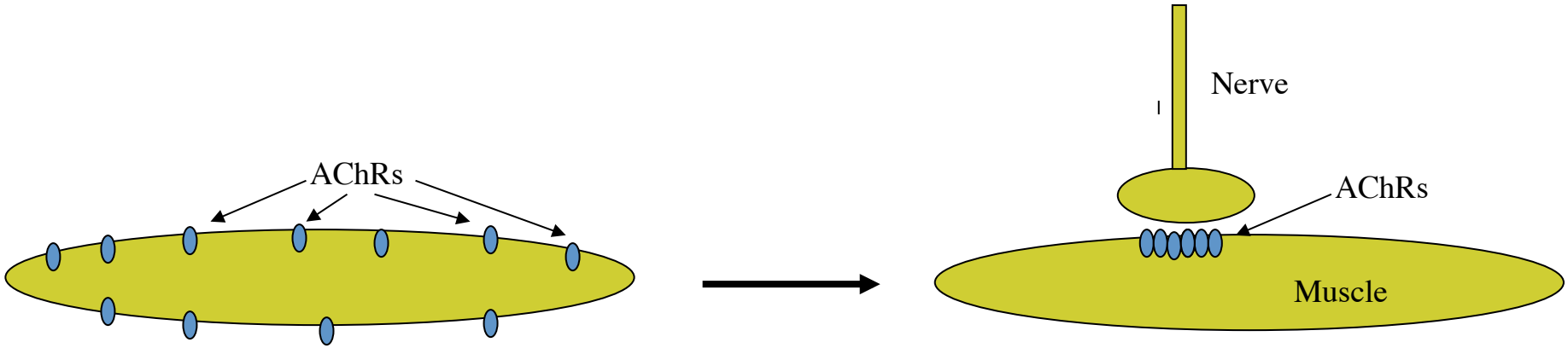
Эмбриональные рецепторы



Взрослые рецепторы



What factors stimulate clustering of AChRs?



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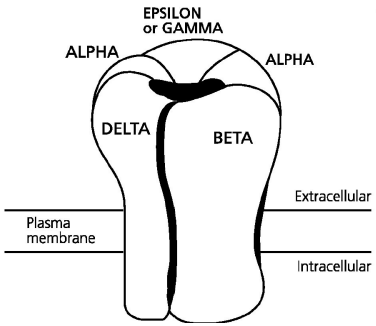
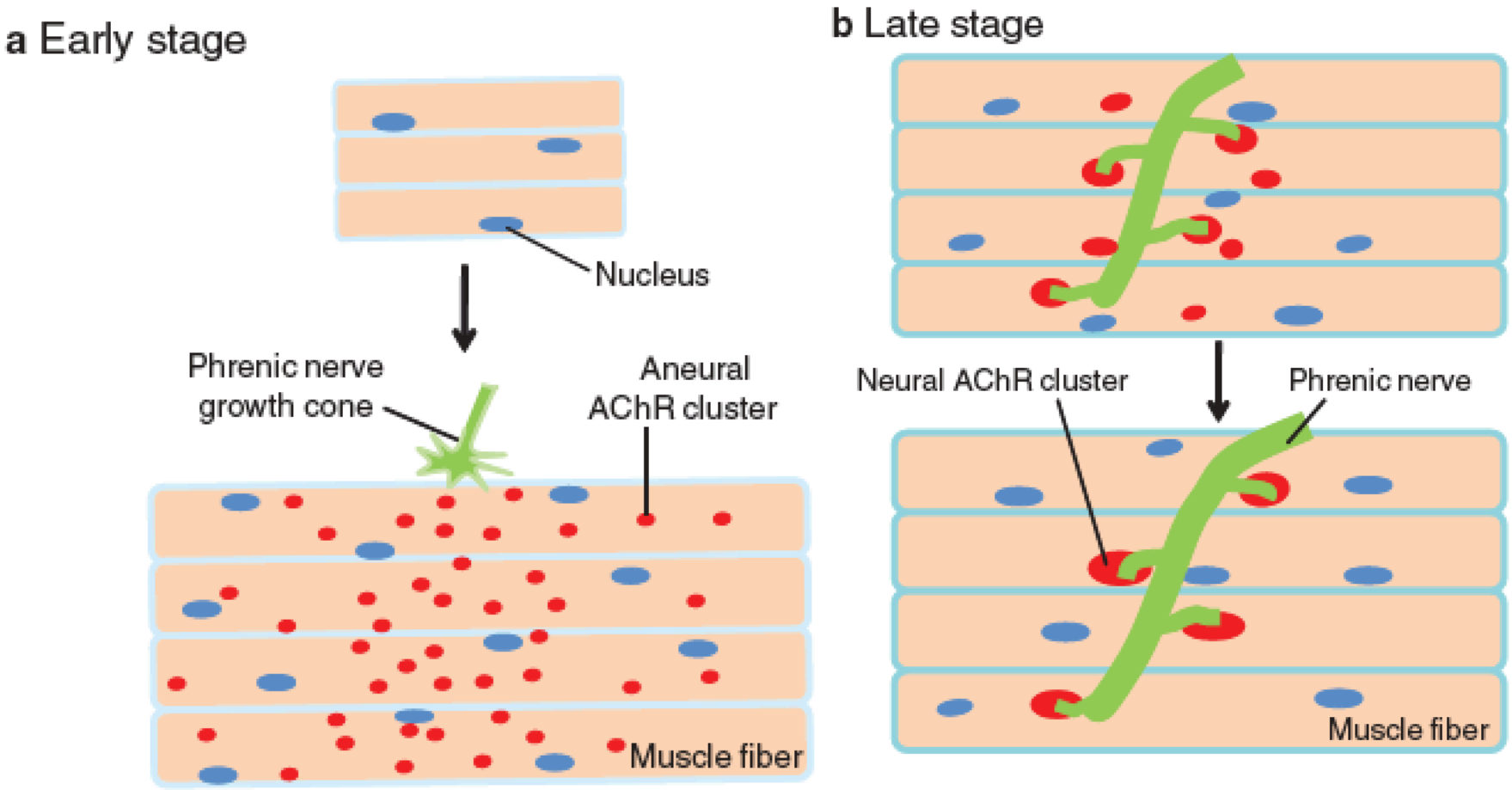
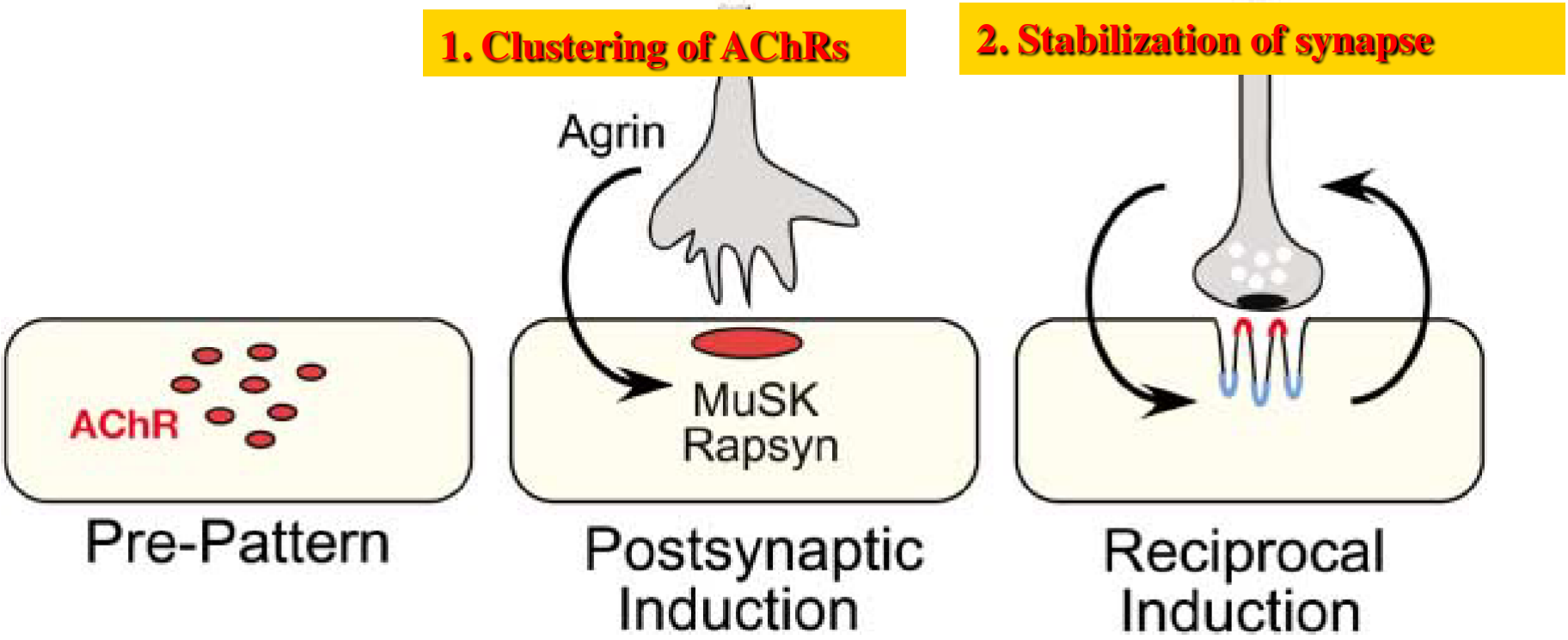
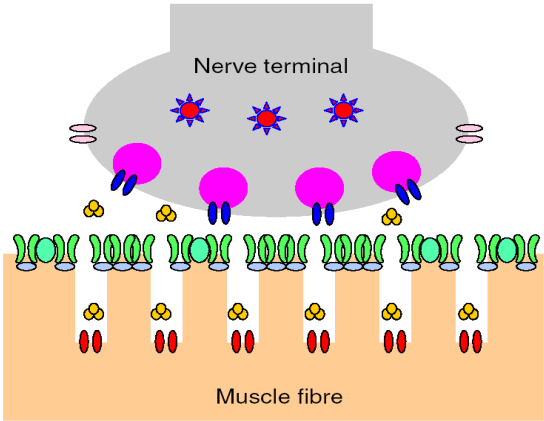



a Early stage
Nucleus
Phrenic nerve
growth cone
Aneural
AChR cluster
Muscle fiber
b Late stage
Neural AChR cluster
Phrenic nerve
Muscle fiber

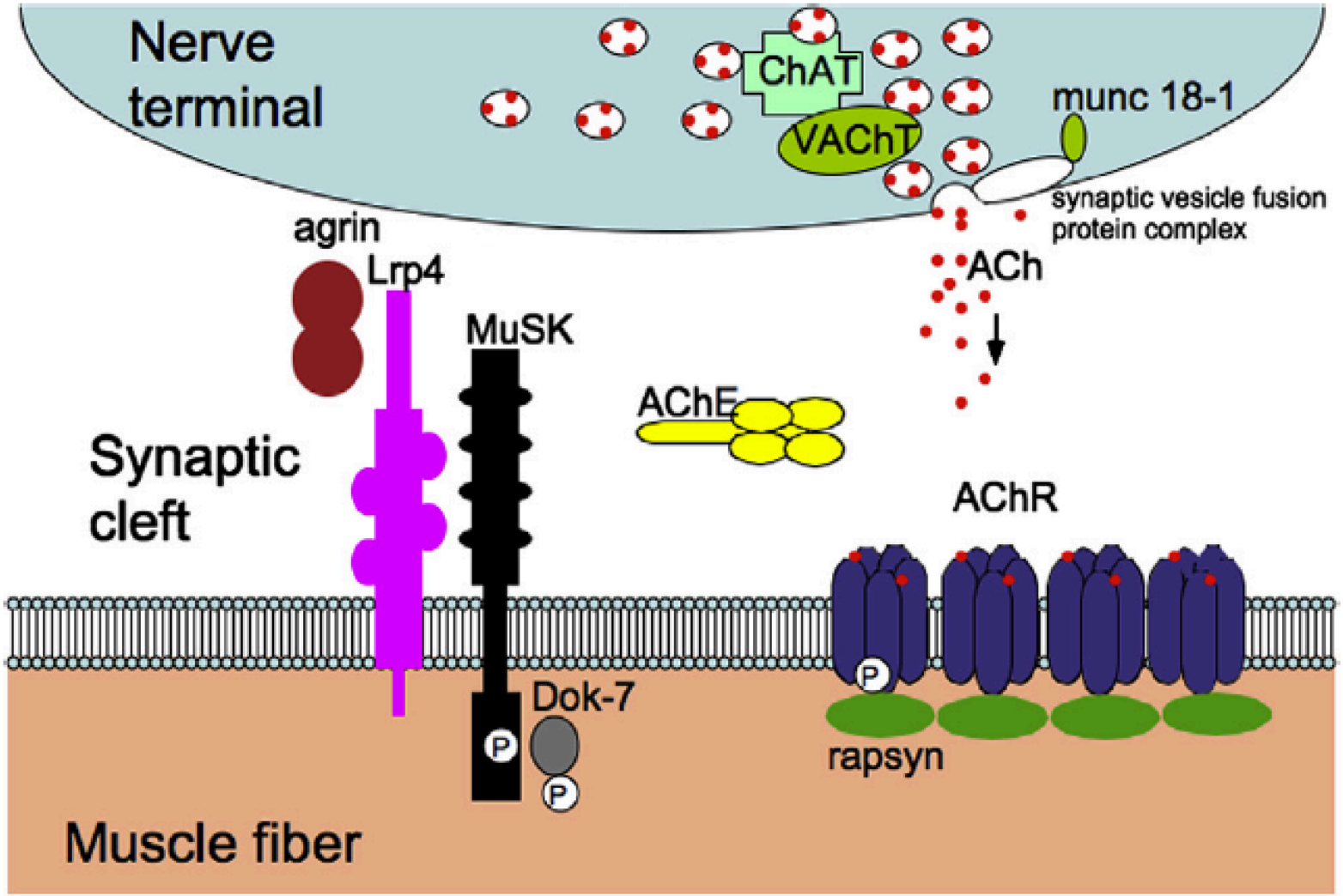
General scheme of synapse self-formation



3. Synapse differentiation

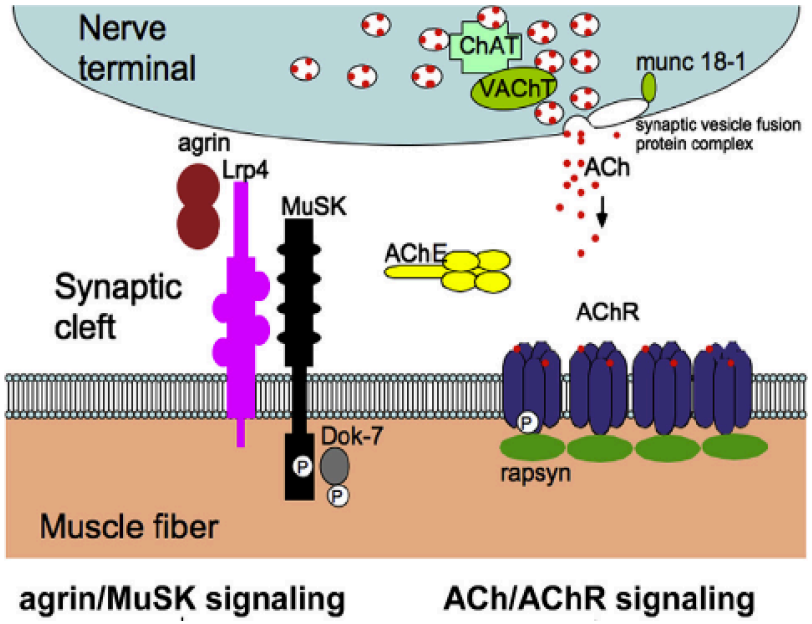


Основные пути пре-/пост-синаптической сигнализации



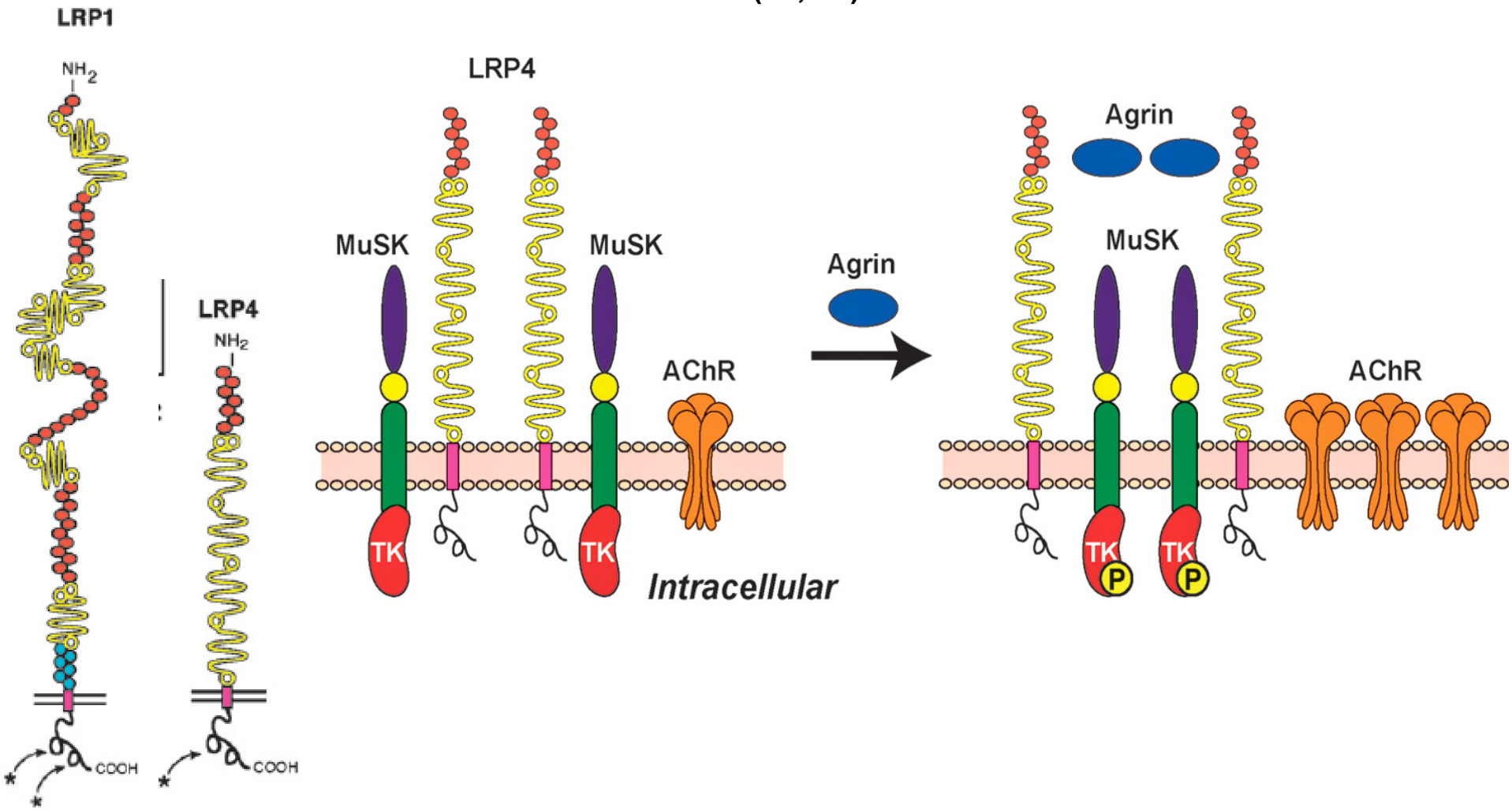
Два основных пути пре/ постсинаптической сигнализации

- **Аргин / MuSK сигнализация:**
  - подготовка кластеризации АХ р-ров
- **АХ / АХ рецептор сигнализация:**
  - деполяризация
  - генерация потенциалов действия
  - Мышечное сокращение
  - стабилизация синапсов



Witzemann et al., 2013

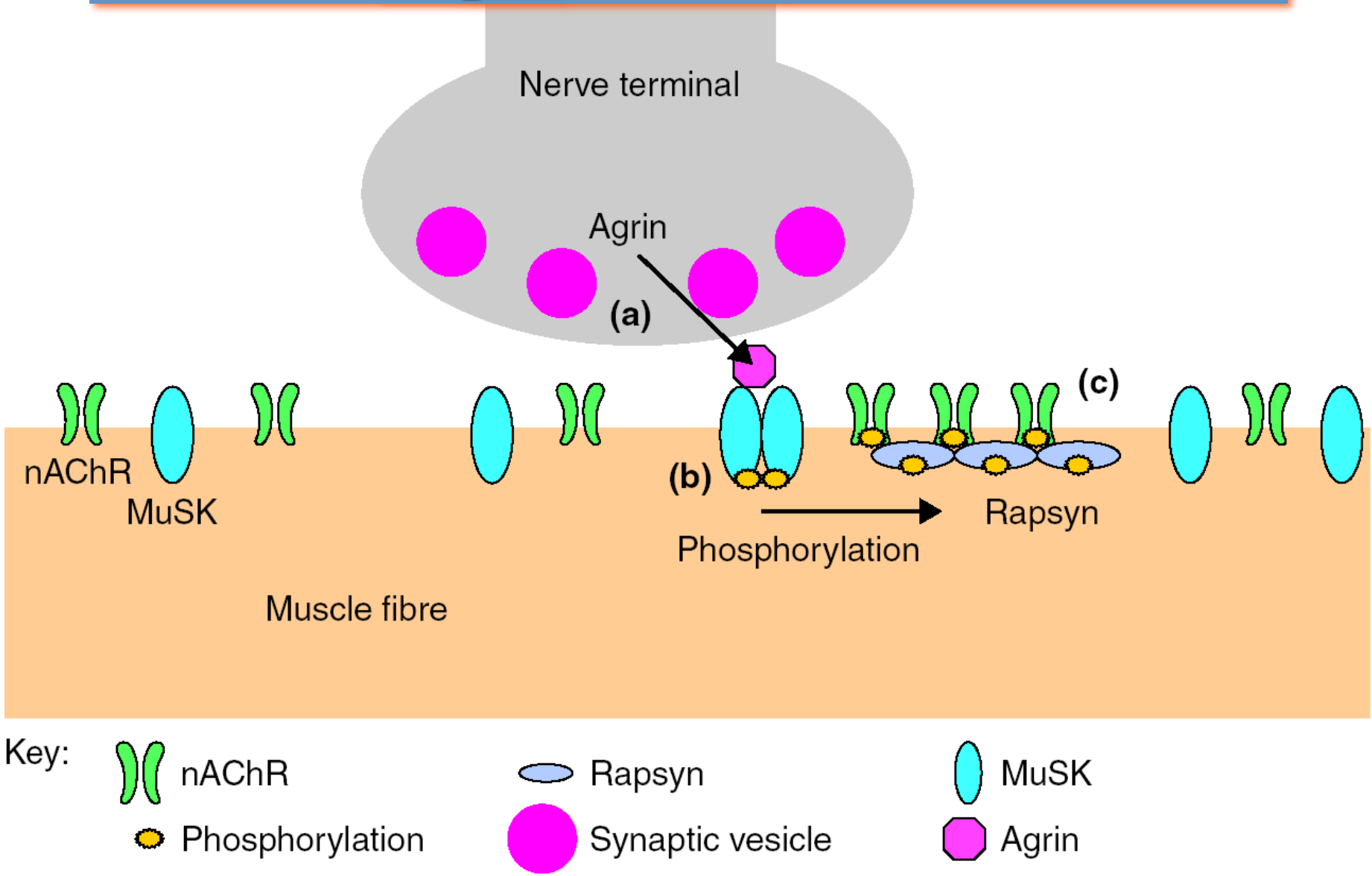
LRP4 serves as a receptor for agrin and a coreceptor for the tyrosine kinase MUSK in the muscle (48, 49).



Joachim Herz et al. J. Lipid Res. 2009;50:S287-S292

The agrin–MuSK–Rapsyn–AChR pathway

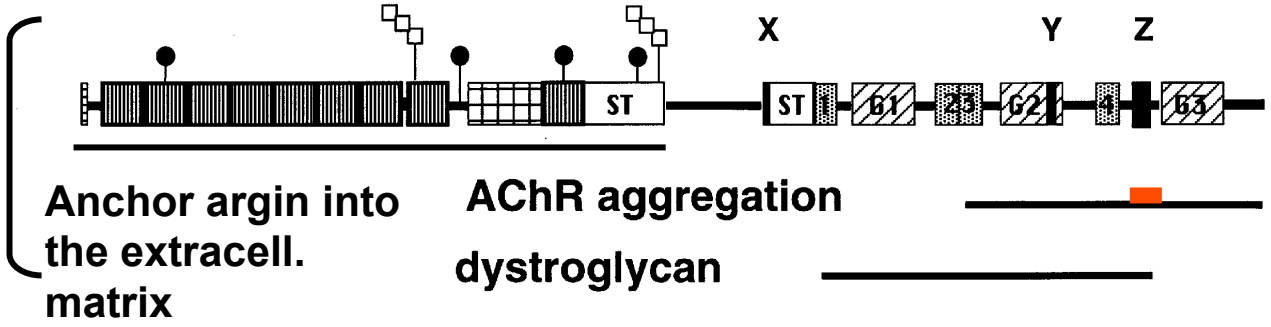
Step 1: Clustering of AChRs



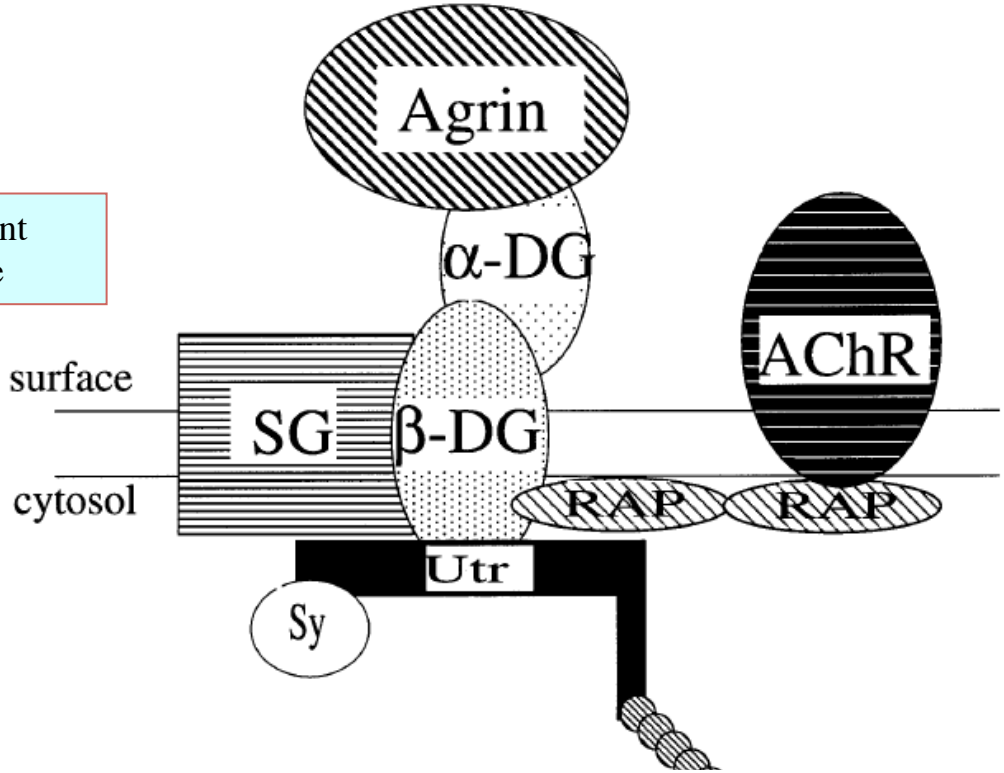
Interaction of agrin with the dystrophin-associated glycoprotein complex.

Step 2: Stabilization of synapse

Agrin

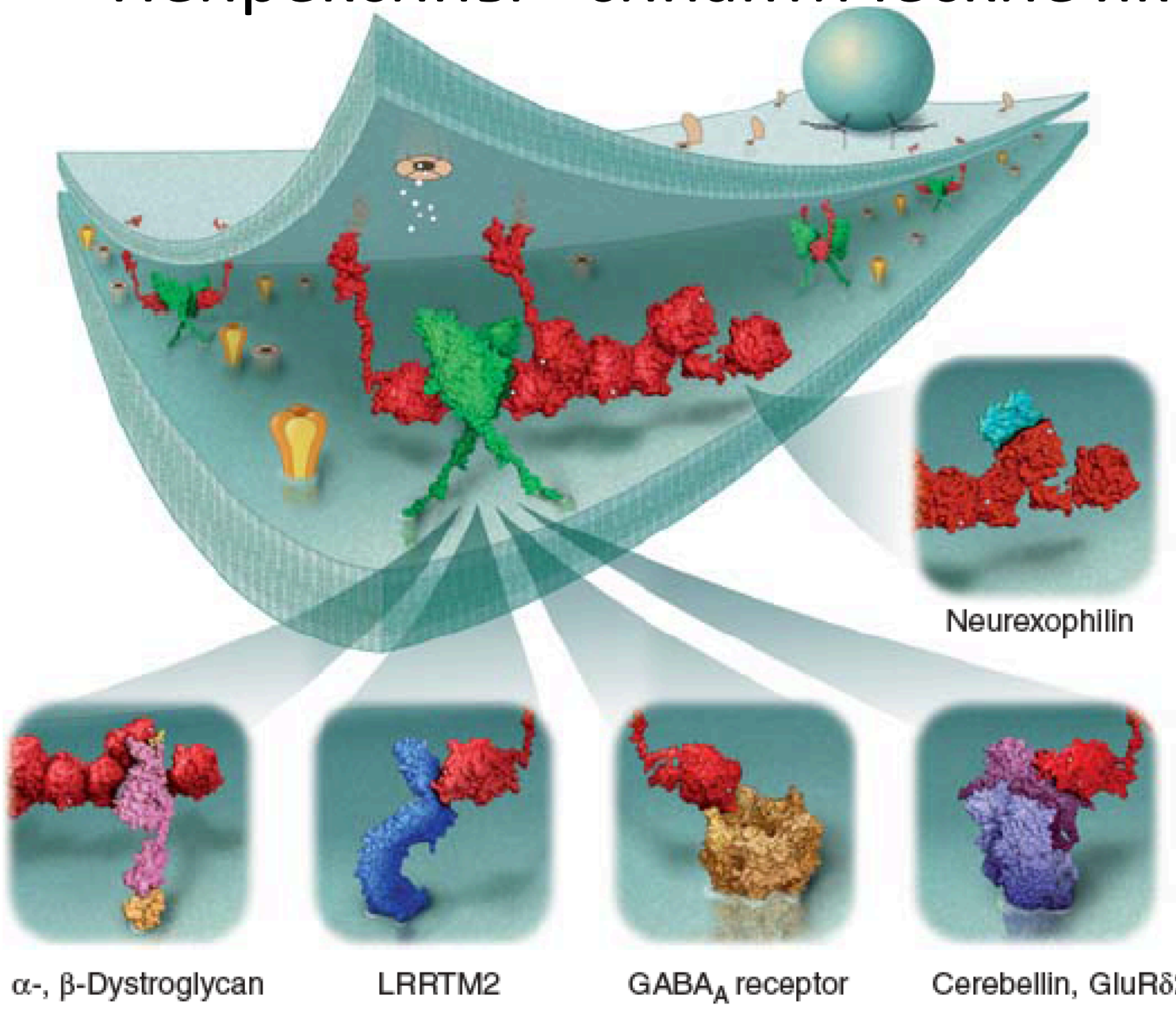


α-dystroglycan (α-DG) – most abundant binding protein on the muscle surface



α-DG	– α-dystroglycan
β-DG	– β-dystroglycan
SG	– Sarcoglycan complex
Sy	– Syntrophin
Utr	– Utrophin
RAP	– rapsin

Этап 2
Нейрексины - синаптические якори



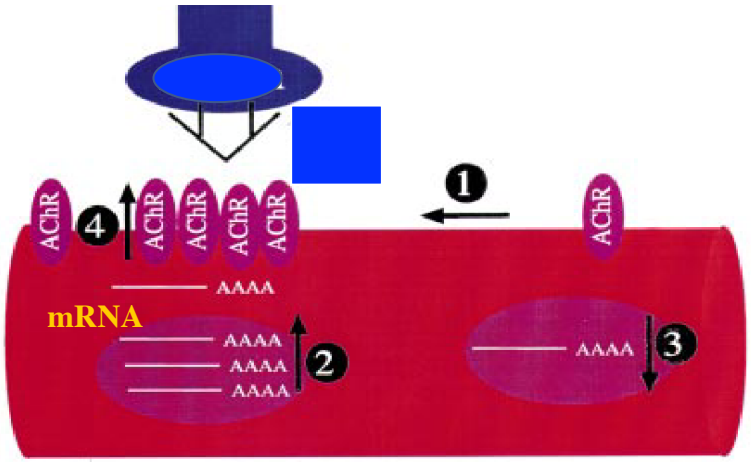
Missler et al., 2012

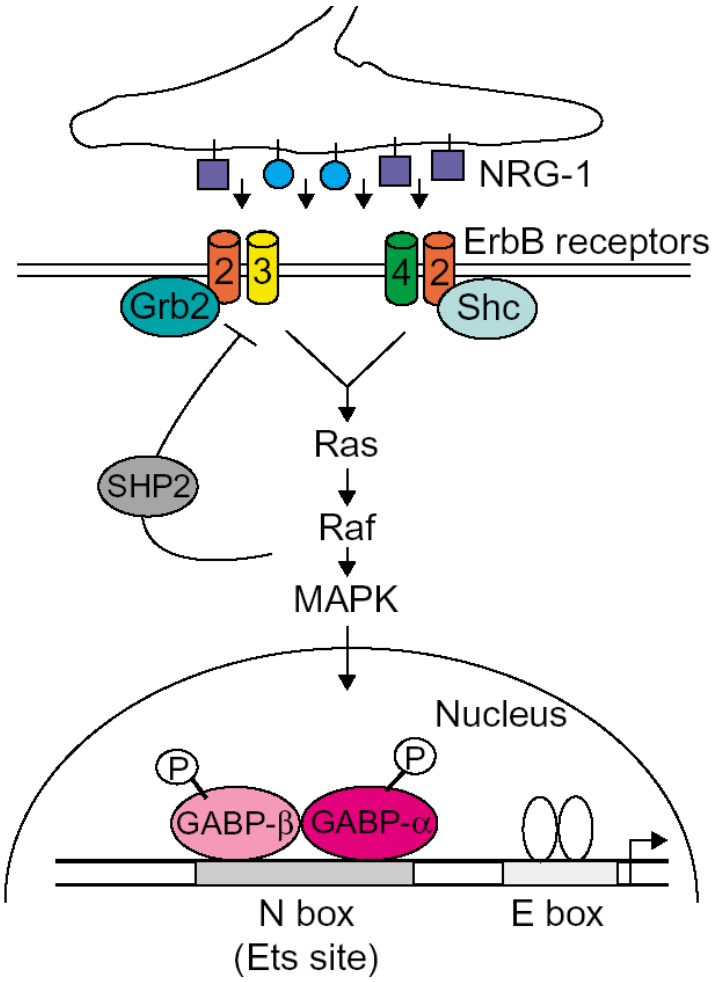
Step 3: Gene expression & Synaptic differentiation

Neuregulin – 1 – a key factor for AChR gene expression

- Increased transcription by synaptic nuclei of mRNA encoding "adult"(αβεδ) AChRs

- Decreased transcription by synaptic nuclei of mRNA encoding "foetal" (αβγδ) AChRs





Nrg –1: -concentrated at n-m synapses;

-induces AChR synthesis;

-activate postsynaptic ErbB recepors;

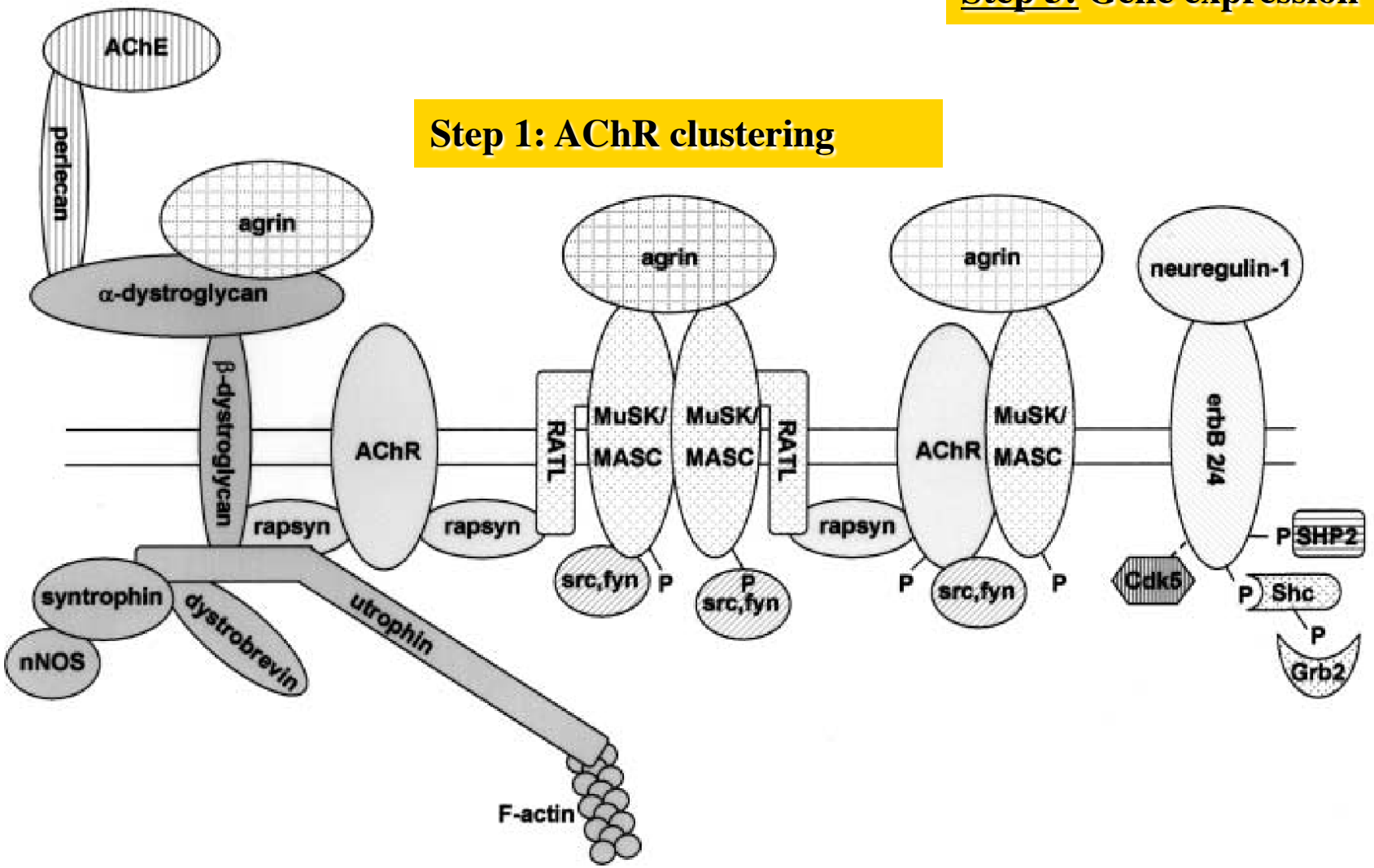
- is a signal of synaptic differentiation

Main steps of AChR clustering

Step 2: Stabilization

Step 3: Gene expression

Step 1: AChR clustering



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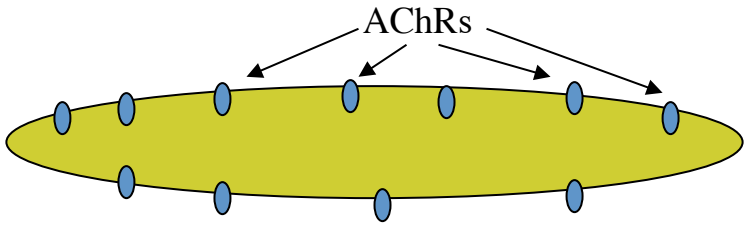

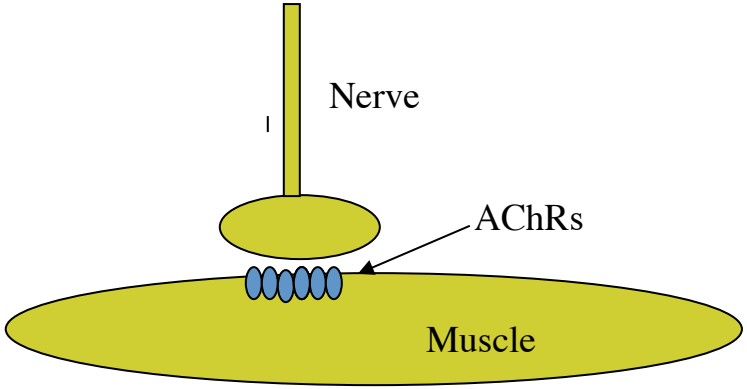

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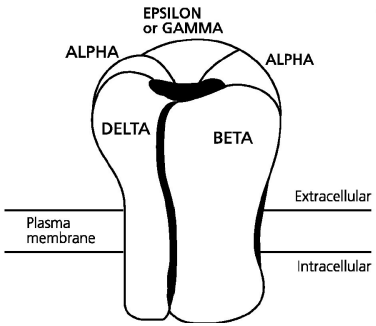
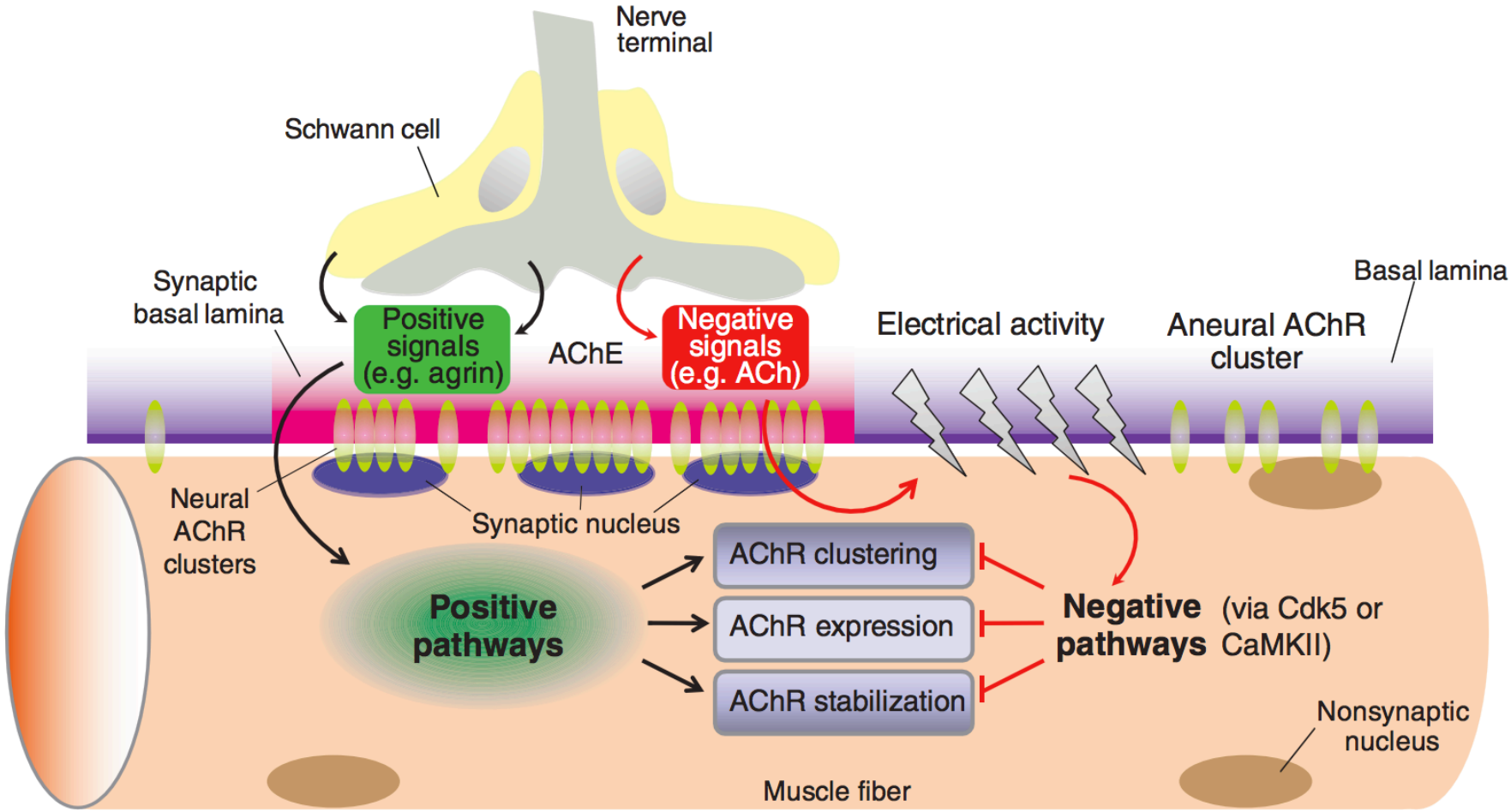
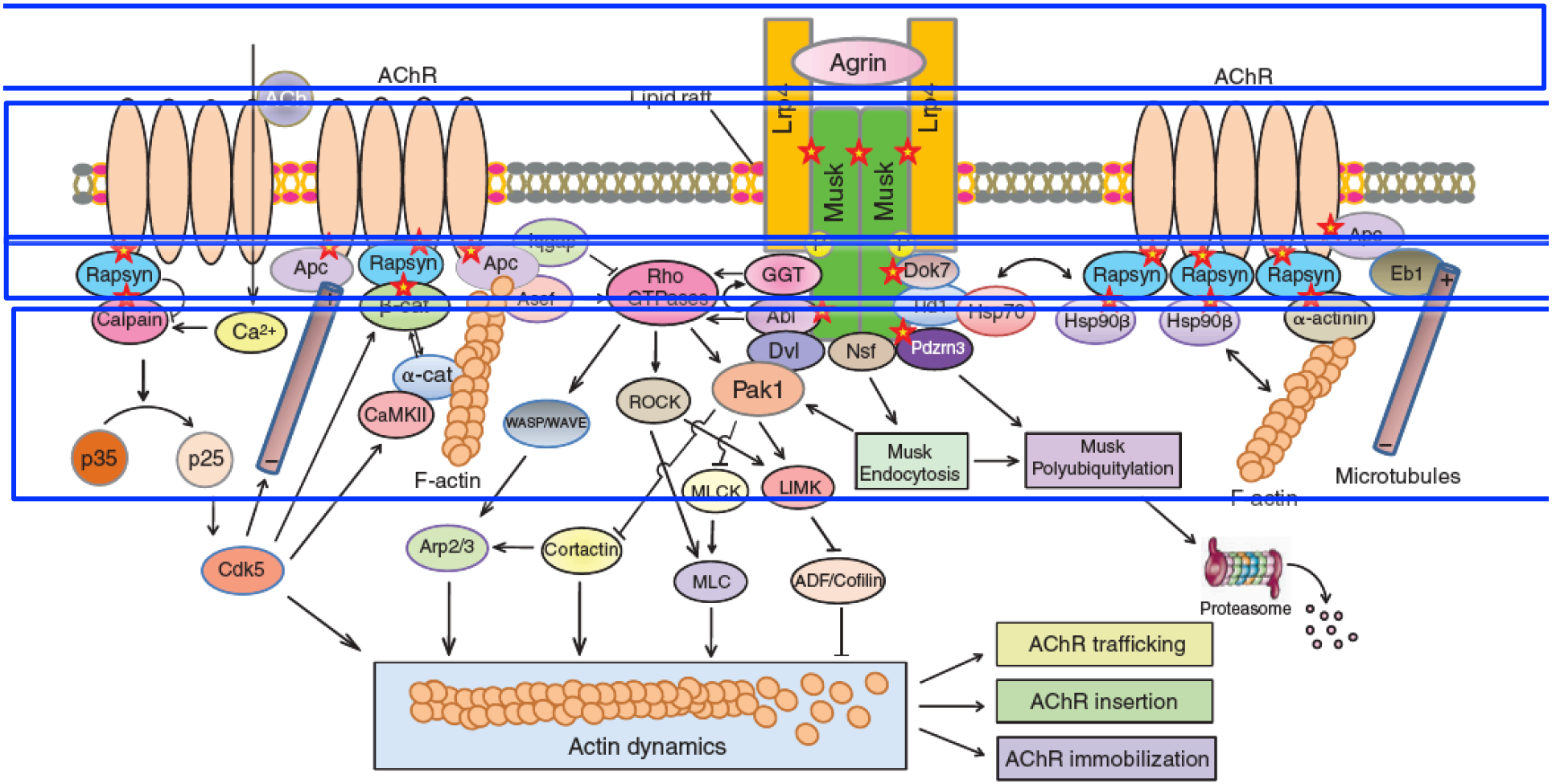
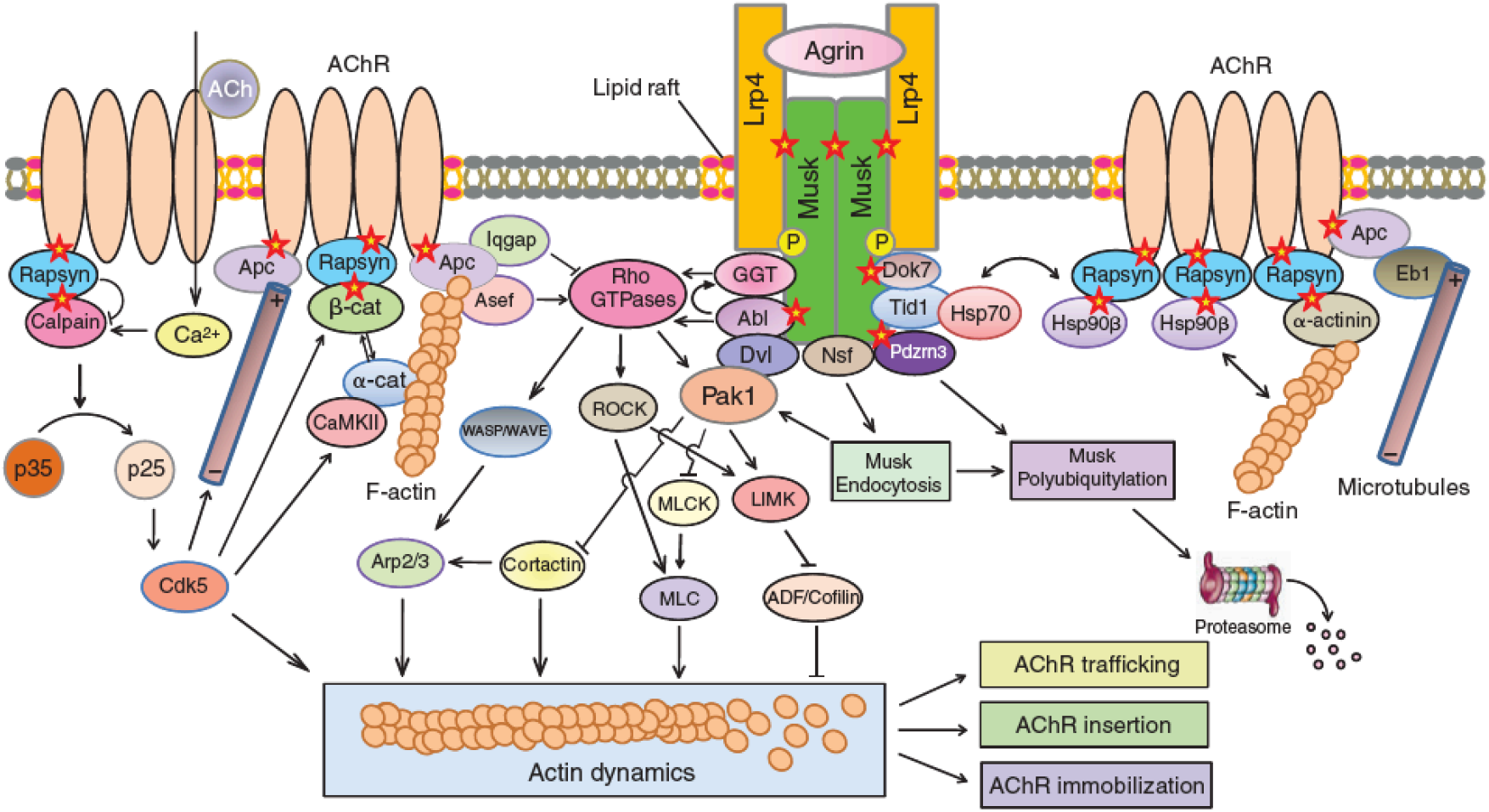


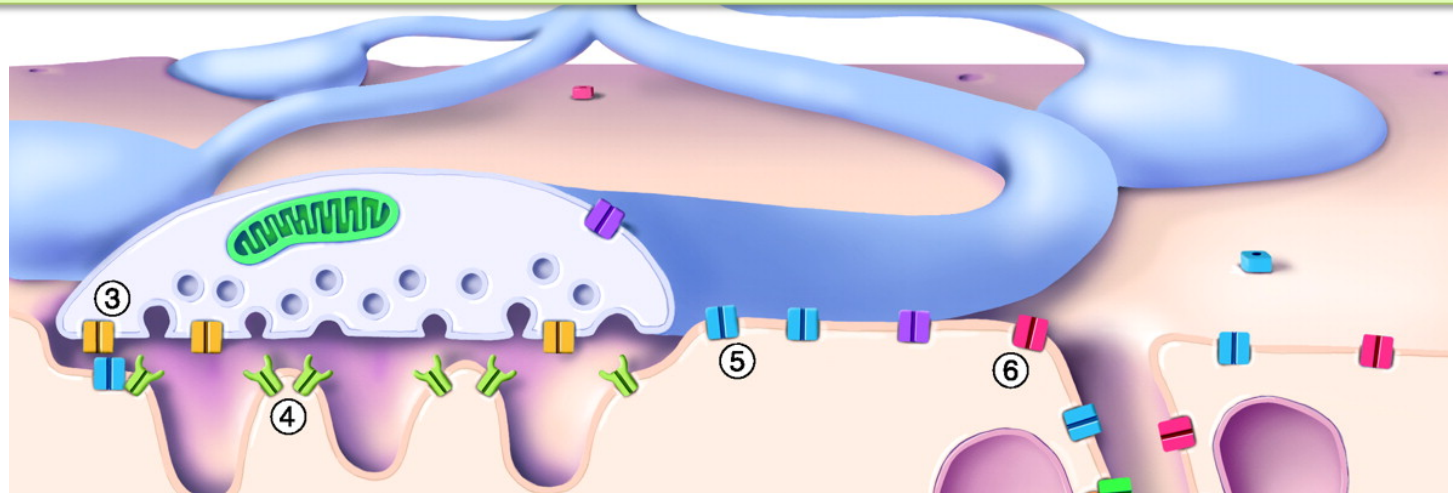

Nerve terminal
Schwann cell
Synaptic basal lamina
Positive signals (e.g. agrin)
AChE
Negative signals (e.g. ACh)
Electrical activity
Aneural AChR cluster
Basal lamina
Neural AChR clusters
Synaptic nucleus
AChR clustering
AChR expression
AChR stabilization
Positive pathways
Negative pathways (via Cdk5 or CaMKII)
Nonsynaptic nucleus
Muscle fiber


AChR
ACh
Agrin
Lipid raft
Lrp4
Musk
Musk
Lrp4
AChR
Rapsyn
Calpain
Ca2+
Apc
Rapsyn
β-cat
Apc
Ascf
α-cat
CaMKII
Rho GTPases
GGT
Abl
Dvl
Nsf
Dok7
Pdzrn3
Hsp70
Rapsyn
Rapsyn
Rapsyn
Hsp90β
Hsp90β
α-actinin
Apc
Eb1
p35
p25
F-actin
WASP/WAVE
ROCK
Pak1
Musk Endocytosis
Musk Polyubiquitylation
F-actin
Microtubules
MLCK
LIMK
Cdk5
Arp2/3
Cortactin
MLC
ADF/Cofilin
Proteasome
Actin dynamics
AChR trafficking
AChR insertion
AChR immobilization


ACh
AChR
Lipid raft
Agrin
Lrp4
Musk
Musk
Lrp4
AChR
Rapsyn
Calpain
Ca2+
Apc
Rapsyn
β-cat
α-cat
CaMKII
Apc
Iqgap
Asef
F-actin
Rho GTPases
GGT
Abl
Dvl
Nsf
Dok7
Tid1
Pdzrn3
Hsp70
Hsp90β
Rapsyn
Rapsyn
Rapsyn
Hsp90β
Apc
α-actinin
Eb1
F-actin
Microtubules
p35
p25
Cdk5
WASP/WAVE
ROCK
Pak1
Musk Endocytosis
Musk Polyubiquitylation
MLCK
LIMK
Arp2/3
Cortactin
MLC
ADF/Cofilin
Proteasome
Actin dynamics
AChR trafficking
AChR insertion
AChR immobilization

Ключевые белки АХ синапсов

- Агрин (2000 а.кислот, выделяется из пресинапса
- Мышечная киназа (MuSK) – около 1000 а.к. – постсинапс
- Рецептор липопротеинов низкой плотности (Lrp4) – около 2000 а.к. - постсинапс
- Рапсин - постсинапс
- Неурегулин – выделяется из пресинапса



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