

Bogomoletz Institute of Physiology,
Kiev, Ukraine
nana@biph.kiev.ua



Molecular Mechanisms of Pain

**Prof. Nana Voitenko
KIEV - 2015**

PAIN

Absence of pain sensation

Chronic pain

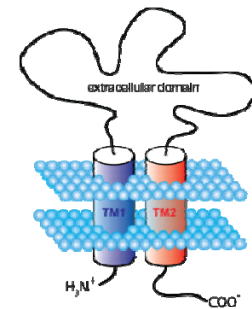
NORMA



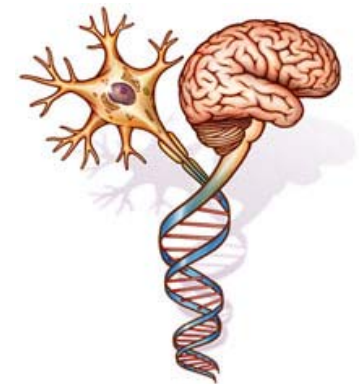
- Pain is a clinical entity rather than a compilation of single disease states.



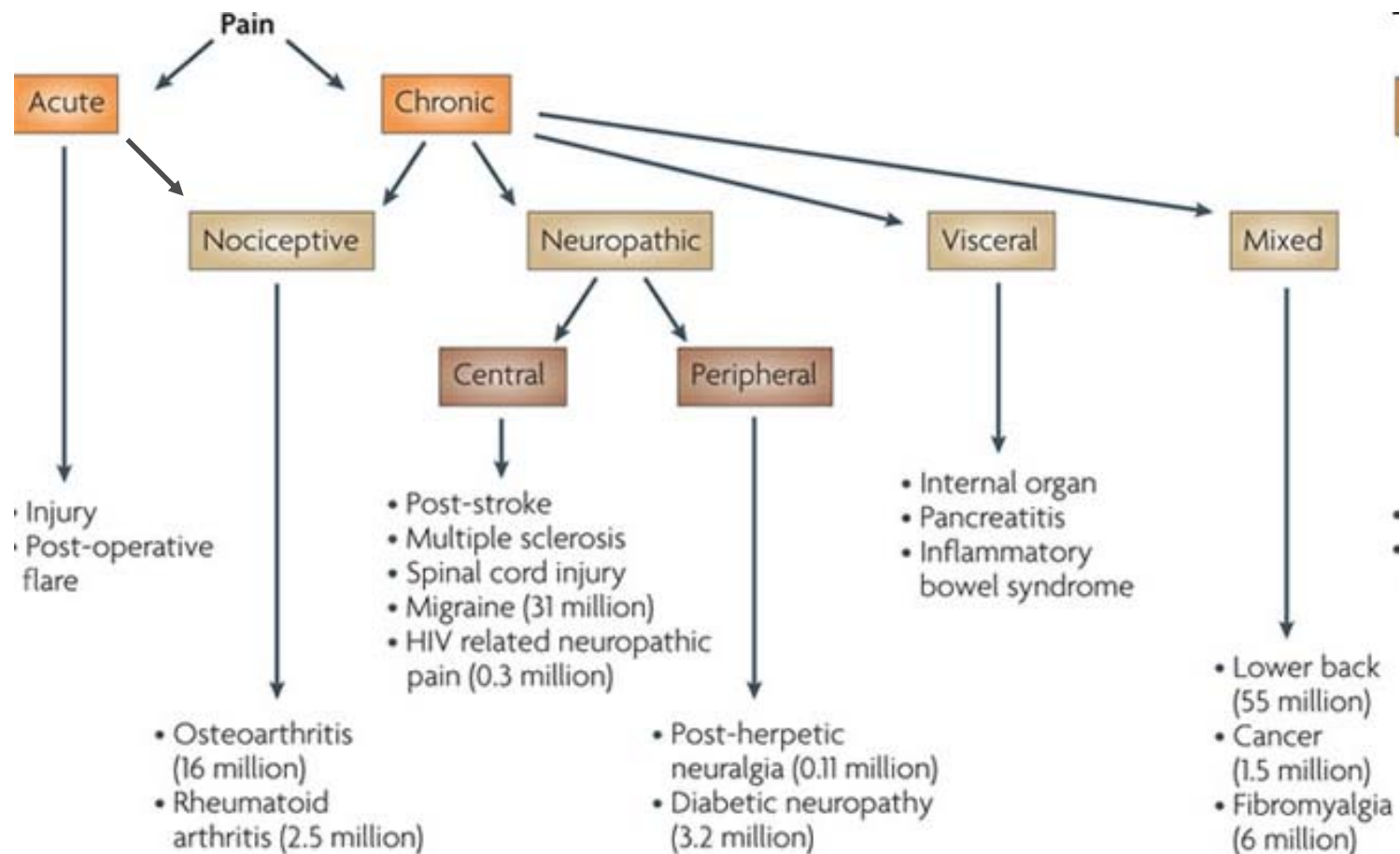
- Molecular mechanisms of pain




- Antisense oligonucleotides – a new strategy of pain treatment



PAIN CLASSIFICATION





Long term chronic pain, mainly inflammatory or neuropathic, afflicts about 25% of the general world population. More than 60% of people aged 65 plus complain of daily pains. This degree of disability has a huge economic toll in terms of loss of employment and disability payments but quality of life is equally compromised. Pain is thus a major medical issue but is not simply a sensation but an event that also triggers aversive and threatening psychological feelings. Intolerable pain is one of the main reason for euthanasia.



Measurements of pain



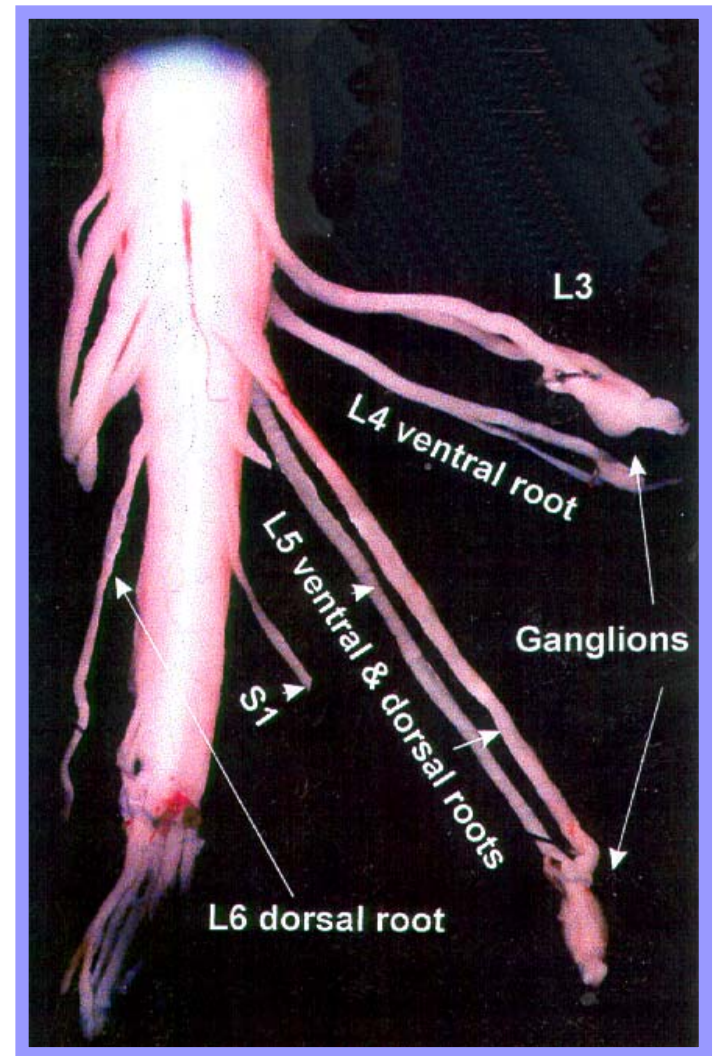
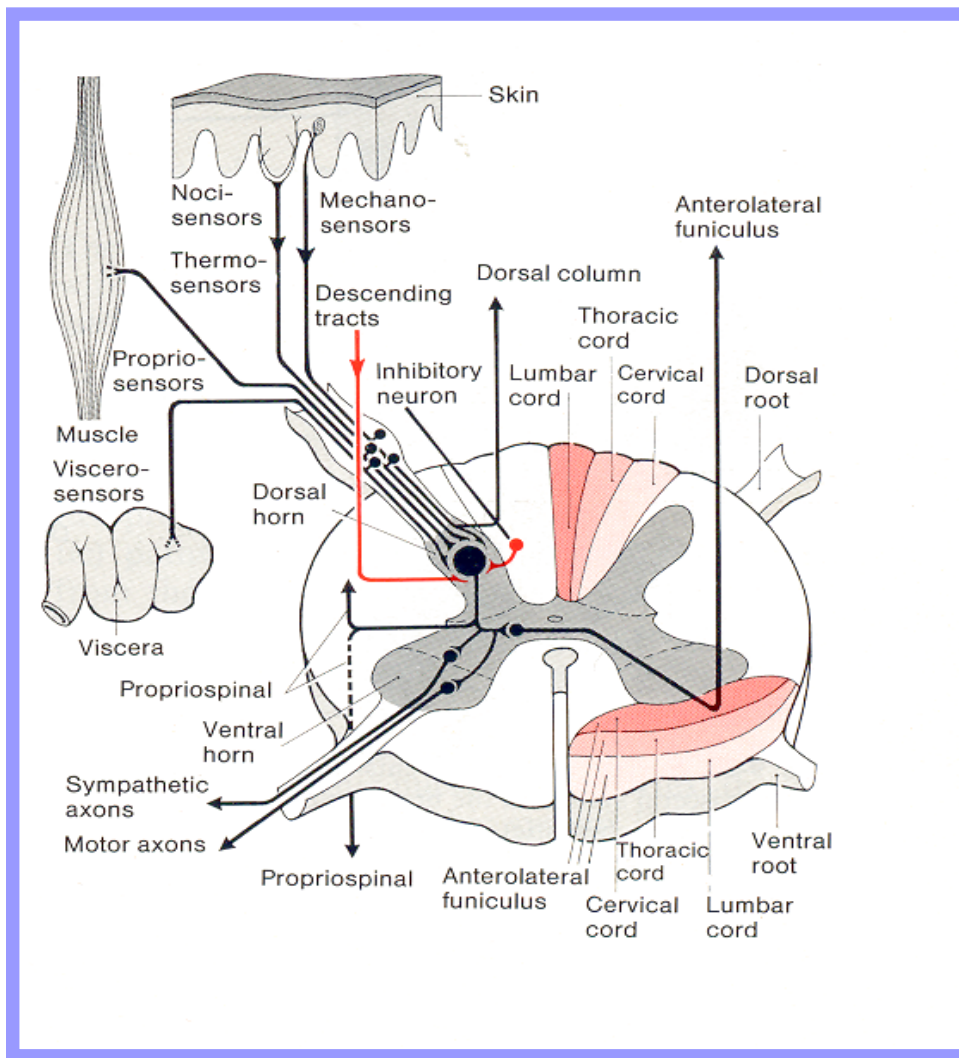
- Hargreaves test – thermal hyper-/ hypoalgesia
- Randall-Selitto test – mechanical hyper-/ hypoalgesia



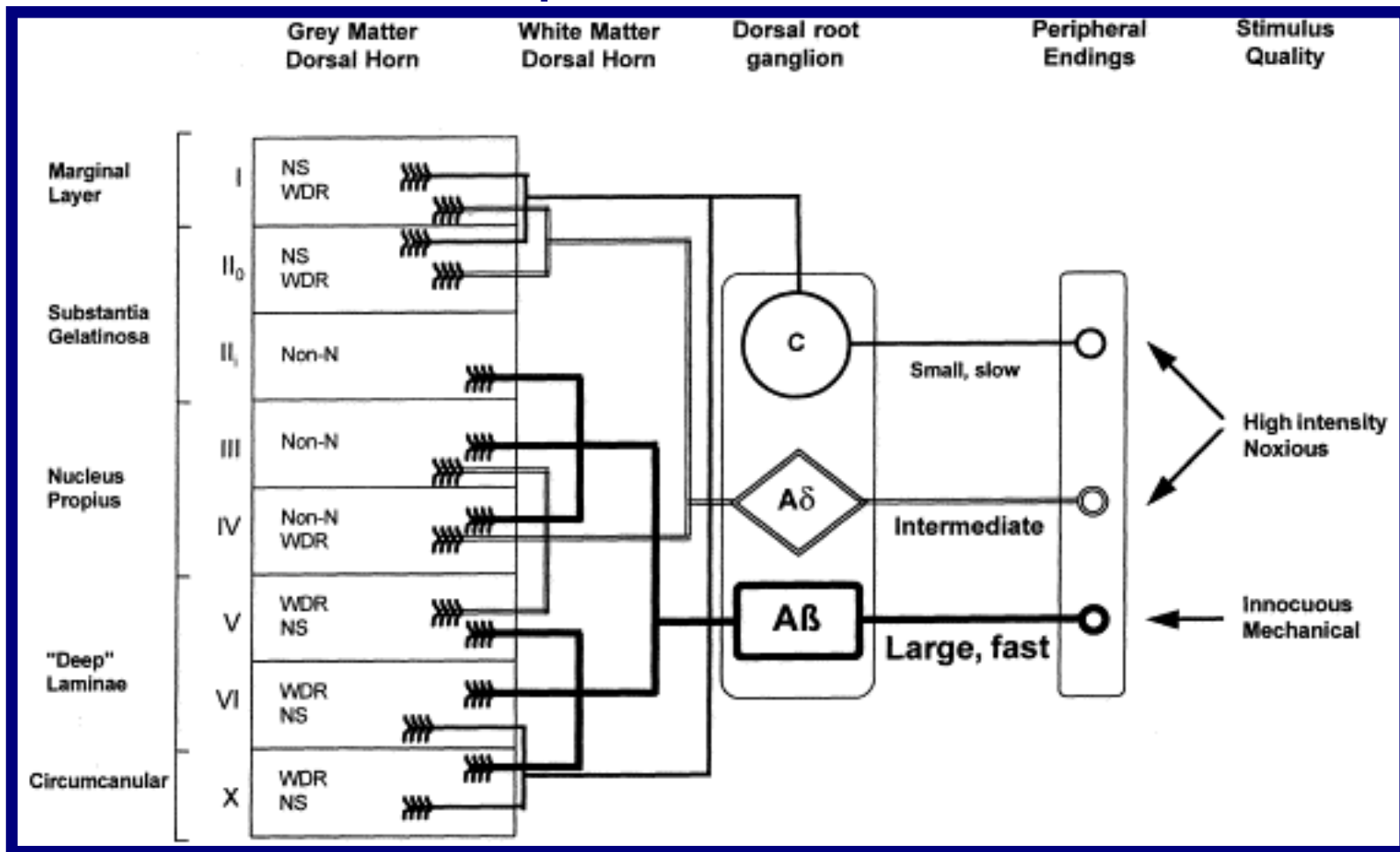
- Hot plate test – thermal allodynia
- Von Frei test - mechanical / tactile allodynia

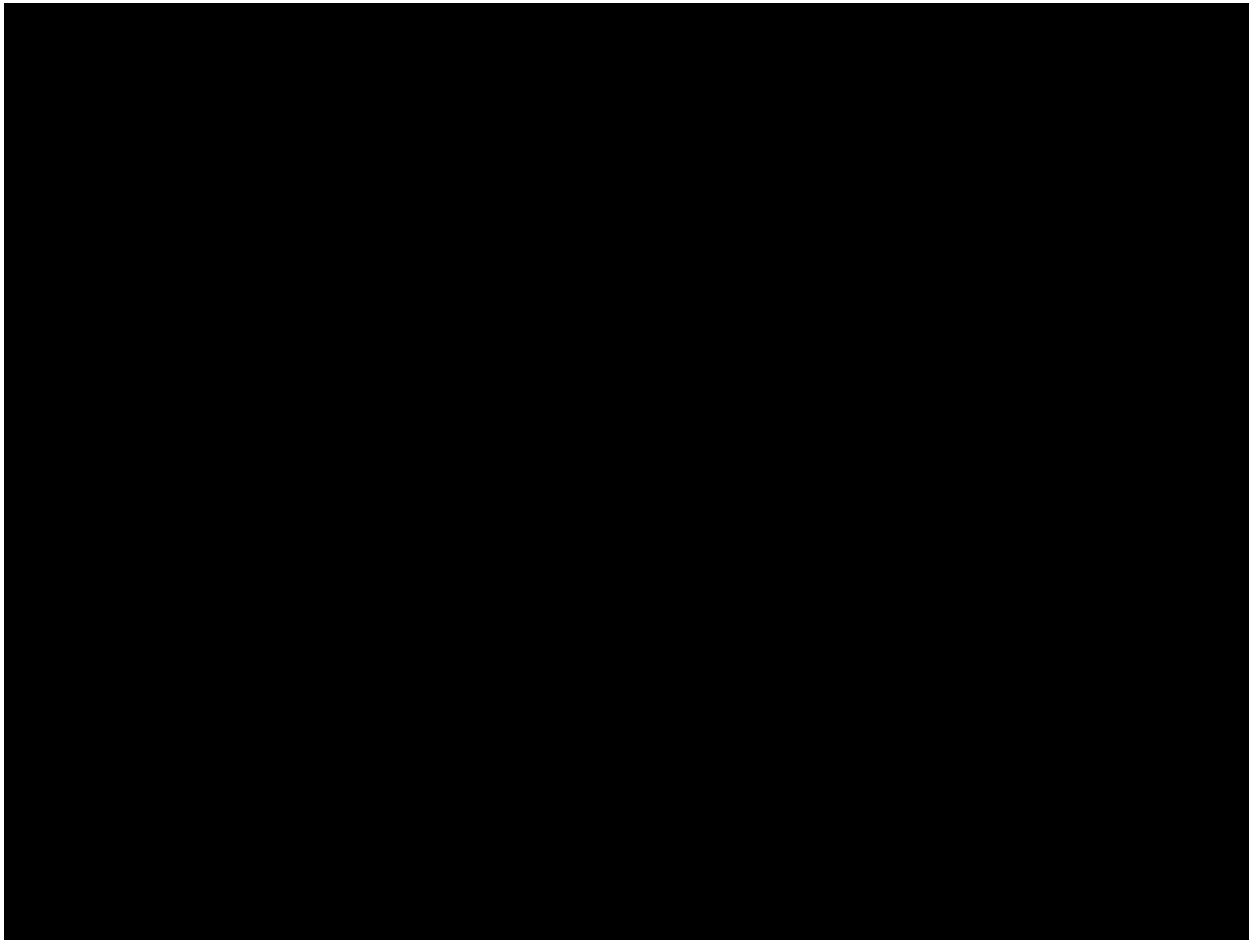


Sensory pathways

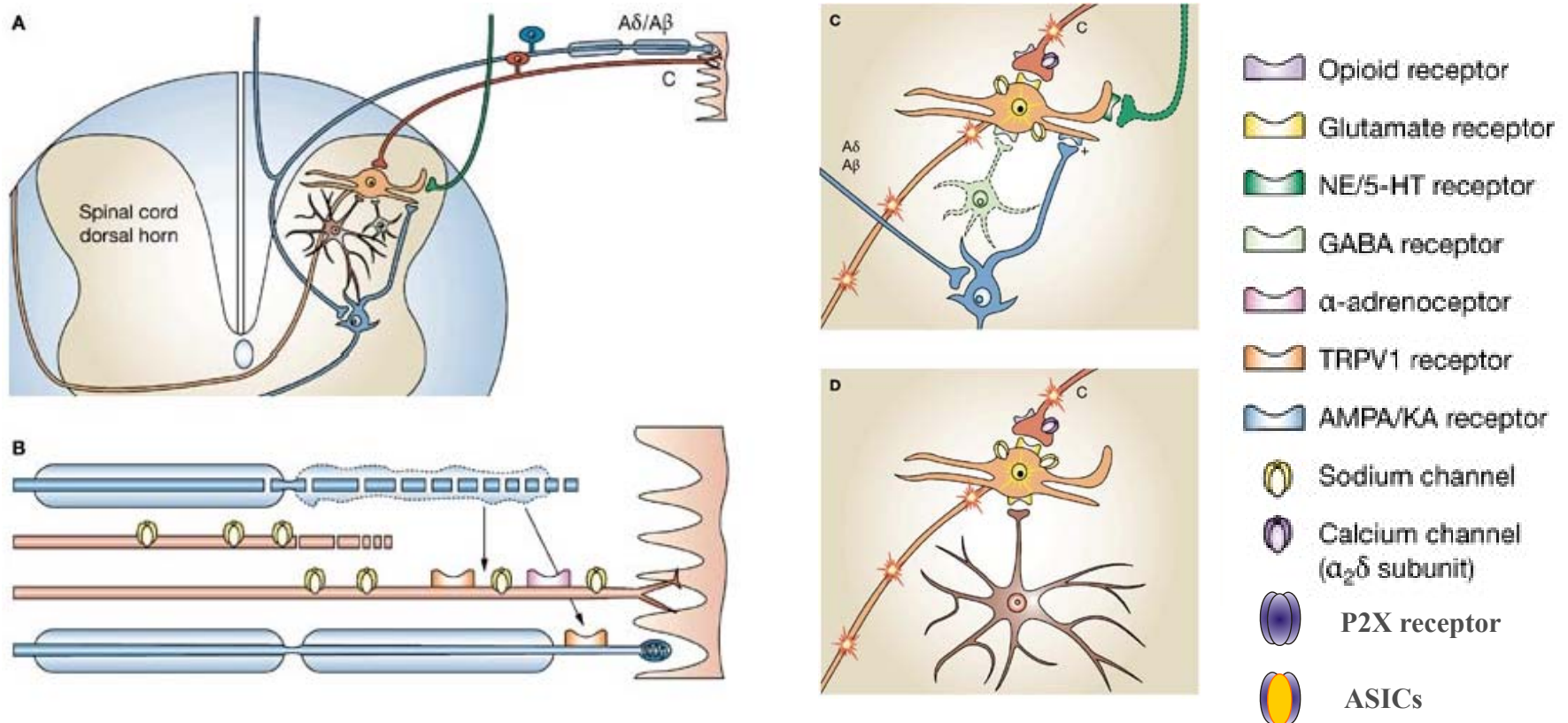


Organization of Cutaneous, Primary Afferent Input to the Dorsal Horn of the Spinal Cord

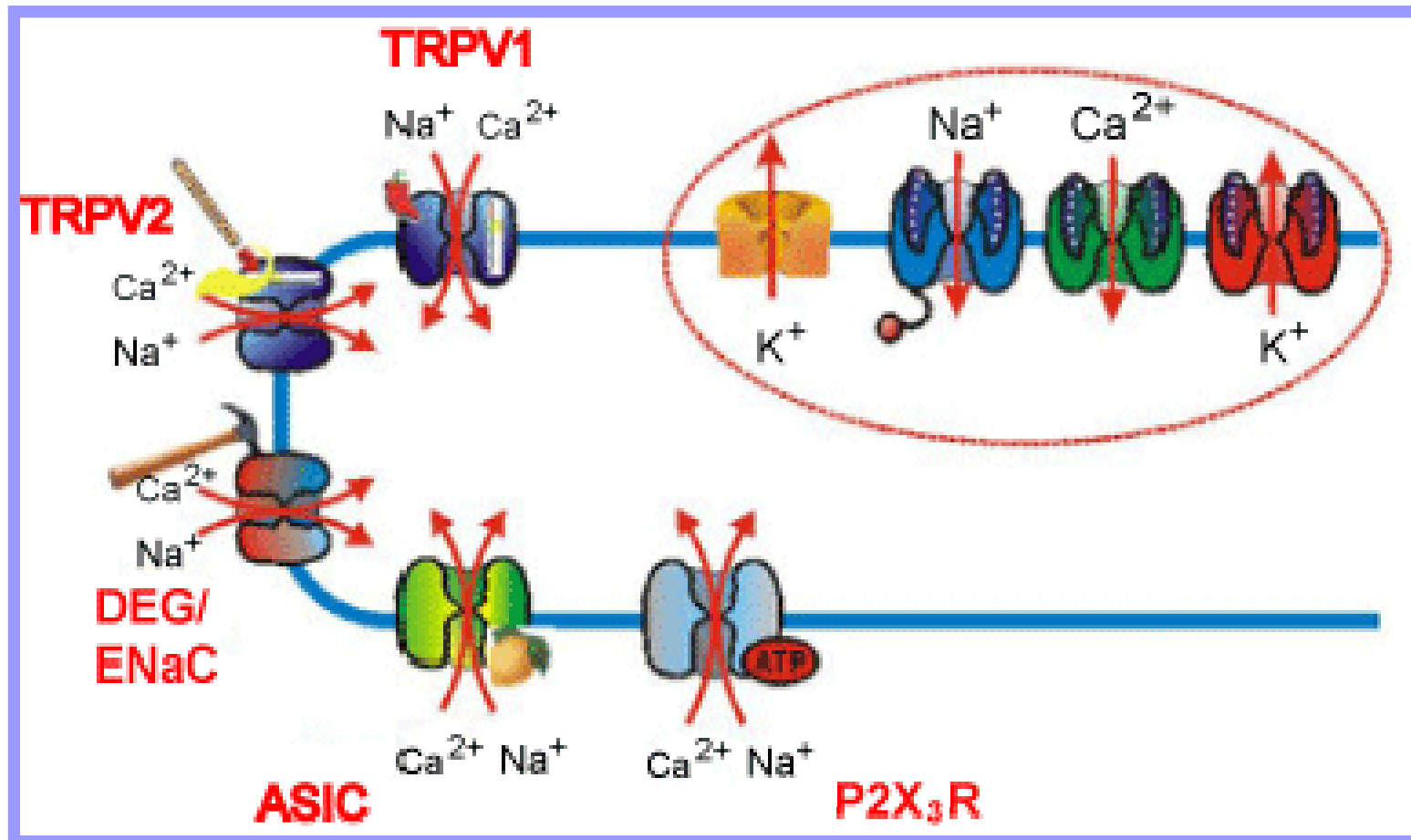




Mechanisms of peripheral and central sensitization in neuropathic pain

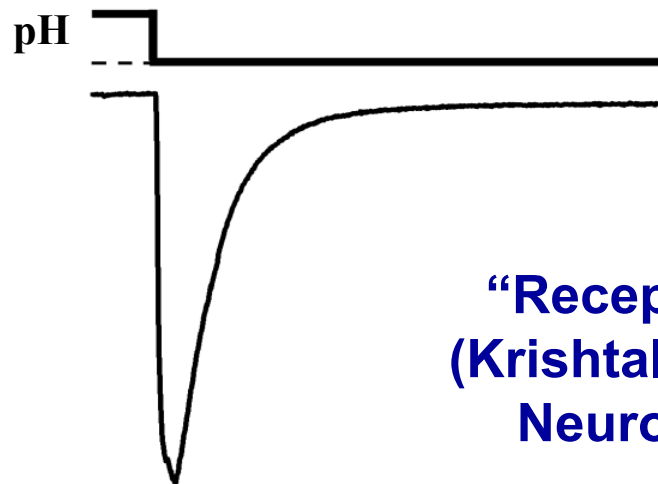


Receptors and Ionic Channels



ASICs

- ASICs — *Acid Sensing Ionic Channels*, are neuronal voltage-insensitive cationic channels activated by extracellular protons. Activation threshold – pH 7.0; maximum current at pH 5.4.
- Acid-sensing ion channels are potential drug targets for treating a wide variety of conditions linked to both the CNS and PNS.



**“Receptor for protons”
(Krishtal and Pidoplichko,
Neurosci. Lett. 1981)**



Oleg Krishtal

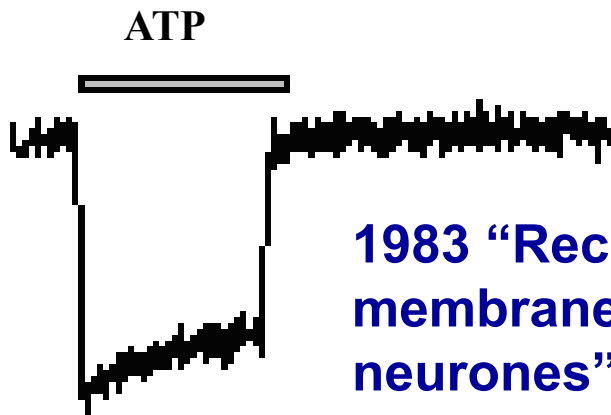


Pathological conditions associated with acidosis:

- ischemia
- inflammation
- tumors
- fractures
- hematomas

P2-(Purino)-receptors

- **P2X receptors** are a family of cation-permeable ligand gated ion channels that open in response to the binding of extracellular **adenosine 5'-triphosphate (ATP)**. In keeping with their wide distribution throughout the body, P2X receptors are involved in a variety of physiological processes, including:
 - Mediation of nociception
 - Modulation of vascular tone
 - Modulation of cardiac rhythm and contractility
 - Contraction of the smooth muscle cells

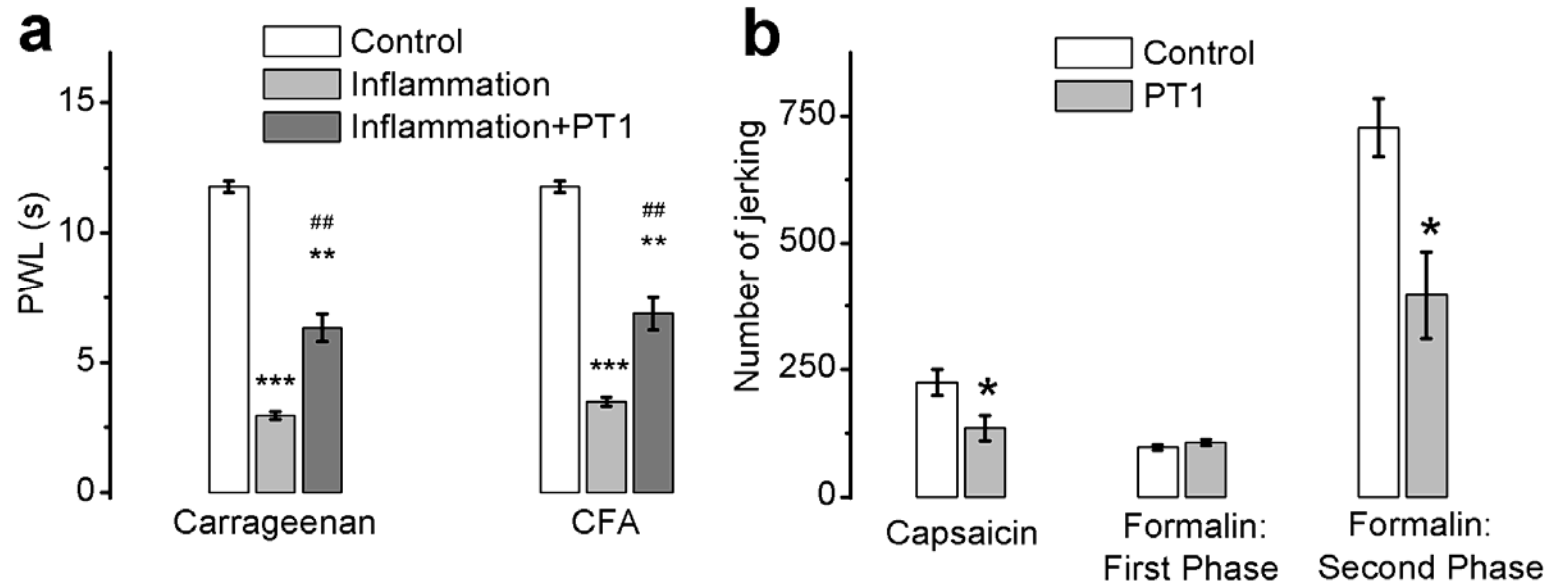


1983 “Receptor for ATP in the membrane of mammalian sensory neurones” (Krishtal et al., Neurosci. Lett. 1983)



Oleg Krishtal

Effect of new P2X3 modulator: purotoxin1 (PT1, spider)



TRPV1 receptor



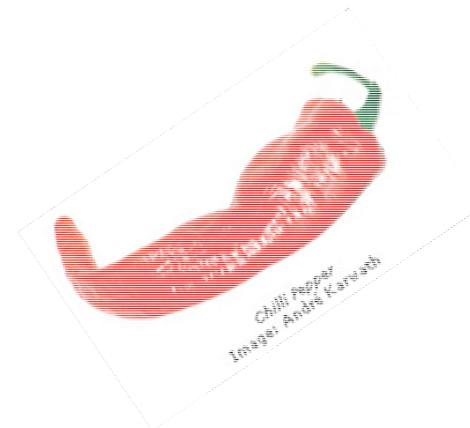
Transient Receptor Potential Vanilloid Vanilloid receptor 1

The best-known activators of TRPV1:

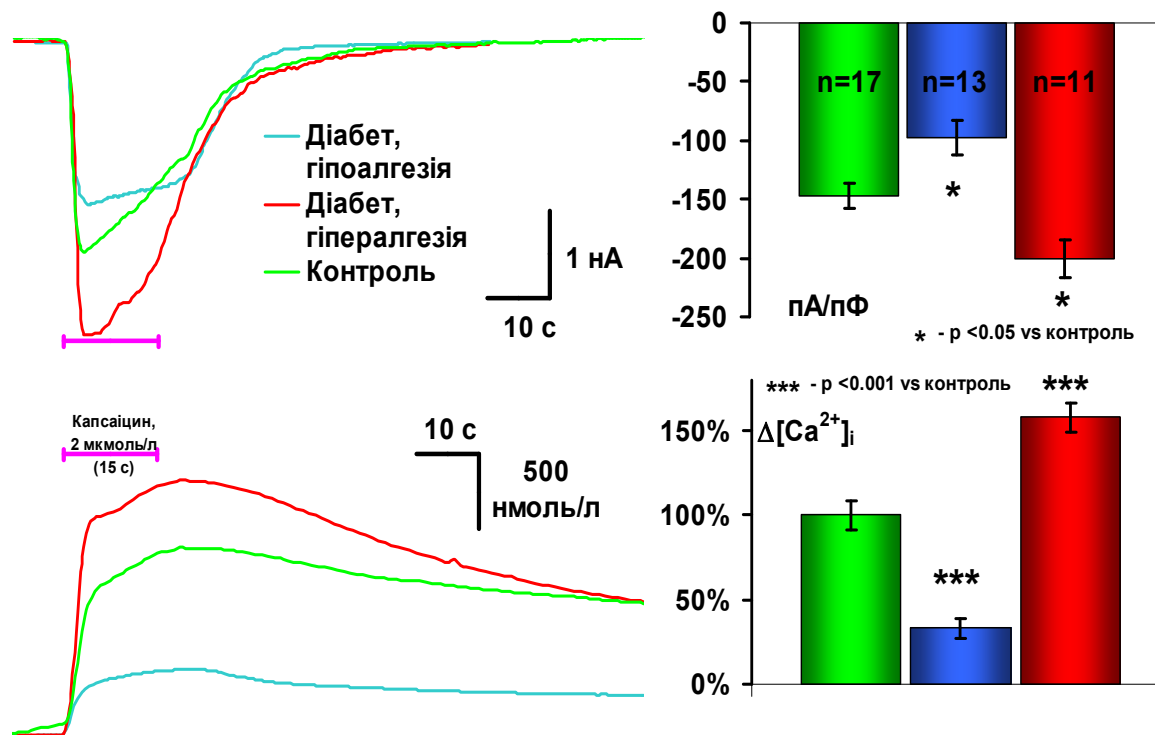
- heat greater than 43°C,
- capsaicin, the pungent compound in hot chili peppers
- allyl isothiocyanate, the pungent compound in mustard and wasabi.

Endogenous activators:

- low pH (acidic conditions),
- endocannabinoid anandamide,
- N-arachidonoyl-dopamine



TRPV1 function under diabetic peripheral neuropathy

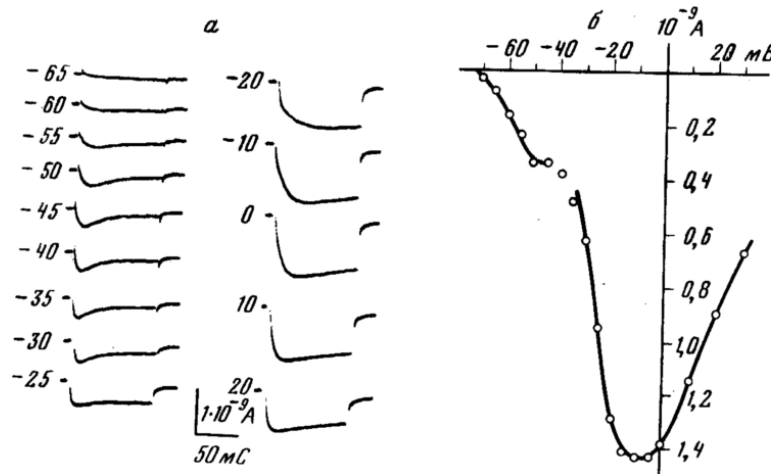


Low-voltage-activated calcium channels



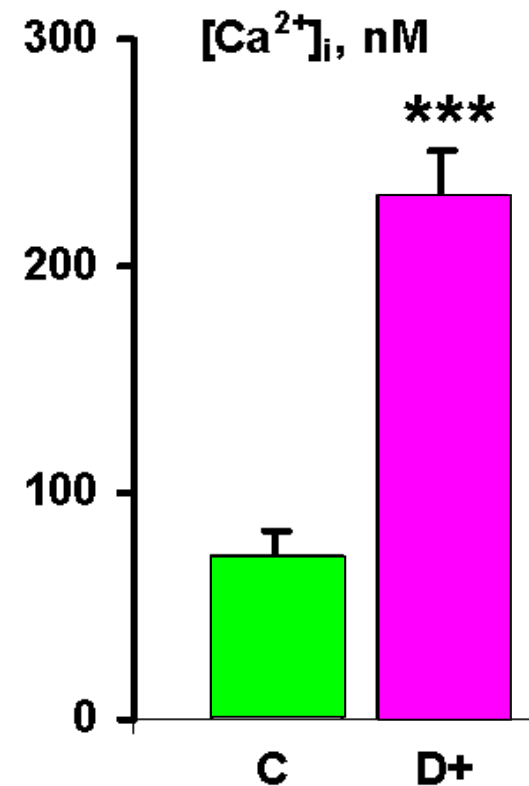
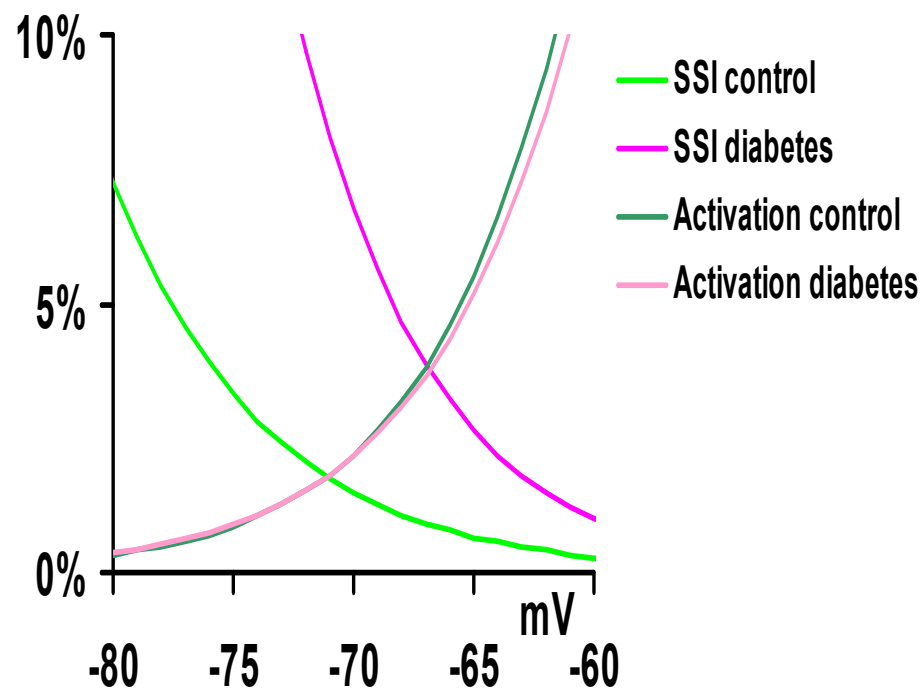
N.S. Veselovsky

The first direct separation of HVA and LVA currents was performed on dorsal root ganglion (DRG) neurons at the Bogomoletz Institute of Physiology (Ukraine) in 1983



**Veselovskii NS, Fedulova SA.
2 types of calcium channels
in the somatic membrane of
spinal ganglion neurons in
the rat. Dokl Akad Nauk SSSR
1983; 268:747-50 (in Russian)**

Increasing of T-type window current and resting $[Ca^{2+}]_i$ in the C-fiber nociceptors of diabetic rats

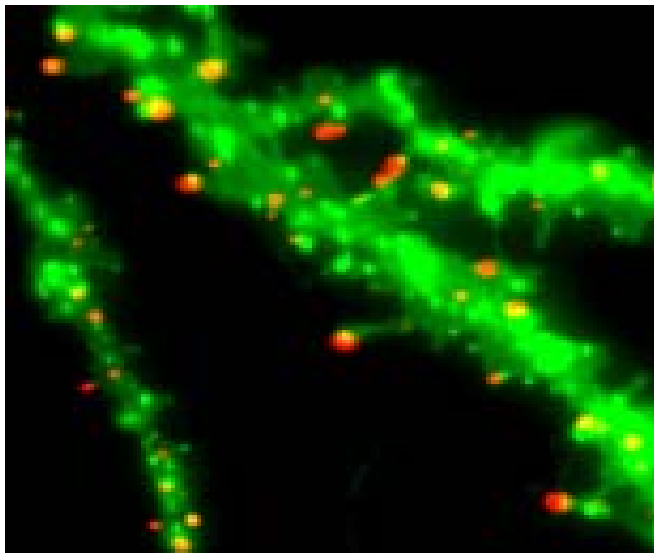


AMPA receptors

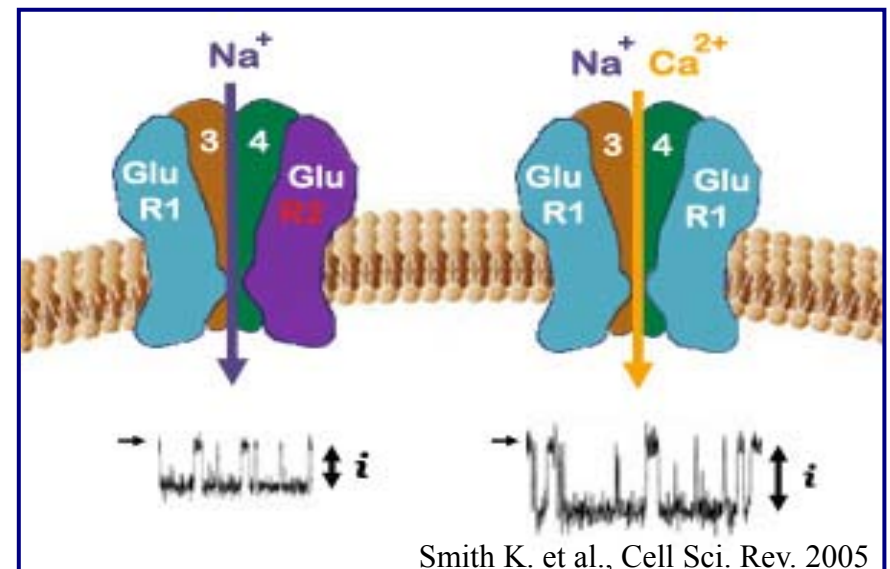
In CNS AMPA receptors:

- found in many parts of the brain
- the most commonly found receptor in the nervous system
- mediate excitatory synaptic transmission
- mediate synaptic plasticity (LTP and LTD)

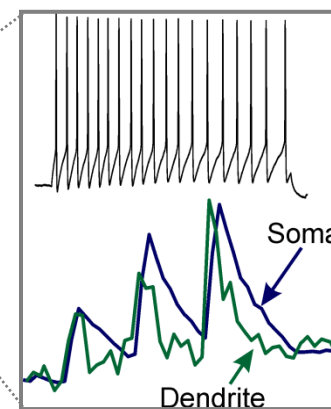
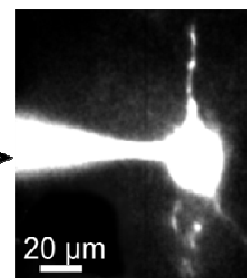
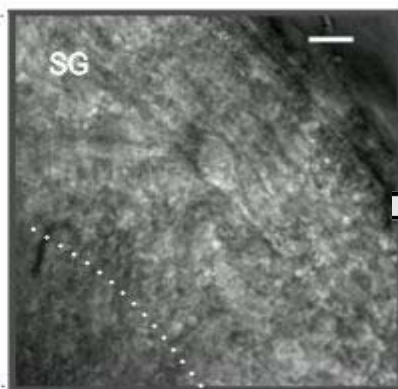
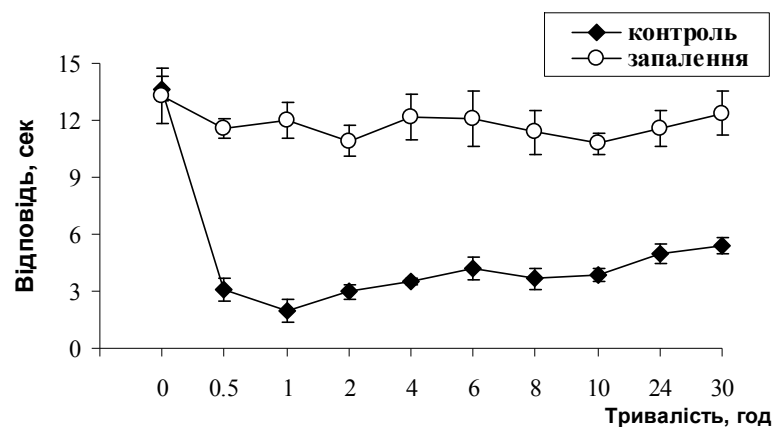
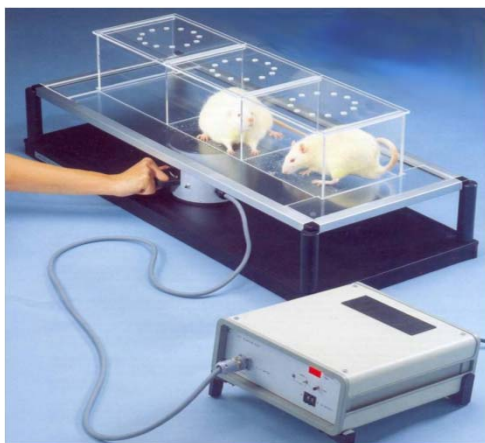
Important feature of AMPA receptors: they are not static.

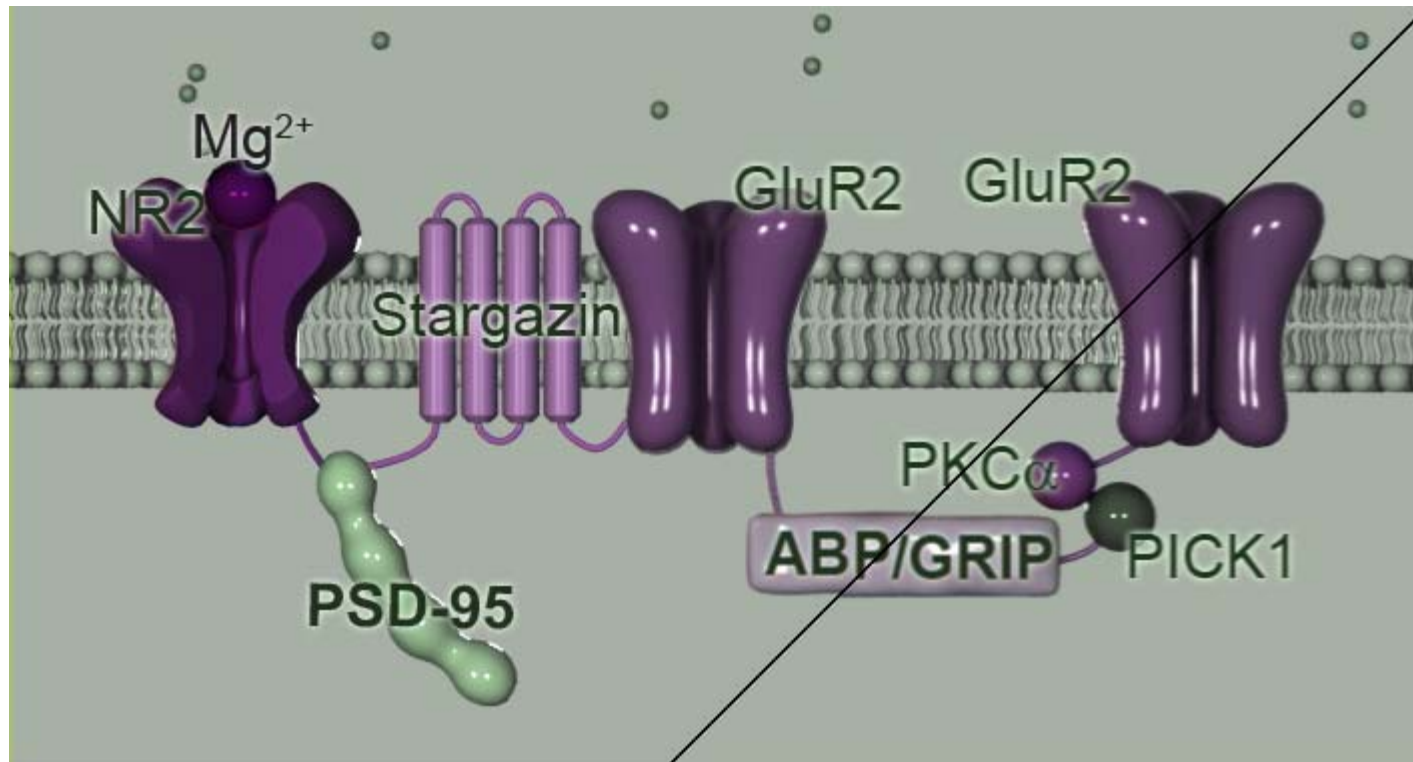


GluR2 subunit determine Ca^{2+} permeability of AMPA receptor

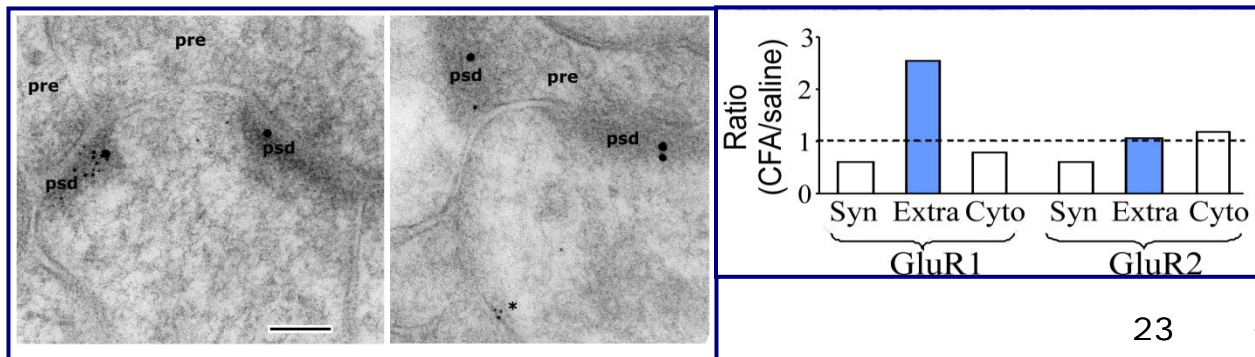
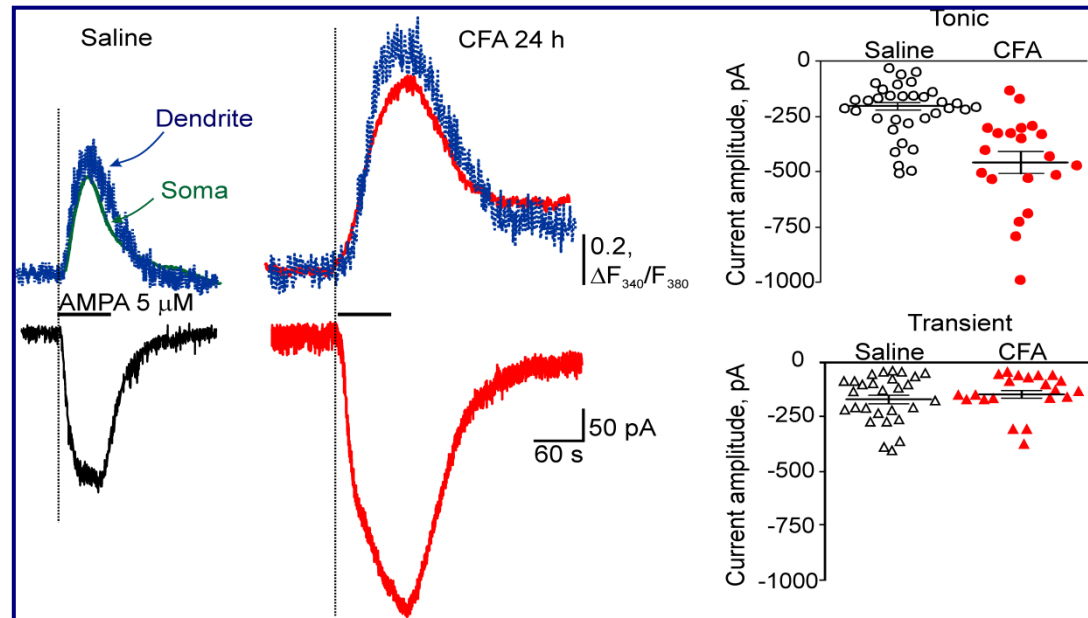


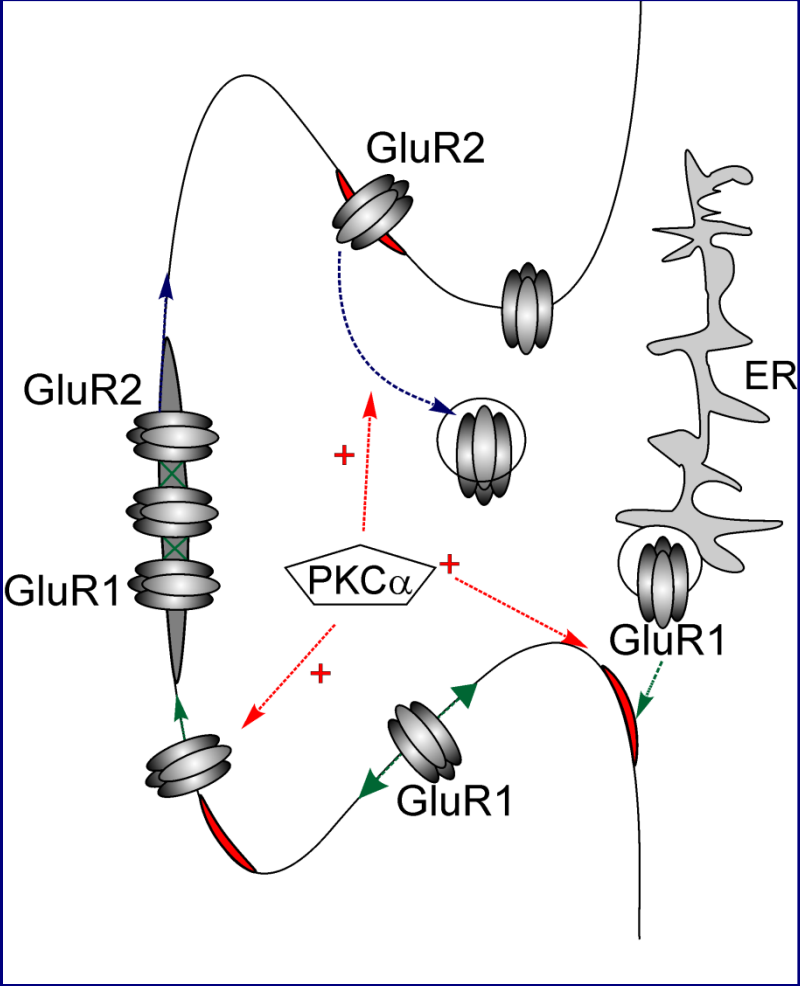
in vivo and *in vitro* registration



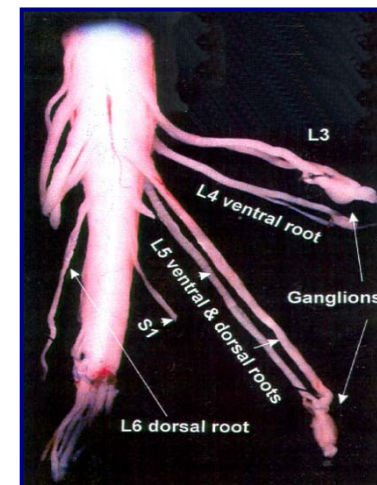
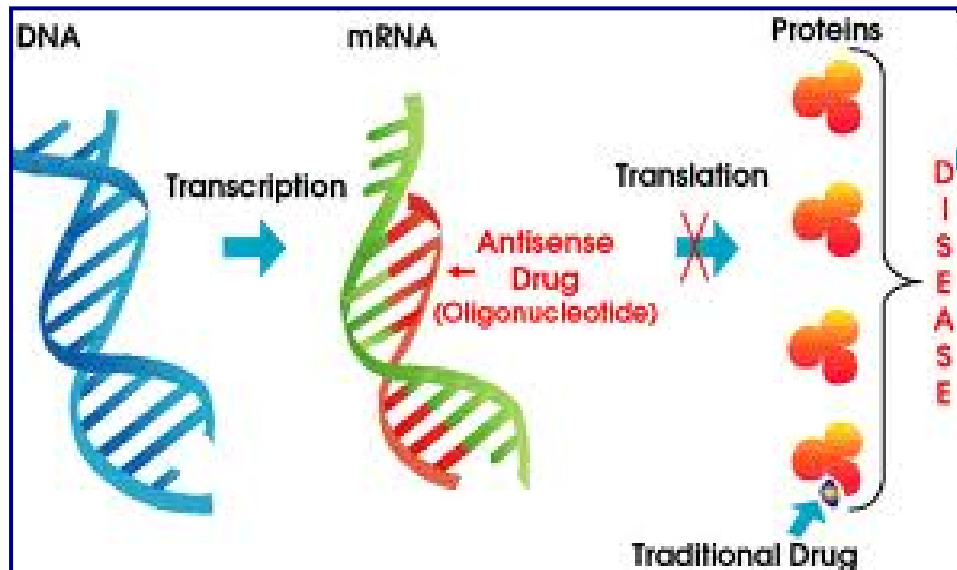


Increasing of Ca²⁺ permeability of AMPA receptors





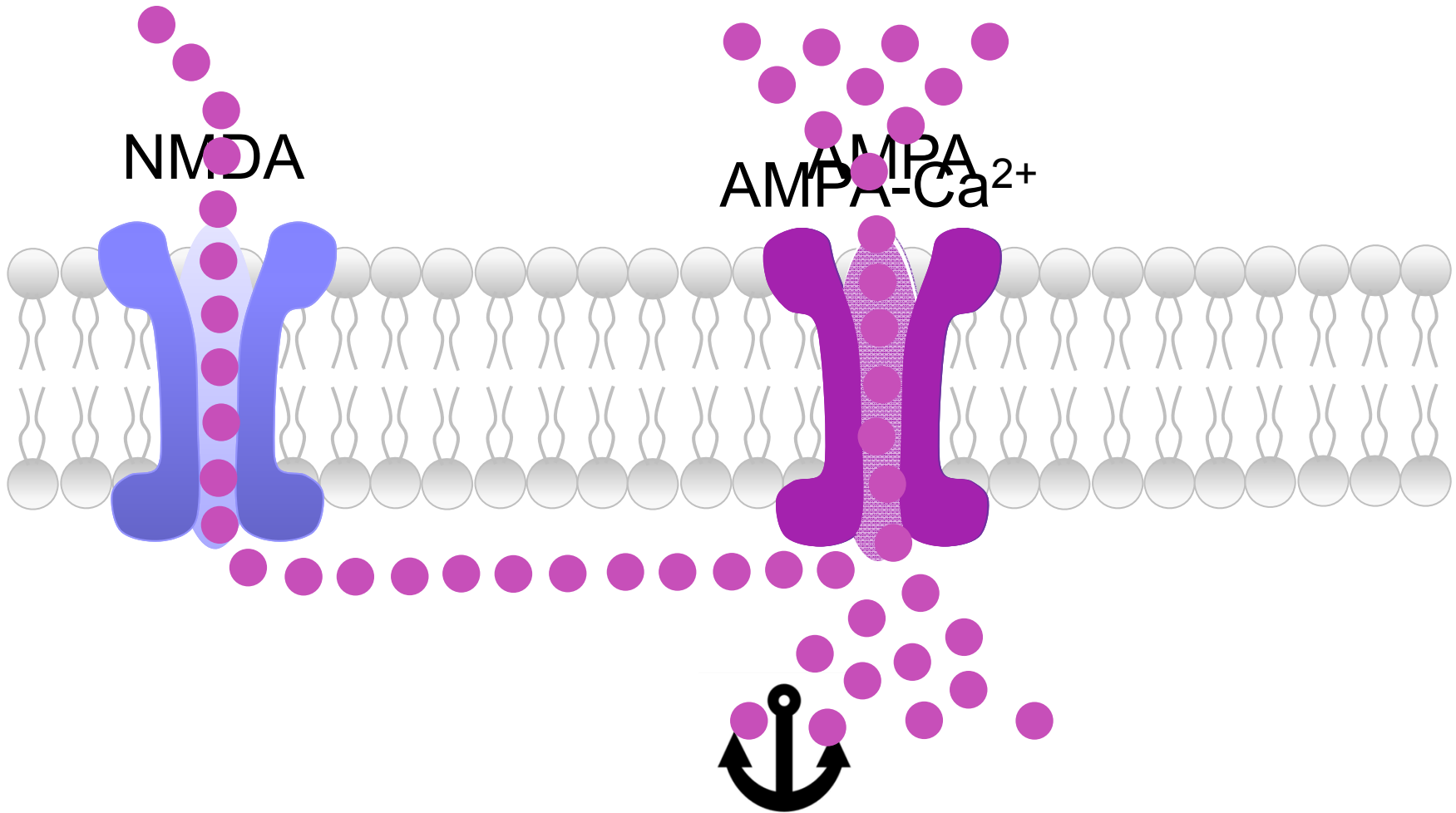
Antisense oligonucleotides: scheme of action





NMDA

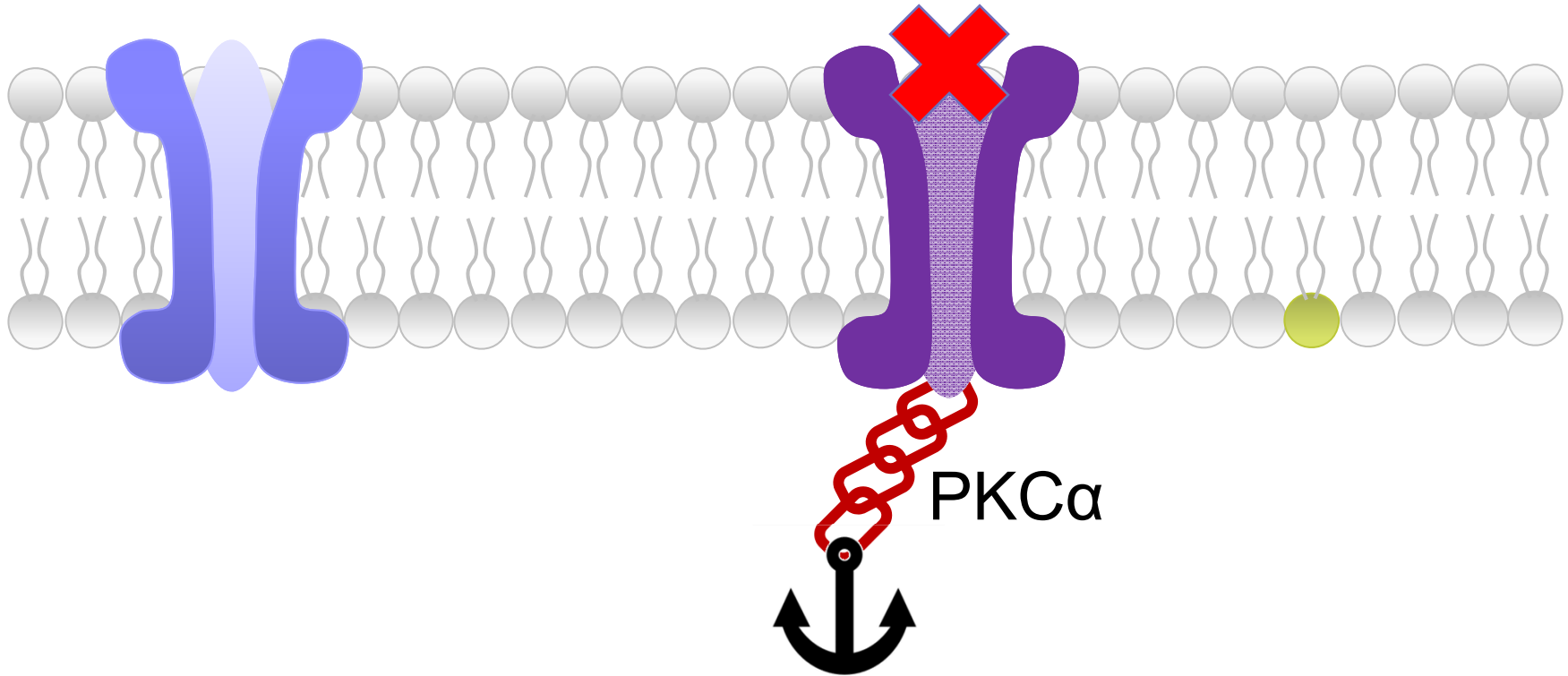
AMPA
AMPA-Ca²⁺





NMDA

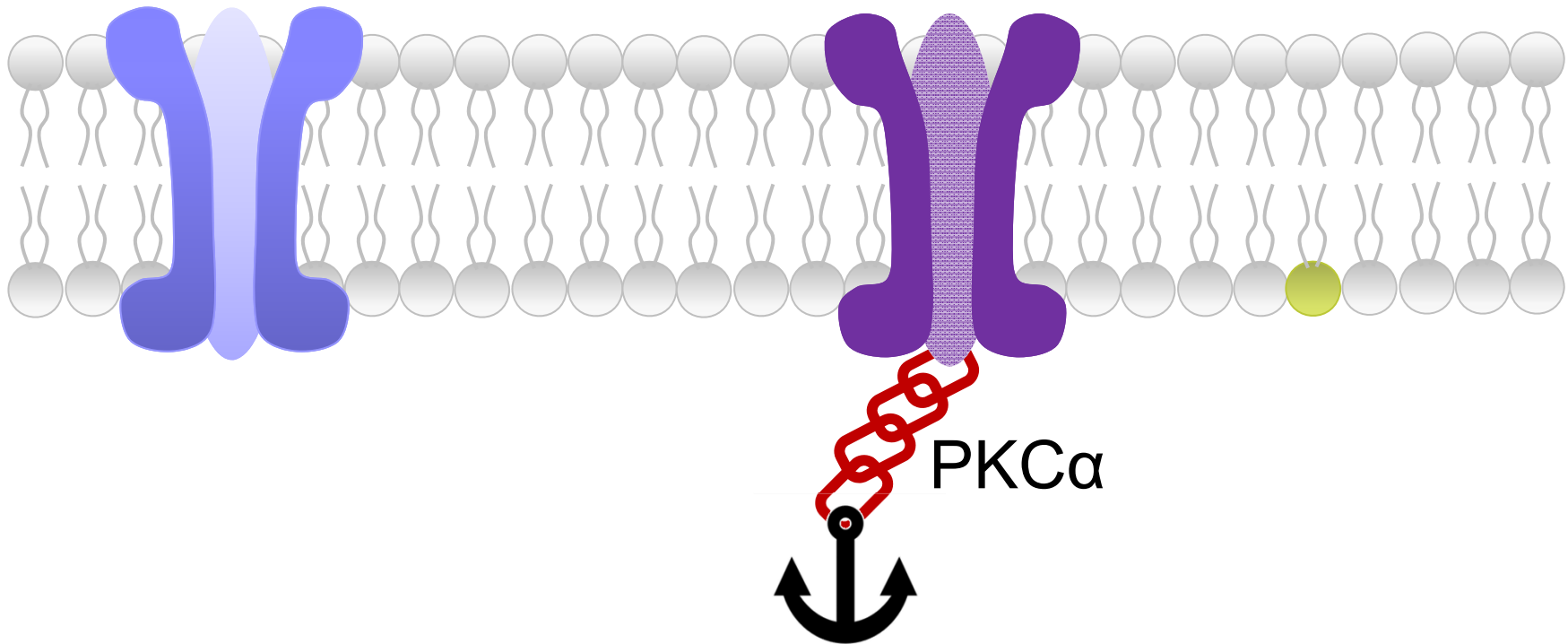
AMPA



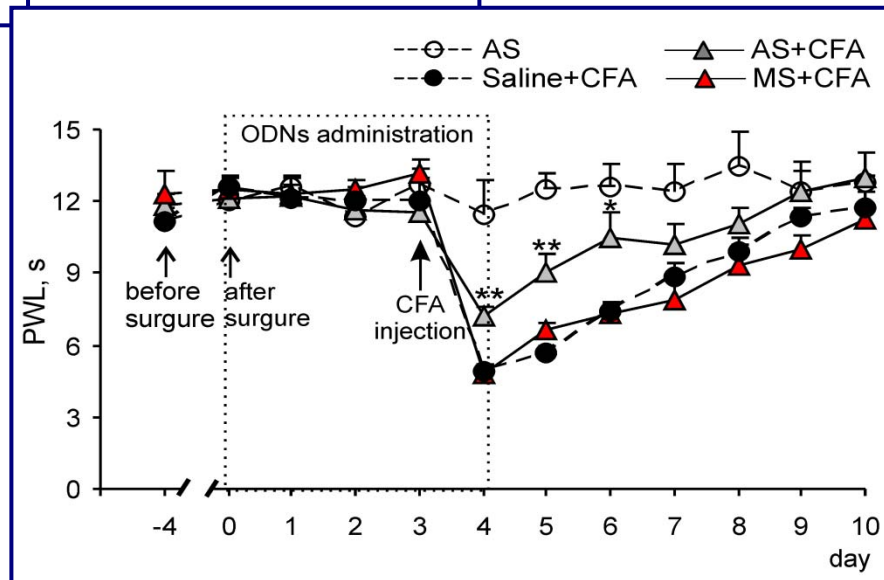
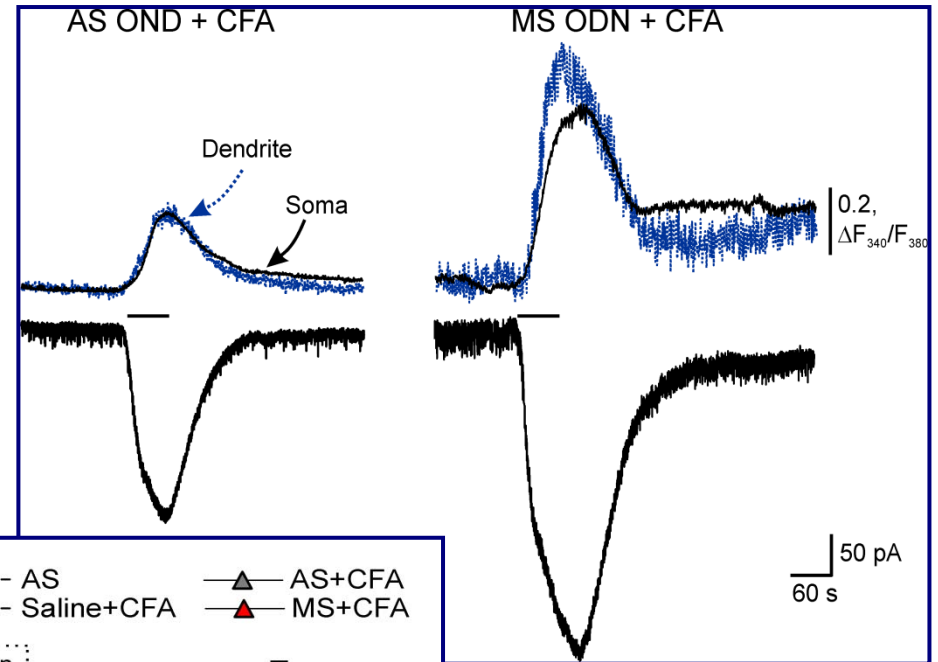
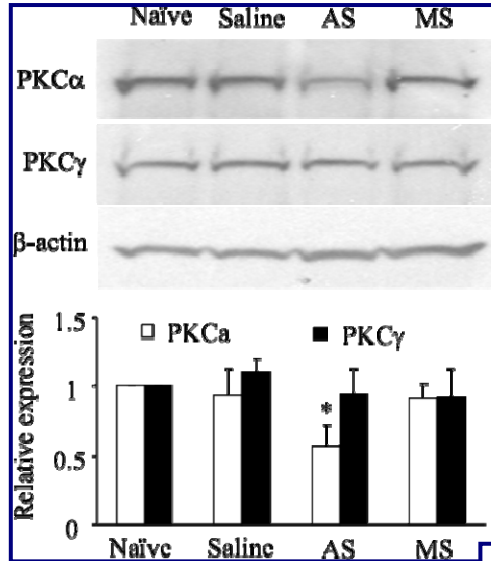


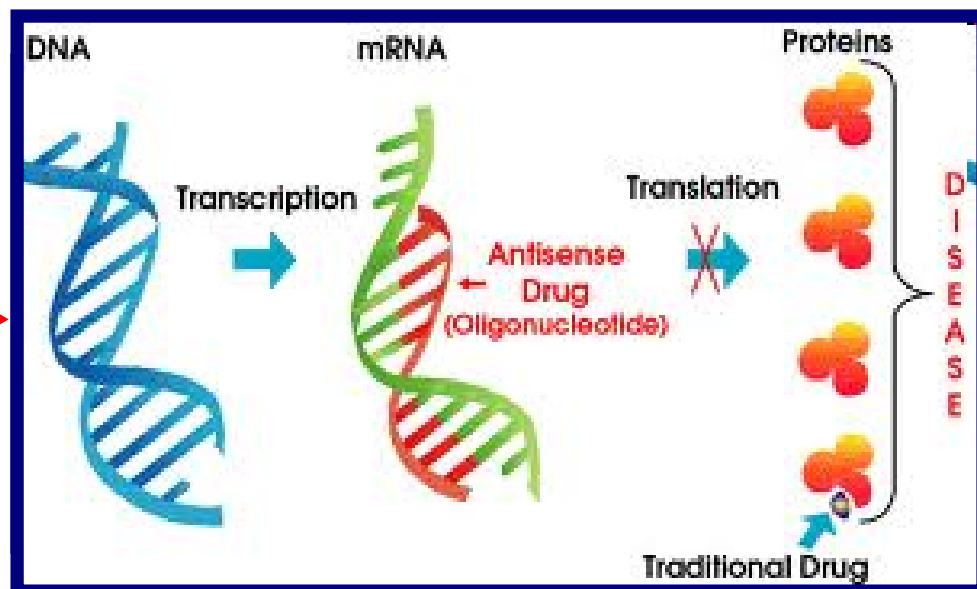
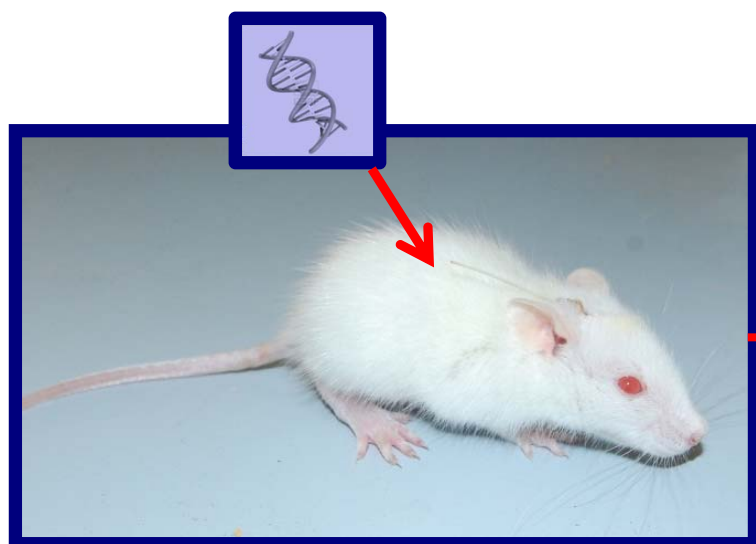
NMDA

AMPA



Вимкнення PKC α у спинному мозку відновлює функціональну експресію AMPA рецепторів та усуває больову гіперчутливість





THANKS!



Artist: Vadim Holovanov