CALCIUM DISORDERS AS A COMMON DENOMINATOR OF DIFFERENT TYPES OF PAIN

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*The research team headed by **Dr. Nana Voitenko** studies molecular mechanisms of chronic pain. Team leader Dr. Nana Voitenko graduated form Moscow Institute of Physics and Technology in 1992. In the same year she began working at the Bogomoletz Institute of Physiology. She defended her Ph.D. thesis in Biophysics in 1995 and became a Doctor of Science in Physiology in 2004.*

Dr. Voitenko is particularly well known for her research and expertise on calcium signaling in nerve cells, especially under conditions of diabetic neuropathy and other types of pain syndromes. In addition to her significant research contributions, she is one of the founders of the Ukrainian Society for Neuroscience and is President of Ukrainian Chapter of the U.S. Society for Neuroscience. Starting from 2008 she has been a vice-chair of Molecular Physiology and Biophysics department at the Kyiv Branch of Moscow Institute of Physics and Technology. Dr. Voitenko teaches students at Taras Shevchenko National University and Kyiv Branch of Moscow Institute of Physics and Technology.

Dr. Voitenko has received numerous awards, including U.S. Civilian Research and Development Foundation (CRDF) honor medal for "support for CRDF in developing international collaboration between the United States and Ukraine". She has received numerous grants including two research grants from the Juvenile Diabetes Research Foundation.

Dr. Voitenko has established world-wide scientific contacts. Profs. B. Hille, M. Randic, and Dr. Y.-X. Tao from USA, Dr. M. Rossier from Switzerland, Dr. E. Bourinet from France, and Prof. A.H. Dickenson from the U.K. have been her collaborative partners. Results obtained by Dr. Voitenko and co-authors have been published in high-rating scientific journals such as "Journal of Neuroscience", "Cell Calcium", "Diabetologia", etc.

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. Patients in pain are

likely to become depressed and anxious, have disturbed sleep patterns and generally have a poor quality of life. The importance of understanding the ways by which the central nervous system can alter incoming signals that relate to pain processing stimulated an increasing number of investigations, many of which are focused on two first elements in the pain pathway, namely dorsal root ganglion (DRG) and dorsal horn (DH) neurones.

Multiple and possibly common mechanisms appear to be involved in generation of chronic pain on the level of primary and secondary sensory neurones independently of aetiological diagnosis of pain. Molecular mechanisms leading to changes in patterns of action potential generation in primary neurones, modification of synaptic transmission between primary central afferents and secondary DH neurones and spinal neurone hyperexcitability acting in concert contribute to generation of chronic pain. In spite of profound difference in patterns of changes or damage in primary and secondary nociceptive neurones, the pain syndromes as observed in numerous studies conducted on different animal models are generally common. Thus, there is a reason to believe that multiple and common mechanisms may be present in chronic pain conditions of all aetiologies.

Calcium is a universal second messenger, and changes in the intracellular cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) triggers a wide spectrum of cellular responses including a long-lasting modification of synaptic transmission and changes in cellular excitability, which may lead to changes in the transmission of nociceptive stimuli. It has been shown in recent works originating from different laboratories that experimental chronic pain conditions (including peripheral inflammation, nerve injury and diabetic neuropathy) do induce significant changes in $[Ca^{2+}]_i$ regulation in DRG and DH neurones participating in transmission of nociceptive signals (Voitenko *et al.,* 1999; Voitenko *et al.,* 2000; Huang *et al.,* 2002; Kruglikov *et al.,* 2004). Thus, impaired cytosolic free calcium regulation may be a basis for abnormal nociceptive signaling during various types of diseases and pain syndromes. Moreover, we have shown that these changes in the calcium regulation are similar in DRG and DH neurones indicating that they might be general for many types of neurones from central and peripheral nervous systems.

Abnormalities in neuronal calcium homeostasis, which lead to impairment of nociceptive neurotransmission, has been detected in many pain models such as diabetic and nerve-legation-induced neuropathies, carrageenan- and CFA-induced inflammation, cancer pain, etc. In particular, we have shown an increase of Ca^{2+} entry to the cytosol via AMPA receptors in neurones of inflamed rats (Voitenko *et al.,* 2004a, Park *et al. 2009*); an increase of Ca^{2+} entry to the cytosol via voltage operated calcium channels in neurones of neuropathic rats (Voitenko *et al.* 2000); a decrease of calcium uptake and release by mitochondria (Kruglikov *et al.* 2004), and a decrease in calcium mobilization from different types of the endoplasmic reticulum (ER) calcium stores (Kruglikov *et al.* 2004) in neurones of both pathologies (Svichar *et al.,* 1998; Voitenko *et al.,* 2004b). It is also important

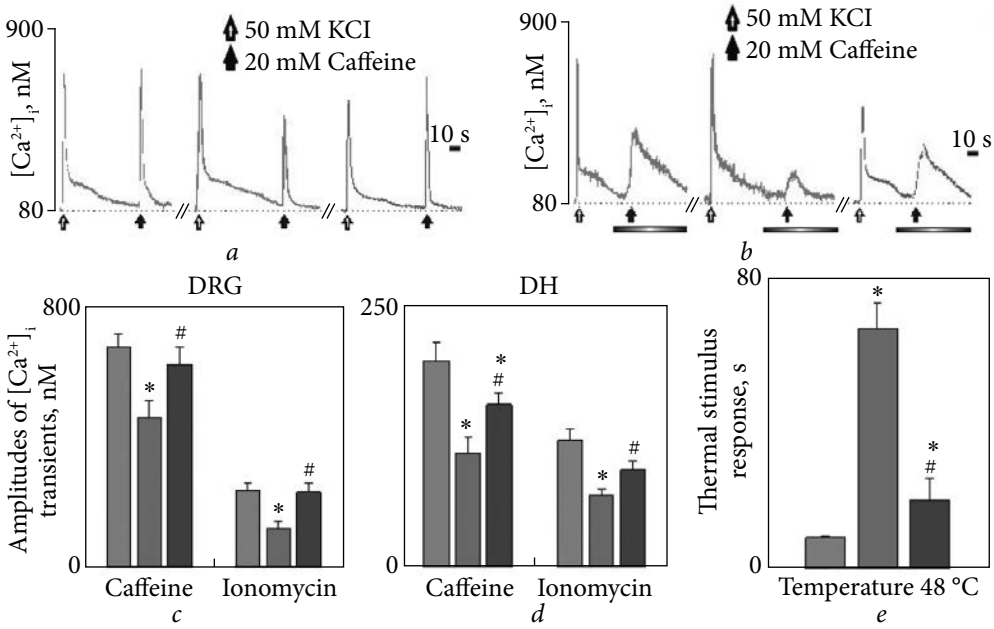

Fig. 1. Nimodipine-induced restoration of calcium signaling and facilitation of diabetes-induced sensory abnormalities: *a* and *b* — representative examples of the effect of nimodipine treatment on amplitudes of $[Ca^{2+}]_i$ transients induced by application of caffeine (*a*) and ionomycin (*b*) in DRG neurons. The traces recorded from a neuron of control animal are shown in green, diabetic — in red, and nimodipine-treated diabetic one — in blue colors. Grey bars in B indicate the use of Ca^{2+}-free extracellular solution; *c* and *d* — average values of amplitudes of caffeine- and ionomycin-induced $[Ca^{2+}]_i$ transients in DRG (*c*) and DH (*d*) neuronal preparations of control (green bars), diabetic (red bars) and nimodipine-treated diabetic (blue bars) rats; *e* — hot plate test: nimodipine treatment (blue bar), partially normalized thermal sensitivity in diabetic rats (red bar) as compared with control animals (green bar). Diagrams reflect a latency of nociceptive reaction at 48 °C. * $P < 0.05$ vs. control, # $P < 0.05$ vs. diabetic animals. In all experiments $n > 10$

to emphasize that calcium abnormalities in these models are well correlated with development of many pain-related symptoms such as thermal and mechanical hyper- and hypoalgesia and changed pain sensitivity, indicating possible relationship between them.

Another corroboration of the calcium theory of pain is the fact that chronic treatment with calcium antagonists may be effective in both the restoration of calcium signaling in DRG and DH nociceptive neurones and the reduction of diabetes-induced sensory abnormalities. We have shown recently (Shutov et al. 2006) that treatment with calcium channel blocker nimodipine was able to restore impaired Ca^{2+} release from the ER, induced by either activation of ryanodine receptors or by receptor-independent mechanism in both DRG and DH neurones (Fig. 1). The beneficiary effects of nimodipine treatment on $[Ca^{2+}]_i$ signal-

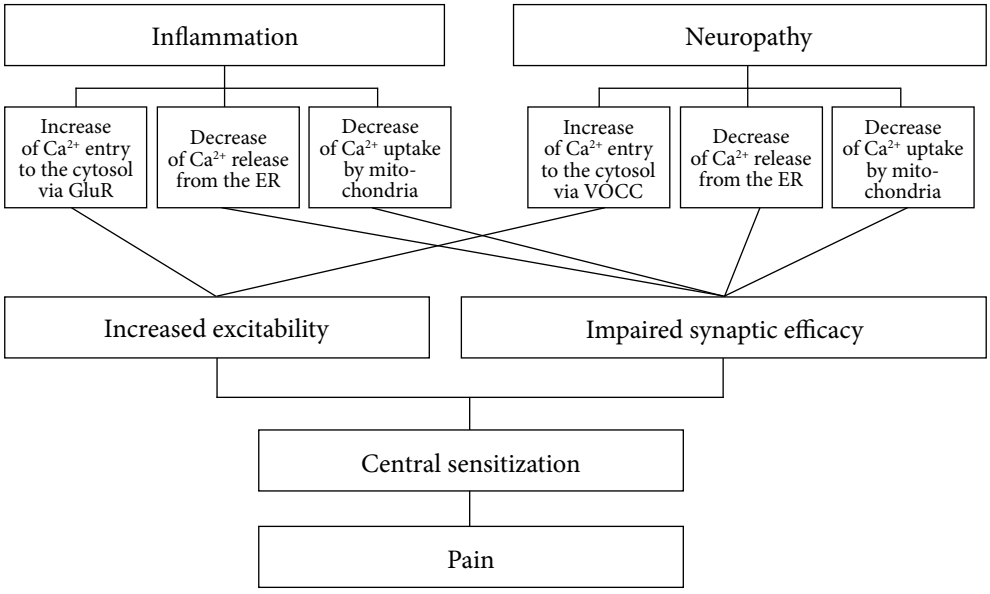

Fig. 2. A simplified scheme of calcium theory of pain. An increase of Ca^{2+} entry into the cytoplasm together with decrease of Ca^{2+} accumulation by ER and mitochondria lead to calcium overloading, which, in turn, results in hyperexcitability of nociceptive DRG and DH neurons and changes of synaptic efficacy between them. All together this may produce central sensitization and pain

ing were paralleled with the reversal of diabetes-induced thermal hypoalgesia and normalization of the acute phase of the response to formalin injection. Nimodipine treatment was also able to shorten the duration of the tonic phase of formalin response to a control value.

It should be also noted that at the present moment there is no theory which can explain the development of allodynia and hyper- and hypoalgesia during diseases of different aetiologies, as well as there is no unified point of view concerning the influence of altered calcium homeostasis on neuronal structures responsible for impaired nociceptive synaptic transmission and induction of pain. Therefore, any advances in development of unifying theory that may explain how different diseases result in common pain abnormalities look very attractive. Basing on many recent observations including ones mentioned above, we venture to suggest the following simplified scheme that might be a basis for this theory: increase of calcium entry via voltage- or ligand gated calcium channels and/or decrease of accumulation of Ca^{2+} by the ER and mitochondria as a result of disease development lead to temporal or permanent calcium abnormalities. That, in turn, results in hyperexcitability of DRG/DH neurones and/or changes of synaptic efficacy between them. All together may produce central sensitization and pain (Fig. 2).

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