**PAVEL T. KRAEVSKY, MD.** ***The Modulation of Nociception and Analgesic Effects by Nonsteroidal and Steroidal Adjuvants. Neuropathic and Inflammatory Experimental Models and Clinical Studies***

PhD Thesis in Pharmacology, incl. Pharmacokinetics and Chemotherapy.
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The treatment of nociceptive and neuropathic pain is a major problem which medicine has been challenging continuously. The intellectual and financial demands for effective pain management are rising constantly. It is known that each one of tree persons in the modern industrial societies has been visiting a doctor because of acute or chronic pain. A rationale approach to optimise and individualise the management of pain is the implementation of analgesics and adjuvant supplement. Such combination could increase the analgesic effect and alleviate/retard the appearance of unwanted adverse reactions.

***Aim:*** (i) In vivo and in vitro investigations of nociception and analgesia in experimental models of acute and chronic pain by advanced pharmacological and EM-histomorphological methods, (ii) Clinical and experimental studies of the potency of classical and new analgesic drugs in the post-operative antinociception, (iii) Pharmacological investigations of the modulation of nociception and development of tolerance/dependence by different adjuvant drugs.

***Experimental Models and Methods:*** (i) NOCICEPTIVE AND INFLAMMATORY PAIN: Carrageenan hyperalgesia and Freund's adjuvant arthritis - Paw pressure test (PPT), Incapacitance test (IT), Plethysmometry. (ii) NEUROPATHIC PAIN: Diabetic neuropathy and constrictive ligature of Sciatic nerve - von Frey hair test (FHT), Heath plantar test (HPT). (iii) OPIOID TOLERANCE/DEPENDENCE AND NOCICEPTION: Morphine-induced tolerance/dependence and Naloxone-pricipitated withdrawal in rats - Tail-Flick test (TFT), Hot plate test (HP). (iv) IN VITRO METHODS: Histochemical investigations - Cell toxicity and stimulus evoked $^{45}Ca^{2+}$-uptake.

***Clinical Methods:*** Evaluation of acute post-operative pain by visual analogue scale in adult female and male patients.

***Statistics:*** GraphPad Prism 5 (Mac OSX). Were used for data processing and statistical analysis.

***Principle Scientific Contributions:*** (i) Experimental model of acute postoperative pain in rats was developed and validated. (ii) The protocols implicated for Parecoxib or Meloxicam treatment proved suitable for post-operative analgesia throughout first 48 hours after major resp. minor orthopedic interventions in female and male adult patients.
It was found that in these patients Benfotiamine supplementation by Parecoxib and Meloxicam is a promising pain management. (iii) It was shown for the first time that in inflammatory hyperalgesia Benfotiamine modulated the analgesic action of COX-inhibitors. (iv) It was shown for the first time that Benfotiamine/Thiamine modulated the analgesic activity of Morphine and alleviated the somatic signs and psychic reactions of opioid tolerance/dependence. (v) It was found that administration of Testosterone/Nandrolone as anabolic steroids might increase or decrease the analgesic effect of Metamizol. (vi) It was found that classic (L-NAME, L-Can) as well as newly synthesized (NoCan, NoCanMe) NOS-inhibitors could modulate opioid tolerance and $^{45}Ca^{2+}$ uptake.

Experiments were conducted: Laboratory of integrative and molecular mechanism of nociception and addiction, Department of Pharmacology and Toxicology, MU Sofia; Department of Neurobiology of Adaptation, BAS; Centre of Molecular Medicine, Karolinska Institutet, Stockholm, Sweden;
The Thesis contains 163 pages incl. 40 figures and 6 tables. The references include 388 titles. The author has published 8 papers and presented 17 communications at national, international or world congresses.