PAIN UNIT AT THE DEPARTMENT OF EXPERIMENTAL BIOLOGY FMUP

Activity Report 2009

1. Objectives and achievements during 2009

1.1. OBJECTIVES defined during 2009:

A) Genetic Determinants

Identify Drg11a/b phosphorylation sites to test their functional relevance on nociceptive system development and characterize the phylogenetically conserved motifs that regulate DRG11 expression.

B) Circuit Organization/Plasticity

Investigate the properties of synaptic connections between spinal substantia gelatinosa excitatory interneurons;

Evaluate the phosphorylation of ERKs in the spinal cord and noradrenergic neurons of the brainstem during neuropathic pain and study the effect of noxious mechanical stimulation;

Characterize the pain-induced disruption of fronto-hippocampal information flow and the plasticity of reward-related prefrontal and amygdalar circuits using neurophysiological recordings from chronically implanted multielectrodes in freely-moving animals.

C) Physiopathology of Pain

Articular: Characterize the changes in primary afferent neurons innervating osteoarthritic joints;

Diabetic neuropathy: Prevent diabetic neuropathy by insulin growth factor 1 (IGF-1), antioxidants or by interfering upon spinal glia;

Visceral: Study the distribution of the high and low affinity receptors of botulinum toxin in human, rat and guinea pig bladders; study the effects of intrathecal administration of different antagonists of neurotrophins receptor in animals with chronic bladder inflammation; study the interaction between TRPV1 and NGF in chronic bladder inflammation.

D) Innovative Therapies

Study the effect of decreasing noradrenaline levels in pain control areas of the brain using gene therapy;

Continue the ongoing multicentre study of botulinum toxin (BoNT/A) versus placebo in patients with overactive bladders of neurogenic aethiology;

Study new oral antagonists of the TRPV1 for bladder overactivity;

Proceed with clinical trials of BoNT/A in patients with painful bladder pathologies.

E) Epidemiology of Pain

Complete the study on the prevalence of chronic pain in Portugal and start a study on post-operative pain in Portuguese hospitals.

1.2. Main Achievements during 2009:

A) Genetic Determinants

Prrxl1 expression of 5´-UTR mRNA variants is controlled by three distinct promoters;

Two adjacent regulatory elements were identified: one presenting capability to strongly reduce the combined activity of the three Drg11 promoters and another with the potential to inhibit the repressive trait of the former motif;

Drg11 expression is enhanced in inflammatory but not in neuropathic pain.

B) Circuit Organization/Plasticity:
Developed a technique of imaging of unstained cells and intracellular structures in isolated spinal cord, brainstem, ganglia and cerebellum;

Neurochemical characterization of cannabinoid synthethizing- primary afferents in the rat;

Glutamatergic synapses formed by excitatory interneurons of the substantia gelatinosa show high transmission efficacy and variable forms of functional plasticity;

Chronic pain alters the thalamocortical flow of information during sleep-wake cycles;

Chronic pain impairs the single cell activity in orbitofrontal cortex during strategic planning and risk assessment;

The spectral coherence of the thalamocortical loop measured from intracranial local field potentials in animals under isoflurane is a promising alternative to other indexes of depth;

ERKs phosphorylation increases in the spinal dorsal horn upon noxious stimulation of naive animals;

ERKs phosphorylation occurs in noradrenergic neurons of the brainstem during neuropathic pain in a pattern that is not altered by noxious stimulation.

C) Physiopathology of Pain

Articular: Osteoarthritic animals showed increased expression of the regeneration marker GAP-43 in sensory neurons expressing ATF-3;
Diabetic neuropathy: glial activation in the spinal cord of diabetic rats is associated with changes in the potassium chloride co-transporter;
Visceral: Blockade of neurotrophin signaling reduces visceral pain and bladder overactivity in cystitis.

D) Innovative therapies
The decrease of noradrenaline in pain control brain areas reverts neuropathic pain;
Injection of botulinum toxin in the bladder trigone reduces bladder pain and urinary neurotrophins in patients with interstitial cystitis;
NGF induces bladder overactivity via TRPV1;
The oral TRPV1 antagonist GRC6211 reduces bladder overactivity in spinal cord injured-rats.

E) Epidemiology of Pain

Indirect costs of chronic pain in Portugal, due to sick leave only, were estimated at more than € 250 million/year;
Data from more than 1.000 patients subject to surgery showed that 73% suffered from post-operative pain (moderate or severe in 23% of them).