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This research is carried out within the PAINCAGE project with the support of the European Union under the 7th framework program GA n. 603191

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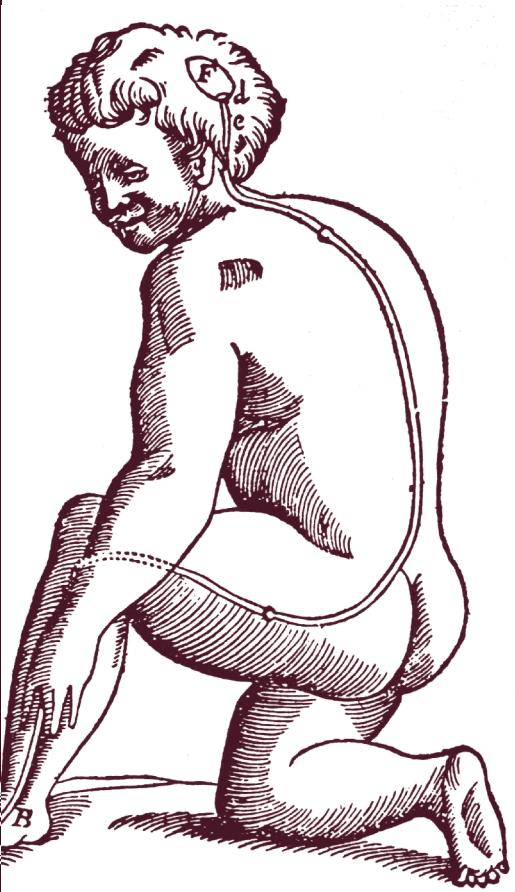
PAINCAGE

The NGF System and its interplay with endocannabinoid signalling, from peripheral sensory terminals to the brain: new targets for the development of next generation drugs for neuropathic pain



SEVENTH FRAMEWORK PROGRAMME

PROJECT CONTEXT AND THE MAIN OBJECTIVES

Chronic pain (CP) is a big unmet medical need and more effective safe drugs are badly needed. Among the most common forms of CP are: i) neuropathic pain (NP) , associated with nerve injury in the peripheral or central nervous system; and ii) osteoarthritis (OA), a progressive degeneration of cartilage of joints, characterized by inflammation and pain. There is no effective treatment for these highly prevalent disabling disease states and current treatments (NSAIDs and opioids) cause serious side-effects. Two molecular systems have recently emerged as central regulators of pain mechanisms, the Nerve Growth Factor (NGF) system and the endocannabinoid (EC) system. NGF is a key player in the onset and progression of CP syndromes, regulating both the neuronal and the inflammatory components of CP. Consistently, genetic mutations in genes encoding NGF or its receptor TrkA cause severe congenital insensitivity to pain in patients. Inhibition of this target system could therefore lead to a new class of painkillers. Therapeutic anti NGF antibodies have been clinically tested in patients, demonstrating a remarkably effective analgesia in patients suffering from OA and low back pain. However, safety concerns, stemming from those trials, need to be addressed and understood, to fully exploit the therapeutic analgesic potential of this target system. The PAINCAGE Project investigates the role of the NGF system in pain mechanisms and its interactions with the EC system, focussing at different levels of pain transmission and perception, from peripheral sensory terminals to the brain.

Questions addressed by PAINCAGE team members include: What is the most effective way of neutralizing the NGF system, to obtain analgesia: targeting the ligand NGF or its receptors (TrkA, p75-NTR and sortilin)? What is the safest approach? How do the NGF and the EC systems interact in regulating pain signalling and perception? How do mutations in genes encoding NGF or its receptor TrkA determine congenital pain insensitivity and what are the central consequences of "suffering without pain"? Can we develop long lasting analgesic drugs that exploit epigenetic mechanisms regulating these systems? A new drug candidate (p75NTR-Fc), based on these ideas, is being studied and developed within the PAINCAGE consortium .

The PAINCAGE project will address the above mentioned questions and provide the mechanistic basis to accelerate the development of a new generation of painkillers

WORK PERFORMED SINCE THE BEGINNING OF THE PROJECT AND THE MAIN RESULTS ACHIEVED SO FAR

Activities have so far focussed mainly on the development and validation of tools and models enabling the planned research. In more detail, focus has been on (1) improving technical aspects (2) producing and analysing mouse models to dissect the role of NGF and EC systems in peripheral and central CP mechanism (3) controlling NP and OA onset, progression and perception by pharmacological treatment with antiNGF, antiTrkA and p75-Fc (NGF scavenger) in different pain models and analysing transcriptomic changes in NP after NGF-based treatments. (4) analysing safety issues related to the anti-NGF therapy.

Following are the main results achieved so far:

A proof of concept of a technological platform based on activity reporters ("TRAP/ permanent access to transiently active neurons") and light-sheet microscopy has been obtained, that will allow mapping pain pathways under different pathological or pharmacological conditions. A computational platform to mathematically simulate the "NGF system" has been designed, for simulating in silico the effects of drugs targeting different points of the complex system.

New mouse models, in which the NGF and the EC pain pathways have been specifically disrupted at different points and in different cells, have been exploited , to study how pain responses will be affected. A transcriptomic gene expression profiling of brain areas from these mice, under different pathological or pharmacological conditions, has been performed, to discover new pathways and targets related to pain. Congenital insensitivity to pain is a rare pathological condition, the other side of the coin of CP. Mouse models of two painlessness genetic disorders in patients, Hereditary Sensory Neuropathies HSAN IV and HSAN V, linked respectively to mutations in the TrkA and NGF genes, have been produced and will be used to dissect the clinical phenotype of HSAN patients and the respective role of TrkA receptor versus NGF in pain responses.

Concerning the EC system, NP determines a decrease in cortical synaptic plasticity, via a reduction of EC receptor CBR1 expression. Consistently, the deletion of CBR1 expression in neurons correlates with a reduced threshold for pain and CBR1 are necessary for the analgesic effect of electroacupunture. A novel form of the CBR1, specifically expressed in mitochondria ($mtCB_1Rs$), has been discovered to mediate the functional effects of EC in the central nervous system, a finding whose relation to pain responses is currently investigated.

Antibodies or ligand scavengers targeting NGF or its receptors TrkA, p75-NTR or sortilin have been used in different pain models, to compare their analgesic properties and study the underlying mechanisms. The analgesic actions by anti NGF and anti TrkA antibodies in a NP model were found to outlast the last dosing by up to three months. The remarkable long lasting analgesia by NGF/TrkA targeting antibodies will be correlated to changes in gene expression and in epigenetic mechanisms occurring in the pain pathways.

Concerning safety, it was found that the adverse event of "accelerated OA" , that had been reported in a subset of patients receiving antiNGF antibodies as a treatment for OA, particularly in association with NSAIDs intake, can be replicated in rodents (clinical-to-preclinical translation), providing a strong basis for a rational investigation of safer approaches targeting the same molecular pathway.

EXPECTED FINAL RESULTS AND THEIR POTENTIAL IMPACTS AND USE

The NGF and the EC systems are crucial regulators of pain pathways. The PAINCAGE project is in the unique position to compare different approaches targeting these systems, in terms of analgesic pharmacological effectiveness, safety and activation of downstream molecular targets. The results of the project will provide a solid basis to accelerate the development of already identified second-generation therapeutics, based on the "NGF target" system, as well as for the identification and validation of new druggable targets emerging from the elucidated mechanisms. It will also identify biomarkers for NP, validated in animal models and clinical samples, that could result in future clinical benefits, for the stratification of patients suffering from different neuropathies.