Plenary lectures

Plenary lecture 2

Neurons and Circuits Contributing to the Pain-Inhibits-Pain Phenomenon

Hanns Ulrich Zeilhofer

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Pain perception is not only a function of peripheral nociceptive input but is heavily influenced by its actual context. Stress-induced analgesia is probably the most well-known example, the so-called “pain-inhibits-pain” phenomenon is another example which is known to many people from daily experience. This phenomenon describes that an acute painful stimulus applied to one body site reduces pain at other sites. It is generally accepted that context dependent modulation of pain experience depends on neural pathways that descend from various brain areas to the spinal cord via the rostral ventromedial medulla. However, the precise circuit basis of this “pain-inhibits-pain” phenomenon, also known as diffuse noxious inhibitory control (DNIC) in animals or conditioned pain modulation (CPM) in humans, is largely unknown. Anatomical and optogenetic circuit tracing methods allowed us to identify a population of descending inhibitory neurons of the rostral ventromedial medulla (RVM) that densely and bilaterally innervate the spinal cord along its entire rostrocaudal axis. Activating these neurons reduced heat and cold sensitivity widely in healthy mice and caused similarly wide-spread antihyperalgesia in chronic pain models. Conversely, their silencing evoked mechanical allodynia and spontaneous pain-like behaviors. Noxious stimuli activated subsets of these neurons in the lateral paragigantocellularis nucleus (LPGi), which inhibited nociception upon chemogenetic reactivation. These spinally projecting inhibitory RVM neurons are hence ideally positioned to function as circuit elements of DNIC and CPM, while their dysfunction may contribute to wide-spread chronic pain syndromes.

Plenary lecture 3:

Implication of the cystine-glutamate exchanger in pain chronicisation

Emmanuel Hermans, Group of Neuropharmacology, Institute of Neuroscience, UCLouvain Belgium

Best known for their metabolic support of neurons, astrocytes are also actively involved in the control of excitatory transmission. Excitatory amino acid transporters at their membrane ensure the reuptake of synaptically released glutamate, thereby limiting excitability or protecting neurons against excitotoxicity. Thus, altered control of extracellular glutamate clearance by astrocytes has been documented in several neurological disorders, including chronic pain, where it contributes to central sensitisation. Also present on astrocytes is the cystine-glutamate exchanger (system xc-), which has received increasing attention during the two last decades. While this exchanger supports glutathione production in glial cells, it also contributes to a substantial non-vesicular release of glutamate maintaining an excitatory tone with potential harmful consequences on neurons. In this context, we have initiated a fundamental research programme to investigate the role of this exchanger in the development or maintenance of chronic pain. In models of chronic pain from neuropathic or inflammatory origin, genetic or pharmacological suppression was found effective in reducing allodynia and hyperalgesia. A reduction in lesion-associated neuroinflammation and central sensitisation is observed in animals lacking system xc-, which is likely to contribute to the reduction in pain. These findings support the search for new drugs targeting this exchanger as valuable pharmacological tools for the management of chronic pain.

Emmanuel Hermans, pharmacist, PhD.

Full professor Faculty of Pharmacy and biomedical sciences

Head of the group of Neuropharmacology at the UCLouvain

Plenary lecture 5:

New tools to probe pain pathways with light

De Koninck Yves (Canada)

The future of pain research hinges on the ability to bridge cellular signaling mechanisms and behaviour. Light-based technologies are enormously enabling in this respect as a growing number of tools emerge to probe and manipulate virtually all aspects of cellular signalling in live cells and tissue. I will present novel fiber-optics tools we are developing that enable multimodal probing and control of individual and small ensemble of cells in the intact brain and illustrate how this is allowing us to identify specific cellular mechanisms underlying chronic pain and comorbid syndromes.

Short communications

ACID-SENSING ION CHANNEL 3 (ASIC3) IN COLD SENSATION

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Background and aims: Acid-Sensing Ion Channels (ASICs) are cationic excitatory ion channels highly expressed in neuronal pain pathways where they appear as emerging key players. Extracellular pH variations are considered as the main activating/gating signal of ASICs, which are essentially seen as proton sensors. However, ASICs have also been reported to be modulated by others factors, including temperature, and ASIC3 has been proposed to behave as a coincident detector. The aim of this study is to explore the regulation of ASIC3 activity by temperature as well as its possible role in cold perception.
Methods: *In vivo* cold sensitivity was measured in adult male and female mice (WT C57Bl6J and ASIC3 $^{-/-}$ mice) using acetone behavioral test. ASIC3 activity was assessed by performing patch-clamp recordings and calcium imaging in HEK293 transfected cells and in cultured DRG neurons. The C-fiber sensitivity to cold temperature was measured in *ex vivo* skin-nerve experiments performed in both WT and ASIC3$^{-/-}$ mice. ASIC3 expression in mice DRGs was evaluated using RNAscope multiplex fluorescent *in situ* hybridization assay.
Results: Male and female ASIC3$^{-/-}$ mice showed reduced cold sensitivity both in the acetone test and the place preference test (25°C/23°C), compared to WT mice. This is in line with the *ex vivo* skin-nerve preparation data showing a reduced firing of C-fibers in response to cold ramps. The calcium response of ASIC3$^{-/-}$ DRGs in primary cultures did not fully explained the loss of cold sensitivity observed *in vivo* and *ex vivo*. Low temperatures increased the amplitude of acid-induced ASIC3 currents *in vitro*, with a slow-down of their inactivation kinetics. However, ASIC3 did not appear to be directly activated by cold temperature as compared to the cold sensor TRPM8. Finally, RNAscope experiments showed little overlapping signals between ASIC3 and the well-known cold sensors TRPM8 and TRPA1 transcripts.
Conclusion: Taken together, these data demonstrate an involvement of ASIC3 to cold sensitivity in mice, which is most probably related to the positive modulation of its activity by cold temperature, although the channel does not appear to behave as a direct cold sensor.

TREK1-POSITIVE NEURONS ARE INVOLVED IN CHLOROQUINE-INDUCED ITCH IN MICE

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Résumé

Background and aims. The TREK1 potassium channel is implicated in polymodal pain perception but its role in itch sensing has never been explored. Our aim is to study the involvement of TREK1-expressing cells in itch transduction and sensation.
Methods. We used chemogenetics to silence the activity of TREK1-positive neurons in mice thanks to TREK1-Cre driven expression of the hM4Di inhibitory receptor. The hM4Di ligand JHU37160 was administered systemically in mice before induction of pruritus using chloroquine injection in the nape. After evaluation of the scratching behavior, c-fos immunohistochemistry was performed in the cervical spinal cord to evaluate neuronal activation. In parallel, the contribution of TREK1-expressing neurons to itch transduction was studied using calcium imaging in DRG (Dorsal Root Ganglia) neurons exposed to chloroquine.

Results. Chemogenetic inhibition of TREK1-positive cells led to a strong increase in scratching while c-fos staining was similar between TREK1-hM4Di and control mice. *In vitro*, JHU37160 did not affect the response of DRG neurons to chloroquine.

Conclusions. TREK1-expressing neurons are involved in itch sensing. Peripheral transduction of itch appears to rely on a different cell population, suggesting a role of central TREK1 channels in chloroquine-induced pruritus. To further explore this hypothesis, we are studying the effect of TREK1 conditional knock-out in the spinal cord and DRGs on itch perception. We will present the development of an automated method for itch scoring in animals using deep learning.
Acknowledgements. We thank the 'Réseau français de recherche sur la douleur (RFRD)' for giving us the opportunity to present our data.

*Intervenant

REDUCED INFLAMMATION-INDUCED VISCERAL SENSITIVITY IN AGED MICE IS ASSOCIATED WITH HIGH POTENCY OF T CELLS TO PRODUCE ENKEPHALINS

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Background and Aims: Aging is closely linked with low-grade inflammation, or "inflammaging", due to immune senescence. Both innate and adaptive immune responses are altered in elderly individuals notably with an increase in activated T lymphocytes. Numerous studies have highlighted the significant role of opioid-producing $CD4^+$ T lymphocytes, upon activation, in the peripheral regulation of inflammation-induced pain. The activation of T lymphocytes leads to the local release of opioids, which impedes the activation of sensory neurons by inflammatory mediators secreted from damaged tissues and infiltrating immune cells. This study aimed to assess whether the opioid-mediated analgesic effect of T lymphocytes is preserved in older mice.

Methods: The intestinal homeostasis of elderly mice was assessed together with the ability of memory T cells to produce opioids (enkephalin). Visceral sensitivity was evaluated by colorectal distension in both basal and inflammatory conditions (DSS (Dextran Sulfate Sodium)-induced colitis).

Results: Our findings show that elderly mice exhibit a higher number of activated memory T-cells and a higher ability to produce enkephalin than young mice. Notably, elderly mice do not display intestinal hypersensitivity typically observed in DSS-induced colitis and develop a milder colitis than young mice.

Conclusions: Because of the higher potency of memory T cells to produce enkephalin, DSS-induced colitis severity including inflammation and related visceral pain is significantly reduced in elderly mice.

Contribution of the satellite glial cells in PACAP-induced migraine-like symptoms

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Résumé

Background and aims. PACAP (pituitary adenylate cyclase-activating polypeptide) has emerged as a key mediator in migraine, but its mechanism remains unknown. The aim of this study is to assess the contribution of the trigeminal satellite glial cells (SGCs) in PACAP-induced migraine.
Methods. Using behavioral testing and measurement of intracellular cyclic adenosine monophosphate (cAMP) concentration in living cells of female rats, we investigated the effects of repeated systemic administration of PACAP38 on changes in cephalic cutaneous mechanical sensitivity and the potential impact of PACAP38 on cAMP levels in cultured SGCs derived from rat trigeminal ganglion.

Results. Repeated injection of PACAP38 induces a persistent cephalic mechanical hypersensitivity, a reliable model for headache. Interestingly, incubation of cultured rat SGCs with graded concentrations of PACAP38 provokes a dose-dependent increase of intracellular cAMP levels. Pre-treatment with M65 or PACAP6-38, antagonists of PACAP receptor type 1 (PAC1) and PAC1/vasoactive intestinal polypeptide (VIP)/PACAP receptor type 2 (VPAC2) respectively, inhibits the PACAP38-induced elevation of cAMP in a concentration-dependent manner. In contrast, blocking VIP/PACAP receptor type 1 (VPAC1) with PG97-269 does not affect the PACAP38-induced cAMP production.
Conclusions. PACAP triggers migraine-like symptoms by increasing intracellular cAMP levels in trigeminal SGCs.

*Intervenant

PLX5622 PREVENTS INFLAMMATION IN A MURINE MODEL OF CORNEAL NEUROPATHIC PAIN

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Résumé

Background and aims
Corneal Neuropathic Pain (CNP) is closely linked to inflammatory responses along corneal pain pathways, involving the trigeminal ganglia and trigeminal brainstem. Recent studies suggest a key role of macrophages and microglia in the pathophysiology of CNP. PLX5622, a colony-stimulating factor 1 receptor (CSF1R) inhibitor, is commonly used to deplete macrophages and microglia. Here, we examined whether PLX5622 can prevent inflammatory responses in a mouse model of CNP.

Methods:
Male C57BL/6JRj mice were divided into four groups: those receiving topical PBS and fed either a normal diet or PLX5622 chow, and those receiving topical 0.2% Benzalkonium chloride (BAC) and fed either a normal diet or PLX5622 chow for 21 days. Tissues from the eyes, trigeminal ganglia, and trigeminal brainstem were collected for immunostaining to assess inflammatory and neuronal responses.

Results

In mice fed with normal chow, topical 0.2% BAC significantly increased the number of Iba1+ and CD68+ cells (macrophages) in the ipsilateral cornea and trigeminal ganglia compared to the PBS group. Additionally, in both PBS and BAC groups, three weeks of treatment with PLX5622 effectively depleted macrophages in the cornea and trigeminal ganglia. Mice fed with PLX5622 chow also exhibited a marked reduction in microglial cells (Iba1+) in the trigeminal brainstem. Preliminary results further suggest that PLX5622 reduced the number of c-Fos+ cells in the trigeminal nucleus in mice with CNP.

Conclusions
These initial findings confirm that PLX5622 depletes macrophages and microglial cells in

*Intervenant

both peripheral and central tissues. Further studies are needed to assess the impact of this cell depletion on corneal pain outcomes.

Fibromyalgia and Small fiber neuropathy: Which prevalence and which relationship with pain?

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Background

Fibromyalgia is a chronic pain syndrome characterized by widespread and severe pain, often accompanied by activity-disturbing symptoms with significant prevalence and socioeconomic impact. However, diagnostic challenges persist due to the lack of objective biomarkers and the subjective nature of symptoms. The involvement of small nerve fibers in fibromyalgia pathogenesis was first proposed in 2013, but the key question—*which comes first, peripheral or central sensitization*—still remains unresolved.

Methods

This study includes 150 participants divided into three age- and sex-matched cohorts. Participants undergo assessment at baseline and at six-month follow-up. By using multimodal approach to investigate small fiber function at the 4 extremities level and small fiber structures at the corneal sub-basal plexus and cutaneous intraepidermal layer: Sudoscan, Quantitative sensory testing (QST), Laser-evoked potentials (LEP), Corneal confocal microscopy (CCM) and anti-PGP 9.5-immunostained skin punch biopsy. Associated clinical symptoms are also assessed using validated questionnaires evaluating pain impact, physical activity, depression, anxiety, fatigue, and sleep quality.

Results

To date, 80% (122/150) of the target population has been included across three groups. 48/50 fibromyalgia patients have been included (42 females [87.5%], 6 males [12.5%]), with a mean age of 46.4±10.0 years (median 47.5) (females: 46.9±10.0 years, median 48.5). As recruitment is ongoing, the current report presents the protocol and several baseline characteristics.

Conclusion

This is the first study aimed at addressing the temporal relationship between peripheral and central sensitization in the primary mechanism of fibromyalgia. Findings are expected to provide new insights into disease pathogenesis and support the development of more accurate and personalized treatment strategies.

VLPAG-SST NEURONS CONTROL PAIN DESCENDING PATHWAY IN A PHYSIOPATHOLOGICAL CONTEXT

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Résumé

Pain is an adaptive and primordial aspect of mammal's physiology whose role is to warn against potential harmful situations and prevent aggravation of actual physical damages. However, many patients suffer from chronic pain, which overpasses pain's adaptive trait becoming pathological. Nociceptive signal transmission is first relayed by the spinal cord before reaching the brain through ascending pathways. The control of descending spinal integration is orchestrated by the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). In the RVM, ON, OFF and neutral cells, are respectively activated, inhibited or unchanged during nociceptive responses. Moreover, the somatostatin neurons of the ventrolateralPAG (vlPAG) are known to be involved in spinal hypersensitivity to nociceptive inputs but their underlying circuits in normal and chronic pain are still unknown. Here, we hypothesize that vlPAG-SST neurons targeting the RVM control pain sensitivity in a physiopathological context. We coupled electrophysiology and optogenetic tools to manipulate and record this pathway during nociceptive stimulation in freely moving animals. Our results first confirm that vlPAG-SST terminal activation in the RVM induces mechanical allodynia and thermal hyperalgesia, while in a chronic pain model (spared nerve injury), the same manipulation alleviates mechanical allodynia. During optostimulation, OFF and neutral cells activity are mostly unchanged while ON cells connected to vlPAG-SST/Glutamatergic neurons are activated during innocuous stimulation. Surprisingly, this same subpopulation becomes non-responsive to noxious stimulation in neuropathy. This work points out ON cells crucial role in neuropathic pain, and vlPAG-SST/Glutamatergic neurons as principle descending pathway controls on this population in a physiopathological context.

*Intervenant

Beyond nociception: towards an understanding of subjective pain perception networks in Humans.

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Background and aims

Activation of the spinothalamic system does not always result in a subjective pain perception. While the cerebral network processing nociception is relatively well known, the one underlying the subjective perception of pain remains poorly described.

The aim of the present study was to identify by intracerebral recordings in humans the regions involved in the subjective perception of pain.

Methods

To do so, we studied the laser evoked responses in ten regions part of the pain matrix, according to the subjective perception of laser stimuli delivered to the hand at a constant intensity, set at the nociceptive threshold.

Results

Despite the constant intensity of stimuli, all patients reported variable subjective perceptions from one stimulus to the other. Responses in sensory areas were identical throughout the experiment, regardless of perception, hence reflecting accurately the stability of the stimulus. In contrast, both anterior insula, amygdala and orbitofrontal cortex responses showed significant enhancement associated with painful perception in the 300-600 ms post-stimulus.

Conclusion

This study highlighted electrophysiological markers of subjective pain perception within regions, reflecting their involvement in the transition from nociception to pain perception.

CORTICAL HYPEREXCITABILITY RELIES ON AXON INITIAL SEGMENT PLASTICITY IN A MURINE MODEL OF FACIAL NEUROPATHIC PAIN

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Neuropathy is a major public health problem affecting 7 to 10 % of the population (Moisset et al., 2020). It mainly results from a primary lesion of the somatosensory nervous system, causing persistent pain even after the lesion has disappeared. Among these conditions, neuropathic facial pains, caused by disease or trauma to the trigeminal nervous system, are one of the most difficult to diagnose and treat (Moreau and Boucher, 2022) and the mechanism by which they emerge is still poorly understood. Several studies suggest that neuropathic pain may arise from primary somatosensory cortex (S1) hyperactivity (Thibault et al., 2016; Xiong et al., 2017). Using behavioral analysis, ex vivo electrophysiology and immunofluorescence, our study aimed to decipher the nature and the cellular origin of S1 hyperactivity in a murine model of orofacial neuropathic pain (infraorbital nerve ligation), focusing on S1 layer V pyramidal neurons (L5PC). Performing patch-clamp experiments in both female and male rats, we observed an increase of L5PC intrinsic excitability in the barrel field cortex of neuropathic animals on the contralateral side of the nerve ligation. This hyperexcitability is associated with a 5-µm-increase axon initial segment (AIS) length in these neurons. These results suggest that orofacial neuropathic pain is associated with exacerbated neuronal activity due to AIS plasticity at the S1 cortical level.

A NEW MODEL FOR STUDYING THE ONSET OF PARKINSON DISEASE RELATED SENSORY DEFICITS

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Background and aims

Parkinson's disease (PD) is a neurological disorder caused by degeneration of the dopaminergic neurons of the substantia nigra *pars compacta* (SNc) and characterized by stereotypic motor symptoms. In addition, patients with PD have sensory abnormalities accompanied by chronic pain that often precede the onset of locomotor deficits, and that are resistant to motor symptom treatments. The early appearance of sensory deficits questions about the link between pain symptoms and SNc degeneration in PD. Unfortunately, early PD symptoms are difficult to study in humans asymptomatic for motor deficits, and pre-clinical models mostly recapitulate the late phase of the disease. Therefore, there is a need to develop a pre-clinical model adapted to the study of PD-related pain symptoms at the onset of dopaminergic neuron degeneration.

Methods

In PD, SNc dopaminergic neurons degenerate primarily through apoptosis following an increase in Caspase-3 activity. Therefore, temporally and locally manipulating Caspase-3 activity in SNc neurons would offer an avenue to study the progressive consequences of dopaminergic neuron apoptosis. To do so, we used local adeno-associated-virus (AAV) viral approach to express a Cre-inducible autocatalytic caspase-3 enzyme (taCasp3) in the SNc of Tyrosine hydroxylase (TH)-CreERt2 genetically modified mice to selectively target dopaminergic neurons. By gradually inducing the expression of taCasp3 expression with increasing tamoxifen doses, we aim to demonstrate the sequential effects of dopaminergic neuron ablation on the sensory and motor symptoms.

Results

The first observations in male and female animals reveals that strong induction of taCasp3 leads to SNc degeneration, causes locomotor deficit, and induces mechanical sensory hypersensitivity. Next, the effects of a progressive targeted dopaminergic neuron ablation with increasing tamoxifen dosage lead to a sequential appearance of somatosensory deficits, including tactile allodynia, largely before the onset of motor symptoms. Pharmacological treatments shows that the use of a brain penetrant T-type calcium channel inhibitor, a molecule in clinical trial for essential tremor and efficient to alleviate PD motor deficits in rats, is able to acutely reverse the tactile hypersensitivity in this model.

Conclusions

Potentially, this preclinical approach may offer a better way to recapitulate the course of clinical sensory and motor signs of PD and notably better asses the underlying pain pathophysiological mechanisms and potential new pharmacological treatments efficient for the distinct symptoms of PD.

Supports: ANR PD Pain, LabEx ICST, Réseau Français de Recherche sur la Douleur (RFRD)

The role of system xc^- in anxiety as a comorbidity and predisposing factor in neuropathic pain

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Background: We have previously documented the role of the cystine/glutamate exchanger (system xc^-) in the pathophysiology of neuropathic pain. The activity of system xc^- also influences anxiety and depressive-like behaviors in rodents, which are known as comorbidities or predisposing factors of chronic pain. This prompted us to examine the implication of system xc^- in the modulation of anxiety in a model of neuropathic pain.

Methods: We have used wild-type mice ($xCT^{+/+}$) and mice lacking xCT ($xCT^{-/-}$), the specific subunit of system xc^-. These mice were subjected to a standardized social defeat stress protocol by confronting them for 10 days to CD1 mice selected for their aggressive behavior. After this anxiety priming, mice were subjected to partial sciatic nerve ligation (PSNL). Animal behaviors were examined for 7 days before sacrifice and tissues were collected for further analyses.

Results: Regarding anxiety as a predisposing factor, data accumulated so far indicate that after priming, $xCT^{-/-}$ mice develop less anxiety than $xCT^{+/+}$ littermates. In addition, priming triggers constitutive pain hypersensitivity which was not observed in $xCT^{-/-}$ mice. Besides, we observed that anxiety priming also tends to exacerbate pain-related behaviors following the sciatic nerve ligature in $xCT^{+}/^{+}$ mice.

Conclusions: Our results suggest that $xCT^{-/-}$ mice show resistance to the development of anxiety-related behaviors in response to social stress. Furthermore, while the xc^- system plays an important role in modulating anxiety, this anxiety appears to promote the chronification of neuropathic pain in this model, although these data need to be consolidated.

PUPILLOMETRY TO EVALUATE DESCENDING NORADRENERGIC CONTROLS OF NOCICEPTIVE TRANSMISSION IN AN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) MOUSE MODEL

Maria-Carmen Medrano, Sandra Sanchez-Sarasua, Thomas Michelet, Marc Landry

Background and Aims: Patients with attention deficit hyperactivity disorder (ADHD) often experience altered pain perception, heightened sensitivity, and difficulty effectively communicating discomfort, complicating diagnosis and treatment. The locus coeruleus (LC) releases noradrenaline (NA), which modulates pain through descending controls to the spinal cord and influences attentional processes in the anterior cingulate cortex (ACC). This study aimed to investigate whether impaired NA modulation in ADHD-like conditions contributes to increased pain perception.

Methods: Electrophysiological recordings were conducted on anesthetized adult control mice and ADHD-like mice (induced by neonatal 6-OHDA injection). Both groups received ACC stimulation or nociceptive stimuli. Pupil-evoked response (PER) was measured to assess NA release induced by the aforementioned stimuli.

Results: In control mice, stimulation of all ACC subregions and nociceptive stimuli significantly increased pupil diameter compared to baseline. However, in mice treated with the LC-NA-specific neurotoxin DSP4, neither ACC stimulation nor nociceptive stimuli altered pupil diameter. ADHD-like mice exhibited a lower nociceptive threshold for pupil dilation than controls. Additionally, the magnitude of diffuse noxious inhibitory control (DNIC) was greater in control mice compared to ADHD-like mice.

Conclusions: This study confirms that pupillometry is a reliable method for evaluating LC-NA-mediated nociceptive responses in mice. The findings suggest that both, pain perception and DNIC may be impaired in ADHD-like conditions, highlighting NA descending control as a potential therapeutic target for addressing the comorbidity of pain and attentional disorders.

THE EFFECT OF PRENATAL STRESS ON DEVELOPEMENT AND FUNCTIONS OF NOCICEPTORS

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General data

Main Category: B (basic research)
Main Topic: Somatosensory and nociceptive systems
Targeted audience: Neuroscientist, Engineer, Pain Specialist, Psychiatrist, Researcher - cellular and molecular neurosciences, Researcher - clinical, Researcher - systems and cognitive neurosciences, Neurologist, Lab Technician, Psychologist

Title

Abstract body

Background and aims: **Nociceptors** are specialized neurons located in the dorsal root ganglia (DRG), responsible for transmitting pain signals from organs to the central nervous system. They are classified into subtypes: **Non-Peptidergic** nociceptors (NP), **Peptidergic** nociceptors (PEP), and non-nociceptive neurons called **c-low-threshold mechanoreceptors** (cLTMRs). These subtypes develop from precursors between embryonic days (E) 11 and E13, achieving transcriptomic maturity by **E13 to post-birth**. As we previously demonstarated that prenatal stress (PS) induces mechanical hypersensitivity, we hypothesized that PS disrupts the transcriptomic development of nociceptors, contributing to **mechanical hypersensitivity** observed in offspring.
Methods: PS was induced in pregnant mice using restraint stress under bright light from E13 to E18. Mechanical sensitivity in 8-week-old mice was assessed using **Von Frey** tests. DRGs were isolated from control (CT) and PS mice for **bulk RNA sequencing**. **Immunohistochemistry** staining identified major nociceptor populations in 8-week-old DRGs. **Single-cell RNA sequencing** (scRNAseq) on sorted nociceptors from CT and PS offspring provided further insights on transcriptomic impacts.
Results: PS offspring showed pronounced **mechanical hypersensitivity** compared to CT offspring. RNA sequencing revealed **300 differentially expressed genes,** including Trpv1 (PEP), Th (cLTMR), and Mrgprd (NP). This **increase of cLTMRs** and decrease of PEP nociceptors in PS offspring has been confirmed by immunohistochemistry. scRNAseq indicated **cLTMRs as the primary affected population**, including genes dysregulated that are known to play a role in Austism spectrum disorders.
Conclusions: Our results show that PS impacts cLTMRs development at the transcriptomic, proteic, and single-cell levels. This impairment is associated with a mechanical hypersensitivity and behavioral disorders (results not shown here).

Conflict of Interest statement

Do you have any conflict of interest to declare (industry support) for the past 3 years related to this work? No

Ethics committee / Approval patient

Has this study been approved by an ethics committee (animal welfare for animal studies)?: Yes
In case of patient case presentations: Do you have approval from the patient/patients? Yes

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MOLECULAR AND CELLULAR ALTERATIONS IN THE DORSAL RAPHE NUCLEUS IN THE CORMOBIDITY OF CHRONIC PAIN AND MOOD DISORDERS.

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General data

Main Category: B (basic research)
Main Topic: Pain and multimorbidity
Targeted audience: Neurologist, Neuroscientist, Neurosurgeon, Nurse, Pain Specialist, Psychologist, Psychiatrist, Researcher - cellular and molecular neurosciences, Researcher - clinical, Researcher - systems and cognitive neurosciences

Title

Abstract body

Background and aims: Neuropathic pain affects 16% of the world's population and is often associated with major depressive disorder (MDD). Compelling evidence from human studies and animal models suggests an important role for the dorsal raphe nucleus (DRN) in both chronic pain and MDD. Therefore, by combining next generation sequencing and fiber photometry with behavioural approaches, we aim to unravel the molecular and physiological changes in the DRN in the development of chronic pain and its comorbidity with MDD.
Methods: Neuropathic pain was induced by implanting a polyethylene tube around the sciatic nerve in male mice. Behavioural characterization was performed using a battery of tests. We used RNA sequencing to study the transcriptomic changes, while fiber photometry recordings were performed to determine whether the response in the DRN to nociceptive and non-nociceptive stimuli is altered by neuropathic pain.
Results: Neuropathic mice developed mechanical hypersensitivity (until 13 weeks) and depressive-like behaviours (until 16 weeks post-surgery). Sequencing data revealed time-dependent alterations within the DRN. Interestingly, strong genomic changes were observed during recovery from hypersensitivity. Calcium-imaging results showed alterations in the calcium dynamics in the DRN during nociceptive stimulation.
Conclusions: Altogether, these data highlight that neuropathic pain induces alterations in the DRN that differ at different stages of the neuropathic pain and that DRN plays an important role in the comorbidity of chronic pain and mood disorders.

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Conflict of Interest statement

Do you have any conflict of interest to declare (industry support) for the past 3 years related to this work? No

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EASYCOG : A DIGITAL COGNITIVE SELF-ASSESSMENT TOOL FOR CHRONIC PAIN PATIENTS.

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General data

Main Category: C (clinical)
Main Topic: Measurement of psychosocial and spiritual aspects of pain
Targeted audience: Neuroscientist, General Practitioner, Internist, Nurse, Pain Specialist, Psychologist

Title

Abstract body

Background and aims: Many pathological conditions, including chronic pain (CP), can impair cognitive functions. CP, defined as persistent or recurrent pain lasting more than three months, produces symptoms that affect the sensory-discriminative, motivo-affective, cognitivo-behavioral dimensions. In CP centers, cognitive assessment is far from being present in the follow-up of CP patients, due to lack of time, appropriate tools or trained health professionals. To fill this gap, our laboratory has developed easyCOG, a digital tool that allows rapid self-assessment of cognitive functions without the help of an experimenter, thanks to speech recognition supported by an artificial intelligence neuronal network.
Methods: In the initial validation steps, we established normative values for 7 cognitive functions on a cohort of 70 healthy subjects. As easyCOG includes a Montreal Cognitive Assessment (MoCA) score, we assessed its reliability in comparison with MoCA normative values. To assess its specificity, we made comparisons with 20 subjects with mild cognitive impairment (MCI) and 20 CP patients selected from a CP center. Finally, we tested the fidelity of easyCOG (i.e. test-retest) by repeating sessions at different intervals.
Results: Compared with normative MoCA scores, easyCOG has excellent age-related reliability. Several cognitive functions were significantly and differentially impaired in MCI subjects and CP patients compared to normative values in healthy subjects, confirming good specificity. Finally, fidelity analysis revealed a zero test-retest effect for a 4-month interval.
Conclusions: In conclusion, easyCOG is a convenient and reliable digital tool for the assessment and monitoring of cognitive function in patients with CP.

Conflict of Interest statement

Do you have any conflict of interest to declare (industry support) for the past 3 years related to this work? No

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Has this abstract been previously presented?: No
Have the results of this abstract been previously published?: No

Dolonersen, a novel therapeutic approach based on the use of an antisense oligonucleotide to relieve pain symptoms of chemotherapy-induced peripheral neuropathy

Dounia Maskini[1], Noelian Soler[1], Patrick Carroll[1], Fabrice Ango[1], Alexandre Pattyn[1], Stephanie Venteo[1]

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- Background/Aims

Oxaliplatin, a chemotherapeutic platinum-based agent is widely used for treating solid tumours. However, it can engender several debilitating aversive side-effects, including Oxaliplatin-induced peripheral neuropathy (OIPN) with painful symptoms difficult to manage. We have established Fxyd2 as a key actor involved in the maintenance of a chronic pain state in neuropathic and inflammatory rodent models. Accordingly, we recently developed an efficient therapeutic protocol using chemically lipid-modified antisense oligonucleotides (LASO-Gapmer) to inhibit FXYD2 expression and alleviate both types of pain. The aim of this study was to assess the efficacy of FXYD2-LASO-Gapmer called Dolonersen on pain symptoms of OIPN.

- Methods

As a model, we chronically treated rats with Oxaliplatin to induce mechanical and cold hypersensitivity over time, and tested the efficiency of two therapeutic approaches. First, we injected Control- or FXYD2-LASO-Gapmer after Oxaliplatin treatment. Second, we injected Control- or FXYD2-LASO-gapmer in preventive before Oxaliplatin treatment. Throughout the experiments, we evaluated animal's hypersensitivity with Randall-Selitto, von Frey, tail immersion and thermal place preference tests.

- Results

First, we showed that OIPN rats post-treated with Fxyd2-LASO-Gapmer do not maintain mechanical and cold hypersensitivity over the long term, in contrast to rats treated with Control-LASO-Gapmer which remain hypersensitive.

Second, we established that animals treated in preventive with the FXYD2-LASO-Gapmer are significantly protected against the induction of mechanical and cold hypersensitivity after Oxaliplatin treatment, in contrast to rats treated with Control-LASO-Gapmer which become hypersensitive.

- Conclusions

Altogether our data establish Dolonersen (FXYD2-LASO-Gapmer) as a new promising preventive and curative therapeutic molecule for pain symptoms of OIPN patients.

ANALGESIC EFFICACY OF NON-INVASIVE NEUROMODULATION TECHNIQUES IN CHRONIC CANCER PAIN: A SYSTEMATIC REVIEW.

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General data

Main Category: C (clinical)
Main Topic: Neuromodulative therapies
Targeted audience: Researcher - clinical, Physiotherapist, Pain Specialist, Oncologist, Neurologist, General Practitioner

Title

Abstract body

Background and aims: Cancer has become a significant source of pain, attributable to both the tumor's and the treatments. Non-invasive brain stimulation (NIBS) is recommended in refractory neuropathic pain; however, its efficacy in chronic cancer-related pain (CRP) remains unknown. A few pilot studies and randomized controlled trials (RCTs) have assessed the effectiveness of NIBS on pain in CRP.
Methods: A systematic review of neuromodulation studies on patients with chronic CRP involving transcranial direct currents stimulation (tDCS) or transcranial magnetic stimulation (TMS) was carried out through PubMed, Cochrane, Web of science and Google Scholar to June 2024. The quality of the evidence was assessed using the PEDro scale.
Results: Keyword-based search and reference tracking identified 9 records that fulfilled the selection criteria (184 patients). In the tDCS protocols, one RCT had an effect size of -1.03 [-1.26; -0.81], and two case reports showed a significant pain intensity (VAS) decreased of -4.3/10 on average. The rTMS protocols provided similar pain relief, with two RCTs showing an effect size of -1.09 [-1.27; -0.90], two observational studies reporting a significant pooled effect on pain intensity (-0.85 [-1.62; -0.08] and -2.30 [-2.73; -1.87]), and two case reports where pain was reduced by -4.8/10 on average.
Conclusions: NIBS could represent an interesting therapeutic strategy to provide pain relief in in individuals with refractory CRP. However, due to the low level of evidence and the high heterogeneity of trials included (i.e., various pain conditions), a randomized controlled trial of high methodological quality is now required to validate these promising results.

Conflict of Interest statement

Do you have any conflict of interest to declare (industry support) for the past 3 years related to this work? No

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In case of patient case presentations: Do you have approval from the patient/patients? No

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Previously presented/published

Has this abstract been previously presented?: No
Have the results of this abstract been previously published?: No

THE THERAPEUTIC EFFECT OF PLATELET-RICH PLASMA ON CHRONIC PAIN

Sarah Jester[1 master's degree], Noémie Willem[1 master's degree], Henrico-Pio Basile[1 master's degree], Stéphanie Magnenat[2 master's degree], Aurélia Cès[1 master's degree], Maxime Thouaye[1 PhD], Yohann Bohren[1,3 MD, PhD], Béatrice Hechler[2 PhD], Mélanie Kremer[1 PhD].

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Résumé

Neuropathic and post-surgical pain are common chronic pain types that are difficult to treat effectively. Recently, platelet-rich plasma (PRP) injections have emerged as a potential therapy. PRP, an autologous blood concentrate rich in growth factors, cytokines, chemokines, adhesion molecules, and serotonin, may promote nerve regeneration and reduce the neuro-immune response, offering potential pain relief. Our study aims to evaluate the preventive and curative potential of PRP in mouse models of neuropathic and post-surgical pain.

We used a model of chronic sciatic nerve constriction in mice by inserting a polyethylene sleeve ("cuff") around the sciatic nerve. Male and female mice underwent either "cuff" placement or a "sham" procedure as controls. Additionally, we employed a postsurgical pain model involving a longitudinal paw incision. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) controls were prepared from citrated whole blood obtained via abdominal aorta draw from anesthetized mice. Mechanical (von Frey filament test), thermal hypersensitivity (Hargreaves test for heat and dry ice test for cold) were assessed to evaluate PRP's impact on pain symptoms in these models.

Our results demonstrate that perioperative administration of PRP prevents the development of mechanical and thermal hypersensitivity in our murine models of neuropathic and post-surgical pain. Moreover, when pain is already established, intrathecal administration of PRP also provides temporary relief.

These results highlight the real preventive potential of PRP against neuropathic and post-surgical chronic pain when administered during surgeries.

Supported by CNRS & Université de Strasbourg (UPR3212), ANR (ANR-23-CE18-0043; Euridol ANR-17-EURE-0022), Région Grand-Est (FRCR CLueDol), SFETD, Institut Analgesia.

MODULATION OF G PROTEIN-COUPLED ESTROGEN RECEPTOR (GPER) AS A THERAPEUTIC STRATEGY FOR OSTEOARTHRISTIS PAIN MANAGEMENT

P. Gousseau[1,2], B. Jouffre[1,2], L. Daulhac[1,2], C. Mallet[1,2]
[1]Neuro-Dol Basics & Clinical Pharmacology Of Pain, Inserm U1107, Université Clermont Auvergne, Clermont-Ferrand, France, [2]Faculty of Medicine, ANALGESIA Institute, Clermont-Ferrand, France

General data
Main Category: B (basic research)
Main Topic: Osteoarthritis, Rheumatoid Arthritis
Targeted audience: Neuroscientist, Pain Specialist, Pharmacologist, Researcher - cellular and molecular neurosciences, Researcher - clinical, Rheumatologist

Title

Abstract body
Background and aims: Osteoarthritis (OA) is the most common musculoskeletal disease, affecting millions of people worldwide. Pain is the dominant symptom of OA and the main reason for medical consultation. Current treatments are often ineffective and/or linked to significant adverse effects. Therefore, new therapeutic approaches are needed.
Our recent studies have highlighted the potential of modulating the G protein-coupled estrogen receptor (GPER) in managing inflammatory pain.
Here, we propose to perform a functional study investigating the involvement of GPER, using genetic and pharmacological strategies, in a murine model of OA.
Methods: Male C57BL/6 mice (10 week-old) underwent destabilization of the medial meniscus (DMM) surgery to induce OA. Mechanical hypersensitivity was assessed using the von Frey test during OA progression. The involvement of GPER was assessed with various pharmacological (GPER inverse agonist and antagonist) and genetic tools.
Results: After DMM surgery, mice developed a significant mechanical allodynia that was reduced after treatment with the GPER inverse agonist. This effect was abolished when the GPER antagonist was co-administered with the inverse agonist. Using genetically modified mice with a specific deletion of GPER in primary nociceptive neurons, we observed a decrease in OA-induced hypersensitivity. A similar result was obtained after the specific knock-out of GPER in the dorsal horn of the spinal cord.
Conclusions: In DMM model, these results demonstrate that GPER, both at peripheral and spinal levels, contributes to OA-induced hypersensitivity. Collectively, these findings highlight that GPER could be a promising new therapeutic target for the management of osteoarthritis pain.

Conflict of Interest statement
Do you have any conflict of interest to declare (industry support) for the past 3 years related to this work? No

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Have the results of this abstract been previously published?: No

ISOLATING BRAIN REGIONS THAT MODULATE THE PAIN EXPERIENCE THROUGH EMOTION AND COGNITION

L. Malaguti Modernell[1], *I. Faillenot*[1], *R. Peyron*[1], *L. Garcia-Larrea*[1], *C. Fauchon*[2]
[1]NEUROPAIN Team, CRNL, CNRS, Inserm, UCBL Lyon1, University of Saint-Etienne, Saint-Etienne, France, [2]Neuro-Dol, Inserm, University Hospital of Clermont-Ferrand, University of Clermont-Auvergne, Clermont-Ferrand, France

General data

Main Category: B (basic research)
Main Topic: Descending pain modulation
Targeted audience: Anaesthetist, General Practitioner, Neurologist, Neuroscientist, Neurosurgeon, Pain Specialist, Physical and Rehabilitation Medicine, Physiotherapist, Psychiatrist, Psychologist, Researcher - clinical, Researcher - systems and cognitive neurosciences, Rheumatologist

Title

Abstract body

Background and aims: Numerous neuroimaging studies have identified brain regions whose activity is associated with the modulation of pain perception through cognitive and emotional tasks. This study aims to identify a potential common brain network underpinning the increase (hyperalgesia) or decrease (hypoalgesia) of experienced pain through these types of tasks.
Methods: a two-step review of neuroimaging studies regarding the cognitive and/or emotional modulation of pain perception was carried out through keyword-based search on PubMed/MEDLINE, Cochrane and Web of Science databases, followed by identification of additional records through reference tracking. In parallel, we applied Multivariate Pattern Analysis (MVPA) to fMRI data from 88 subjects receiving constant nociceptive stimulation, while undergoing cognitive and emotional tasks modulating pain perception.
Results: Keyword-based search and reference tracking identified a total of 133 records, of which 35 fulfilled completely the selection criteria (888 participants). Analysis of the activation peak coordinates revealed a recurrent but inconsistent participation of the anterior and mid-insulae, mid and anterior cingulate cortices, orbitofrontal cortex and caudate during hypoalgesia as well as hyperalgesia. Some of those regions were also shown to have a role in predicting pain modulation in a preliminary MVPA model based on data from 36 participants, with a significant correlation coefficient between predicted and true pain ratings ($p<0.001$).
Conclusions: Brain regions associated to emotional/cognitive pain modulation are not primarily sensory areas but multimodal structures integrating important information from the context, highly interconnected with higher order networks. They can modulate how we perceive a constant noxious stimulus and may represent interesting neuromodulation targets.

Conflict of Interest statement

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