XIXth SYMPOSIUM OF THE FRENCH PAIN RESEARCH NETWORK

April 12 & 13th, 2024

8:30 am to 7:00 pm
and 8:30 am to 12:30

Grand Château

28 Avenue de Valrose
06103 Nice

PROGRAM

SPEAKERS

Dr Kirsty Bannister

Wolfson Sensory, Pain and Regeneration Centre, King's College London, UK)

Pr Tor D. WAGER

Presidential Cluster in Neuroscience and Department of Psychological and Brain Science, Dartmouth College, NH, USA

Registration

https://rfrd2024.sciencesconf.org/

Programme RFRD 2024

Grand Château, Parc Valrose

Vendredi 12 avril / Friday, April 12

9h00 : Accueil des participants / Welcome

9h15 : Ouverture du symposium / Symposium opening

9h30 -10h30 : **Communications orales / Oral communications - Session 1**
chair : Raphaële Le Garrec / Cyril Goudet

- Alexandre Charlet (INCI Strasbourg)
  Parvocellular oxytocin neurons project to the periaqueductal gray to induce anti-hyperalgesia
- Aurélie Leplus (CHU -FHU Nice)
  Somatotopy of the human somatosensory thalamus: inputs from directional deep brain stimulation in patients with refractory neuropathic pain
- Guillaume Robert (IBDM Marseille)
  C-Low-Threshold-MechanoReceptors (C-LTMRs): from pleasant touch to pain modulation
- Lauriane Delay (Neuro-Dol Clermont-Ferrand)
  Functional connectivity changes in preclinical models of migraine-like headaches using a new approach of neuroimaging: the functional ultrasound imaging (fUSi)

10h30-11h00 : Laurent Misery (LIEN, Brest) " Translational research on pruritus "
chair : Michel Lanteri-Minet

11h00-11h30 Pause-café / Coffee break

11h30-12h30 : **Conférence plénière 1 / Keynote 1– Dr Kirsty Bannister** (Wolfson Sensory, Pain and Regeneration Centre, King's College London, UK)
chair : Eric Lingueglia

"The top down control of pain in health and disease: from bench to bedside"

12h30-14h00 Déjeuner / Lunch

14h00-15h00 : **Communications orales / Oral communications - Session 2**
chair : Christine Courteix / Nicolas Cenac

- Marc Landry (IMN Bordeaux)
  Anti-Nociceptive Role of The Relaxin-3/RXFP3 Peptidergic System
- Hélène Bastuji (NeuroPain Lyon)
  Intracranial EEG spectra: a pathway to optimise neurostimulation?
- Gawain Grellier (IGF Montpellier)
  A new model for studying the onset of Parkinson disease related sensory deficits
- Romane Boyer (Neuro-Dol Clermont-Ferrand)
  TREK1 channels expressed in peripheral nervous system participate to thermonociception

15h00-16h00 : **Session FHU InovPain 2.0**
chair : Emmanuel Deval

- Denys Fontaine (CHU, Nice) "Safety and feasibility of deep brain stimulation of the anterior cingulate and thalamus in chronic refractory neuropathic pain"
- Guillaume Sandoz (iBV, Nice) "Optopharmacology of two-pore domain potassium channels in pain"

16h00-16h30 Pause-café / Coffee break

16h30-18h00 : **Communications orales / Oral communications - Session 3**
chair : Sophie Pezet / Emmanuel Bourinet

- Raphaële Le Garrec (LIEN Brest)
  The mouse cheek test to study some neuropathic disorders of ciguatera
- Ahmed Negm (Neuro-Dol Clermont-Ferrand – current: IGF Montpellier)
  Sensory plasticity of dorsal horn neurons: a new mechanism for neuropathic pain.
- Pascal Fossat (IMN Bordeaux)
  Role of vlPAG SST neurons in fear conditioning analgesia
- Océane Boyer (BSC Strasbourg)
  The PrRPR and PrRP system modulates nociception, inflammatory pain and neuropathic pain in mice
- Léa Rey (IRSD Toulouse)
  Reduced inflammation-induced visceral sensitivity in aged mice is associated with high potency of T cells to produce enkephalins
- Présentation société Bioseb (partenaire)

18h00-19h00 : Actualités du réseau douleur / News from the network

20h00 Dîner de Gala / Gala Dinner (Hôtel ASTON LA SCALA, 12 avenue Félix Faure 06000 Nice)
Tram ligne/line 1, arrêt/stop « Opéra Vieille Ville » face à l'hôtel/across from the hotel.

<u>Samedi 13 avril / Saturday, April 13</u>

8h30-9h30 : **Communications orales / Oral communications Session 4**
chair : Dominique Massotte / Cedric Peirs

- Sophie Pezet (ESPCI Paris)
  Comprehensive study of the sex-specific alterations of the brain vascular responsiveness in a preclinical model of migraine, using whole brain ultrafast Doppler imaging
- Rachel Bourdon-Alonzeau (IGF Montpellier)
  A quest for Cav3.2 interactome to gain insight in chronic pain mechanisms
- Nicolas Gilbert (IPMC Valbonne)
  Exploring the role of THIK potassium channels in nociceptive pathway
- Nazarine Mokhtar (Neuro-Dol Clermont-Ferrand)
  Blockade of 5-HT6 receptor/mTOR activity differentially attenuates neuropathic pain and cognitive comorbidity in male and female diabetic rats

09h30-10h00 : Ipek Yalcin (INCI, Strasbourg) "Reaching circuitry level of understanding of the comorbidity between chronic pain and mood disorders"
chair : Marc Landry

10h00-10h30 Pause-café / Coffee break

10h30-11h30 **Conférence plénière 2 / Keynote 2 – Pr Tor D Wager** (Presidential Cluster in Neuroscience and Department of Psychological and Brain Science, Dartmouth College, NH, USA)
chair : Denys Fontaine

"The brain in pain: Pathways, neuromarkers, and interventions"

11h30-12h30 : **Communications orales / Oral communications - Session 5**
chair : Delphine Bichet / Alexandre Charlet

- Arnaud Landra-Willm (iBV Nice)
  Dual effect of TRESK-C317F mutation related to epilepsy
- Nadine Gheziel (IRSD Toulouse)
  The effect of prenatal stress on development and functions of nociceptors
- Jacques Noel (IPMC Valbonne)
  Acid-Sensing Ion Channel 3 mediates pain hypersensitivity associated with high-fat diet consumption in mice
- Yasmine Brik (LNCA Strasbourg)
  Impact of neonatal maternal separation stress in neuropathies induced by chronic constriction of the sciatic nerve.

12h30 : Prix de la communication orale, conclusions et déjeuner (sachets repas) / Oral Communication Award, conclusions and lunch (lunch bags)

Informations pratiques / Useful information

Contacts : Eric Lingueglia (06 20 42 52 91), Maeva Meynier (06 30 40 76 51)

Lieu/ Location : Théâtre du Grand Château, Parc Valrose, sur le Campus de la faculté des Sciences de l'Université Côte d'Azur, 28 Avenue Valrose, 06108 Nice (GPS : 43.717099128897736, 7.267021536827088 ; https://maps.app.goo.gl/TjiTjtb3iKS5ZsZG9).

Transport/Transportation: Tram: ligne/line 1, arrêt/stop "Valrose Université ".

Voiture/Car: Le parking sur le campus vendredi sera compliqué, privilégiez le covoiturage ou le tram. Le samedi, vous pourrez vous garer dans le campus (sous réserve d'enregistrement préalable de la plaque d'immatriculation du véhicule) / Parking on campus on Friday will be tricky, so carpool or take the Tram. On Saturday, you'll be able to park on campus (subject to prior registration of the vehicle's license plate).

Oral communication

Session 1

Chair : Raphaële Le Garrec & Cyril Goudet

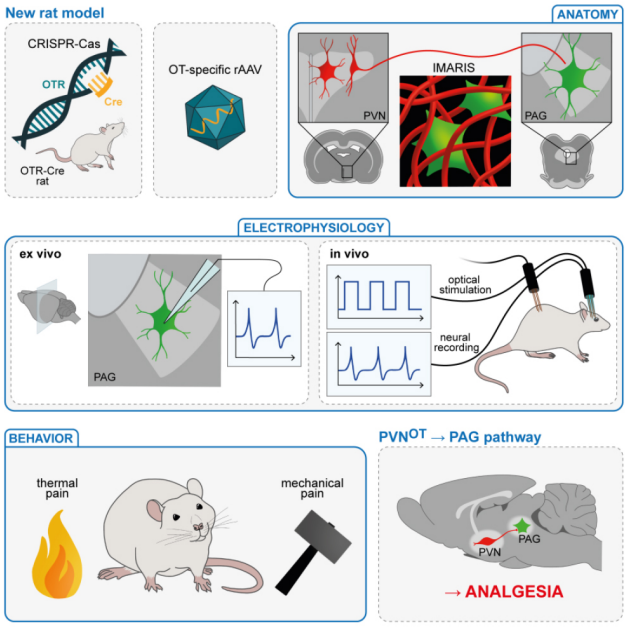
Parvocellular oxytocin neurons project to the periaqueductal gray to induce anti-hyperalgesia

Alexandre Charlet*[1]

[1]Institut des Neurosciences Cellulaires et Intégratives – université de Strasbourg, Centre National de la Recherche Scientifique – France

Résumé

The hypothalamic neuropeptide oxytocin (OT) exerts prominent analgesic effects via central and peripheral action. However, the precise analgesic pathways recruited by OT are largely elusive. Here we discovered a subset of OT neurons whose projections preferentially terminate on OT receptor (OTR)-expressing neurons in the ventrolateral periaqueductal gray (vlPAG). Using a newly generated line of transgenic rats (OTR-IRES-Cre), we determined that most of the vlPAG OTR expressing cells targeted by OT projections areGABAergic. Ex vivo stimulation of parvocellularOT axons in the vlPAG induced local OT release, as measured with OT sensor GRAB. In vivo, optogeneticallyevoked axonal OT release in the vlPAG of as well as chemogenetic activation of OTR vlPAG neurons resulted in a long-lasting increase of vlPAG neuronal activity. This lead to an indirect suppression of sensory neuron activity in the spinal cord and strong analgesia in both female and male rats. Altogether, we describe an OT-vlPAG-spinal cord circuit that is critical for analgesia in both inflammatory and neuropathic pain models.



*Intervenant

Somatotopy of the human somatosensory thalamus: inputs from directional deep brain stimulation in patients with refractory neuropathic pain

Aurelie Leplus*[1], Petru Isan[1], Anne Balossier[2], Anne Donnet[3], Theo Papadopoulo[4], Jean Regis[2], Michel Lantéri-Minet[5], and Denys Fontaine*[1]

[1]Neurosurgery, UR2CA (PIN), FHU INOVPAIN 2.0, CHU de Nice – Centre Hospitalier Universitaire de Nice, Université Côte d'Azur – France

[2]Neurosurgery – Assistance publique - Hôpitaux de Marseille (AP-HM) – France

[3]Pain Clinic, FHU INOVPAIN 2.0 – Assistance publique - Hôpitaux de Marseille (AP-HM) – France

[4]INRIA – L'Institut National de Recherche en Informatique et e n Automatique (INRIA), Université Côte d'Azur (UCA) – France

[5]Pain Clinic, UR2CA (PIN), FHU INOVPAIN 2.0, CHU de Nice – Centre Hospitalier Universitaire de Nice, Université Côte d'Azur – France

Résumé

The sensory ventroposterior (VP) thalamic nuclei display a mediolateral somatotopic organization (respectively head, arm, leg). We studied this somatotopy using directional VP deep brain stimulation (DBS) in patients treated for chronic neuropathic pain.
Six patients with central (4) or peripheral (2) neuropathic pain were treated by VP DBS using directional leads in a prospective study (clinicaltrials.gov NCT03399942). Lead-DBS toolbox was used for leads localization, visualization and modelling of the volume of tissue activated (VTA). Bipolar stimulation was delivered in each direction, 1 month after surgery and correlated to the location of stimulation-induced paresthesias. The somatotopy was modelled by correlating the respective locations of paresthesias and VTAs.

We recorded 48 distinct paresthesia maps corresponding to 48 VTAs (including 36 related to directional stimulation). We observed that, in a single patient, respective body representations of the trunk, upper limb, lower limb and head were closely located around the lead. These representations differed across patients, did not follow a common organization and were not concordant with the previously described somatotopic organization of the sensory thalamus.
Thalamic reorganization has been reported in chronic pain patients compared to non-pain patients operated for movement disorders in previous studies using intraoperative recordings and micro-stimulation. Using a different methodology, namely 3D representation of the volume of thalamic tissue activated by the directional postoperative stimulation through a stationary electrode, our study brings additional arguments in favor of a reorganization of the sensory thalamic nuclei somatotopy in patients suffering from chronic neuropathic pain of central or peripheral origin.

*Intervenant

C-Low-Threshold-MechanoReceptors (C-LTMRs): from pleasant touch to pain modulation

Guillaume Robert*[1], Aziz Moqrich , and Ana Reynders

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Résumé

The sense of touch is our most recruited sense at birth, and remains essential throughout our lives for various functions, including pain. How pain and touch pathway interact at the spinal level was well explained in the Gate Control Theory (GCT) of pain. The GCT stipulates that propagation of touch and pain information from the periphery to the central nervous system, is strongly modulated by a particular class of spinal cord interneurons called " Gating Neurons ". The core of this theory predicts that injury induces a disruption in the efficacy of these gating neurons, allowing both innocuous and noxious stimuli to access the pain pathway. For a long time, it was thought that tactile sensitivity relies solely on Low-Threshold Mechanoreceptors (LTMRs) with large myelinated (Aβ) afferents, and they have been postulated to be the only touch-sensing neurons to play a role in this process.
1939 was a breakthrough year in the field of touch with the discovery of the neuronal substrate for the pleasant aspect of touch: The C-LTMRs. These unmyelinated primary afferent fibers, found in both humans and mice, exclusively innervate the hairy skin. Recently, in both species, these pleasant touch neurons have also been proposed to play a critical role in the modulation of injury-induced pain. However, this last function remains to be demonstrated. To address this question, we developed an intersectional genetic strategy allowing us to selectively ablate this enigmatic population of sensory neurons in vivo. Ablation of C-LTMRs leads to a decrease in the second phase of formalin evoked-pain and conversely to a decrease in the baseline mechanical threshold in naive condition and a prolonged mechanical hypersensitivity in a model of postsurgical pain. Our preliminary RNAseq data suggest that C-LTMRs may modulate surgical-induced pain by regulating neurotrophin/BDNF induced sensitization in DRG. Further ultrastructure (immuno electron microscopy) and transcriptomic (RNAseq) approaches on the dorsal horn of the spinal cord will further provide central mechanistic insights into this chronic surgical pain phenotype.
Data emanating from this project will, for the first time, validate the dogma on pleasant touch neurons and pain modulation, providing a new basis for the development of suitable new treatments to different types of pain and adding this new touch component to the well-known Gate Control Theory.

*Intervenant

Functional connectivity changes in preclinical models of migraine-like headaches using a new approach of neuroimaging: the functional ultrasound imaging (fUSi)

Lauriane Delay*[1,2], Stéphanie Ravaillault[1], Samuel Diebolt[1], Nathalie Ialy-Radio[1], Fabien Marchand[2], Lénaïc Montconduit[2], Thomas Deffieux[1], Mickaël Tanter[1], and Sophie Pezet[1]

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[2]Neuro-Dol – Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne – France

Résumé

Background: Affecting approximately 15 % of the global population, migraine is a complex neurovascular disorder characterized by headache crises and associated sensory hypersensitivities, such as allodynia. As an alternative to functional magnetic resonance imaging in preclinical settings, we employ an innovative neuroimaging technique: functional ultrasound imaging. Due to its high sensitivity to cerebral blood volume (CBV) changes, along with its superior spatial and temporal resolutions, this method has resulted in significant advancements in the field of neuroscience. Functional connectivity (FC) is a descriptive measure of spatiotemporal correlations between distinct cerebral regions and a readout of the intrinsic network organization of the brain, undergoes changes across pathological states such as migraine. Our objective is to investigate functional connectivity changes of two relevant preclinical models of migraine induced by nitric oxide donors, using functional ultrasound imaging.
Methods: Chronic migraine-like models were induced in Sprague-Dawley male rats using repetitive intraperitoneal injections of nitric oxide donors: nitroglycerin (NTG) or isosorbide dinitrate (ISDN). Facial mechanical threshold sensitivity was monitored using von Frey hair filaments before model induction and five days after. A functional ultrasound imaging session was performed on day 5 to characterize interictal resting-state FC changes in these two preclinical models of migraine.

Results: Consistent with the literature, repetitive injections of nitric oxide donors induced facial mechanical allodynia. In our study, bilateral FC changes were observed in the two migraine-like models compared to the control group, with relevance to clinical data. Repetitive administrations of NTG induced slight changes compared to repetitive administrations of ISDN. Both showed a decreased FC of the amygdala and the auditory, primary somatosensory, somatosensory barrel field, parietal, and retrosplenial cortex compared to the control group. Repetitive administrations of ISDN led to an increase in FC in various parts of the brain related to migraine symptomatology.

*Intervenant

Conclusions: Our results validated the use of functional ultrasound imaging to explore functional connectivity in preclinical models of migraine-like headaches. Additionally, these data show more pronounced changes in ISDN-injected rats compared to NTG-injected rats, prompting the question of which model is the most relevant for preclinical migraine studies.

Translational research on pruritus

Laurent Misery

Univ Brest, Laboratoire Interactions Epitheliums-Neurones (LIEN), F-29200 Brest
Université de Bretagne Occidentale (UBO) : EA4685

Laurent Misery's lab is dedicated to translational research on itch (and pain). All aspects, from basic research to clinical trials, clinical research and sociopscyhological research are addressed. In vitro cocultures of neurons and skin that are routinely performed in this lab and allow better understanding of itch pathophysiology. Neurokeratinocytic synapses were evidenced. In clinical research, a focus will be given on neuropathic and psychogenic/pruriplastic itch then the burden of itch will be discussed.

*Intervenant

KEYNOTE 1

Dr. Kirsty Bannister

Wolfson Sensory, Pain and Regeneration Centre, King's College London, UK

Chair : Eric Lingueglia

The top down control of pain in health and disease: from bench to bedside

Descending modulatory controls underpin the way in which the brain talks to the spinal cord, exerting bi-directional control over nociceptive processing. Defining the discrete circuits that are encompassed by the descending pain modulatory system in a translational manner will lend itself to improved analgesia thanks to overcoming the issue of invalid targets and limitations of currently used methods to measure pain/nociception. Here, the functional (pharmacological and anatomical) definition of a naturally occurring pain inhibitory control in health is revealed alongside a foundation of studies that will pinpoint dysfunction in disease through understanding the translational value of electrophysiological neuronal and psychophysical sensory correlates.

Chair : Christine Courteix & Nicolas Cénac

Anti-Nociceptive Role Of The Relaxin-3/RXFP3 Peptidergic System

Marc Landry*[1,2], Cynthia Alkhoury-Abboud[3], Rémi Kinet[3], Sandra Sanchez Sarasua De La Barcena[3], Akhter Hossain[4], Andrew Gundlach[4], and Thibault Dhellemmes[3]

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[2]Université de Bordeaux – IMN, UMR CNRS 5293 – France

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Résumé

Affecting around 10% of world population, chronic pain and its related psychiatric comorbidities are major health issues. Implication of neuropeptides in modulation of pain remains poorly described in the brain. The relaxin-3 (RLN3) neuropeptide displays antidepressant and anxiolytic effects, and our preliminary results indicated an antinociceptive role in rodents. RLN3 is expressed by Nucleus Incertus (NI) neurons that project to different cortical (e.g. anterior cingulate cortex (ACC)) and subcortical (e.g. amygdala) areas of the pain matrix.
We aim at studying the pain modulatory effects of RLN3 release and RXFP3 (RLN3 receptor) activation by using pharmacological, behavioral and anatomical approaches in a mouse model of persistent inflammatory pain.

Inflamamtory pain is induced by injection of Complete Freund's Adjuvant (CFA) in the paw of C57Bl6 mice. Intra-amygdalar injection of RXFP3 agonists alleviated both mechanical and thermal pain in CFA mice, while intra-ACC injection had an effect only on mechanical sensitization. Effects are suppressed by the coinjection of an RXFP3 antagonist. The effect of AAV-mediated chronic release of another RXFP3 agonist (R3/I5) confirmed these antinociceptive effects in the ACC and amygdala. Tracing experiments (eGFP) of NI RLN3 neurons showed a dense network innervating most of the forebrain areas. Patch-clamp experiments suggested that pain conditions alter excitability of NI neurons.

In situ hybridization experiments demonstrated RXFP3 mRNA expression in somatostatin interneurons both in the ACC and amygdala, with an increase of RXFP3 expression in pain condition. 3D quantification in the ACC indicated an increase in the number RLN3 profiles, but a decrease in their volume under inflammatory conditions.
Our data highlight the plasticity of the RLN3/RXFP3 system and a novel antinociceptive role for this peptide family, suggesting its therapeutic potential in persistent pain conditions.

*Intervenant

Intracranial EEG spectra: a pathway to optimise neurostimulation?

Hélène Bastuji*[1,2], Maeva Daoud[3], Clara Gazagnaire[3], Charbel Salameh[3], and Luis Garcia-Larrea[3]

[1]Centre de recherche en neurosciences de Lyon - Lyon Neuroscience Research Center – Université Claude Bernard Lyon 1, Université de Lyon, Université Jean Monnet - Saint-Etienne, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique – Centre Hospitalier Le Vinatier, Bâtiment 462 Neurocampus Michel Jouvet, 95 boulevard Pinel, 69500 Bron, France

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[3]Centre de recherche en neurosciences de Lyon - Lyon Neuroscience Research Center – Université Claude Bernard Lyon 1, Université de Lyon, Université Jean Monnet - Saint-Etienne, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique – France

Résumé

Repetitive Transcranial Magnetic Stimulation (rTMS) for neuropathic pain is commonly applied over the precentral cortex at frequencies of 10 or 20 Hz. Since these frequencies are close to the spontaneous oscillatory rhythm of sensorimotor cortices (the 'mu' rhythm) or its harmonics, it has been hypothesised that such oscillatory match may contribute to rTMS efficacy. New potential targets for cortical stimulation are currently being considered for patients not responding to standard rTMS, notably the posterior and anterior insulae and the cingulate gyrus, but the oscillatory characteristics of neural networks in these areas are barely known in humans. The aim of the present project is to characterise the oscillator activity of these potential cortical targets using field potential intracranial recordings (iEEGs) in patients implanted with intracranial electrodes for diagnostic purposes. This is still a work in progress, with preliminary results. The spontaneous activity in motor and somatosensory primary cortices showed prominent peaks, respectively at 8 ± 0.6 Hz and 10 ± 0.9 Hz consistent with the 'mu' rhythm. In contrast, spontaneous activity in the insular and cingulate cortices did not show such prominent, regular oscillatory activity, but rather a surcharge of slow (delta) oscillations on which small spectral 'bumps' could be identified, whose peak frequency varied considerably across subjects. The posterior (sensory) insula showed two such spectral swellings, one at roughly the same frequency as the sensorimotor cortices (8-9 Hz), and a second at higher frequencies of 13-15 Hz, which was also the only clearly appearing in the anterior insula and anterior cingulate gyrus. No frequency peak of activity could be individualised from the posterior cingulate cortex. Hebbian models postulate that phase locking between the intrinsic activity of a network and an external driving stimulus (rTMS) increases synaptic efficacy, as this strengthens the impact of the synchronously firing neurons onto common targets. Adapting rTMS of new targets to their intrinsic frequency may be one relatively simple way to increase the efficacy of rTMS in neuropathic pain.

*Intervenant

A new model for studying the onset of Parkinson disease related sensory deficits

Gawain GRELLIER*, Amaury FRANCOIS, and Emmanuel BOURINET

Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, Montpellier, France,

Résumé

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. 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 viral approach to express a Cre-inducible autocatalytic caspase-3 enzyme (taCasp3) in the SNc of Th-CreER mice to target dopaminergic neurons. By gradually inducing the expression of taCasp3 expression with varying tamoxifen doses, we aim to demonstrate the sequential effects of dopaminergic neuron ablation on the sensory and motor symptoms. The first observation reveals that strong induction of taCasp3 leads to SNc degeneration, causes locomotor deficit, and induces mechanical sensory hypersensitivity. The ongoing project aims now to study the effects of a progressive targeted cell ablation. 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.

Supports: ANR PD Pain, Labex ICST

*Intervenant

TREK1 channels expressed in peripheral nervous system participate to thermonociception

Romane Boyer*[1]

[1]NeuroDol – Université d'Auvergne - Clermont-Ferrand I – France

Résumé

Background. The TREK1 potassium channel plays a crucial role in polymodal pain and morphine-induced analgesia. Several studies show that pharmacological activation of this channel produces analgesia in different rodent pain models. Yet, TREK1 is expressed in both the peripheral and central nervous systems, raising uncertainty about whether selectively targeting peripheral TREK1, considered safer due to the widespread central expression of this channel, is sufficient to induce pain relief. **Methods.** To investigate the contribution of peripheral TREK1 channels in nociception, we measured calcium transients produced in response to capsaicin with/without co-treatment with the TREK1 activator ML335 in cultured sensory neurons from WT, TREK1 knock-out and TREK1-Tomato Cre-dependent reporter mice. Additionally, chemogenetic inhibition of TREK1-positive neurons obtained from TREK1-hM4Di mice was performed using the hM4Di activator JHU37160. Sensitivity to noxious heat was also evaluated *in vivo* in TREK1 global and conditional knockouts (restricted to Nav1.8-positive neurons) as well as in TREK1-hM4Di mice following JHU37160 treatment. **Results.** Immunostaining of TRPV1 in DRG slices from TREK1-Tomato mice revealed that 56% of TREK1-positive neurons express TRPV1 and 16% of TRPV1-positive neurons express TREK1. ML335 treatment and chemogenetic inhibition of TREK1-positive cells decreased the average intensity of calcium transients triggered by capsaicin in cultured DRG neurons, while neurons from TREK1 knockout mice exhibited a higher response to capsaicin. Also, over 90% of TREK1-positive neurons responded to capsaicin, supporting the role of TREK1 channels in reducing the excitability of a population of putative heat-sensitive nociceptors. *In vivo*, we confirmed that TREK1 global knockout mice are more sensitive to noxious heat (46∘C) than wild-type mice. Conditional (Nav1.8-Cre) TREK1 knockouts show intermediate pain thresholds, suggesting that TREK1 channels in nociceptors are necessary but not sufficient for thermonociception. Conversely, intraperitoneal injection of JHU37160 increased pain thresholds of TREK1-hM4Di mice. **Conclusion.** Our findings highlight the involvement of TREK1 in heat sensitivity, implicating a reduction of nociceptors excitability at the periphery together with a contribution of central TREK1 channels that remains to be explored.

*Intervenant

INOVPAIN 2.0
DOULEURS CHRONIQUES RÉFRACTAIRES
SOLUTIONS INNOVANTES

SESSION FHU INOVPAIN 2.0

Chair : Emmanuel Deval

Safety and feasibility of deep brain stimulation of the anterior cingulate and thalamus in chronic refractory neuropathic pain

Denys Fontaine*[1], Aurelie Leplus[2], Anne Donnet[3], Anne Balossier[4], Benoit Simonet[2], Petru Isan[2], Jean Regis[4], Michel Lantéri-Minet[5]

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[3]Pain Clinic, FHU INOVPAIN 2.0 Assistance publique - Hôpitaux de Marseille (AP-HM)
[4]Neurosurgery Assistance publique - Hôpitaux de Marseille (AP-HM)
[5]Pain Clinic, UR2CA, FHU INOVPAIN 2.0 CHU de Nice, Université Cote d'Azur

Objectives: Our objective was to evaluate the feasibility and safety of unilateral thalamic and bilateral anterior cingulate Deep Brain Stimulation (DBS) in patients suffering from medically-refractory chronic unilateral neuropathic pain.

Methods: We conducted a bicentric study (clinicaltrials.gov NCT03399942) to evaluate successively: sensory thalamic stimulation only, combined thalamic and anterior cingulate stimulation, cingulate “on” and “off” stimulation periods in a randomized cross-over double-blinded phase and a 1-year open phase. Safety and efficacy were evaluated by repeated neurological examination, psychiatric assessment, comprehensive assessment of cognitive and affective functioning. Changes on pain intensity (Visual Analogic Scale) and quality of life were used to evaluate DBS efficacy.

Results: Eight patients (2 women; mean age 52,1, mean pain duration 7,1 years) were included and completed the study. One patient had an intraoperative epileptic seizure but no patient developed permanent epilepsy. Several patients presented transient motor or attention disturbances, reversible after cingulate stimulation intensity decrease. Persistent adverse effects were gait and balance disturbances (1 case) and sleep disturbances (1 case). No patient displayed significant changes cognitive or affective change. We observed a significant improvement of quality of life at the end of the cingulate ON stimulation period and at the end of the study, compared to baseline, without significant concomitant pain intensity change.

Conclusion: This pilot study confirmed the safety of anterior cingulate DBS alone or in combination with thalamic stimulation and suggested that it might improve quality of life of patients with chronic refractory pain.

*Intervenant

INOVPAIN 2.0
DOULEURS CHRONIQUES RÉFRACTAIRES
SOLUTIONS INNOVANTES

SESSION FHU INOVPAIN 2.0

Optopharmacology of Two-Pore-Domain Potassium Channel in Pain

Guillaume Sandoz*[1]

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By endowing light control of neuronal activity, optogenetics and photopharmacology are powerful methods notably used to probe the transmission of pain signals. However, costs, animal handling and ethical issues have reduced their dissemination and routine use. Here we report LAKI (Light Activated K+ channel Inhibitor), a specific photoswitchable inhibitor of the pain-related two-pore-domain potassium TREK and TRESK channels. In the dark or ambient light, LAKI is inactive. However, alternating transdermal illumination at 365 nm and 480 nm reversibly blocks and unblocks TREK/TRESK current in nociceptors, enabling rapid control of pain and nociception in intact and freely moving mice and nematode. These results demonstrate, in vivo, the subcellular localization of TREK/TRESK at the nociceptor free nerve endings in which their acute inhibition is sufficient to induce pain, showing LAKI potential as a valuable tool for TREK/TRESK channel studies. More importantly, LAKI gives the ability to reversibly remote-control pain in a non-invasive and physiological manner in naive animals, which has utility in basic and translational pain research but also in in vivo analgesic drug screening and validation, without the need of genetic manipulations or viral infection.

*Intervenant

Oral communication

Session 3

Chair : Sophie Pezet & Emmanuel Bourinet

The mouse cheek test to study some neuropathic disorders of ciguatera

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Résumé

Ciguatoxins (CTXs) are the neurotoxins causing ciguatera poisoning. The most prevalent and distressing symptoms are neuropathic-like sensory disturbances, including paresthesia, cold allodynia and an intense generalized pruritus. Pain in the muscles, joints, teeth, and urogenital tract, as well as taste disturbances, ataxia and fatigue are also commonly described. Ciguatera itch and fatigue commonly last for weeks or months after a single poisoning. Mechanistically, CTXs are potent activators of voltage-gated sodium (Nav) channels. Besides the overall involvement of these channels, knowledge on molecular actors involved is limited and no specific treatment currently exists. This project aims to complement the limited knowledge on the pathophysiological bases of ciguatera sensory disturbances, especially itch.
We used the mouse cheek test, which distinguishes between itch- and pain-related behaviors, to characterize the spontaneous sensory behaviors elicited by a pure CTX injected intradermally. Nanomolar and sub-nanomolar doses of Pacific-CTX-1 were injected into the cheek of C57BL/6 mice. Video recordings of behavioral responses were analyzed to count the numbers of sensory behaviors reflecting itch and pain. In addition, the other evoked behaviors were noted and/or their durations were measured. Selected knockout mice or pretreatments were used to investigate underlying mechanisms.

The expected and unexpected behaviors induced will be presented and discussed. The dose-response relationships determined for each behavior analyzed allow to highlight the first measurable effect occurring in response to increasing doses. These data suggest that CTX applied to the mouse cheek test is a singular tool for studying some major symptoms of ciguatera.
This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 101026260.

*Intervenant

Sensory plasticity of dorsal horn silent neurons: a new mechanism for neuropathic pain.

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Résumé

Our capacity to discriminate between painful and non-painful sensory stimulation is crucial for our survival. Under maladaptive conditions this discriminative sensory perception is dramatically disrupted leading to misperception of light touch as painful referred as **mechanical allodynia** (3). Mechanical allodynia is a common symptom of neuropathic pain representing one of the highest causes of disability (1). Indeed, despite the growing body of investigations on neuropathic pain, most current treatments have modest efficacy with distressful symptoms highlighting the deficit in our knowledge of the complex neuronal mechanisms precipitating this condition (Finnerup et al., 2018).
Several mechanisms have been proposed to explain the transition from physiological to neuropathic pain conditions among which is the disruption of the functional sensory circuit in the dorsal horn of the spinal cord (DH) (2,6). Indeed, the DH is considered a major hub for sensory integration and processing which is interplayed by **excitatory and inhibitory interneurons** with few (1%) output projection neurons (2,4,5).

Here we aimed at investigating the functional sensory profiles of DH neurons in normal control conditions and how these sensory profiles are altered during neuropathic conditions. To do so, we developed a somatosensory *ex vivo* preparation combined with 2-Photon Ca2+ imaging of the excitatory DH neurons allowing us to analyze the substantial activation of a group of individual neurons by peripheral sensory stimulations. We found that during control conditions most of DH neurons responded to **noxious stimulation** and a large population of neurons being **silent**, irresponsive to any peripheral stimulation. After spinal disinhibition or neuropathy, many neurons became **WDR** responding indifferently to noxious and innoxious peripheral stimulations. These WDR neurons originated from shifting the tuning of the noxious specific neurons and the recruitment of a population silent WDR neurons. This data reveals a new mechanism for the development of neuropathic pain and help in defining new therapeutic targets for the treatment of mechanical allodynia.

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*Intervenant

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Role of vlPAG SST neurons in fear conditioning analgesia

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Résumé

In mammals, threat-related behavior is typically induced by a noxious physical stressor and is associated with a broad range of behavioral responses such as freezing and avoidance. These behavioral responses are associated with the regulation of pain responses allowing individuals to cope with noxious stimuli. Whereas the structures and mechanisms involved in pain behavior are well documented, little is known about the precise neuronal circuits mediating the emotional regulation of pain behavior. Here we used a combination of behavioral, anatomical, optogenetic, and electrophysiological approaches to show that somatostatin-expressing neurons in the ventrolateral periaqueductal gray matter (vlPAG SST cells) are involved in fear and pain. Long range vlPAG SST cells enhance nociceptive responses through downstream control of rostral ventromedial descending pathways to the spinal cord while local vlPAG SST cells are involved in fear expression. Indeed, we show that activation of vlPAG SST cells mediating descending facilitation suppress fear conditioning analgesia without affecting freezing while activating the whole vlPAG SST population also suppress fear expression. These results identify a midbrain circuit composed of vlPAG SST cells specifically projecting to the RVM and mediating FCA to regulate pain responses during threatful situations.

*Intervenant

The PrRPR and PrRP system modulates nociception, inflammatory pain and neuropathic pain in mice

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Résumé

Chronic pain is a major health problem. This debilitating condition is considered a disease and affects up to one third of the adult population (Steingrímsdóttir *et al.*, 2017). Existing treatments are often poorly effective and display numerous adverse side effects highlighting the urgent need to identify and validate novel targets for drug development. In this project, we have studied the role of a novel GPCR target Prolactin Releasing Peptide Receptor (PrRPR or GPR10) and its endogenous ligand Prolactin Releasing Peptide (PrRP) in the modulation of pain. The PrRP receptor belongs to the RF-amide receptor family and has been proposed to be involved in the modulation of different functions including metabolism and feeding as well as modulation of nociception and opioid analgesia (Quillet *et al.*, 2016; Fuji *et al.*, 1999; Laurent *et al.*, 2005). However, the absence of pharmacological tools (antagonists) is severely limiting the study of the functions of this receptor/ligand system *in vivo*. In this project, we have identified a potent and selective PrRPR antagonist, RF1340, and showed that this compound efficiently blocks the activity of the PrRPR both *in vitro* and *in vivo*. We have further used this compound to study in mice the consequences of the pharmacological blockade PrRPR/PrRP system in different model of pain. Our results show that activation of PrRPR/PrRP is essential for the development of hyperalgesia induced by opiates, inflammatory and neuropathic pain. Moreover, we have shown by ISH that PrRPR is expressed in the outer layers of the dorsal horn spinal cord as well as dorsal root ganglia indicating a potential role in the modulation of nociceptive inputs both in the peripheral and central nervous systems. Altogether, these data make the proof of concept that pharmacological blockade of PrRPR is an interesting strategy to develop novel treatment for chronic pain. In order to go forward in the development of a novel drug targeting PrRPR

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we have recently screened and identified patentable compounds that efficiently block PrRPR activity *in vitro*. Among them RF4442 displays a good activity in different models of chronic pain, as well as low toxicity suggesting that it could represent a future preclinical candidate.

Reduced inflammation-induced visceral sensitivity in aged mice is associated with high potency of T cells to produce enkephalins

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Résumé

Aging is intricately associated with a state of low-grade inflammation known as inflammaging, which arises as a consequence of immune system senescence. While both innate and adaptive immune responses undergo alterations in elderly individuals, T lymphocytes are particularly vulnerable to the effects of aging, notably exhibiting a higher number of 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 nociceptive neurons by inflammatory mediators from damaged tissues and infiltrating immune cells. Our study aimed to assess whether the opioid-mediated analgesic effect of T lymphocytes remains preserved in older mice, considering the impact of aging on both the quantity and functionality of T lymphocytes. Our findings reveal an increased production of enkephalins by activated T lymphocytes, along with a higher proportion of activated T-cells, in 1-year-old mice. Notably, these mice seem to be shielded from the visceral hypersensitivity typically observed following DSS treatment. Moreover, under inflammatory conditions induced by treatment with DSS, 1-year-old mice exhibit milder colitis compared to their younger counterparts. In summary, our results suggest that the low-grade inflammation commonly seen in elderly individuals triggers a faster immune reaction to DSS treatment, leading to a reduction in the severity of colitis. Additionally, it's worth noting that elderly individuals, whether healthy or afflicted with IBS, experience decreased abdominal pain, which could further contribute to their overall resilience against colitis.

*Intervenant

Comprehensive study of the sex-specific alterations of the brain vascular responsiveness in a preclinical model of migraine, using whole brain ultrafast Doppler imaging

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Résumé

Background: Migraine is one of the most prevalent and disabling neurovascular disorders worldwide. However, despite the increase in awareness and research, the understanding of migraine pathophysiology and treatment options remain limited. For centuries, migraine was considered to be a vascular disorder. In fact, the throbbing, pulsating quality of the headache is thought to be caused by mechanical changes in vessels. Moreover, the most successful migraine treatments act on the vasculature and induction of migraine can be accomplished with vasoactive agents. Since, the vascular nature of migraine is still debated, and the emphasis has now shifted to the neural imbalances associated with migraine.
Aim: Taking advantage of the high sensitivity of ultrafast Doppler imaging to cerebral blood volume (CBV), along with its high spatial and temporal resolutions and its large field of view, this study aimed at studying the changes of cerebral blood volume in a large part of the brain during the development of sensitization in an animal model of migraine (induced by repetitive injections of nitroglycerin), and once sensitized, during inter-ictal periods and during migraine attacks. Existence of a possible dimorphisms was studied through inclusion of two cohorts of male/female rats.

Methods: The chronic migraine-like model was induced in Sprague-Dawley male rats using repetitive intraperitoneal injections of nitroglycerin (NTG). Facial mechanical threshold sensitivity was monitored using von Frey hair filaments before the model induction and before each imaging session. Ultrafast Doppler imaging sessions were performed in anaesthetized animals through a chronically implanted cranial window before and several hours following the 1st, 4th and 5th injection of NTG.

Results: In addition, with the short-term vasodilation induced by NTG, previously reported, our study reveals that the acute injection of NTG in naïve animals induces a long-lasting

*Intervenant

(2-3 hours) hyperperfusion in groups of brain areas (including the cingulate, retrosplenial and medial visual areas). Once sensitized, female rats display a very strong unilateral hyperperfusion in these same brain regions. In sensitized animals, NTG injection induced an exacerbation over time of the CBV in these areas. In male in contrary, these changes were present, but comparatively modest.
Conclusions: Our results show, for the first time in this translational animal model of migraine, clear zones of the cerebral vasculature that are the center of altered vascular tone. The exacerbation observed overtime, its unilateral nature, and its location in mediomedial visual areas are consistent with clinical observations. Our results also point also towards a strong dimorphism in these pathophysiological changes.

A quest for Cav3.2 interactome to gain insight in chronic pain mechanisms.

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Résumé

Many ion channels are involved in the pathophysiology of pain, with an important pronociceptive role of Cav3.2 voltage-gated calcium channels in rodents. Cav3.2 channels activate at low membrane potential before the threshold of action potentials and therefore are important contributors to cell excitability. While Cav3.2 is unique in modulating pain signals, the two other low-voltage-gated calcium channels, Cav3.1 and Cav3.3, have similar biophysical properties, overlapping expression, and close sub-cellular distribution including within the spinal cord, the first relay of nociceptive information processing. Therefore we hypothesize that, in addition to its electrogenic impact, Cav3.2 is specifically present in some signaling complexes associated with membrane or submembrane partners that could explain its pro nociceptive functions. Documentation of interactors for this channel family is sparse; and the specific Cav3.2-channelosome is largely unknown. This study aims to identify Cav3.2-associated signaling complexes with the hope of finding specific interactors. To do so, we use Affinity Purification associated with Mass Spectrometry (AP-MS) on tissues from Cav3.2-GFP KI mice using a set of commercial and homemade high affinity anti-GFP nanobodies. The combined use of genetically tagged channel, high affinity anti-tag trapping, and customized buffers improved the enrichment of lowly expressed Cav3.2 to an extent compatible with MS analysis. The preliminary set of partners obtained validate this discovery pipeline. The most co-enriched partners show promising perspectives in the context of pain circuits. We believe that applying this non-biased strategy in models of chronic pain compared to control situations will enable us to pinpoint perturbations of Cav3.2 complexes that could be targeted by future innovative analgesic therapies for chronic pain management. *Supported by ANR interacT / FHU inovpain / Labex ICST*

*Intervenant

Exploring the role of THIK potassium channels in nociceptive pathway

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Résumé

Title : Exploring the role of THIK potassium channels in nociceptive pathway
Nicolas Gilbert, Franck Chatelain, Florian Lesage, Delphine Bichet

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Potassium channels play a crucial role in the nervous system, as they can affect resting membrane potential and modulate action potentials making them important targets for the search for new neuronal modulators. The K2P group of potassium channels are involved in various physiological functions mostly cardiac and neuronal. Recently, several K2P channels have been linked to the regulation of pain and mutation in K2P channels are associated with migraine and neurodevelopmental disorders. K2P channels are known to finely regulate neuronal excitability by hyperpolarizing their membrane.

Members of the Tandem pore-domain Halothane-Inhibited K+ channels subfamily (THIK1 and THIK2) are highly expressed in the Central and Peripheral Nervous System (CNS and PNS), but their role in the control of pain sensation has not been studied yet. Using in-situ hybridization technique (RNAscope), we have recently shown that THIK channels are co-expressed by non-peptidergic nociceptive neurons that express the Purinergic Receptor 2X3 (P2RX3) in PNS. These unmyelinated neurons are known to be involved in the transmission of slow nociceptive messages in Dorsal Root Ganglia (DRG) such as inflammatory and chronic ones. Moreover, RNAseq data shows that THIK1 and THIK2 are the most highly expressed K2P channels in microglial cells of the CNS, in which THIK1 has been linked to inflammasome activation. This suggests that these channels might play a role in inflammatory pain.

We are now investigating their role in transmitting sensory and nociceptive messages and whether these channels function as homomers or heteromers. Initial studies have shown that THIK2 knockout mice exhibit thermal allodynia and inflammatory hyperalgesia. We aim to further explore the functions of THIK1 and THIK2 in nociception and differentiate the roles of homomeric and heteromeric forms of the THIK channels. This distinction is crucial for the development of specific pharmacology and targeted therapy.

*Intervenant

Blockade of 5-HT6 receptor/mTOR activity differentially attenuates neuropathic pain and cognitive comorbidity in male and female diabetic rats

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Résumé

Chronic neuropathic pain is a major complication of diabetes with, in France no less than 20.3% of diabetic patients (type 1 and type 2 diabetes) suffering from chronic neuropathic pain. Regarding the increased number of diabetic patients worldwide (537 million in 2021 versus 783 million estimated in 2045), the impact of pain on quality of life and the poor efficacy of recommended treatments, we have focused our efforts on new options for the management of diabetic neuropathic pain, proposing 5-HT6 receptor inverse agonists as new candidates. Our previous data obtained in male diabetic rats show that blocking the constitutive activity of the 5-HT6 receptor, inhibiting the mTOR signalling pathway and disrupting the interaction between the 5-HT6 receptor and mTOR, improve pain behavior and cognitive performance. To increase the relevance of this finding and to explore pharmacokinetics/pharmacodynamic differences between males and females, we examined the effect of 5-HT6receptor inverse agonists, rapamycin (an mTOR inhibitor) and a mimetic peptide (Tat-VEPE) on mechanical hyperalgesia and cognitive deficits in streptozocin (STZ)-induced diabetic female rats. The complete (PZ1388, PZ1386, SB258585) and partial (PZ1179) inverse agonists intraperitoneally injected reduced mechanical hyperalgesia in females as well as rapamycine and TAT-VEPE intrathecally injected. Compared with their respective antihyperalgesic effects previously observed in male rats, the magnitude and duration of the effect were smaller and shorter respectively. Regarding comorbid cognitive deficits associated with neuropathic pain, PZ1386, SB258585, rapamycin and TAT-VEPE but not PZ1179 restored novel object discrimination in females as previously observed in males. These results therefore suggest that 5-HT6 receptor signalling pathways are differentially sensitive to pharmacological agents depending on gender, and prompt further investigation and comparison of downstream effectors in the two sexes in order to better understand the differential effects on diabetic neuropathic pain.

*Intervenant

Reaching circuitry level of understanding of the comorbidity between chronic pain and mood disorders

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Uncontrolled and persistent pain is strongly associated with anxiety and depressive disorders and is one of the most common causes of disability and impaired quality of life. Over the last 10 years, our group has established and validated paradigms to model this comorbidity in the mouse. We have then used this model to uncover individual brain structures and molecular mechanisms affected by chronic pain. Among the candidates, the anterior cingulate cortex (ACC), a structure shared by the default mode, salience and reward networks, appears to be critical for pain and emotional processing. Our rodent studies further support the involvement of the ACC in pain processing, particularly in the comorbidity between chronic pain and mood disorders.

It is now recognized that most central nervous system pathologies involve changes in brain networks rather than in a single structure. Thus, beyond identifying specific changes in individual brain regions, recent studies and our results suggest that chronic pain and its comorbidities are more likely to result from changes in brain networks, particularly the circuits of the ACC. To take this a step further, we now aim to gain a network level understanding of this comorbidity. Our resting state functional magnetic resonance imaging (fMRI) results clearly showed alterations in the circuitry of the basolateral amygdala (BLA)-ACC and corticomesolimbic regions in our rodent model of comorbid chronic pain and depression. By combining optogenetic approaches, behavioral and transcriptomic analyses, we are now further dissecting the functional role of these distinct circuits to deepen our understanding of the mechanisms underlying the comorbidity of depression and chronic pain.

*Intervenant

KEYNOTE 2

Pr. Tor D. Wager

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Chair : Denys Fontaine

The brain in pain: Pathways, neuromarkers, and interventions

The ability to experience pain is an ancient and fundamental capacity. It is a primary motivator of behavior and driver of learning. While pain serves vital adaptive functions, it can also become decoupled from injury and persist long after it is needed. How pain becomes chronic, and the role of the brain in this process, are vitally important questions for improving the human condition. A trove of new research across species implicates neuroplasticity in brain circuits responsible for four key processes: Nociception, fear and avoidance, reward and enjoyment, and the sense of self and personal meaning. In this task, I discuss these processes through the lens of human neuroimaging studies and mechanistic studies in nonhuman animals. Together, these studies are beginning to characterize the nature of pain beyond nociception and identify new targets for psychological, behavioral, and neuromodulatory treatments. They also permit, for the first time, a comparison of the effects of diverse treatments on the neurophysiological systems underlying pain.

ORAL COMMUNICATION

Session 5

Chair : Delphine Bichet & Alexandre Charlet

Dual effect of TRESK-C317F mutation related to epilepsy

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Résumé

The two hallmarks of seizure generation are neuronal hyperexcitability and hypersynchrony. Neuronal excitability is under the control of a leak potassium current carried by the Two-Pore-Domain Potassium channels (K2Ps). Here, we report a new epilepsy-related mutation of the K2P18.1 channel called TRESK-ME. As expected for an epilepsy-related mutation, when introduced in mice, the mutation led to a decrease of the endogenous leak potassium current which was leading to neuronal hyperexcitability, fitting with the epileptic phenotype observed in human. When expressed in heterologous system the mutation, expected to decrease channel activity, led to a strong increase of the TRESK current. We hypothesized that such discrepancy may be related to a differential effect of the mutation on TREK heterodimers. Using photopharmacology and single molecule we found that TRESK-ME acts as a dominant negative on TREK1 and TREK2 channels. All together, these data show that the channels which could represent a target to treat epilepsy are K2P2.1 and K2P10.1 more than K2P18.1. Furthermore, this example demonstrates that one mutation may carry two opposite effects : gain of function and dominant negative, depending on the protein environment.

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*Intervenant

The effect of prenatal stress on developpement and functions of nociceptors

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Résumé

Nociceptors are specialized neurons of the peripheral nervous system that have their cell body in the dorsal root ganglia (DRG) and are responsible for transmitting painful signals from peripheral organs to the central nervous system. Historically defined as non myelinated medium/small size neurons within the dorsal root ganglia, the advent of next generation sequencing has allow to reveal their high transcriptomic diversity and their classification into several subtypes: Non-Peptidergic nociceptors (NP, three subpopulations), Peptidergic nociceptors (PEP, two subpopulations), and a population of non-nociceptive neurons called c-low-threshold mechanoreceptors (cLTMRs). This cellular diversity supports functional diversity, enabling them to respond to a wide range of mechanical, thermal, or chemical stimuli. These nociceptors differentiate from neuronal precursors between embryonic days (E) 11 and E13 and acquire their final transcriptomic maturity from E13 to after birth

Developmental defect in nociceptors can alter the processing of peripheral stimuli. In particular, it has been shown that perinatal stress can both induce hypersensitivity and leads to neuronal transcriptomic alterations within the offspring's nervous system. In a mouse model, we previously shown that prenatal stress (PS), a stress endured by the mother during pregnancy, generates mechanical visceral hypersensitivity in adult offspring. We thus hypothesized that a disturbance in the transcriptomic development/maturation of nociceptors during PS could explain, at least in part, this phenotype.

To induce PS, pregnant mice are subjected to restraint stress under bright light. This protocol is repeated in 30-minute sessions, three times per day, between embryonic days E13 and E18, a period corresponding to the onset of nociceptor neurogenesis.

To evaluate the effect of PS on somatic mechanical sensitivity we conducted Von Frey experiments on 8-week-old mice. We observed that PS offspring show a pronounced mechanical somatic hypersensitivity as compared to non-stressed CT offspring, suggesting that the hypersensitivity is generalized to all the body. To explore the possible cause of this hypersensitivity, we isolated the dorsal root ganglia (DRG) from CT or PS mice and compared the whole transcriptome of (DRG) from adults born to control or stressed mothers

*Intervenant

using bulk RNAseq. Our results showed that 300 genes are differentially expressed between control and PS conditions, among which several are marker genes of the different nociceptor populations such as Trpv1 (PEP), Th (cLTMR), or Mrgprd (NP). We then conducted immunohistochemistry staining on 8-week-old mice DRGs, to evaluate the repartition of the major populations of small nerve fibers: c-LTMRs (Th staining), NP (IB4 staining) and PEP (Tac1 staining). We observed that PS offspring show an increased proportion of c-LTMRs nociceptors and a decreased proportion of Peptidergic nociceptors, with no changes observed in all or NP as compared to non-stressed CT offspring. To gain insight in the effect of PS on the different population of nociceptors, we performed single-cell RNA sequencing (scRNAseq) on sorted Nav1.8-Tdtomato+ nociceptors from CT or PS offspring. After identifying the cellular types present in our samples, we applied bioinformatics methods to determine differentially expressed genes in each population and to study the activity of transcription factor-associated regulons between the two conditions. Our preliminary results thus suggest that NP and cLTMRs are the two populations of small fiber that are transcriptionally affected by PS.

The continuation of our study will identify the specific developmental stage during which nociceptor neurogenesis is affected and explore the molecular actors likely to be responsible for this dysregulation.

High fat diet causes hyperlipidemia and systemic inflammation associated with thermal hyperalgesia, role of ASIC3 channels.

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Résumé

Diet induced obesity is a major risk factor for many diseases. It is associated with chronic systemic low grade inflammation leading to serious health consequences. We have investigated the effect of high-fat diet induced obesity (DIO) on the activity of nociceptive dorsal root ganglion (DRG) neurons and pain perception. We show that mice fed a high-fat diet develop obesity associated with metabolic syndrome and prediabetes. This pathophysiological state presents a deregulation of glucose homesotasis, hyperlipidemia and systemic inflammation. Obese mice suffer from hypersensitivity to thermal pain, while mechanical sensitivity is unaffected. We have previously shown that Acid Sensing Ion Channels (ASIC channels) expressed in DRG neurons are important mediators of neuropathic and inflammatory pain. ASIC3 knockout mice fed a high-fat diet become obese and develop signs of metabolic syndrome and prediabetes identical to control mice. However, both gene deletion and in vivo pharmacological inhibition of ASIC3 protected the mice from obesity-induced thermal hypersensitivity. We then found that lipids present in high concentration in the serum of diet-induced obese mice increase the excitability of small-diameter DRG neurons in wild type mice, but not in the absence of ASIC3 channels. This observation is linked to the direct activation of ASIC3 by lysolipids and pro-inflammatory lipids, which we found in high concentration in the serum of obese mice. We propose that direct activation of ASIC3 by lipids present in serum potentiates the activity of non myelinated fibers of nociceptive DRG neurons, resulting in sensory hypersensitivity.

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Impact of neonatal maternal separation stress in neuropathies induced by chronic constriction of the sciatic nerve

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Résumé

ENGLISH : Among many stressors existing in the intensive care unit environment of preterm infants, parental separation is an additional factor increasing the risk of developing behavioral disorders and pain hypersensitivity in adulthood.Neonatal maternal separation (NMS), (3h per day from P2 to P12) in rodents has been described as a model of neonatal stress reflecting human prematurity.NMS is known to induce social, behavior and anxiety disorders, disturbances of the nociceptive system and pain responses, as well as cognitive deficits in adult animals. However, little is knows of its impact on the development of neuropathies. Here we sought to evaluate it with a model of neuropathy induced by chronic constriction of the sciatic nerve (cuff model). The hypothesis was that NMS would constitute an aggravating factor in the case of chronic pain in terms of sensory, emotional and cognitive symptoms and would promote aggravated anxio-depressive comorbidities which are usually not detectable in control rats (CTRL) subjected to this model.
We therefore characterized the thermal and mechanical nociceptive responses, anxiety and depressive behaviors and cognitive abilities of NMS animals in adulthood following the establishment of the cuff induced neuropathy.

Following cuff placement, NMS rats presented a delayed and less marked development of cold allodynia and mechanical hyperalgesia compared to CTRL animals. Regarding the assessment of anxiety and depressive behaviors, neuropathic NMS animals did not show significant differences compared to the CTRL group. Results, contrary to the first hypothesis, seem to demonstrate that NMS stress, rather than being an aggravating factor in neuropathies and associated comorbidities, makes individuals resilient to it.

FRENCH : La séparation maternelle néonatale (SMN) chez le rongeur est un modèle de stress reflétant la prématurité humaine et induisant des altérations nociceptives, une anxiété accrue, ainsi que des troubles des comportements sociaux.

Cependant, l'impact de la SMN sur le développement de douleurs chroniques reste méconnu. L'hypothèse étant que la SMN constituerait un facteur aggravant dans le cas de douleurs chroniques au niveau des symptômes sensoriels, émotionnels ainsi que cognitifs et favoriserait l'apparition de comorbidités anxio-dépressives aggravées et d'ordinaire non détectables chez des rats contrôles (CTRL) soumis au modèle de neuropathie induite par constriction

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chronique du nerf sciatique par pose d'un cuff.

Nous avons donc caractérisé à l'âge adulte les réponses thermiques et mécaniques nociceptives, les comportements anxieux et dépressifs et les capacités cognitives des animaux SMN suite à l'établissement de la neuropathie.

Suite à la pose du cuff les rats SMN ont présenté un développement retardé et moins marqué de l'allodynie au froid et de l'hyperalgésie mécanique par rapport aux animaux CTRL. Concernant l'évaluation des comportements anxieux et dépressifs, les animaux SMN neuropathiques ne montrent pas de différences significatives comparativement aux groupes CTRL.

Les résultats dans nos conditions expérimentales, contrairement à la première hypothèse, semblent démontrer que le stress précoce plutôt que d'être un facteur aggravant des neuropathies et comorbiditées associées, rend les individus résilients face à cette dernière.

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