XVIII^{ème} Symposium du Réseau Inserm de Recherche sur la Douleur

Montpellier, 24-25 Mars 2023

Conférenciers invités:
Dr Franziska DENK (UK)
Dr. Michael HILDEBRAND (Canada)
Dr. Sarah ROSS (USA)
Prof. Mathieu ROY (Canada)

https://rfrd2023.sciencesconf.org/

Programme (MAJ 23/3/2023 AM)

Vendredi 24 mars

9h00 : Accueil des participants
9h15 : Ouverture du symposium

9h30 -11h00 : Communications orales - Session 1
Modérateurs : Pierrick Poisbeau et Cédric Peirs

1. Functional brain and trigeminovascular changes in migraine using a new approach of neuroimaging: the functional ultrasound imaging. **Delay Lauriane** - Physics for Medicine, Paris. **visioconférence**
2. Gut microbiota promotes pain chronicity in Myosin1A deficient male mice. **Reynders Ana** - Institut de Biologie du Développement de Marseille, Marseille. **Visioconférence**
3. La planaire comme modèle émergent pour le développement de molécules antinociceptives. **Reho Guillaume** - Institut des Neurosciences Cellulaires et Intégratives, Strasbourg. **visioconférence**
4. Contribution of ASIC1a channels in the spinal processing of pain information by deep projection neurons.**Toft Maurizio** - Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne.
5. Disrupting HCN channels - TRIP8b interaction is an efficient strategy to decrease acute oxaliplatin-induced peripheral neuropathy symptoms. **Morez Margaux** - Neuro-Dol, Clermont-Ferrand.
6. Dual ENKephalinase Inhibitor (DENKI) PL37 as a potential novel treatment of migraine-like symptoms. **Rossignol Jeanne** Pharmaleads, Paris.
7. **Présentation sponsor: Bioseb**

11h00-11h30 Pause-café

11h30-12h30 : Conférence plénière 1
Dr Franziska Denk (King's College London, UK): "A neuro-immunological perspective on chronic pain - what if nerves aren't to blame?"
Modérateurs : Pierrick Poisbeau et Cédric Peirs

12h30-14h00 Déjeuner

14h00-15h00 : Conférence plénière 2 visioconférence
Dr. Michel Hildebrandt (Ottawa, Canada): « Translational human tissue approaches to understand and target spinal mechanisms of pain »
Modérateur : Emmanuel Bourinet

15h00-16h30 : Communications orales - Session 2
Modérateurs : Nadine Attal et Fabien Marchand

1. Phenotyping for better treatment. **Garcia-Larrea Luis** - Centre de Recherche en Neurosciences de Lyon, Bron.
2. Interaction between anitimicrobial peptide Reg3g and IL-22 pathway on intestinal and central disturbances following Citrobacter rodentium infection. **Daugey Valentine** - Neuro-Dol, Clermont-Ferrand.
3. Exploring the role of THIK potassium channels in nociceptive pathway. **Gilbert Nicolas** - Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne.
4. Involvement of serotonergic descending pathways in pain in a mouse model of Parkinsonism. **Grivet Zoé** - Institut des Maladies Neurodégénératives, Bordeaux. **visioconférence**
5. LRP1 in sensory neurons is required for the pain killing effect of TAFA4. **Charron Aude** - Institut de Biologie du Développement de Marseille, Marseille. **visioconférence**
6. Tofacitinib-induced analgesia in mouse model of inflammatory pain. **Tuifua Marie** - Institut des Maladies Neurodégénératives, Bordeaux. **visioconférence**

« 16h30-17h Pause-café

17h30-18h30 : Conférence plénière 3 visioconférence
Dr. Sarah Ross (Pittsburg, USA) : « The Spinal Circuits of Pain and Itch »
Modérateurs : Nadine Attal et Fabien Marchand

18h30-19h00 : Actualités du réseau douleur *: Radhouane Dallel.*

20h Dîner de Gala

Samedi 25 mars

8h30-10h00 : Communications orales - Session 3
Modérateurs : Delphine Bichet et Luis Garcia-Larrea

1. Nociception and itch hypersensitivity in a mouse model of autism associated with peripheral mechanosensory dysfunctions. **Huzard Damien** - Institut de Génomique Fonctionnelle, Montpellier.
2. Optical control of PIEZO1 channels. **Balcon Melaine** - Université de Strasbourg, Faculté de Pharmacie, Illkirch.
3. Peripheral and central delta opioid receptors regulate the migraine-like headache in rats. **Dussol Manon** - Neuro-Dol, Clermont-Ferrand.
4. Reconnaitre la douleur d'un bébé qui pleure : Etude des corrélats cérébraux chez des adultes experts. **Corvin Siloé** - Centre de Recherche en Neurosciences de Lyon, Bron.
5. Ultrasonic stimulation of dorsal root ganglion neurons at 20 MHz. **Elena Brunet** - Institut de Biologie du Développement de Marseille, Marseille.
6. Evaluation of TACAN as a new target for treating osteoarthritis pain. **Gilbert Alice** - Neuro-Dol, Clermont-Ferrand.

10h00-11h00 : Conférence plénière 4
Dr. Mathieu Roy (McGill University, Canada) : « Comment le cerveau produit-il notre expérience de douleur ? »
Modérateur : Patrick Ginies

11h00-11h30 Pause-café

11h30-12h30 : Communications orales - Session 4
Modérateurs : Rémy Schlichter et Eric Lingueglia

1. Chronic neuropathic and inflammatory pain: implication and therapeutic potential of the FXYD family members. **Maskini Dounia** - Institut des Neurosciences de Montpellier
2. Pyridin-2(1H)one derivatives: A new class of therapeutics for trigeminal pain. **Murail Pauline** - Neuro-Dol, Clermont-Ferrand.
3. Thalamo- and cortico-cortical functional connectivity as predictor of arousal to noxious stimuli during sleep in humans. **Bastuji Hélène** - Centre de Recherche en Neurosciences de Lyon, Bron.
4. The constitutive activity of spinal 5-HT6 receptors contributes to diabetic neuropathic pain in rats. **Mokhtar Nazarine** - Neuro-Dol, Clermont-Ferrand.

12h30 : Prix de la communication orale, conclusions et déjeuner

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Informations pratiques

Pour nous contacter : 06 09 53 93 22 (Lauriane Ulmann) 06 28 59 61 53 (Cyril Rivat)

Adresse symposium *:Salle Puaux, Théâtre d'Ô, entrée Sud, Rond-point du Château d'Ô, Avenue des Moulins 34080 Montpellier.*
https://www.domainedo.fr/domaine-do/espaces/theatre-d-o

Transport: Tramway: ligne 1, arrêt "Chateau d'Ô" / Voiture: Parking sur place
Google maps: https://goo.gl/maps/DBfUe91xCeQMHsUX6

Repas de Gala : *Hôtel Mercure Montpellier Centre Antigone, 285 Bd de l'Aéroport international.*
Transport : Tram 1 arrêt Léon Blum ou Place de l'Europe.

Abstracts

Contribution of ASIC1a channels in the spinal processing of pain information by deep projection neurons

Maurizio Toft [1],

1 : Institut de pharmacologie moléculaire et cellulaire
Université Nice Sophia Antipolis (1965 - 2019), Centre National de la Recherche Scientifique, Université Côte d'Azur
CNRS-IPMC 660 Route des lucioles 06560 VALBONNE - France

The dorsal horn of the spinal cord represents a critical junction in the pain neuraxis where peripheral sensory-nociceptive inputs are integrated and processed within the central nervous system. ASICs (Acid-Sensing Ion channels) are voltage-independent homo- or hetero-trimeric cationic channels expressed along the pain pathway, including within spinal cord neurons where their pharmacological inhibition is known to produce potent analgesia.
We used a combination of in vivo and ex vivo electrophysiological recordings and computational modeling to explore the role of ASIC1a-containing channels in windup, a short-term spinal pain facilitation process. We demonstrate that pharmacological inhibition of spinal ASIC1a-containing channels through the application of venom peptides (PcTx1 and mambalgin-1) leads to a significant decrease in the ability of deep wide dynamic range (WDR) neurons to undergo windup in vivo.
Our results further show that deep WDR-like neurons recorded from spinal slices exhibit ASIC currents with biophysical kinetics and pharmacological sensitivities consistent with functional expression of ASIC1a homomeric channels, as shown by characterization of the properties of different ASIC1a channel subtypes in heterologous expression system. Positive contribution of these channels to windup is further supported by a computational model of WDR neuron that accurately reproduces experimental data through the incorporation of ASIC1a parameters.
Our findings provide evidence for the expression of ASIC1a channels in deep laminae projecting neurons where they contribute to the windup process.

Disrupting HCN channels - TRIP8b interaction is an efficient strategy to decrease acute oxaliplatin-induced peripheral neuropathy symptoms

Margaux Morez [1], Laetitia Prival [1], Youssef Aissouni [1], Emmanuel Bourinet [2], Olivier Roy [3], Claude Taillefumier [3], Eric Wersinger [1,*], Jérôme Busserolles [1*]

1 : Neuro-Dol
Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne
UFR Médecine Pharmacie, TSA 50400, 28 Place Henri Dunant, 63001 Clermont-Ferrand // Faculté de Chirurgie Dentaire, 2 Rue de Braga, 63100 Clermont-Ferrand - France
2 : Institut de Génomique Fonctionnelle
Centre National de la Recherche Scientifique, Université de Montpellier
141, Rue de la Cardonille 34094 Montpellier cedex 5 - France
3 : Institut de Chimie de Clermont-Ferrand
Institut de Chimie du CNRS, Centre National de la Recherche Scientifique, Université Clermont Auvergne, Institut national polytechnique Clermont Auvergne
Campus universitaire des Cézeaux, TSA 60026 - CS 60026, 24 avenue Blaise Pascal, 63178 Aubière - France
* : Auteur correspondant

Peripheral Neuropathy, a common adverse effect of anticancer agents, such as oxaliplatin, negatively influences quality of life and may lead to therapy discontinuation. To date, there is no treatment available and hence an unmet medical need. Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channels are widely expressed throughout the pain pathway and specific blockers have been shown to reverse pain symptoms in acute oxaliplatin-induced peripheral neuropathy (OIPN) in mice, but their cardiac side effects limit their clinical use. Interestingly, TRIP8b, an auxiliary protein of HCN regulating its surface expression and function, is not expressed in the heart, suggesting that disrupting their interaction could decrease OIPN symptoms, without any cardiac effect. The aim of this project is (1) to study HCN isoforms and TRIP8b transcripts and proteins expression in dorsal root ganglia (DRG) and trigeminal ganglia (TG) tissues from control mice as compared to tissues fromoxaliplatin-treated mice, and (2) to evaluate the pharmacological efficacy of compounds targeting HCN-TRIP8b on this model. We performed standard qPCR as well as western blot analysis and we observed for the first time the presence of TRIP8b mRNA and protein in both DRG and TG neurons in mice. Immunofluorescence staining showed a strong co-localization between TRIP8b and both HCN1 and HCN2 channels. Moreover, we showed that HCN1, HCN2 and TRIP8b mRNA and protein levels are increased in DRG and TG from acute OIPN mice as compared to control ones. Chemists from the chemistry institute of Clermont-Ferrand synthesized series of peptoids (synthetic oligomers mimicking peptides) targeting specifically HCN-TRIP8b interaction, using a rational drug design based on the co-cristal X-Ray structure of the tetratricopeptide repeat region (TPR) of TRIP8b with the C-terminus sequence of HCN2. A hit compound demonstrated a dose-dependent anti-hyperalgesic effect on distal and perioral cold hypersensitivity, that was lost in TRIP8b knock-out mice. Our results provide the proof of concept that pharmacological disruption of TRIP8b-HCN interaction is analgesic in a mouse model of acute OIPN, while, contrary to non-selective HCN blockers, it did not affect cardiac HCN current.

Dual ENKephalinase Inhibitor (DENKI) PL37 as a potential novel treatment of migraine-like symptoms

Jeanne Rossignol [1, 2], Radhouane Dallel [2], Hervé Poras [1], Philippe Luccarini [2]

1 : Pharmaleads
Université Clermont Auvergne, CHU Clermont-Ferrand, Inserm, Neuro-Dol, Clermont-Ferrand F-63000, France
11 rue Watt 75013 Paris - France
2 : Neuro-Dol
Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne
UFR Médecine Pharmacie, TSA 50400, 28 Place Henri Dunant, 63001 Clermont-Ferrand // Faculté de Chirurgie Dentaire, 2 Rue de Braga, 63100 Clermont-Ferrand - France

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Migraine is a debilitating disorder, with patients primarily suffering from cutaneous allodynia and improving their clinical management is considered a high priority since available treatments are not effective in a high proportion of patients. One direction may be to enhance the efficacy of enkephalins that preferentially target the delta-opioid receptors. Indeed, it has been recently shown that blockade of their enzymatic degradation by a Dual ENkephalinase Inhibitor (DENKI®, PL37) provides an anti-allodynic effect in a rat model of migraine induced by a nitric oxide donor, *i.e*. Iso-Sorbide-Di-Nitrate (ISDN). As sumatriptan, one of specific antimigraine agents, could lead to latent sensitization and medication overuse headaches, our study aims to investigate the cutaneous sensitivity after PL37 repetitive oral administrations and the potential synergistic effect of PL37 co-administrated with sumatriptan.

Using the facial von Frey test, we showed that repetitive oral administrations of PL37 (one injection every 2 days over 11 days) did not modify the cutaneous mechanical sensitivity whereas repetitive sumatriptan (10 mg/kg) induced a chronic allodynia after 6 days that was recovered 21days after the beginning of the experiment. To assess the latent sensitization, at day 21, ISDN was administered. Animals prior submitted to sumatriptan developed a stronger allodynia than controls whereas those receiving PL37 did not. Moreover, the co-administration of PL37 and sumatriptan (ED50 PL37/4+ ED50 sumatriptan/4; ED50 PL37/8+ ED50 sumatriptan/8 ED50 PL37/16+ ED50 sumatriptan/16) induced anti-allodynic effects, showing that PL37 presented a synergistic action with sumatriptan.

These data suggest that PL37 does not induce central sensitization when administered repetitively, neither latent sensitization after an ISDN injection and the combination of PL37/sumatriptan could constitute a useful option for the acute treatment of migraine. Hence, these data reinforce the potential treatment of interest of PL37 for episodic migraine.

Functional brain and trigeminovascular changes in migraine using a new approach of neuroimaging : the functional ultrasound imaging.

Lauriane Delay [1,*], Samuel Diebolt [1], Nathalie Ialy-Radio [1], Thomas Deffieux [1], Mickael Tanter [1], Sophie Pezet [1]

1 : Physics for Medicine
INSERM U1273, ESPCI Paris - PSL Research University - CNRS
Paris Santé Campus, 4-10 rue Oradour sur Glane, 75015 Paris - France
* : Auteur correspondant

As a leading cause of disability worldwide, migraine is a neurovascular disorder characterized by headaches crisis and sensory hypersensitivities such as photophobia and/or allodynia. Migraine pathophysiology is complex and still partially understood. As a source of new findings, we use a novel brain neuroimaging modality that is particularly interesting for vascular diseases: the functional ultrasound imaging (fUSi). As an alternative to functional magnetic resonance imaging (fMRI), this modality of neuroimaging enables the measurement of cerebral blood volume with a high sensitivity and spatio-temporal resolution (100 µm and 1 ms, respectively). Due to the vascular aspect of the pathophysiological alterations previously observed in migraine patients, this study aims at deciphering the sequence of vascular dynamic changes on the whole brain and the trigeminovascular system in relevant animal models of migraine induced by systemic administrations of nitric oxide donors. This study adds new insights in migraine pathophysiology and proves the potential of fUS imaging as an important new technology to decipher nociceptive components of neurovascular diseases such as migraine.

Gut microbiota promotes pain chronicity in Myosin1A deficient male mice

Ana Reynders [1],

1 : Institut de Biologie du Développement de Marseille
Aix Marseille Université, Collège de France, Centre National de la Recherche Scientifique
Case 907 - Parc Scientifique de Luminy 13288 Marseille Cedex 9 - France

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Over the past decade, the gut microbiota has emerged as an important regulator of nervous system's health and disease states. Yet, its contribution to the pathogenesis of chronic somatic pain remains poorly documented. Chronic pain is a heavily debilitating disease affecting more than 1.5 billion people worldwide, that can manifest through a long-lasting hypersensitivity to mechanical and/or thermal stimulations. Maladaptive responses of dorsal root ganglia (DRG) neurons and spinal cord (SC) interneurons to tissue injuries and also of non-neuronal cells including DRG macrophages and SC microglia, are acknowledged as important drivers of sensory symptoms underlying chronic pain. Recent evidence shows that signals from gut microbiota are required for the initiation of injury-induced sensory hypersensitivity, via the ability to interact with the immune system. However, whether and how gut microbiota promotes pain chronicity remains unknown.

Here, we report that male mice knock-out (KO) for myosin 1a (Myo1a)12 raised under single genotype (KO-SGH) but not mixed genotype housing (KO-MGH) conditions exhibit a persistent mechanical hypersensitivity in response to inflammatory, post-operative and neuropathic tissue insults. We demonstrate that the acquisition of the vulnerability to injury-induced chronic pain in KO-SGH is achieved through the inheritance of a dysbiotic microbiota. Parental antibiotic treatment completely rescues the chronic pain phenotype, modifies the gut microbiota composition and resolves the neuropathy-induced inflammatory response in the DRG, in KO-SGH male offspring.

Evaluation of TACAN as a new target for treating osteoarthritis pain.

A. Gilbert[1,2,3,7], L. Rabiller[1,2,3], L. Miraucourt[2,3], M. Georgiopoulos[4], I. Colmegna[5,6], J. Ouellet[4], R. Dallel[7], C. Peirs[7], R. Sharif-Naeini[2,3].

[1]These authors contributed equally to this work.

[2]Department of Physiology and Cell Information Systems, McGill University, Montreal, QC, Canada

[3]Alan Edwards Center for Research on Pain, McGill University, Montreal, QC, Canada

[4]Spine Surgery Program, Department of Surgery, McGill University, Montreal, Canada

[5]The Research Institute of the McGill University Health Centre (MUHC), 1001 Decarie Blvd, Montreal, QC, Canada

[6]Division of Rheumatology, Department of Medicine, McGill University, Montreal, QC, Canada

[7]Université Clermont Auvergne, CHU Clermont-Ferrand, Inserm, Neuro-Dol, Clermont-Ferrand, France

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Joint pain is the most prominent symptom of osteoarthritis (OA). Patients with OA experience mechanical allodynia which is due in large part to a dysfunction in nociceptors. We previously demonstrated that during OA, mechanosensitive ion channels, which convert high-intensity mechanical stimuli into electrical signals, become sensitized and are contribute to mechanical allodynia, where light stimuli are perceived as painful. However, the molecular identity of these channels was unknown, which prevented any progress toward improved pain management in OA patients. We recently identified an ion channel expressed in mouse nociceptors, called TACAN, essential to the sensation of mechanical pain. Here, we examined whether TACAN is necessary to the development of mechanical allodynia in OA.

We used behavioural tests to assess primary mechanical allodynia and pain in a preclinical model of knee OA in both male and female mice. We decreased TACAN expression by injecting adenoassociated viral vectors encoding control or TACAN shRNA in the knee capsule. Deletion of TACAN

in nociceptors of OA mice significantly decrease primary mechanical allodynia. In electrophysiology experiments, we characterized the contribution of TACAN to the mechanosensitivity of both mouse and human nociceptors from recently deceased donors incubated with control media or synovial fluid (SF) obtained from OA patients. Mechanically evoked responses are potentiated following a 24h incubation period with OA-SF : Mean amplitude, percentage of active patch are significantly increased. Further investigation will assess whether the inflammatory mediators contained in the SF can lead to the sensitization of mechanical responses in human nociceptors via the TACAN channel and modulate pain associated symptoms during OA.

Interaction between anitimicrobial peptide Reg3g and IL-22 pathway on intestinal and central disturbances following Citrobacter rodentium infection

Valentine Daugey [1], Maëva Meynier [1,2], Mathieu Meleine [1], Jean-Marc Chatel [3], Denis Ardid [1,], Nicolas Barnich [2], Valérie Livrelli [2], Mathilde Bonnet [2,*], Frédéric Carvalho [1,*]

1 : Neuro-Dol
Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne
UFR Médecine Pharmacie, TSA 50400, 28 Place Henri Dunant, 63001 Clermont-Ferrand // Faculté de Chirurgie Dentaire, 2 Rue de Braga, 63100 Clermont-Ferrand - France
2 : Microbes, Intestin, Inflammation et Susceptibilité de l'Hôte
Institut National de la Santé et de la Recherche Médicale, Centre de Recherche en Nutrition Humaine d'Auvergne, Institut National de Recherche pour l'Agriculture, l'Alimentation et l'Environnement, Université Clermont Auvergne
UFR de Médecine et de Pharmacie, 28 Place Henri Dunant, BP 38, 63001 Clermont-Ferrand Cedex - France
3 : MICrobiologie de l'ALImentation au Service de la Santé
AgroParisTech, Université Paris-Saclay, Institut National de Recherche pour l'Agriculture, l'Alimentation et l'Environnement
Domaine de Vilvert 78352 JOUY-EN-JOSAS CEDEX - France
* : Auteur correspondant

Background and Aims. Irritable bowel syndrome is characterized by colonic hypersensitivity (CHS) and comorbidities such as anxiety or depression. When IBS occurs following a gastrointestinal infection, it is called post-infectious IBS. These patients present abdominal pain months or years after infection resolution. *Citrobacter rodentium* infection in mice leads to the development of IBS-like symptoms as CHS, anxiety-like behavior and cognitive impairment 8 days after pathogen clearance. Moreover, recent data have shown that the induction of colonic IL-22 expression during the post-infectious phase allows the correction of IBS-like symptoms induced by *C. rodentium* infection. Thus, our first objective was to study the overtime chronicization of PI-IBS symptoms in this *C. rodentium* infection mouse model. In addition, since, the cytokine IL-22 is involved in *C. rodentium* clearance *via* regulation of Reg3γ antimicrobial peptide expression, the second objective was to evaluate the effect of Reg3γ expression on IBS-like symptoms in *C. rodentium*-infected mice.

Methods. Wild-type C57Bl6/J mice were infected with *C. rodentium* reference strain DBS100. Colonic sensitivity and anxiety- or depression-like behaviors were evaluated by colorectal distension (CRD) and several behavioral reference tests, respectively, at different days post-infection (DPI): 24, 42, 56, 84 or 112. In addition, a treatment with IL-22 or Reg3γ colonic vectorization expression were evaluated on IBS-like symptoms. This treatment was administered daily between 16 and 24 DPI, using a *Lactococcus lactis* strain allowing Reg3γ (*L. lactis*Reg3γ) or IL-22 (*L. lactis*IL-22) expression in the colonic mucosa. The fecal microbiota was also analyzed by 16S rRNA sequencing.

Results. CHS persisted in a subgroup of *C. rodentium* infected mice until 84 DPI, despite anxiety-like behavior was observed only until 42 DPI. No cognition impairment was noticed after 24 DPI. However, several post-infected animals developed depressive-like behavior at 42 DPI, which persisted over time. Finally, *L. lactis*IL-22 and *L. lactis*Reg3γ treatments corrected CHS and anxiety-like behavior induced by *C. rodentium* infection at 24 DPI. In addition, fecal microbiota sequencing data suggested that Reg3γ-colonic induced expression, like IL-22, modified the microbiota composition in the PI-IBS model. The effectiveness of Reg3γ delivery on long-term depressive-like behavior symptoms is being evaluated.

Conclusions. *C. rodentium* infection induced long-term IBS-like symptoms as chronic CHS associated with transient anxiety- and depression-like behaviors which is consistent with clinical symptoms observed in PI-IBS patients. Moreover, these initial data suggest that recovery of PI-IBS symptoms correlated with the correction of gut dysbiosis and that Reg3γ would represent an interesting therapeutic target to relieve these IBS-like symptoms.

Involvement of serotonergic descending pathways in pain in a mouse model of Parkinsonism

Zoé Grivet [1],

1 : Institut des Maladies Neurodégénératives [Bordeaux]
Université de Bordeaux, Centre National de la Recherche Scientifique
Centre Broca Nouvelle Aquitaine, 146 Rue Léo Saignat 33076 Bordeaux - France

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Parkinson disease (PD), a multi-factory disorder leading to well-known motor but also to non-motor symptoms, is induced by dopamine (DA) depletion in basal ganglia (BG) especially in the substantia nigra and the striatum. The major non-motor symptom is chronic pain which is only partly explained by DA depletion in BG. Beyond DA, it is also known that other monoaminergic systems such as serotonergic are altered in PD. Moreover, serotonergic (5-HT) descending neurons coming from the nucleus raphe magnus (NRM) and acting at the level of the dorsal horn (DH) of the spinal cord exert important pain control. Thus, we hypothesized that pain disorders in PD may be associated to a modification of 5HT descending pain pathways. Using a mouse model of Parkinsonism in which the DA depletion is induced by the injection of 6-OHDA into the right mid forebrain bundle (MFB), we first showed that unilateral DA depletion induces a bilateral pain hypersensitivity associated to an increase activity of the 5-HT neurons in the NRM and an increased level of spinal serotonin. We then used transgenic mice expressing cre-recombinase in 5-HT neurons to specifically express inhibitory light dependent opsins in the NRM and showed that optogenetic inhibition of 5-HT projecting fibers induced a partial mechanical pain relief. These results demonstrate that NRM 5-HT system is altered in 6-OHDA mice and open the way for the development of 5-HT inhibitors in the treatment of chronic pain syndromes in PD pain.

Planarians as an emergent model for the development and screening of antinociceptive drugs.

Guillaume Reho [1,*], Yannick Menger [1], Yannick Goumon [1], Vincent Lelievre [1], Hervé Cadiou [1*]

1 : Institut des Neurosciences Cellulaires et Intégratives
université de Strasbourg, Centre National de la Recherche Scientifique
8 Allée du Général Rouvillois 67084 Strasbourg - France
* : Auteur correspondant

Planarians represent a class of non-parasitic flatworms and constitute an excellent model for the study of tissue regeneration and development. However, this animal has gained popularity in other fields of biology and neuroscience due to its easy handling and the availability of molecular biology tools. Recent studies have shed light on various nociceptive aspects in this animal. Just as in other invertebrates models of nociception such as insects, nematodes, leeches or mollusks, planarians show stereotypical reactions to aversive stimuli, well conserved nociceptive ion channels (TRPs) and responses modulated by antinociceptive agents (morphine, NSAIDs, etc). However, to date, the description of their nociceptive system is not complete yet eventhough several drugs acting on nociception or pain have been tested on this model. Our work is focusing on adapting classical nociceptive tests, both from the limited literature on planarians, and from much more common tests used on other animal models. We have set up multiple complementary tests, both for behavioral analysis on worms exposed to drugs of interest in an arena, and for observing the way these drugs modulate the place preference of the worms under different conditions. For example, exposure of worms to AITC, a well-known TRPA1 ion channels agonist, induced an avoidance muscular gait (‘scrunching') in a largely reproducible fashion (from 0 to 60% at 50µM). These reactions were shown to be modulated by common antinociceptive drugs such as opioids (morphine application reduces scrunching behaviors by approx. 50%) or NSAIDs (approx. 60% with meloxicam). In order to test thermotaxis, a simple place preference assay was set. Without heat (homogenous 22°C), animals spent an equal amount of time on both sides of the racetrack. When a gradient from 22 to 36°C was applied, worms were found 80% of the time in the colder side. Here again, thermotaxis could be modulated by antinociceptive agents. For instance, worms exposed to 10-100µM of meloxicam were found 40 to 60% of the time in the colder side only. In conclusion, we have successfully established an assay for chemical and thermal nociception in an invertebrate animal model which could potentially be used for new antinociceptive drug screening.

LRP1 in sensory neurons is required for the pain killing effect of TAFA4

Aude Charron [1], Francis Castets [1], , Aziz Moqrich [1]

1 : Institut de Biologie du Développement de Marseille
Aix Marseille Université, Collège de France, Centre National de la Recherche Scientifique
Case 907 - Parc Scientifique de Luminy 13288 Marseille Cedex 9 - France

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Pain, whether acute or persistent, is a serious medical problem worldwide. However, its management remains unsatisfactory, and new analgesic molecules are required. We demonstrated recently that TAFA4 (a neurokine selectively expressed in C-Low Threshold Mechanireceptors C-LTMRs) reverses inflammatory, postoperative, and Spared nerve injury (SNI)-induced mechanical hypersensitivity in male and female mice. TAFA4 requires functional low-density lipoprotein receptor-related protein 1 (LRP1). Indeed LRP1 inhibition by RAP (receptor-associated protein) dose-dependently abolishes the anti-hypersensitive action of TAFA4. During my presentation, I will discuss our strategy to identify the different cell types expressing LRP1 that are required for TAFA4 painkilling action.

Exploring the role of THIK potassium channels in nociceptive pathway

Nicolas Gilbert **1**, Franck Chatelain, Florian Lesage, Delphine Bichet

1 : Institut de pharmacologie moléculaire et cellulaire
Université Nice Sophia Antipolis (1965 - 2019), Centre National de la Recherche Scientifique, Université Côte d'Azur CNRS-IPMC 660 Route des lucioles 06560 VALBONNE - France

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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.
Members of the THIK subfamily (THIK1 and THIK2) are highly expressed in the central and peripheral nervous system, but their role in the control of pain sensation has not been studied yet. Using RNAscope technique we have recently shown that THIK channels are co-expressed in non-peptidergic nociceptive neurons that express the purinergic receptor P2RX3. These unmyelinated neurons are known to be involved in the transmission of slow nociceptive messages such as chronic or inflammatory ones. Moreover, THIK1 and THIK2 are the most highly expressed K2P channels in microglial cells, and 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 differential sensitivity to thermal stimulation. 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.

Phenotyping for better treatment

Luis Garcia-Larrea

Centre de Recherche en Neurosciences de Lyon, Bron.

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease of somatosensory systems. Although this definition still poses some problems, it does delineate a series of pain entities with common characteristics in terms of pathophysiology, clinical presentation and words used by the patient. Pain being a private and exclusively subjective symptom, the patients' discourse on their pain is necessarily equivocal and may lead to false diagnoses of neuropathic pain, by excess or by default. A simple physiological phenotyping with calibrated stimulations and cortical and vegetative recordings can quickly determine, in clinical routine, the alteration of somatosensory transmission. It verifies the concordance or discordance between verbal reports and their physiological concomitants, as well as possible fluctuations of these functions over time. Physiological phenotyping goes beyond quantified sensory testing (QST) in that it is based on objective data that can be compared with the patient's discourse. It often allows the patient to be proved right in the face of the clinician's doubts, authorizing the formal diagnosis of neuropathic pain and therefore the therapeutic orientation. Finally, in the case of discordance between the subjective discourse and the objective data, it can distinguish a simulation from a probable dissociative conversion syndrome.

Nociception and itch hypersensitivity in a mouse model of autism associated with peripheral mechanosensory dysfunctions.

Damien Huzard [1,*], Mélanie Marias, Vanessa Soubeyre, Gawain Grellier, Emmanuel Bourinet, Amaury Francois

1 : Institut de Génomique Fonctionnelle
Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Université de Montpellier
141, Rue de la Cardonille 34094 Montpellier cedex 5 - France
* : Auteur correspondant

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent difficulties in social interaction, increased repetitive behaviors, restricted and repetitive behaviors, as well as altered sensory perception. So far, most of the literature investigating the mechanisms involved in the behavioral and somatosensory alterations observed in mice modes focuses on central circuits. However, recent findings suggest that somatosensory, nociceptive and behavioral deficits occurring in ASD models may also arise from differences occurring at the periphery. We focused our research on the screening of somatosensory and nociceptive responses in the Shank3Δex21 mouse model. We also performed analysis of the physiological functioning and pharmacological responses, from somatosensory neurons from the skin or from the dorsal root ganglion respectively. We suggest that differences occurring in somatosensory fibers within the skin may be, in part, responsible for some behavioral and developmental alterations in somatosensation in ASD.

OPTICAL CONTROL OF PIEZO1 CHANNELS

Melaine Balcon **1,**

1 : Université de Strasbourg – Faculté de pharmacie
Université de Strasbourg
74 route du Rhin - CS 60024 - 67401 Illkirch Cédex - France

Sensing mechanical forces in the environment is vital for organism's survival. In 2010, the discovery of Piezo ion channels in vertebrates showed that they are the molecular sensors of mechanical sensitivity, the least known sense. Activation of Piezo channels requires sophisticated and non-specific methods of mechanical stimulation of the cell. The development of alternative activation methods able to specifically and rapidly activate these channels *in vivo* is challenging and therefore needs new technologies.

Using biomolecular engineering combined with patch-clamp electrophysiology, we have developed an opto-chemical technology that makes the mouse Piezo1 channel sensitive to light. By covalently tethering an azobenzene-based photoswitch to a cysteine introduced by site-directed mutagenesis, we showed that light irradiation at 365 nm rapidly opened the pore. The reprogramming of this channel allows, in the absence of mechanical stimulus, to rapidly modulate its activity by light, without changing its mechanical sensitivity. Furthermore, this tool could provide a basis for understanding the mechanism of Piezo channels.

Peripheral and central delta opioid receptors regulate the migraine-like headache in rats

Manon Dussol [1], Gisela Borges [1], Claudie Beaulieu [2], Philippe Luccarini [1], Louis Gendron [2], Radhouane Dallel [1]

1 : Université Clermont Auvergne, CHU Clermont-Ferrand, Inserm, Neuro-Dol
Université Clermont Auvergne
Clermont-Ferrand - France
2 : Département de Pharmacologie-Physiologie
Université de Sherbrooke, Sherbrooke, Québec - Canada

Migraines are incapacitating diseases, and improving their clinical management is of high priority. Treatments available, including those newly developed, may not be effective in a proportion of patients. Moreover, most commonly used treatments are either associated with contraindications or poorly tolerated: thus, most current acute headache treatments can lead to medication overuse headache. This highlights the need for new medications. The delta opioid receptor (DOP) has emerged as a promising therapeutic target for migraine. In mice, DOP agonists inhibit the allodynia associated with migraine. There are however species differences in the DRG distribution of DOP between rats and mice. Therefore, this study explores the antimigraine potential of a DOP agonist using a new rat model of migraine in which cutaneous mechanical hypersensitivity is a surrogate of headache.

Using a new ISH technology called RNA-scope, we show that DOP is expressed in all types of neurons within the rat's trigeminal ganglia (TG), a key structure involved in migraine: namely, large and medium size myelinated neurons (NF200-positive), small nonpeptidergic (IB4) and peptidergic C-fibers (Calca). DOP mRNA is predominantly expressed by myelinated neurons. The rat TG and DRGs exhibit similar proportions of small nonpeptidergic C-fibers expressing DOP mRNA but less than mouse DRGs. In vivo electrophysiological recordings reveal that systemic administration of SNC80, a selective DOP agonist, inhibits noxious, but not innocuous, mechanical stimuli-evoked responses of wide-dynamic range (WDR) neurons in the trigemino-cervical complex (TCC). Behavioral testing shows that intracisternal and systemic administration of SNC80 can prevent partially and completely, respectively, the cephalic mechanical allodynia induced by systemic administration of the nitric oxide donor, isosorbide dinitrate. Finally, the peripherally-restricted opioid receptor antagonist, naloxone-methiodide, is able to reverse this anti-allodynic effect.

In conclusion, as in mice, activation of DOP appears to have an antimigraine potential in rats. Nevertheless, we report species differences in the mechanisms of action of DOP agonist: whereas they act mainly through central opioid receptors in mice, they rather act through both peripheral and central opioid receptors in rats.

Reconnaitre la douleur d'un bébé qui pleure : étude des corrélats cérébraux chez des adultes experts

Siloé Corvin [1, 2], Isabelle Faillenot [1], David Reby [2], Nicolas Mathevon [2], Roland Peyron [1], Camille Fauchon [1],

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
Intégration Centrale de la Douleur, Faculté de Médecine, Bâtiment Recherche, 10 rue de la Marandière, 42270 Saint-Priest en Jarez, France - France
2 : Ecologie et Neuro-Ethologie Sensorielles
Université Jean Monnet - Saint-Etienne
Faculté des Sciences et Techniques 23 rue Paul Michelon 42023 Saint-Etienne cedex 2 - France

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Repérer la douleur des bébés est essentiel pour les soins pédiatriques. Nous avons montré récemment que les adultes sont capables d'identifier la douleur d'un bébé à partir de l'écoute de ses pleurs. Néanmoins, cela nécessite un apprentissage qui se gagne grâce à l'expérience à prendre soin de nourrissons, qu'elle soit professionnelle ou parentale (*1*, *2*). De manière remarquable, les parents de jeunes enfants sont également capables d'identifier la douleur pour un bébé totalement inconnu. Le but de cette étude est de confirmer ces résultats et d'étudier les corrélats cérébraux de cette identification de la douleur chez des participants experts (parents ou professionnels de santé), pour des bébés familiers ou non.

Méthodes

29 participants ont été inclus (sur les 60 planifiés : 8/20 pères, 13/20 mères et 8/20 femmes professionnelles sans enfants travaillant en pédiatrie). Huit bébés de 2 mois ont été enregistrés pendant le bain (pleurs d'inconfort) ou une vaccination de routine (pleurs de douleur). Chaque participant était assigné à un bébé et a suivi :

1) Une session d'entrainement : écoute de pleurs d'inconfort du bébé assigné pour devenir familier avec celui-ci ;

2) Une session test en IRM fonctionnelle : écoute de 64 pleurs randomisés incluant des pleurs d'inconfort ou de douleur, de leur bébé assigné ou de bébés inconnus. Ils devaient déterminer pour chaque pleur s'il était produit par leur bébé assigné ou non, et dû à de l'inconfort ou de la douleur.

Nous utilisons des modèles linéaires bayésiens pour analyser les réponses comportementales. Les analyses préliminaires d'imagerie utilisent des contrastes de l'activité cérébrale (BOLD) entre les conditions.

Résultats

Les participants ont eu 71.6% de réussite dans l'identification de l'identité du bébé (intervalle de crédibilité (CI) de 95% [68.0, 75.0], avec 100% de la distribution postérieure (PD) au-dessus du niveau de chance de 50%). Concernant la reconnaissance du contexte, ils ont eu 65.7% de réussite (95% CI [61.7, 69.4], 100% de la PD > 50%).

Dans une autre étude, nous avons mis en évidence que les pleurs de bébés entrainent l'activation de différents réseaux cérébraux, allant de réseaux de bas niveau impliqués dans le traitement de l'information auditive (cortex auditif primaire, gyrus temporal supérieur) à des réseaux cognitifs de plus haut niveau, permettant d'identifier la valence du pleur. L'écoute de pleurs de douleur, comparés à des pleurs d'inconfort, induisait une activité cérébrale plus importance dans des aires impliquées dans l'empathie, comme l'insula antérieure (*3*). Ici nous faisons l'hypothèse que l'écoute de pleurs de douleur du bébé assigné, donc familier, modifiera l'activité dans les régions comme le gyrus frontal inférieur, l'amygdale et les régions cingulo-insulaires, favorisant la compréhension, la régulation des émotions et la résonance avec la douleur du bébé.

Ces résultats d'imagerie fonctionnelle aideront à comprendre comment l'expérience parentale et professionnelle façonne l'activité cérébrale et fait des adultes des experts de l'identification de la douleur dans les cris.

1. S. Corvin et al, 2022
2. A. Koutseff et al, 2018
3. C. Fauchon et al, in prep

Tofacitinib-induced analgesia in mouse model of inflammatory pain

Marie Tuifua [1], Louison Brochoire [1], Thibault Dhellemmes [1], Thomas Barnetche [2], Thierry Schaeverbeke [2], Marc Landry [1]

1 : Institut des Maladies Neurodégénératives [Bordeaux]
Université de Bordeaux, Centre National de la Recherche Scientifique
Bât. 3b 1er étage 146 Rue Léo Saignat 33076 Bordeaux - France
2 : Service de Rhumatologie - CHU de Bordeaux Pellegrin [Bordeaux]
Hopital Pellegrin - CHU Bordeaux
Place Amélie Raba-Léon, 33000 Bordeaux - France

Inflammatory rheumatism exposes patients to pain over a long period of time. This promotes a restructuring of the nervous system responsible for central and peripheral sensitization to pain. These sensitization phenomena are involved in the genesis of so-called nociplastic pain that explains the persistence of diffuse pain and chronic fatigue despite the control of inflammation. Some mediators of neuroplasticity involved in these pain sensitization phenomena, ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), and oncostatin M (OSM), act via the JAK/STAT signaling pathway.

Here, we used an inflammatory pain model obtained by injecting Complete Freund's Adjuvant (CFA) into the mouse hind paw to test the effect of Tofacitinib, a JAK/STAT inhibitor. We assessed mechanical and thermal sensitivities using the von Frey and plantar tests, respectively. We further investigated the Tofacitinib effect on the activity of dorsal horn neurons of the spinal cord (Wide Dynamic Range neurons) using extracellular in vivo electrophysiological recordings.

Tofacitinib administration in CFA animals showed an increase in the mechanical threshold suggesting a decrease in nociception. This effect was not found in sham animals demonstrating that Tofacitinib does not have an analgesic effect *per se*. Moreover, electrophysiological recordings reported a decrease of C-fibers evoked response in CFA animals treated with tofacitinib. Tofacitinib has an anti-nociceptive effect in a model of persistent pain, but not in control conditions. We show that it acts at the spinal level by decreasing the excitability of dorsal horn neurons, thus reducing central sensitization. This effect is in agreement with the results of clinical trials conducted in rheumatoid arthritis patients and suggests that JAK/STAT inhibitors have a greater impact than anti-TNF agents on pain, independently of their anti-inflammatory effect.

Ultrasonic stimulation of dorsal root ganglion neurons at 20 MHz

Elena Brunet [1, 2], Sungjae Yoo [1], Eric Debieu [2], Olivier Macherey [2], Aziz Moqrich [1], Andrew Saurin [1], Emilie Franceschini [2]

1 : Institut de Biologie du Développement de Marseille
Aix Marseille Université, Centre National de la Recherche Scientifique, Turing Center for Living Systems
Case 907 - Parc Scientifique de Luminy 13288 Marseille Cedex 9 - France
2 : Laboratoire de Mécanique et d'Acoustique de Marseille
Aix Marseille Université, Ecole Centrale de Marseille, Centre National de la Recherche Scientifique, Turing Center for Living Systems
4 impasse Nikola TeslaCS 4000613453 Marseille Cedex 13 - France

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Background, Motivation and Objective

More than 100,000,000 people worldwide suffer from chronic pain. Pain is considered chronic when it has lasted for at least three months. It is more or less acute in intensity and can lead to a profound alteration in the quality of life of those who suffer from it. This project is part of the development of a treatment to relieve chronic pain using ultrasound stimulation of sensory neurons.

Focused UltraSound (US) is a promising non-invasive technology for stimulating neuronal activity. However, the underlying mechanisms are not well understood. At the cellular scale, US-evoked responses have generally been assessed on single transfected cells or on brain slices by recording membrane currents or calcium activity. This study aims to explore the direct stimulation of individual dorsal root ganglion (DRG) neurons by combining focused US with live-cell calcium imaging.

Statement of Contribution/Methods

An experimental set-up based on calcium imaging has been developed to monitor changes in calcium signals in individual DRG neurons subjected to US stimuli. The US transducer was positioned with a tilted angle to reduce interference/standing waves between the cavity formed by the transducer and the rigid surface. The US stimulus consisted of a 20 MHz sinusoidal signal with a peak acoustic pressure of 5 MPa, and a pulse duration of 1 ms. Calcium images were recorded before, during and after US stimulation.

Results/Discussion

We found that US activated 46 % of DRG neurons (N=203). These results demonstrate that focused ultrasound at 20 MHz is capable of activating a small fraction of DRG neurons. To determine the identity of the ultrasound-sensitive neurons and the underlying molecular mechanisms, we performed single-cell RNA sequencing of 45 ultrasound-positive and 11 ultrasound-negative DRG neurons. Our results showed that specific subgroups of DRG neurons are sensitive to ultrasound.

Chronic neuropathic and inflammatory pain: implication and therapeutic potential of the FXYD family members

Dounia Maskini [1], Alexandre Derre [1], Noelian Soler [1], Valentine Billoux [1], Sébastien Benizri [2], Brune Vialet [2], Cyril Rivat [1], Philippe Barthélémy [2], Patrick Carroll [1], Alexandre Pattyn [1], Stephanie Venteo [1],

1 : Institute for Neurosciences of Montpellier U1298 Univ Montpellier, Inserm 34000 Montpellier - France
2 : ARNA Laboratory University of Bordeaux, INSERM U1212, UMR CNRS 5320 33076 Bordeaux - France

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Elucidating the mechanisms underlying the establishment of chronic pain and developing new therapeutic strategies still constitute major challenges for public health and for the fields of fundamental and clinical research. In that context, we have revealed Fxyd2 as a novel important molecular actor involved in the maintenance of a chronic pain state in neuropathic and inflammatory rodent models. This protein which is so far mainly known as a regulatory subunit of the Na,K-ATPase pump, is expressed by discrete subtypes of somatosensory neurons of the dorsal root ganglia in rodents and Humans. We recently set up a therapeutic protocol based on the use of chemically-modified antisense oligonucleotides (ASO) to inhibit FXYD2 expression and treat chronic pain. We identified an ASO targeting a 20 nucleotides-stretch in the *FXYD2* mRNA that is evolutionary conserved between rats and humans and is a potent inhibitor of FXYD2 expression. We used this sequence to synthesize lipid-modified forms of ASO (FXYD2-LASO) to facilitate their entry into dorsal root ganglia neurons. We established that intravenous injections of FXYD2-LASO in rat models of neuropathic or inflammatory pain led to a virtually complete alleviation of their pain symptoms, without causing obvious side effects. Remarkably, by using 2′-*O*-2-methoxyethyl chemical stabilization of the antisense oligonucleotide (FXYD2-LASO-Gapmer) we could significantly prolong the therapeutic action of a single treatment up to 9 days. This establishes FXYD2-LASO-Gapmer administration as a novel promising and efficient therapeutic strategy for long-lasting relief of chronic pain conditions in human patients. Based on these recent findings, our perspectives are: 1) to extend our understanding of the mechanisms by which Fxyd2 affects the physiological properties of somatosensory neurons in normal and pathological states by notably identifying its molecular partners through a proteomic approach; 2) to more generally address the potential role(s) of other FXYD family members in the diverse somatosensory neuronal sub-types of the dorsal root ganglia in both, normal and pathological conditions. This will bring new insights into the role of the FXYD family in chronic pain.

Pyridin-2(1H)one derivatives: A new class of therapeutics for trigeminal pain

Pauline Murail [1], Amélie Descheemaeker [1], Nicolas Pinto-Pardo [1], Gisela Dasilva-Borges [1], Alexia Visseq [2], Fabrice Anizon [2], Pascale Moreau [2], Alain Artola [1], Radhouane Dallel [1]

1 : Neuro-Dol
Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne
UFR Médecine Pharmacie, TSA 50400, 28 Place Henri Dunant, 63001 Clermont-Ferrand // Faculté de Chirurgie Dentaire, 2 Rue de Braga, 63100 Clermont-Ferrand - France
2 : Institut de Chimie de Clermont-Ferrand
Institut de Chimie du CNRS, Centre National de la Recherche Scientifique, Université Clermont Auvergne, Institut national polytechnique Clermont Auvergne
Campus universitaire des Cézeaux, TSA 60026 - CS 60026, 24 avenue Blaise Pascal, 63178 Aubière - France

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Mechanical Allodynia (MA), a frequent chronic pain symptom caused by normally innocuous stimuli, constitutes an unmet medical need, as treatments using the analgesics available today are not always effective and can be associated with important side-effects. Recently, we found that a newly synthetized compound, the 3-(2-Bromophenyl)-5-(phenylamino)pyridin- (1H)-one 69 (C69), is effective in reducing pain hypersensitivity in a rat model of inflammatory MA. C69 appears to inhibit p38a MAPK, a protein kinase known to contribute to pain hypersensitivity in animal models. The present study aimed at characterizing the anti-allodynic effect of C69 in different models of chronic pain in male and female rats and at identifying its mechanism of action.

Using a behavioral approach in rats, we show that intracisternally (IC) applied C69 dose-dependently attenuates MA in the facial CFA model. IC C69 can also prevent formalin-induced facial MA and reverse neuropathic facial MA in both sexes. Notably, such anti-allodynic effect appears to be long-lasting (>24h) in both inflammatory and neuropathic pain models. Moreover, C69 is also effective when orally applied. Using *in vivo* electrophysiological single-unit recordings, we show that IC C69 inhibits both innocuous and noxious stimulus-evoked responses as well as the wind-up phenomenon of wide dynamic range (WDR) neurons in the medullary dorsal horn (MDH)**.** Two hours after CFA injection, touch can evoke c-Fos expression in the superficial laminae (laminae I and II) of the ipsilateral, but not contralateral, MDH, a manifestation of MDH central sensitization. Treatment with C69 prevents such c-Fos expression. Hence, both central and systemic injections of C69 appear to be able to inhibit MA in different animal models of chronic pain, supporting a central effect of C69, thus consistent with its p38 inhibition. Our electrophysiological data suggest that C69 exerts its anti-allodynic effect through both presynaptic and postsynaptic actions. Importantly, IC C69 neither has any effect on motor behavior, nor inhibits hERG channel activity, nor exhibits any cytotoxic effect on normal and tumor cell lines. In conclusion, 3,5-disubstituted pyridin-2(1H)-one compounds may represent a novel class of analgesic for the treatment of MA.

Thalamo- and cortico-cortical functional connectivity as predictor of arousal to noxious stimuli during sleep in humans.

Hélène Bastuji [1]

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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Phasic noxious stimuli delivered during sleep may or not induce arousal reactions. interruption of sleep by a nociceptive stimulus is favoured by an increase in the pre-stimulus functional connectivity between sensory and higher-level cortical areas. In addition, stimuli inducing arousal also trigger a widespread EEG response reflecting the coordinated activation of a large cortical network. Since functional connectivity between distant cortical areas is thought to be underpinned by trans-thalamic connections involving associative thalamic nuclei, we investigated the possible involvement of one principal associative thalamic nucleus, the medial pulvinar (PuM), in the sleeper's responsiveness to nociceptive stimuli in 8 epileptic patients. The spectral coherence between the PuM and 10 cortical regions grouped in networks was computed during 5 seconds before and one second after the nociceptive stimulus, and contrasted according to the presence or absence of an arousal EEG response. Pre- and post-stimulus phase coherence between the PuM and all cortical networks was significantly increased in instances of arousal, both during N2 and paradoxical (REM) sleep. Thalamo-cortical enhancement in coherence involved both sensory and higher-level cortical networks and predominated in the pre-stimulus period. The association between pre-stimulus widespread increase in thalamo-cortical coherence and subsequent arousal suggests that the probability of sleep interruption by a noxious stimulus increases when it occurs during phases of enhanced trans-thalamic transfer of information between cortical areas.

The constitutive activity of spinal 5-HT6 receptors contributes to diabetic neuropathic pain in rats

Nazarine Mokhtar [1], Florian Jacquot [1], Sylvain Lamoine [1], Eric Chapuy [1], Laetitia Prival [1], Youssef Aissouni [1], Philippe Marin [2], Stéphane Doly [1], Christine Courteix [1 *]

1 : Neuro-Dol
Institut National de la Santé et de la Recherche Médicale, Université Clermont Auvergne
UFR Médecine Pharmacie, TSA 50400, 28 Place Henri Dunant, 63001 Clermont-Ferrand // Faculté de Chirurgie Dentaire, 2 Rue de Braga, 63100 Clermont-Ferrand - France
2 : Institut de Génomique Fonctionnelle
Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Université de Montpellier
141, Rue de la Cardonille 34094 Montpellier cedex 5 - France
* : Auteur correspondant

Background and Aims. Chronic neuropathic pain, regardless of its etiology (toxic, traumatic, metabolic, iatrogenic...) is difficult to manage and characterized by inadequate control by first-line agents (tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, gabapentinoids). In patients, neuropathic pain has a significant impact on quality of life, cognitive performance and is often associated with depression and anxiety. The prevalence of painful neuropathy in patients with type 1 and type 2 diabetes mellitus is estimated at 20% and, considering the 537 million people with diabetes worlwide, it constitutes a major humanistic and economic burden. The Serotonin type 6 (5-HT6) receptor, recently emerges as a pain and cognitive functions modulator. In addition to its "classical" Gs protein coupling, the 5-HT6 receptor interacts with intracellular proteins including mTOR (mechanistic Target Of Rapamycin), also involved in neuropathic pain and in the regulation of cognitive functions. The aim of the present study is to addressed the involvement of 5-HT6 receptor constitutive activity and mTOR signaling in an experimental model of diabetic neuropathic pain.
Methods. Sprague-Dawley male rats received a single intraperitoneal (i.p) injection of streptozocin (STZ) (75mg.kg-1). One week after STZ injection, diabetes was confirmed by measuring blood glucose levels. Rats with blood glucose higher than 14 mM, received a subcutaneous (s.c) injection of insulin every other day until the pharmacological experiments. The animals were divided in groups according to treatment and 5-HT6 receptor ligands (inverse agonists and antagonist) injected before behavioral (paw pressure test) or cognitive (novel object recognition test) tests.
Results. In STZ diabetic rats, mechanical hyperalgesia and associated cognitive deficits were reduced by the administration of serotonin 5-HT6 receptor inverse agonists but not with neutral antagonist. This decrease is also observed after administration of the mTOR inhibitor rapamycin or by disrupting the physical interaction between spinal 5-HT6 receptors and mTOR with a peptidyl mimetic peptide.
Conclusions. These results suggest that constitutive activity of the 5-HT6 receptor has a harmful influence in diabetic neuropathic pain. Thus, targeting 5-HT6 receptors with inverse agonists or targeting 5-HT6 receptor/mTOR complex activity might be new strategies to treat the painful diabetic neuropathy and associated cognitive co-morbidities.

Liste des participants

Abdeddaim	Inès	abines00@gmail.com
Aissouni	Youssef	youssef.aissouni@inserm.fr
Alba-Delgado	Cristina	cristina.alba_delgado@uca.fr
Albisetti	Amélie	ameliealbisetti@yahoo.fr
Ango	Fabrice	fabrice.ango@inserm.fr
Picot	Antoine	antoine.picot@umontpellier.fr
Aparicio Arias	Juri	juri.aparicio-arias@umontpellier.fr
Attal	Nadine	nadine.attal@aphp.fr
Balcon	Melaine	melaine.balcon@etu.unistra.fr
Barrot	Michel	mbarrot@inci-cnrs.unistra.fr
Bastuji	Hélène	bastuji@univ-lyon1.fr
Bertin	Juliette	juliette.bertin@inserm.fr
Bichet	Delphine	bichet@ipmc.cnrs.fr
Bondon	Christelle	christelle.bondon@etu.umontpellier.fr
Bouhassira	Didier	didier.bouhassira@inserm.fr
Bourdon	Rachel	r.alonzeau.bourdon@gmail.com
Bourinet	Emmanuel	emmanuel.bourinet@igf.cnrs.fr
Bourki	Hugo	hugo.bourki@hotmail.fr
Boyer	Océane	oceaneboyer17@gmail.com
Boyer	Romane	romane.boyer2@uca.fr
Brunet	Elena	elena.brunet@gigaplanet.com
Brunet	Elena	elena.brunet@univ-amu.fr
Busserolles	Jérôme	jerome.busserolles@uca.fr
Carroll	Patrick	patrick.carroll@umontpellier.fr
Carvalho	Frédéric	frederic.carvalho@uca.fr
Cazzanelli	Silvia	silvia.cazzanelli@gmail.com
Charbonnier	Tatiana	charbonnier@ipmc.cnrs.fr
Charmes	Valentine	valentine.charmes@etu.umontpellier.fr
Charron	Aude	aude.charron@univ-amu.fr
Chassot	Anne Amandine	Amandine.CHASSOT@univ-cotedazur.fr
Chaussy	Alexis	alexis.chaussy@etu.umontpellier.fr

Muller	Claire	claire.muller3@etu.unistra.fr
Corvin	Siloé	siloe.corvin@yahoo.fr
Cuculière	Célia	celia.cuculiere@igf.cnrs.fr
Dallel	Radhouane	radhouane.dallel@udamail.fr
Daugey	Valentine	valentine.daugey@uca.fr
Delay	Lauriane	lauriane.delay@gmail.com
Deval	Emmanuel	deval@ipmc.cnrs.fr
Diochot	Sylvie	diochot@ipmc.cnrs.fr
Dussol	Manon	manondussol@wanadoo.fr
Fauchon	Camille	camille.fauchon@univ-st-etienne.fr
Fossat	Pascal	pascal.fossat@u-bordeaux.fr
Francois	Amaury	Amaury.francois@igf.cnrs.fr
Garcia-Larrea	Luis	larrea@univ-lyon1.fr
Gaveriaux-Ruff	Claire	c.gaveriaux@unistra.fr
Gazard	Chloé	chloe.gazard@umontpellier.fr
Gerber	Yannick	yannick.gerber@umontpellier.fr
Gilbert	Alice	alice.gilbert@doctorant.uca.fr
Gilbert	Nicolas	gilbert@ipmc.cnrs.fr
Goetz	Eva	goetz-eva@outlook.fr
Goudet	Cyril	cyril.goudet@igf.cnrs.fr
Grellier	Gawain	gawain.grellier@igf.cnrs.fr
Greuet	Denis	denis.greuet@inserm.fr
Grivet	Zé	zoe.grivet@u-bordeaux.fr
Guiraud	Clara	clara.guiraud@igf.cnrs.fr
Haetty	Aline	aline.haetty@inserm.fr
Huzard	Damien	damien.huzard@igf.cnrs.fr
Kaeffer	Juliette	juliette.kaeffer@etu.unistra.fr
La	Amanda	thuy.la@etu.umontpellier.com
Labatut	Marlysa	marlysalabatut@gmail.com
Landry	Marc	marc.landry@u-bordeaux.fr
Lingueglia	Eric	lingueglia@ipmc.cnrs.fr
Lioutaud	Robin	robin.lioutaud@etu.umontpellier.fr

Lolignier	Stéphane	stephane.lolignier@uca.fr
Luccarini	Philippe	philippe.luccarini@uca.fr
Magalon	Karine	karine.magalon@univ-amu.fr
Malhaire	Fanny	fanny.malhaire@igf.cnrs.fr
Marchand	Fabien	fabien.marchand@uca.fr
Marias	Mélanie	melanie.marias@igf.cnrs.fr
Maskini	Dounia	dounia.maskini@inserm.fr
MECHALY	ILANA	ilana.mechaly@umontpellier.fr
Merabet	Nesrine	nesrine.merabet@igf.cnrs.fr
Meynier	Maéva	maeva.meynier@live.fr
Zbili	Mickael	mickael.zbili@uca.fr
Mokhtar	Nazarine	nazarine.mokhtar@uca.fr
Morez	Margaux	margaux.morez@uca.fr
Mrad	Yara	yara.mrad@uca.fr
Murail	Pauline	paulinemurail35@gmail.com
Néel	Eloise	eloise.neel@etu.umontpellier.fr
Negm	Ahmed	ahmed.negm@uca.fr
Oliva	Giulia	giulia@oliva.fr
Peirs	Cedric	cedric.peirs@inserm.fr
Perez	Jean-Christophe	jean-christophe.perez@etu.umontpellier.fr
Perrin	Florence	florence.perrin@inserm.fr
Phamban	Tanya	tanya.phamban@inserm.fr
Poisbeau	Pierrick	poisbeau@inci-cnrs.unistra.fr
Quittet	Clémence	clemence.quittet@etu.umontpellier.fr
Réaux - Le Goazigo	Annabelle	annabelle.reaux@inserm.fr
Ranchon-Cole	Isabelle	isabelle.ranchon-cole@uca.fr
Reho	Guillaume	guillaume.reho@etu.unistra.fr
Reynders	Ana	ana.reynders@univ-amu.fr
Rivat	Cyril	cyril.rivat@umontpellier.fr
Robert	Guillaume	guillaume.robert.1@etu.univ-amu.fr
Rossignol	Jeanne	jeanne.rossignol@doctorant.uca.fr
Salinas	Miguel	salinas@ipmc.cnrs.fr

Schlichter	Rémy	schlichter@inci-cnrs.unistra.fr
Simonin	Frédéric	simonin@unistra.fr
Soler	Noélian	noelian.soler@inserm.fr
Soubeyre	Vanessa	vanessa.soubeyre@igf.cnrs.fr
Toft	Maurizio	toft@ipmc.cnrs.fr
Tourdot	Quentin	tourdot.quentin@gmail.com
Tournois	Laura	lauratournois8@gmail.com
Travert-Jouanneau	Youenn	youenn.travert@gmail.com
Truong	Iona	iona.truong@igf.cnrs.fr
Tuifua	Marie	marie.tuifua@u-bordeaux.fr
Ulmann	Lauriane	lauriane.ulmann@igf.cnrs.fr
Valmier	Jean	jean.valmier@umontpellier.fr
Velez	Aragorn	aragornvelez@hotmail.fr
Ventéo	Stéphanie	stephanie.venteo@inserm.fr
VIEL	Eric	eric.viel@chu-nimes.fr
Yalcin	Ipek	yalcin@unistra.fr
Zassot	Tess	tess.zassot@etu.umontpellier.fr

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