13ème Symposium National du Réseau de Recherche sur la DOULEUR

Conférenciers invités
Dr L. Garcia-Larrea (Lyon)
Dr R. Kuner (Heidelberg)

Marseille, 17-18 Mars 2017
Campus Saint-Charles, AMU

NOUS REMERCIONS POUR LEUR SOUTIEN

COMITE D'ORGANISATION

SERGE ALONSO
NADINE CLERC
BERTRAND COSTE
ANNE DONNET
IRENE MARICS
AZIZ MOQRICH
FRANCOISE PADILLA

13ème SYMPOSIUM NATIONAL DU RESEAU RECHERCHE SUR LA DOULEUR

17-18 Mars 2017 à la Faculté Saint-Charles (Marseille)

Programme

VENDREDI 17 MARS 2017

A partir de 8h00	**Accueil des participants et bienvenue (Salle de Conférences, Faculté Saint-Charles)**
8h45-9h00	**Ouverture du symposium par le comité d'organisation (Amphi de Sciences Naturelles, Faculté Saint-Charles)**
9h00-10h00	**MIGRAINE** Chairman: Anne DONNET
9h00-9h20	Hyperexcitability of GABAergic interneurons can trigger cortical spreading depression: a new pathological mechanism of migraine? Sarah ZERIMECH (IPMC, Valbonne, France)
9h20-9h40	Locus coeruleus involvement in migraine progression Jérémy SIGNORET-GENEST (Neuro-Dol, Clermont-Ferrand, France)
9h40-10h00	Analgesic effects of mambalgin, an inhibitor of ASIC channels, in a rat model of migraine. Clément VERKEST (IPMC, Valbonne, France)
10h00-11h00	**CLINICAL INVESTIGATION** Chairman: Didier BOUHASSIRA
10h00-10h20	Influence of environmental parameters on the placebo response. Christian DUALE (CHU Clermont-Ferrand, Centre de Pharmacologie Clinique (Inserm CIC1405), Clermont- Ferrand, France.)
10h20-10h40	Supernatants from colonic biopsies of IBS patients activate PARs receptors expressed in Human sensory neurons. Cléo DESORMEAUX **(**IRSD, Toulouse, France.)
10h40-11h00	Characterization of bioactive lipids produced by a pathogenic Escherichia coli bacteria: role in visceral hypersensitivity. Julien PUJO **(**IRSD, Toulouse, France.)
11h00-11h30	**PAUSE ET VISITE DES EXPOSANTS**
11h30-12h30	**PLENARY CONFERENCE**

Soyons électriques : demandons l'impossible. L'électrophysiologie chez l'Homme pour détecter, prévenir et traiter la douleur.
Luis GARCIA-LARREA (NeuroPain - Centre de Recherches en Neurosciences de Lyon , France)

12h30-14h00 REPAS (Salle de Conférences, Faculté Saint-Charles)

14h00-15h20 PAIN PROCESSING IN BRAIN
Co-Chairs : Emmanuel BOURINET et Pierrick POISBEAU

14h00-14h20 A key role for amygdala astrocytes in regulation of negative affective processing by oxytocin.
Alexandre CHARLET (INCI, Strasbourg, France)

14h20-14h40 Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4.
Cyril GOUDET (IGF, Montpellier, France)

14h40-15h00 Rac-1 dependent structural plasticity of the anterior cingulate cortex regulates the emotional aspect of chronic pain.
Sophie PEZET (Laboratoire de plasticité du cerveau, ESPCI, Paris, France)

15h00-15h20 Functional ultrasound imaging of the functional connectivity in the rat submitted to short lasting inflammatory pain.
Line RAHAL (Laboratoire de Plasticité du Cerveau, ESPCI, Paris, France)

15h20-16h30 FREE COMMUNICATION SESSION 1
Co-Chairs: Eric LINGUEGLIA et Jerôme BUSSEROLLES

15h20-15h40 Loss of inhibitory tone on spinal cord dorsal horn spontaneously and non-spontaneously active neurons in a mouse model.
Matilde CORDERO-ERAUSQUIN (INCI, Strasbourg, France)

15h40-16h00 Loss of MYO protein facilitates the transition from acute to chronic pain through a selective alteration of spinal ionotropic GABAergic neurotransmission.
Ana REYNDERS (IBDM, Marseille, France)

16h00-16h20 TAFA4: A first-in-class chemokine-like protein for prevention of chronic pain development.
Catarina SANTOS (IBDM, Marseille, France)

16h20-16h30 Présentation de la Société BIOSEB (Benoit Godard, Vitrolles, France)

16h30-17h00 PAUSE ET VISITE DES EXPOSANTS

17h00-18h40 FREE COMMUNICATION SESSION 2
Co-Chairs : Jean VALMIER et Patrick CARROLL

17h00-17h20 Implication des voies de signalisation NGF/TrkA dans l'arthrite chez les souris knock-in TrkAC: approche multimodale.
Lauriane DELAY (Neuro-Dol, Clermont-Ferrand, France)

17h20-17h40 Le MS-275, un inhibiteur d'HDACs, pour prévenir la neuropathie chronique induite par l'oxaliplatine.
Sylvain LAMOINE (Neuro-Dol, Clermont-Ferrand, France)

17h40-18h00 Topical instillations of Benzalkonium Chloride alter the corneal mechanical sensitivity and the extracellular activity of the ciliary nerve.
Fanny JOUBERT (UPMC, Paris, France)

18h00-18h20 Therapeutic effects of Mesenchymal Stromal Cells on anxiety and depression-like behavior in a model of radiation-induced persistent visceral hypersensitivity.
Alexandra SEMONT (IRSN, Fontenay-aux roses, France)

18h20-18h40 What are the strengths and limits of mouse models of fibromyalgia, a meta-analysis of the literature.
Melina BEGOU (Neuro-Dol, Clermont-Ferrand, France)

18h40-19h00 ACTUALITES ET PROJETS DU RESEAU
Radhouane DALLEL (Neuro-Dol, Clermont-Ferrand, France)

20h00 DINER
Les Arcenaulx (Cours D'Estienne D'Orves, 13001 Marseille)

SAMEDI 18 MARS 2017

9h00-10h00 OPIOIDS 1
Chairman: Aziz MOQRICH

9h00-9h20 Morphine-induced hyperalgesia requires mu opioid receptorClaire GAVERIAUX-RUFF (IGBMC, Illkirch, France)

9h20-9h40 Dual acting opioid – neuropeptide FF ligands: screening and pharmacological characterization.
Armand DRIEU LA ROCHELLE (ESBS, Illkirch, France)

9h40-10h00 Involvement of GPR103A in opioid-induced hyperalgesia and tolerance.
Safia AYACHI (UMR7242- Strasbourg, France)

10h00-11h00 PLENARY CONFERENCE

The plastic spinal cord: structural and functional remodeling as a basis for pathological pain.
Rohini KUNER (Department of Pharmacology, INF 366, Heidelberg, Germany)

11h00-11h30 PAUSE ET VISITE DES EXPOSANTS

11h30-12h30 OPIOIDS 2

Chairman: Bertrand COSTE

11h30-11h50 Heavy drugs as a tool for metabolic studies in chronic treatment paradigms: investigating morphine metabolism in tolerant mice.
Ivan WEINSANTO (INCI, Strasbourg, France)

11h50-12h10 Antiallodynic treatment with antidepressants partially reverses neuropathy-induced changes in peripheral delta opioid receptor distribution.
Dominique MASSOTTE (INCI, Strasbourg, France)

12h10-12h30 In a murine model of neuropathic pain, independent peripheral and central mechanisms mediate allodynia relief by antidepressants.
Michel BARROT (INCI, Strasbourg, France)

12h30-14H00 FIN DU COLLOQUE ET COLLATION DE CLOTURE

Communication

Sarah ZERIMECH

Titre : Hyperexcitability of GABAergic interneurons can trigger cortical spreading depression: a new pathological mechanism of migraine?

Chever Oana, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR 7275 & Université Côte d'Azur
Ayrault Marion, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR 7275 & Université Côte d'Azur
Duprat Fabrice, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR 7275 & Université Côte d'Azur
Mantegazza Massimo, Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS UMR 7275 & Université Côte d'Azur

Resume

Migraine is a highly prevalent episodic brain disorder with dramatic socio-economic implications. 30% of patients have transient neurological disturbances before the headache, called aura. Several studies on a genetic form of migraine with aura, familial hemiplegic migraine type 3 (FHM3), suggest a disturbance of GABAergic neurons' physiology. Indeed, FHM3 mutations have been identified in the gene encoding Nav1.1 sodium channels, which are important for action potential generation in these neurons. Interestingly, these mutations cause Nav1.1 gain of function, consistently with hyperexcitability of GABAergic neurons. However, until now, no causal link between GABAergic hyperexcitability and aura generation or migraine attacks has been demonstrated.

To this aim, we performed in mouse brain slices studies of the neurophysiological correlate of aura, cortical spreading depression (CSD): a slow wave of long-lasting neuronal depolarization that could also be implicated in the generation of migraine headache. Using electrophysiology and imaging techniques, combined with selective optogenetic stimulations of GABAergic neurons and use of selective pharmacological blockers, we here demonstrate that increased activity of GABAergic neurons can by itself trigger CSD. Activation of GABAergic or glutamatergic ionotropic receptors is not necessary for CSD initiation, whereas efflux of K+ ions caused by interneurons' firing can induce [K+]out build-up, eventually leading to initiation of CSD.

Our results show that interneurons can be a target to prevent FHM3 attacks and more generally highlight a novel mechanism underlying CSD generation, which may have a general relevance for migraine with aura.

Communication

Signoret-Genest Jérémy

Titre : Locus coeruleus involvement in migraine progression

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Resume

Migraine progression from an episodic to a chronic form was associated with persistent sensitization of trigeminovascular nociceptive neurons (Sp5C) and an impairment of descending inhibitory controls as shown by altered diffuse nociceptive inhibitory controls (DNIC). As the beta-adrenergic receptor antagonist propranolol is the mostly used migraine prophylaxis, and the locus coeruleus (LC) is involved in descending noradrenergic control of pain, we hypothesized that maladaptation in the LC is involved in migraine progression. Monitoring neuronal activity within the LC with Fos expression, we found that a single dural stimulation with inflammatory soup (IS) induces Fos expression in the LC that was significantly increased upon repetition (every two days for 10 days). Using in vivo electrophysiological recordings, we showed that both noxious mechanical and electrical stimulation of facial skin as well as meninges could activate LC neurons. A single dural application of IS also activated LC; however, upon repetition, LC neurons became less responsive to this specific stimulus.
This study demonstrates that recurrent dural nociception could induce specific neuronal plasticity in the LC that results in a state of latent sensitization, which may underlie migraine progression.

Communication

Clément Verkest

Titre : ANALGESIC EFFECTS OF MAMBALGIN, AN INHIBITOR OF ASIC CHANNELS, IN A RAT MODEL OF MIGRAINE

Clément Verkest1,2, Emilie Piquet3,4, Sylvie Diochot1,2, Amélie Descheemaeker3, Mélodie Dauvois1, Philippe Luccarini3, Radhouane Dallel3, Eric Lingueglia1,2, Anne Baron1,2
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4 : CHU Nice, Hopital Cimiez, Département d'évaluation et de traitement de la douleur, Nice, France.

Resume

A recurrent symptom associated to migraine is cutaneous allodynia. It can afflict facial and also extra-facial territories, especially in chronic migraine (≥15 days of headache/month) which is particularly disabilating and difficult to treat. Acid Sensing Ion Channels (ASICs) are emerging as new therapeutic targets and mambalgins, peptides isolated from snake venom, have recently shown analgesic effects against inflammatory and neuropathic pain in mice by specifically blocking ASIC1-containing channels (Diochot et al., 2016). In this study we investigated the analgesic effects of mambalgin-1 (Mamb-1) on a rat model of acute and chronic migraine.
Isosorbide dinitrate (ISDN), a therapeutically used nitric oxide donor is known to trigger headache as an adverse side effect. We used a rat migraine model induced by systemic (i.p) injections of ISDN (Ramos et al., 2017). The facial and extra-facial (hindpaw) mechanical sensitivity were measured with von Frey filaments and dynamic von Frey apparatus, respectively. In vivo pharmacological experiments were realized with Mamb-1compared to clinically-effective molecules.

A single ISDN injection induced acute migraine-like symptoms, characterized by a facial and extra-facial mechanical hypersensitivity. Intravenous injection of Mamb-1 or amiloride, a non specific ASICs antagonist, reversed the mechanical facial allodynia and attenuated the extra-facial one. This effect was stronger than the one with sumatriptan, the reference drug for acute migraine treatment. It also delayed the settlement of chronic migraine induced by repeated ISDN injections. Mamb-1 injected prior ISDN displayed no preventive effect.
Repeated ISDN injections induced a chronic allodynia state, lasting several days. Subsequent injection of Mamb-1 or amiloride reversed the facial allodynia and attenuated the extra-facial one. As expected from previous studies, sumatriptan failed to exert any effect whereas topiramate, the reference treatment for chronic migraine, showed similar effects than Mamb-1.
Taken together, these results support a role for ASIC1-containing channels in facial and extra-facial acute and chronic migraine allodynia. Finally, these data highlight and also broaden the therapeutic potential of ASICs inhibitors like amiloride and mambalgins that could lead to new anti-migraine drugs.

References :

Diochot, S., Alloui, A., Rodrigues, P., Dauvois, M., Friend, V., Aissouni, Y., Eschalier, A., Lingueglia, E., and Baron, A. (2016). Analgesic effects of mambalgin peptide inhibitors of acid-sensing ion channels in inflammatory and neuropathic pain. Pain 157, 552–559.
Ramos, J.M.F., Devoize, L., Descheemaeker, A., Molat, J.-L., Luccarini, P., and Dallel, R. (2017). The nitric oxide donor, isosorbide dinitrate, induces a cephalic cutaneous hypersensitivity, associated with sensitization of the medullary dorsal horn. Neuroscience.

Communication

Christian Dualé

Titre : Influence of environmental parameters on the placebo response.

Alvaro Pereira 1 ; Christian Dualé 2 ; Fréderic Clermont 1, Pierre Gramme 3 ; Samuel Branders 1 ; Chantal Gossuin 1 ; Dominique Demolle 1
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Resume

Those studies on peripheral neuropathic pain (PNP) patients investigate the potential influence of the investigator on the placebo response in RCTs while manipulating different variables, including patient expectation, conditioning and prior experiences, observational and social learning.
Patients were given a blinded placebo (presented as “new treatment”) in addition to their regular analgesic treatment. They were randomized to follow an “Influenced” or “neutral” procedures designed to assess the environmental factors that may influence the placebo response when administrating a drug.
99 patients completed the study in 5 centers (mean age 58 ± 11; 44% females). They suffered from PNP based upon medical examination for at least 6 months. The median history of PNP was 5.0 years.
The 49 patients in the “Influenced” group followed the studied placebo-reinforcing procedure consisting of positive expectation directed information about the placebo in the form of a video. They then underwent pre-treatment heat pain stimuli. After the pain stimuli, patients were given their first placebo capsule and underwent a new heat pain conditioning approximately one hour after dosing. The post-treatment heat pain conditioning protocol was intentionally modified from the pre-treatment, one as the mean intensity was reduced to induce the patient’s belief in analgesic efficacy.
The 50 patients randomized to the “neutral” group followed the procedure consisting of no expectation of improvement, neutral social observational learning and no modulation of pain stimuli. Those patients watched a video presenting only neutral properties of the placebo drug.
Both groups were given capsules to be taken twice a day over 4 weeks as add-on therapy to their regular analgesic.
The weekly mean of the average pain score (APS; 11-point numerical scale) at baseline was 5.4. After four weeks of placebo treatment, across groups, 28 patients (28.3%) had an important decrease of their average pain of more than a 20% from baseline. Overall, the mean APS decreased significantly by 0.48 ($p=0.0057$) to 4.9. The differences between the two procedures was not significant ($p=0.7859$) with a decrease of 0.53 and 0.43 respectively for the “Influenced” and “neutral” groups.
To control the increasing placebo response affecting the assay sensitivity in RCTs, many study level factors have been studied such as number and type of patients, study design and outcome measurement. We investigate here the potential influence of environmental parameters on the placebo response while manipulating the patient expectation and conditioning through two different procedures. Our results tend to show that the external factor effect is marginal compared to the intrinsic placebo fluctuations. This advocates for a better characterization of the individual placebo response. The prediction of the placebo responders may be used in RCTs to stratify patients within groups, and thereby to increase the assay sensitivity.

Communication

Cléo Désormeaux

Titre : Supernatants from colonic biopsies of IBS patients activate PARs receptors expressed in Human sensory neurons.

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2 Departments of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy.

Resume

Background: IBS is a functional bowel disorder characterized by abdominal pain, associated with constipation and/or diarrhea. Among the mediators studied in IBS, increased colonic proteolytic activity appears as a common feature in all IBS sub-groups. Through Protease-Activated Receptors (PARs) activation, proteases can activate primary afferents and act on visceral pain pathways in rodents, but the relevance of PARs activation in human sensory neurons still has to be determined. Thus, the objective of our study was to decipher the PARs pharmacology in human sensory neurons.
Methods: Cryo-protected or fresh human thoracic dorsal root ganglia (DRG) were obtained from the national disease resource interchange (NDRI). Expression of PAR1, PAR2 and PAR4 was studied on slices of DRG (DRG T12, n=3) by co-staining immunochemistry with a pan-neuronal marker (pgp9.5) and PARs antibodies. Calcium signaling responses to PARs agonist peptide (PAR-AP): PAR1-AP (TFLLR; 1, 10 and 100 µM), PAR2-AP (SLIGRL; 100 µM) and PAR4-AP (AYPGKF; 100 µM), their irrelevant peptides (PAR-IP; 100 µM), proteases: trypsin (1 and 10 U) and thrombin (1 and 10 U) or supernatants from colonic biopsies of IBS and HCs (Healthy Controls) patients were studied in cultured human DRG neurons, which were fixed thereafter, to study PARs expression.
Results: In fixed human DRG, PAR1, PAR2 and PAR4 were respectively expressed in 20, 40 and 40% of human sensory neurons. PARs expression was not modified after culture. PAR1-AP increased intracellular calcium concentration in a dose-dependent manner. This increase was inhibited by PAR1 antagonist (SCH79797, 10µM). In contrast, PAR2-AP, PAR4-AP and PAR-IP did not cause calcium mobilization. PAR1-AP-induced calcium mobilization was significantly reduced by pre-incubation with PAR4-AP, but not with PAR2-AP or any of the PAR-IP. Thrombin (PAR1 and PAR4 agonist) but not trypsin (PAR2 and PAR4 agonists) increased calcium flux in human sensory neurons. This thrombin increased is reversed by PAR1 antagonist (SCH79797, 10µM) and potentiated with PAR4 antagonist (ML-354, 10µM) pre-treatment. Only supernatants from colonic biopsies of IBS patients increased calcium flux. This effect is reversed by PAR1 antagonist (SCH79797, 10µM) pre-treatment.
Conclusion: Our study demonstrates that PAR1, PAR2 and PAR4 are expressed in human sensory neurons. In contrast to PAR2 and PAR4, PAR1 activation induced calcium increase in human sensory neurons. PAR4 activation reduced PAR1 induced calcium mobilization. Moreover, thrombin activates both PAR1 and PAR4. Supernatants from colonic biopsies of IBS patients induced intracellular calcium increase via PAR1. Thus, in Human PAR1 and PAR4 seem to play an important role in neuronal activation and could be a target in IBS therapy.

Communication

Pujo Julien

Titre : Characterization of bioactive lipids produced by a pathogenic Escherichia coli bacteria: role in visceral hypersensitivity.

Pujo Julien1, Pérez-Berezo Teresa1, Martin Patricia1, Le-Faouder Pauline2, Riols Fabien2, Oswald Eric1, Bertrand-Michel Justine2, Cenac Nicolas1
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2: MetaToulLipidomics Facility, INSERM UMR1048, Toulouse, France

Resume

Irritable Bowel Syndrome (IBS) is the most common gastrointestinal disorder which is characterized by visceral hypersensitivity. Several studies have shown that polyunsaturated fatty acids (PUFA) metabolites were involved in visceral hypersensitivity associated with IBS. In parallel, intestinal microbiota dysbiosis seems to participate to the symptoms generation. The aim of our study was to identify whether pathogenic bacteria could be the source of PUFA metabolites able to activate sensory neurons.
Lipid profiling was performed by liquid chromatography coupled to mass-spectrometry (LC-MS) on lipids extracted from two strains of bacteria: one pathogenic Escherichia coli, NC101, and a probiotic Escherichia coli Nissle 1917. Calcium signaling experiments have been performed in primary culture of sensory neurons from mice dorsal root ganglia in response to PUFA metabolites overexpressed by pathogenic bacteria. Then, we have assessed the ability of these lipid compounds to cross the intestinal barrier in vitro, across a monolayer of epithelial cells cultivated in transwell, ex vivo, performing ussing chamber experiments with colon biopsies of mice and in vivo, by LC-MS/MS quantification of the bacterial lipids in mice.
Overproduced by pathogenic bacteria compared to probiotic, we identified several hydroxylated metabolites of linoleic and a-linolenic acid: hydroxyoctadecadienoic acid (HODE), dihydroxyoctadecenoic acid (DiHOME), trihydroxyoctadecenoic acid (TriHOME) and fatty acids composed by 12 to 19 carbons that share a hydroxylation on the third carbon (Cx-3OH). Interestingly, in addition to 9- and 13-HODE, the C18-3OH increased significantly the intracellular concentration of calcium in sensory neurons by the activation of a calcium channel. Moreover, the C18-3OH did not diffuse through the epithelial cells and neither through colon biopsies in vitro and ex vivo respectively. In contrast, in vivo, the C18-3OH was quantified in the colon, the blood, and in the brain of mouse.
Pathogenic bacteria produce hydroxylated fatty acid metabolites able to activate sensory neurons. Even if more experiments are needed, we demonstrate that bacteria could interact with sensory neurons via the production of PUFA metabolites.

Soyons électriques : demandons l'impossible.

L'électrophysiologie chez l'Homme pour détecter, prévenir et traiter la douleur.

Luis Garcia-Larrea

Les techniques d'électrophysiologie aident au diagnostic, à la prédiction et au traitement de la douleur chronique, en particulier neuropathique. Nous passerons rapidement en revue ces différentes approches, ainsi que les possibilités nouvelles d'une réflexion « translationnelle inverse », où les résultats obtenus chez l'Homme pourront inspirer la recherche sur des modèles animaux.

Diagnostic différentiel : affirmer le diagnostic de douleur neuropathique (DN) nécessite la confirmation d'une lésion ou d'une maladie des systèmes somesthésiques ; l'exploration électrophysiologique permet d'obtenir cette confirmation. Les lésions responsables des DN concernent essentiellement les fibres périphériques de petit calibre A-delta et C, le système spino-thalamo-cortical au niveau central. Parmi les méthodes pour activer sélectivement les voies thermo-algiques, les potentiels évoqués par laser (PEL) o par thermode de contact (CHEPs) sont simples et fiables. Son efficacité diagnostique augmente par le couplage avec des réflexes végétatifs, des réponses psychophysiques (temps de réaction, analyse sensorielle quantitative), et par l'exploration concomitante des systèmes non-nociceptifs, car certaines douleurs paroxystiques peuvent dépendre d'une altération sélective des fibres de gros calibre. L'exploration électrophysiologique doit répondre aux questions : (a) la douleur est-elle liée à une atteinte des voies somesthésiques ? (b) quel est le degré d'altération des différents sous-systèmes ? ; (c) les résultats sont-ils en accord avec l'imagerie ? et (d) les résultats seront-ils utiles au suivi thérapeutique ?

Prédiction / prévention de la douleur : L'identification et/ou l'évitement d'une lésion nerveuse au cours d'interventions peut prévenir la survenue de douleurs postopératoires. L'analyse conjointe des réponses nociceptives corticales et de l'imagerie IRM permet de classer correctement ~90% des patients ayant développé o non des douleurs après accident vasculaire du tronc cérébral ou du thalamus. Tous ces éléments suggèrent que l'analyse électrophysiologique précoce des patients à risque pourrait détecter ceux avec la plus forte probabilité de développer une douleur, ouvrant ainsi la voie à des interventions thérapeutiques préventives.

Objectiver la douleur ? L'enregistrement des réponses orthosympathiques cutanées ou pupillaires permet d'évaluer l'éveil végétatif provoqué par une douleur, et par là même attester de sa réalité subjective. La correspondance entre réponses végétatives et corticales, ainsi que leur possible dissociation, s'avère extrêmement utile pour déterminer la réalité d'un phénomène allodynique, ou pour vérifier des anomalies de perception cliniquement douteuses. Des techniques se développent actuellement pour objectiver la nociception chez le patient non-communicant, dans le coma ou sous anesthésie générale.

Traitement électromagnétique : La stimulation corticale par électrodes implantées chirurgicalement s'est positionnée comme une thérapie efficace chez environ 50% de patients réfractaires à la pharmacothérapie. Des modalités non-invasives de stimulation, par le biais d'impulsions magnétiques répétitives (rTMS) ou par courant électrique sur le scalp (tDCS, tACS) sont actuellement utilisées non seulement pour prédire l'efficacité de la stimulation implantée, mais de plus en plus comme des thérapies à part entière, permettant dans certains cas l'utilisation au domicile du patient, contrôlées depuis l'hôpital via une interface internet.

Références

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Communication

A Charlet

Titre : A key role for amygdala astrocytes in regulation of negative affective processing by oxytocin

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Resume

Complex integrations by astrocyte-neuron networks in both the temporal and spatial domains are crucially involved in brain circuits and functions. Oxytocin orchestrates social and emotional behaviors through modulation of brain circuits such as the central amygdala (CeA). We hypothesize that oxytocin effects in the CeA arise from modulation of such astro-neuronal networks. We found that a subpopulation of CeA astrocytes expresses the oxytocin receptor and responds to its activation by long-lasting increase in calcium transients. Those responses are necessary for oxytocin effects on neuronal activity in the CeA and astrocytic light-evoked calcium transients are sufficient to drive the neuronal network activity. Astrocyte-neuronal communication occurs through release of D-Serine and subsequent activation of NMDA receptors. Accordingly, impairing astrocytes in the CeA abolishes effects of oxytocin on both pain and anxiety. Thus, astrocytes play a critical role in the oxytocinergic modulation of CeA neuronal network and its beneficial modulation of emotional experiences.

Communications

Cyril Goudet

Titre : Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4

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Resume

Contrary to acute pain, chronic pain does not serve as a warning signal and must be considered as a disease per se. This pathology presents a sensory and psychological dimension at the origin of affective and cognitive disorders. Being largely refractory to current pharmacotherapies, identification of endogenous systems involved in persistent and chronic pain is crucial. The amygdala is a key brain region linking pain sensation with negative emotions. Here, we show that activation of a specific intrinsic neuromodulatory system within the amygdala associated with type 4 metabotropic glutamate receptors (mGlu4) abolishes sensory and affective symptoms of persistent pain such as hypersensitivity to pain, anxiety- and depression-related behaviors, and fear extinction impairment. Interestingly, neuroanatomical and synaptic analysis of the amygdala circuitry suggests that the effects of mGlu4 activation occur outside the central nucleus via modulation of multisensory thalamic inputs to lateral amygdala principal neurons and dorso-medial intercalated cells. Furthermore, we developed optogluram, a small diffusible photoswitchable positive allosteric modulator of mGlu4. This ligand allows the control of endogenous mGlu4 activity with light. Using this optopharmacological approach, we rapidly and reversibly inhibited behavioral symptoms associated with persistent pain through optical control of optogluram in the amygdala of freely behaving animals. Together, our data identifies amygdala mGlu4 signaling as a mechanism that bypasses central sensitization processes to dynamically modulate persistent pain symptoms. Our findings help to define novel and more precise therapeutic interventions for chronic pain, and exemplify the potential of optopharmacology to study the dynamic activity of endogenous neuromodulatory mechanisms in vivo.

Communication

Sophie PEZET

Titre : Rac-1 dependent structural plasticity of the anterior cingulate cortex regulates the emotional aspect of chronic pain

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Resume

Painful experiences are multi-layered, composed of sensory, affective, cognitive and behavioural facets. While it is well accepted that the development of chronic pain is due to maladaptive neuronal changes, the underlying molecular mechanisms and their relationship to the different pain modalities is still not well understood. We have previously shown that a BDNF (Brain-Derived Neurotrophic Factor) – dependent plasticity takes place in the anterior cingulate cortex in a inflammatory model of chronic pain induced by intraplantar injection of Complete Freund ‘s Adjuvant (CFA). In this brain area, BDNF is a key mechanism in the development and maintenance of the affective-emotional aspect of chronic pain, while it does not modify the sensory discrimivative aspect (Thibault et al., 2014). In the current study we explored i) the presence of structural plasticity in the ACC in this animal model and ii) the putative role of the Rac-1 signaling pathway. Using Golgi- and immune-staining for several pre- or post-synaptic components, as well as behavioural tests that explore specifically the sensory discriminative (Von Frey hairs, cold plate) or the emotional aspect of pain (passive avoidance tests to either mechanical or cold stimuli), we show that the anterior cingulate cortex is indeed the site of structural plasticity, through a Rac-1 dependent mechanism and that pharmacological blockade of Rac-1 specifically prevents the development of the emotional aspect of chronic pain.

Communication

Line RAHAL

Functional ultrasound imaging of the functional connectivity in the rat submitted to short lasting inflammatory pain

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Resume

Introduction
Neurophysiological, neurobiological and medical imaging techniques permitted to bring to light the neuroanatomic pathways implied in the transmission of nociceptive information in the peripheral and central nervous systems. However, many questions remain to be answered, such as like the changes in the pain pathways underlying the chronification of pain in some chronic pain disorders. A novel imaging technique developed by the Langevin Institute, called functional ultrasound (fUS) imaging, allows the study of the i) brain hemodynamics, ii) microvasculature dynamics and iii) functional connectivity with unequaled spatial and temporal resolutions. The aim of our study is to determine, using FUS imaging, the brain areas involved in acute pain and their alteration in chronic pain condition. The final aim of this work is to define the alterations in neuronal network in chronic pain condition and, by defining the molecular mechanisms, develop new therapeutical strategies. We started using an inflammatory pain model induced by intraplantar injection of CFA (Complete Freund's Adjuvant).
Methods
Functional ultrasound (fUS) imaging was performed using Ultrafast Doppler (Bercoff et al., 2011) based on compounded plane-wave ultrasound imaging (Tanter et al., 2002; Montaldo et al., 2009). This technique has sufficiently high sensitivity to detect subtle hemodynamic changes due to the neurovascular coupling with a high spatio- temporal resolution (1 ms, 100 μm). The scanning sequence consisted of 11 tilted planar ultrasonic waves (-10° to 10° angles, with a step of 5°) with a pulse repetition frequency of 5500 Hz. We used an Aixplorer and a linear ultrasonic probe (128 elements, 0.1 mm pitch, 15 MHz). Doppler acquisitions were obtained in coronal planes for a dozen of thinned-skull and anesthetized rats. Inflammation was induced by intraplantar injection of CFA (Freund's Complete Adjuvant) in the hind paw.

Results
We initially compared several anesthetics in order to obtain a sustained, reproducible experimental design. We found out that a mix of Ketamine and Domitor was the optimal anesthetic, providing very robust and stable results with low inter- and intra-animal variability. Analysis of changes in functional connectivity in one frontal and one saggital plan showed statistically different connectivity in a small number of brain areas. This, result is consistent with the recently published article of Le Blanc's team (Pain, 2016) that observed (using EEG in freely moving rats) lack of significant alteration in the Fc when pain lasted less than 2 weeks.

In conclusion: Forty-eight hours of peripheral inflammation is therefore not long enough to after pain brain networks and see significant changes of functional connectivity. We are currently turning to a more chronic model of inflammatory pain (arthritis), where these changes are being studied in a larger number of plans (i.e. brain areas).

Communication

Matilde Cordero-Erausquin

Titre : Loss of inhibitory tone on spinal cord dorsal horn spontaneously and non-spontaneously active neurons in a mouse model of neuropathic pain

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Resume

Plasticity of inhibitory transmission in the spinal dorsal horn (SDH) is thought to be a key mechanism responsible for pain hypersensitivity in neuropathic pain syndromes. However in vivo recordings performed in rats have provided controversial data concerning the plasticity of inhibitory transmission in neuropathic models, arguing for either a decrease or an increase of GABAergic tone. Most studies so far have focused on SDH neurons responding to natural peripheral stimulations but showing no spontaneous ongoing activity between stimuli (non-spontaneously active or NSA neurons). However, some SDH neurons display considerable ongoing activity in the absence of experimentally-applied stimuli (spontaneously active or SA neurons). In the present study, we systematic analyzed both SA and NSA neurons to provide an exhaustive characterization of the neurons involved in sensory processing of mechanical information and their plasticity after nerve injury in mice.
Our study reveals a dramatic loss of spinal inhibitory tone in neuropathic conditions. In addition, it suggests that a shift in the reversal potential for anions is an important component of the abnormal mechanical responses and of the loss of inhibitory tone recorded in this model of nerve injury-induced neuropathic pain.

Communication

Ana Reynders

Titre : Loss of MYO protein facilitates the transition from acute to chronic pain through a selective alteration of spinal ionotropic GABAergic neurotransmission

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Resume

The transition from acute to chronic pain represents a major clinical problem. The factors and mechanisms underlying pain chronicity are still largely unknown. Recently, we identified an atypical Myosin (MYO) that is expressed in dorsal root ganglia sensory neurons. We showed that loss of function of MYO, converted a short lasting and reversible inflammatory, neuropathic and postoperative mechanical pain into a long lasting and irreversible chronic pain. Using behavioral pharmacology and RNA deep sequencing, we found that loss of MYO resulted in a selective impairment of spinal ionotropic GABAergic signaling and an intriguing selective upregulation of the α2 subunit of the GABAA-R in DRG and spinal cord. Together, our results identified Myo gene as a predictive genetic factor to develop chronic pain, and uncovered a unique preclinical animal model to study the mechanisms responsible for chronic pain development.

Communication

Catarina Santos

Titre : TAFA4: a first-in-class chemokine-like protein for prevention of chronic pain development

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Resume:

Chronic pain affects approximately 20% of the European population and currently there is no effective treatment. TAFA4 is a chemokine-like protein that is highly expressed and released from C-low threshold cutaneous mechanoreceptors. It has recently been shown to have a transient antalgic effect after a single intrathecal injection in two different models of transient pain, one inducing a fast inflammatory pain (Carrageenan 1%) and the second one that induces a slow progressing neuropathic pain triggered by chronic constriction injury of the sciatic nerve.

In this work we aim to explore further the potential antalgic effect of TAFA4 in chronic pain by using different mice models of pain.

First, to evaluate if this antalgic effect depends only on spinal mechanisms or involves also peripheral mechanisms, we injected TAFA4 intrathecally (i.t) or subcutaneously (s.c) at the peak of the pain induced by Carrageenan treatment. Both procedures resulted in a 4-6 hours antalgic effect in a dose-dependent way (12.5, 50, 200 µg/mL and 100, 300 µg/kg for i.t and s.c injections respectively).

TAFA4 effects in chronic pain were then tested using the model of spared nerve injury (SNI) that induces a persistent neuropathic pain. At day 7 post-surgery, both i.t. and s.c injections had an approximate 4 hour antalgic effect, peaking at 30 minutes and 2 hours, respectively. This antalgic effect was much longer than the 1-2-hour relief obtained in the same model with Baclofen (agonist of $GABA_B$ receptors) and DAMGO (µ-opioid receptors).

We then investigated whether TAFA4 can be efficient for long-term treatments. For that purpose we used Myosin KO mice that are so highly susceptible to pain that they develop chronic pain even when they are submitted to protocols that generate very transient pain. We chose to trigger chronic pain in these mice by performing a paw incision (Brennan model). In addition to TAFA4 (100µg/kg), Gabadoxadol (5 mg/kg), Ketamine (5 mg/kg), Pregabalin (3 mg/kg), SNC80 & DAMGO (10 mg/kg and 0,2 mg/kg), N-tert-butyl-α-phenylnitrone (PBN) (50 mg/kg) and Celecoxib (20 mg/kg) were tested by s.c single daily injections applied 10 days after surgery. Only Pregabalin and TAFA4 treatments induced significant results. However, whereas Pregabalin treatment transiently decreased the pain at day 1 post-surgery, TAFA4 treatment decreased pain from day 3 to day 30 post-surgery.

This work shows the potential of TAFA4 as a therapeutic drug for pain treatment in both acute and chronic conditions with longer lasting effects than commonly used drugs.

Communication

Delay Lauriane

Titre : Implication des voies de signalisation NGF/TrkA dans l'arthrite chez les souris knock-in TrkAC: approche multimodale.

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Resume

La polyarthrite rhumatoïde est une maladie auto-immune qui se caractérise par une inflammation articulaire, des altérations cartilagineuses et osseuses communément accompagnées de douleurs chroniques difficiles à traiter par les thérapeutiques actuelles. Le Nerve Growth Factor (NGF) est une neurotrophine connue comme une cible thérapeutique prometteuse de la polyarthrite rhumatoïde mais de par son action pléiotropique, elle conduit à certains effets indésirables importants. Le but de notre étude est de mieux comprendre l'implication des voies de signalisation intracellulaires spécifiquement associées à l'activation du récepteur au NGF, le récepteur tyrosine kinase de type A (TrkA), dans la physiopathologie de la polyarthrite rhumatoïde. Pour cela, nous avons réalisé une étude multimodale chez des souris knock-in TrkA/C, exprimant un récepteur chimérique composé de la partie extracellulaire native du récepteur TrkA et des parties transmembranaires et intracellulaires fonctionnelles du récepteur à la neurotrophine 3 : le récepteur TrkC. En parallèle d'un suivi du comportement nociceptif, nous avons effectué un suivi longitudinal par imagerie scintigraphique in vivo (99mTc-NTP 15-5 et 99mTc-HMDP, traceurs ciblant respectivement les remodelages du cartilage et de l'os) ainsi que des marquages immunohistochimiques de l'articulation tibio-tarsienne dans un modèle de monoarthrite (MoAr) induit par l'administration intra-articulaire d'adjuvant complet de Freund (CFA). Nous avons pu démontrer que les souris TrkA/C présentaient une diminution spécifique de l'allodynie mécanique, corrélée à une réduction de l'augmentation de l'innervation des fibres peptidergiques CGRP+ par rapport aux souris sauvages. En outre, nous avons observé une diminution uniquement du remodelage osseux en imagerie chez ces souris TrkA/C ainsi qu'une baisse de l'infiltration articulaire des cellules CD68+ sans que la taille de l'œdème ne soit affectée. En collaboration avec l'institut Karolinska, nous avons complété notre étude en utilisant un modèle plus pertinent cliniquement de polyarthrite rhumatoïde : le modèle CAIA qui utilise un cocktail arthritogénique d'anticorps monoclonaux anti-collagène de type II. De manière intéressante, les souris TrkA/C semblent résistantes à l'immunisation par ce cocktail d'anticorps comparées à des souris sauvages.
L'ensemble de nos résultats montrent une implication des voies spécifiquement liées à TrkA, à la fois dans la douleur, particulièrement l'allodynie mécanique, et dans le remodelage osseux associés à l'arthrite inflammatoire. Nos derniers résultats dans le modèle CAIA suggèrent aussi un rôle de cette signalisation dans l'inflammation liée à l'auto-immunité. Nos études en cours permettront d'identifier plus spécifiquement quels sont les effecteurs de ces voies responsables de ces changements dans un contexte d'arthrite inflammatoire afin d'identifier de nouvelles cibles thérapeutiques.

Communication

Sylvain LAMOINE

Titre : Le MS-275, un inhibiteur d'HDACs, pour prévenir la neuropathie chronique induite par l'oxaliplatine

Sylvain LAMOINE, Vanessa PEREIRA, Youssef AISSOUNI, Laetitia PRIVAL, Julie BARBIER, Alain ESCHALIER, Jérôme BUSSEROLLES.

Resume

L'oxaliplatine, un sel de platine de 3ème génération, fait partie du traitement de référence des cancers colorectaux. L'effet indésirable majeur de ce composé est le développement d'une neuropathie douloureuse se caractérisant par des paresthésies et des dysesthésies apparaissant chez 90% des patients dès la première cure de chimiothérapie. Une neuropathie chronique se développe suite à la répétition des cures chez plus de 20% des patients, pouvant conduire à une diminution de dose ou à l'arrêt du traitement. De plus, les symptômes de cette dernière peuvent durer plusieurs mois après l'arrêt de la chimiothérapie. Des données préliminaires obtenues au laboratoire ont montrées l'implication de processus épigénétiques dans l'apparition de cette neuropathie. Nous avons également démontré un effet antalgique du MS-275 ou Entinostat, un inhibiteur des histones désacétylases (HDAC) de classe I, chez un modèle murin de neuropathie aiguë induite par l'oxaliplatine. Une surexpression de plusieurs HDACs appartenant à la Classe I ayant été observée dans des biopsies de patients cancéreux, et l'entinostat ayant également des propriétés antiprolifératives, nous avons recherché à tester l'efficacité de ce composé sur un modèle murin de neuropathie chronique et d'évaluer l'impact de cet inhibiteur, en présence ou non d'oxaliplatine, sur des lignées cellulaires de cancer colorectal.
Des souris mâles C57Bl6/J et APCMin/+ (mutation conduisant au développement de polypes intestinaux) ont été utilisées pour les expérimentations in vivo. L'oxaliplatine (3mg/kg, i.p) a été administrée deux fois par semaine durant 3 semaines. Le MS-275 (15mg/kg, p.o) était administré 30 minutes avant chaque injection d'oxaliplatine. La sensibilité douloureuse des animaux a été évaluée chaque semaine par différents tests de douleur provoquée par des stimulations thermique et mécanique. Deux lignées de cellules humaines de cancer colorectal, HT29 et T84 ont été utilisées pour les expérimentations in vitro. La toxicité des composés sur les cellules cancéreuses a été analysée par le test du MTT et par cytométrie en flux.
Nos résultats montrent que l'inhibition des HDACs de la Classe I permet de prévenir l'apparition de l'hypersensibilité thermique et mécanique des animaux traités par des administrations répétées d'oxaliplatine. De plus, l'oxaliplatine et le MS-275, utilisés seuls, présentent une activité anti-proliférative sur les deux lignées cellulaires de cancer colorectal utilisées. Lorsque co-administrés, le MS-275 n'a pas d'effet délétère vis-à-vis de l'effet antiprolifératif de l'oxaliplatine sur la lignée HT29 mais l'améliore sur les cellules T84.
Nos résultats suggèrent ainsi que la combinaison de l'oxaliplatine avec le MS-275 pourrait présenter un double bénéfice pour les patients souffrant d'un cancer colorectal, en prévenant l'effet neurotoxique de l'oxaliplatine

Communication

Fanny Joubert

Titre : Topical instillations of Benzalkonium Chloride alter the corneal mechanical sensitivity and the extracellular activity of the ciliary nerve

Fanny Joubert (1,2,3), Laurence Bodineau (5), M Carmen Acosta (6), Juana Gallar (6), José Sahel (1,2,3,4), William Rostène (1,2,3), Christophe Baudouin (1,2,3,4), Stéphane Mélik Parsadaniantz (1,2,3) and Annabelle Réaux- Le Goazigo (1,2,3)
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Resume

Ocular surface diseases are among the most frequent ocular pathologies, with prevalence ranging between 10 and 20% of the general population. Benzalkonium chloride (BAK) as a preservative in eye drop is a major cause of dry eye in patients treated over the long term. Here we described the electrophysiological set-up to record ciliary nerve activity in mice and we investigated the effect of BAK corneal exposure i) in vivo, on the corneal mechanical sensitivity and ii) ex vivo, on the extracellular ciliary nerve activity using an isolated mouse whole eye preparation.
Adult male C57BL/6 mice were used. For electrophysiological experiments, eye was placed in the two-compartment chamber to isolate the cornea to the rest of the eye and the extracellular spontaneous activity of the ciliary nerve was recorded. Repeated corneal topical instillations of PBS 1X or 0.02% BAK were performed (1 instillation every 5 min – 15 times) and two types of application were used: i) ex vivo: instillations were directly performed during the ciliary nerve recording and ii) in vivo: mice received repeated instillations and after, eyes were removed and ciliary nerve activity was recorded. The blinking behavior in response to corneal mechanical stimulation was evaluated using von Frey filaments (0.008 – 0.07g).
Our electrophysiological set up gave accurate and reliable extracellular recordings. Under basal condition, the multiunuit activity of the mouse ciliary nerve is around 28.8±2.4 imp/sec. After in vivo repeated topical instillations of 0.02% BAK, we observed a corneal mechanical hypersensitivity (-0.016±0.001g (~ -40%); $p<0.001$) whereas repeated PBS instillations did not alter mechanical threshold (-0.003±0.003g (~ -7%)). Interestingly, we observed a significant increase of basal activity of the ciliary nerve in BAK-treated mice compared to PBS-treated animals (39.6±3.7 vs 29.1±0.7 imp/sec respectively; $p<0.05$).
Ex vivo repeated application of 0.02% BAK significantly increased the ciliary nerve activity 30 minutes after the first instillation (127.9±8.0%; $p<0.05$) compared to PBS instillations (83.0±0.3%; $p<0.05$). This effect was still observed after 70 minutes of BAK treatment (15 instillations, 123.4±27.2% vs 80.6±9.7%; $p=0.0714$). Similarly to in vivo experiments, we observed a decreased of mechanical threshold in BAK-treated eye (-0.021±0.007g (~ -50%); $p<0.05$) compared to PBS-treated eye (0.004±0.003g (~ +10%); $p<0.01$).
In conclusion, this work presents the methodology to record the ciliary nerve activity in mouse preparation. This set up allowed us to provide the first evidence that corneal exposure to BAK altered the extracellular activity of ciliary nerve fibers and may explain the ocular pain observed after a chronic treatment with BAK, a preservative commonly used in eye drops.

Communication

Sémont Alexandra

Therapeutic effects of Mesenchymal Stromal Cells on anxiety and depression-like behavior in a model of radiation-induced persistent visceral hypersensitivity.

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Resume

Each year, millions of people worldwide are treated for primary or recurrent pelvic malignancies, involving radiotherapy in almost 50% of cases. Therapeutic doses of radiation used lead to the damage of healthy tissue around the tumor with high incidence that may lead to undesirable persistent toxic effects. Many cancer survivors exhibit overlapping symptoms resulting from multiple organ dysfunctions which have been recently recognized as a new pathology called “pelvic radiation disease”. Persistent abdominal pain can affect those patients’s quality of life and may be a factor in the development of psychiatric co-morbidity. Using our model of radiation-induced visceral hypersensitivity, we have yet shown that mesenchymal stromal cell (MSC) treatment decreases mechanical allodynia. The aim of the present study was to assess, in this model, (i) anxiety and depression-like behavior and (ii) to test on those parameters MSC therapeutic strategy.
A 29 Gy colorectal irradiation (CI) were performed on Sprague-Dawley rats. Time-dependent effects of radiation (at 7, 14 and 28 days) on anxiety and depression-like behavior was first analyzed using different tests. The anxiety-like behavior assessment was performed using Marble Burying (MB), Elevated Plus Maze (EPM) and Sociabilization (S) tests. For depression symptoms, Forced Swimming Test (FST) was used. To test MSC efficiency, 5 millions of cells were administered intravenously 3 weeks after irradiation and 1 week later MB, EPM, S tests and FST were realized.
In our model, irradiated rats buried more balls, spent less time in open arm of EPM, had fewer interactions between us compared to control rats. Concerning FST, irradiated rats spent more time immobile in the water and had many difficulties to swim in comparison with control rats. CI, associated with persistent visceral hypersensitivity, seems to cause a predisposition to anxiety and depression-like behavior. The anxiety-like behavior appears very early after irradiation (at 7 days) and get worse over time. For the first time, we showed that administration of MSC decreased most of anxiety and depression-like behavior.
This work provides new insights into the potential use of MSC as cell therapy in the treatment of visceral hypersensitivity and co-morbidities associated to “pelvic radiation disease”.

Communication

Mélina BEGOU

What are the strengths and limits of mouse models of fibromyalgia, a meta-analysis of the literature

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Resume

Fibromyalgia is a condition of diffuse, chronic pain characterized by extreme sensitivity of muscles in several parts of the body. Due to the unknown etiology of this disease, the development of animal models is difficult and until now very limited. Nonetheless, three mouse models are commonly used: the intermittent cold stress, the intramuscular acidic saline injection and the reserpine-induced myalgia models. We made the assumption that the neonatal maternal separation model could also be considered as an animal model of fibromyalgia.
Using the data of literature, the purpose of this study was to compare the different animal models on their ability to meet the criteria of: 1) construct validity i.e. induction of the disease state in accordance with the fibromyalgia etiology, 2) face validity i.e. presence of fibromyalgia-like symptoms, 3) predictive validity i.e. improvement of symptoms by treatments used in the clinical setting. We then compiled data from these 4 mouse models using the technique of systematic review and meta-analysis to highlight their strengths and limits.
We performed a systematic search with Medline, manual literature review, and a review of expert bibliographies. After examining all eligible studies, we extracted results about 1) muscular, somatic and visceral pain; 2) anxiety and depression related behaviors; 3) hypothalamic-pituitary-adrenal axis dysfunction; 4) markers of inflammation; 5) efficacy of pharmacological drugs. Weighted and standard mean difference random effects meta-analysis was used to measure overall effects in each models. Statistical heterogeneity between results was assessed by examining forest plots, confidence intervals and using I^2.
On the 269 studies identified, 41 were eligible. First the meta-analysis showed that all the models met the construct, face and predictive validity criteria with more or less accuracy. For the three commonly used animal models, they all exhibit pain behaviors associated with comorbidities both responding to drugs used in fibromyalgia among which pregabalin or amitriptyline. One main limits of these models is that muscular pain is little if not studied and that long term follow-up is often missing. Concerning the neonatal maternal separation, despite for somatic and muscular pain, the effects on behavioral and biochemical markers of fibromyalgia as well as pharmacological sensitivity are as strength if not better than those observed in the classical models.
This meta-analysis study then confirmed that the three classical models of fibromyalgia could be interesting but still need further characterization in order to ensure they are really suitable notably to identify muscular pain and more dedicated pharmacological treatment. Concerning the neonatal maternal separation model, this study strongly indicates that it can mimic a large range of fibromyalgia symptoms even if a detailed characterization of somatic and muscular pain is needed to draw a definitive conclusion.

Communication

Claire Gaveriaux-Ruff

Titre : Morphine-induced hyperalgesia requires mu opioid receptor

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Resume

Opiates are potent analgesics but their clinical use is limited by adverse events including analgesic tolerance and opioid-induced hyperalgesia (OIH). Opiates trigger analgesia and other adverse effects through mu opioid receptor (MOR) activation. However, the involvement of MOR in OIH remains uncertain and a matter of debate as Toll like receptor-4 (TLR4), a key innate immunity receptor, has been shown as the OIH mediator. We examined the involvement of mu opioid receptors in OIH by comparing chronic morphine effect in wild-type (WT) mice and MOR knockout (KO) mice. Repeated morphine administration produced analgesic tolerance and OIH in WT animals. However, no OIH was detected in mu receptor KO mice. These behavioural results have been observed in tests exploring mechanical, heat and cold pain modalities. Requirement for MOR in OIH was found in both female and male mice. Also, the morphine metabolite morphine-3-glucuronide (M3G) previously shown to mediate OIH, did produce hyperalgesia in WT but not in MOR KO animals. Moreover, in radioligand binding and ligand-activated GTPγS binding assays, both morphine and M3G were shown binding to and activating MOR. Altogether, our in vivo findings on WT and MOR KO mice and in vitro assays indicate that MOR is required for hyperalgesia induced by both chronic morphine and M3G acute administration.

Communication

Drieu la Rochelle A

Dual acting opioid – neuropeptide FF ligands: screening and pharmacological characterization

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Resume

Opioid analgesics, such as morphine and fentanyl, continue to be the cornerstones for treating moderate to severe pain. However, upon chronic administration, their efficiency is limited because of prominent side effects such as tolerance and dependence. One hypothesis for the occurrence of these side effects is that the chronic stimulation of the opioid system may trigger its endogenous counterparts, anti-opioid systems, producing hyperalgesia (opioid-induced hyperalgesia, OIH) and analgesic tolerance. Previous data from our lab and others have shown that RF9, an antagonist of neuropeptide FF receptors (NPFF1R and NPFF2R), efficiently blocks opioid-induced hyperalgesia and tolerance when co-administered with fentanyl or morphine in rodents. In this study multi-target molecules, that display mu-opioid receptor (MOR) agonist activity, as well as NPFF receptor antagonist properties, were designed. To this purpose a set of peptidic ligands was generated, which combines an already known high affinity mu-opioid receptor agonist together with the carboxyl-terminal RF-amide signature of NPFF. First, the affinity and activity of these molecules were determined for MOR. We identified high affinity ligands (<1nM) in binding competition studies with membranes from CHO cells stably expressing MOR. The MOR-agonist activity was confirmed in cAMP assay (Glo-sensor) in HEK cells stably expressing this receptor and furthermore the β-arrestin recruitment was investigated by BRET in HEK cells stably expressing MOR-luciferase. We then examined the NPFF receptor component in binding competition studies with membranes from CHO cells stably expressing NPFF1R or NPFF2R. Molecules that displayed good affinity for both NPFF1 and NPFF2 receptors were further evaluated in GTPγS and cAMP functional assays. This study allowed to identify one hybrid molecule that displays high affinity for and full agonist activity at MOR, NPFF1R and NPFF2R (compound 1) and a second hybrid molecule that shows full agonist activity at MOR as well as antagonist properties for both NPFF1 and NPFF2 receptors (compound 2). In accordance with in vitro results, we observed that acute s.c. administration of compounds 1 and 2 at low doses produced strong and long-lasting (> 5 hrs) antinociceptive effects in mice. After 7 days of chronic s.c. administration of compound 1, mice developed hyperalgesia and analgesic tolerance, two effects that were not observed upon chronic treatment with compound 2. Further in vivo evaluation of analgesic properties in an inflammatory pain model of these two compounds and additional adverse side effects are currently in progress.

Communication

Ayachi Safia

Titre : Involvement of GPR103A in opioid-induced hyperalgesia and tolerance.

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Resume

Pain is a major health problem that reduces quality of life. Opiates remain the most effective way of reducing moderate to severe pain, but their chronic administration induces the development of tolerance to their analgesic effects and hypersensitivity to pain (hyperalgesia), which lead to the decrease of treatment efficacy over time. It has been proposed that opioid-induced tolerance and hyperalgesia (OIH) may result from the activation of anti-opioid systems, which would occur in opiates chronic administration (Simonnet and Rivat, 2003; Ayachi and Simonin, 2014). RF-amide neuropeptide receptors are G-protein-coupled receptors described as part of an anti-opioid system involved in the modulation of nociception and opiate analgesia (Ayachi and Simonin, 2014). Their respective role and their mechanism of action in the modulation of nociception are, however, still poorly understood. In order to address this issue, we generated knockout (KO) mice for the six RF-amide receptors. We observed that fentanyl-induced hyperalgesia is attenuated in NPFF1R, NPFF2R and GPR103a KO mice. We further showed that GPR103a KO mice also show a decrease in morphine analgesic tolerance and that hyperalgesia induced by the administration of GPR103 endogenous ligand, 26RFa, was absent in these mice. We then identified and characterized a selective antagonist of this receptor, RF1156. We were able to show that RF1156 blocked the hyperalgesia induced by 26RFa or by opiates as well as analgesic tolerance induced by chronic morphine administration. Overall, these results indicate that GPR103a and its ligand participate in a pro-nociceptive anti-opioid system that is in part responsible for the development of pain hypersensitivity and analgesic tolerance induced by opiates. They further suggest that pharmacological blockade of GPR103 could represent an interesting strategy to decrease side effects associated with chronic opiate treatments without compromising their analgesic potency.

The plastic spinal cord: structural and functional remodelling as a basis for pathological pain

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The spinal dorsal horn is an important seat of pathophysiological processes that initiate and drive chronic pain. In particular, synapses between nociceptive afferents and second order spinal neurons in the superficial spinal laminae show are highly plastic and the tuning of their input-output performance plays a major role in triggering and maintaining plasticity at downstream centers in nociceptive pathways. Over the past years, we have worked on understanding processes that amplify the output of spinal neurons in response to nociceptive activity and identify molecular mediators thereof.

This talk will discuss mediators that act at presynaptic or post-synaptic avenues at spinal synapses to regulate synaptic long-term potentiation and induction of inflammatory hypersensitivity. Moreover, I will present data that indicate that not only do these synapses undergo functional plasticity in the form of long-term potentiation, but also show marked structural remodelling in an activity-dependent manner. An increase in the density of synaptic spines in the superficial spinal cord has been reported in mouse models of pathological pain. We hypothesized that synaptic proteins recruited by glutamatergic receptors that are capable of dynamically modulating the actin cytoskeleton play a role in coordinating structural and functional plasticity at spinal synapses. Our recent work has identified Kalirin-7, a multifunctional guanine-nucleotide-exchange factor (GEF) that interacts physically with NMDA receptor, as a key molecule orchestrating functional and structural plasticity during the course of inflammatory pain. Moreover, our results indicate that structural plasticity of spinal synapses in inflammatory pain states is brought about by a disruption of balance between excitatory and inhibitory neurotransmitters and I will present new data on cannabinoidergic modulation.

Communication

Ivan Weinsanto

Heavy drugs as a tool for metabolic studies in chronic treatment paradigms: investigating morphine metabolism in tolerant mice

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Resume

Monitoring drug metabolism in patients undergoing chronic treatment remains a major challenge due to the residual presence of precursors and metabolites from previous administrations. We have developed a protocol using heavy drugs carrying deuterium isotopes associated with a liquid chromatography-tandem mass spectrometry (LC-MS/MS) approach to study potential alterations of drug metabolism following chronic administration. To validate our methodology, we investigated whether morphine analgesic tolerance is linked to alterations in its metabolism. UDP-glucuronosyltransferase enzymes (UGTs) of the liver and the brain convert morphine into its main pronociceptive metabolite morphine-3-glucuronide (M3G), which could be involved in antinociceptive tolerance.
We treated C57BL6/J mice with morphine (10 mg/kg i.p.) or saline for 8 days, and injected a mixture of morphine (85%) and deuterated-morphine (15%, d3-morphine) to both groups on the last day of treatment. Then, we quantified morphine, M3G, d3-morphine and deuterated-M3G (d3-M3G) in the liver, brain, spinal cord, plasma and urine of morphine-tolerant and control animals using LC-MS/MS. No significant alteration in morphine metabolism was found in tolerant animals. In all samples, comparison of the metabolic ratios of morphine (M3G/morphine) and d3-morphine (d3-M3G/d3-morphine) showed a significant reduction in the glucuronidation of d3-morphine compared to that of natural morphine.
In this communication, we validate a novel approach for the study of drug metabolism in chronic treatment paradigms and discuss potential benefits and pitfalls arising from the use of deuterated drugs. Additionally, we use our methodology to show that analgesic tolerance to morphine in the mouse is not linked to an alteration in morphine metabolism and does not involve M3G overproduction. Finally, we report for the first time in the mouse central and peripheral morphine and M3G levels following acute and chronic morphine administration.

Communication

Dominique Massotte

Titre : Antiallodynic treatment with antidepressants partially reverses neuropathy-induced changes in peripheral delta opioid receptor distribution.

Ceredig Rhian Alice, Pierre Florian, Yalcin Ipek, Barrot Michel and Massotte Dominique

Resume

Peripheral delta opioid (DOP) receptors represent novel attractive targets for chronic pain management and are essential for anti-allodynic effect of antidepressants. We therefore addressed the impact of neuropathic pain on DOP receptor distribution in dorsal root ganglia using a knock in mouse expressing a fluorescent version of the DOP receptor (DOPeGFP). In our model, we observed neuronal loss 8 weeks after cuff surgery that affected small size neurons. Also, remaining small peptidergic and non-peptidergic neuronal populations expressing DOPeGFP were decreased. Oral chronic treatment with the antidepressant duloxetine reversed mechanical allodynia in wild type animals but not in conditional knock out mice that do not express DOP receptors in Nav 1.8 positive neurons establishing that DOP receptor expression in this population is required for treatment effectiveness. More precisely, we observed that treatment with duloxetine partially reversed neuropathy-induced changes. Also, we found that chronic neuropathy increased DOPeGFP translocation to the plasma membrane, which was reversed by the anti-allodynic treatment. These data confirm the critical involvement of DOP receptors in the relief of mechanical allodynia in the context of neuropathic pain.

Communication

Michel BARROT

Titre : In a murine model of neuropathic pain, independent peripheral and central mechanisms mediate allodynia relief by antidepressants

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Resume

In the early 1960's, it has been fortuitously observed that a tricylic antidepressant used in the psychiatry field might also relieve neuropathic pain, which is a pain consecutive to a lesion or pathology of the somatosensory system. Since confirmed of this action by controlled studies, some antidepressants became recognized as first line treatments against neuropathic pain. However, the detailed mechanism by which these drugs relieve painful symptoms remains elusive, or, more accurately, the scientific literature reports apparently contradictory mechanisms. Here, we postulated that many of these discrepancies might just be apparent, and could depend on the procedure that is used to deliver and test the action of the antidepressants in models of neuropathic pain. To test this hypotheses, we studied the antiallodynic action of the selective serotonin and noradrenaline reuptake inhibitors duloxetine and of the trcicylic antidepressant amitriptyline according to two different paradigm, and, in a translational effort, compared plasma concentration of duloxetine to the ones observed in patients relieved of their neuropathic pain. Data evidence 2 independent mechanisms, one peripheral and one central, which display different therapeutic onsets, depend on different adrenoceptors and on different opioid receptors.

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Composition :

Enseignants-Chercheurs/Hospitaliers	22 (9.2 EQTP)
Chercheur Inserm	1
ITA	11 (11 EQTP)
Doctorants/Post-Doctorants	11

Thématiques :

Mécanisme d'action et modalité de prescription des analgésiques
Nouvelles stratégies dans le traitement de la douleur chronique

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	
Pharmacologie	Modèles animaux : rats, souris
Douleurs viscérales	Analyses comportementales
Douleurs neuropathiques	Biologie moléculaire
Moelle épinière	Biologie cellulaire
Contrôles descendants	Immunohistochimie
Systèmes monoaminergiques	Modèles cliniques d'hypersensibilité
Acides aminés	Tests de quantification sensorielle
Canaux ioniques	Pharmacologie clinique
Physiopathologie	Techniques analytiques
Antalgiques	Microdialyse
Antidépresseurs	Pharmacogénétique

Principales publications :

1. Pichon X,Wattiez AS,Becamel C,Ehrlich I,Bockaert J,Eschalier A,Marin P,Courteix C. Disrupting 5-HT(2A) receptor/PDZ protein interactions reduces hyperalgesia and enhances SSRI efficacy in neuropathic pain. **Mol Ther.** 18(8):1462-70, 2010.
2. Guastella V,Mick G,Soriano C,Vallet L,Escande G,Dubray C,Eschalier A. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. **Pain** 152(1):74-81, 2011.
3. Marger F,Gelot A,Alloui A,Matricon J,Ferrer JF,Barrere C,Pizzoccaro A,Muller E,Nargeot J,Snutch TP,Eschalier A,Bourinet E,Ardid D. T-type calcium channels contribute to colonic hypersensitivity in a rat model of irritable bowel syndrome. **Proc Natl Acad Sci USA** 108(27):11268-73, 2011.
4. Devilliers M. Busserolles J. Lolignier S. Deval E. Pereira V. Alloui A. Christin M. Mazet B. Delmas P. Noel J. Lazdunski M. Eschalier A. Activation of TREK-1 by morphine results in analgesia without adverse side effects. **Nat Commun** 4:2941, 2013.
5. Lolignier S, Gaudosio C, Amsalem M, Bonnet C, Ferrier J, Rodas-Despoix L, Aissouni Y, Chapuy E, Padilla F, Eschalier A, Delmas P, Busserolles J. The Nav1.9 channel is a key element of cold pain signaling. **Cell reports** 11:1-12, 2015.

Responsable : **Michel BARROT (DR1**)

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Composition :

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Chercheurs	3 (2 DR, 1 CR, CNRS)
ITA	2 (2 CNRS)
Master/Doctorants/ Post-Doctorants	10

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Modèles animaux (rats, souris, transgéniques)
Nociception	Tests comportementaux (nociception)
Neuropathies	Tests comportementaux (anxiété/dépression)
Antidépresseurs	Pharmacologie du comportement
Bêta-mimétiques	Neuroanatomie (traçage)
Troubles de l'humeur	Immunohistochimie
Circuits supraspinaux et neuroanatomie	Electrophysiologie in vivo
Amygdale étendue	qPCR
Système mésolimbique	
Récepteurs opioïdes	

Principales publications :

1. Yalcin I, Choucair-Jaafar N, Benbouzid M, Tessier LH, Muller A, Hein L, Freund-Mercier MJ, Barrot M. Beta2-adrenoceptors are critical for antidepressant treatment of neuropathic pain. **Ann Neurol** 65:218-225, 2009.
2. Kaufling J, Veinante P, Pawlowski SA, Freund-Mercier MJ, Barrot M. γ-aminobutyric acid cells with cocaine-induced ΔFosB in the ventral tegmental area innervate mesolimbic neurons. **Biol Psychiatry** 67:88-92, 2010.
3. Jalabert M*, Bourdy R*, Courtin J, Veinante P, Manzoni OJ, Barrot M**, Georges F**. Neuronal circuits underlying morphine action on dopamine neurons. **Proc Natl Acad Sci USA** 108:16446-16450, 2011.
4. Yalcin I, Bohren Y, Waltisperger E, Sage-Ciocca D, Yin JC, Freund-Mercier MJ, Barrot M. A time-dependent history of mood disorders in a murine model of neuropathic pain. **Biol Psychiatry** 70:946-953, 2011.
5. Bourdy R, Barrot M. A new control for dopaminergic systems: pulling the VTA by the tail. **Trends Neurosci** 35:681-690, 2012.
6. Yalcin I, Barthas F, Barrot M. Emotional consequences of neuropathic pain: insight from preclinical studies. **Neurosci Biobehav Rev** 47:154-164, 2014.
7. Barthas F, Sellmeijer J, Hugel S, Waltisperger E, Barrot M, Yalcin I. The anterior cingulate cortex is a critical hub for pain-induced depression. **Biol Psychiatry** 77:236-245, 2015.
8. Erbs E, Faget L, Scherrer G, Matifas A, Filliol D, Vonesch JL, Koch M, Kessler P, Hentsch D, Birling MC, Koutsourakis M, Vasseur L, Veinante P, Kieffer BL, Massotte D. A mu-delta opioid receptor brain atlas reveals neuronal co-occurrence in subcortical networks. **Brain Struct Funct** 220:677-702, 2015.
9. Fillinger C, Yalcin I, Barrot M, Veinante P. Afferents to anterior cingulate areas 24a and 24b and midcingulate areas 24a` and 24b` in the mouse. **Brain Struct Funct** in press, 2017.
10. Barthas F*, Humo M*, Gilsbach R, Waltisperger E, Karatas M, Leman S, Hein L, Belzung C, Boutillier AL, Barrot M, Yalcin I. Cingulate overexpression of mitogen-activated protein kinase phosphatase-1 as key factor for depression. **Biol Psychiatry** in press, 2017.

Responsables : **Dan BENHAMOU (PU-PH)**

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Composition :

Enseignants-Chercheurs/Hospitaliers	4
Technicienne à plein temps	1
Master/Doctorants	1

Organigramme et Thématiques:

1. Pharmacologie des antalgiques et des anesthésiques locaux (Dan BENHAMOU)
2. Douleur inflammatoire (Dan BENHAMOU)
3. Hyperalgésie liée aux opiacés, opiorphine (Philippe Sitbon)
4. Douleur viscérale (Toni Kfoury)

Principaux mots clés

Thématiques	***Méthodologiques***
Douleur inflammatoire	Comportement
Inflammation et immunité	Biologie moléculaire
Douleur viscérale	Stimulations PBMCs, monocytes, PN, sang total
Hyperalgésie, opiorphine	Immunohistologie: c-Fos, TNFα

Principales publications :

1. Van Elstraete AC, Sitbon P, Benhamou D, Mazoit JX. The median effective dose of ketamine and gabapentin in opioid-induced hyperalgesia in rats: an isobolographic analysis of their interaction. **Anesth Analg** 113(3):634-40, 2011.
2. Kariya N, Cosson C, Mazoit JX. Comparative effect of lidocaine, bupivacaine and RAC 109 on myocardial conduction and contractility in the rabbit. **Eur J Pharmacol**. 15;691(1-3):110-7, 1012.
3. Van Elstraete AC, Sitbon P. Median effective dose (ED50) of paracetamol and nefopam for postoperative pain: isobolographic analysis of their antinociceptive interaction. **Minerva Anestesiol** 79(3):232-9, 2013.
4. Dureau P, Charbit B, Nicolas N, Benhamou D, Mazoit JX. Effect of Intralipid® on the dose of ropivacaine or levobupivacaine tolerated by volunteers: a clinical and pharmacokinetic study. **Anesthesiology** 125(3):474-83, 2016.
5. Sitbon P, Van Elstraete A, Hamdi L, Juarez-Perez V, Mazoit JX, Benhamou D, Rougeot C. STR-324, a stable analog of opiorphin, causes analgesia in postoperative pain by activating endogenous opioid receptor-dependent pathways. **Anesthesiology** 125(5):1017-1029, 2016.

Responsable : **Bruno BONAZ (PU/PH)**

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Attachée Scientifique (CHU)	1
ITA	0,5
Doctorants	3 (dont 1 AHU)

Organigramme :

1. Adaptation comportementale à la douleur et à l'inflammation (F. Canini, S. Pellissier)
2. Activité cérébrale associée à la douleur viscérale digestive chez l'Homme (S. Pellissier, A. Rubio, B. Bonaz)
3. Neurostimulation vagale et inflammation/douleur (D. Clarençon, V. Sinniger, C. Picq, B. Bonaz)
4. Stress, inflammation, CRF digestif et perméabilité intestinale (M. Jacquier-Sarlin, M. Lainé, B. Ducarouge, M. Pelissier)
5. Etude de la balance sympatho-vagale (S. Pellissier, N. Mathieu, B. Bonaz)

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Immunocytochimie, Neuroanatomie (traçage)
Nociception	Hybridation in situ, RT-PCR quantitative
Stress, Inflammation	Analyse comportementale
CRF (corticotropin-releasing factor)	Distension du tube digestif, modèles de stress
Moelle épinière, Hypothalamus, Locus coeruleus, IRMf	
Nerf vague, NTS	Télémétrie (paramètres végétatifs)
Modélisation neuronale	Algésimétrie clinique, Simulation numérique
Fibromyalgie, Neuro-Gastroentérologie	Neurostimulation vagale
Troubles fonctionnels digestifs	Balance sympatho-vagale (HRV : Heart rate
Maladie inflammatoires chroniques de l'intestin	variability)
Perméabilité intestinale	Hypnose
	Etude de la perméabilité intestinale

Principales publications :

1. Pellissier S, Dantzer C, Canini F, Mathieu N, Bonaz B. Toward a definition of a global psycho-physiological criterion of vulnerability to relapse in inflammatory bowel diseases. **Am J Gastroenterol** 105:1446-7, 2010.
2. Meregnani J, Clarençon D, Vivier M, Peinnequin A, Mouret C, Sinniger V, Picq C, Job A, Canini F, Jacquier-Sarlin M, Bonaz B. Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease. **Auton Neurosci** 160:82-9, 2011.
3. Chartier NT, Lainé MG, Ducarouge B, Oddou C, Bonaz B, Albiges-Rizo C, Jacquier-Sarlin MR. Enterocytic differentiation is modulated by lipid rafts-dependent assembly of adherens junctions. **Exp Cell Res** 317:1422-36, 2011.
4. Rubio A, Van Oudenhove L, Pellissier S, Ly HG, Dupont P, de Micheaux HL, Tack J, Dantzer C, Delon-Martin C, Bonaz B. Uncertainty in anticipation of uncomfortable rectal distension is modulated by the autonomic nervous system--a fMRI study in healthy volunteers. **Neuroimage** 107:10-22, 2015.
5. Bonaz B, Sinniger V, Hoffmann D, Clarençon D, Mathieu N, Dantzer C, Vercueil L, Picq C, Trocmé C, Faure P, Cracowski JL, Pellissier S. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. **Neurogastroenterol Motil**. (In press) 2016.

Responsable : **Didier BOUHASSIRA (DR1 Inserm)**

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Principaux mots clés :

Thématiques	***Méthodologies***
Douleur	Psychophysique
Douleurs chroniques	Evaluation Sensorielle Quantifiée
Douleurs neuropathiques	Psychométrie
Douleurs postopératoires	Electrophysiologie clinique
Douleurs viscerales	Pharmacologie
Douleurs cancéreuses	Neuroimagerie fonctionnelle
Fibromyalgie	Neuropsychologie
Neuropathies	Psychologie
Accidents Vasculaires	Stimulations magnétiques transcraniennes
Lésions médullaires	Epidémiologie
Analgésie	
Evaluation clinique	
Evaluation thérapeutique	
Outils diagnostiques	

Principales publications :

1. Hatem SM, Attal N, Ducreux D, Gautron M, Parker F, Plaghki L, Bouhassira D. Clinical, functional and structural determinants of central pain in syringomyelia. **Brain** 133: 3409-22, 2010.
2. Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. **Pain** 152: 1478-85, 2011.
3. Attal N, Masselin-Dubois A, Martinez V, Jayr C, Albi A, Fermanian J, Bouhassira D, Baudic S. Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. **Brain** 137(Pt 3):904-17, 2014.
4. Bouhassira D, Wilhelm S, Schacht A, Perrot S, Kosek E, Cruccu G, Freynhagen R, Tesfaye S, Lledó A, Choy E, Marchettini P, Micó JA, Spaeth M, Skljarevski V, Tölle T. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. **Pain**. Oct;155(10):2171-9, 2014.
5. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Glahardoni R, Raicher I, Üceyler N, Sommer C, Bouhassira D. Efficacy and safety of repeated injections of botulinum toxin a in peripheral neuropathic pain and predictors of treatment response: a randomised double blind placebo controlled study. **Lancet Neurol** 2016.

Responsable : **Emmanuel BOURINET (DR1 CNRS)**

Intitulé de l'équipe : *Canaux calciques et physiopathologie de la nociception*

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Composition :

Chercheurs	3 (1 DR, 1 CR, 1 MCU)
ITA	1
Master/Doctorants/Post-Doctorants	3

Principaux mots clés :

Thématiques	***Méthodologiques***
Canaux calciques et pathologies de la douleur	Système d'expression fonctionnelle, cultures primaires neurones, tranche de moelle épinière, comportement de la douleur chez la souris
Etudes structure-fonction des canaux calciques	Enregistrements électrophysiologiques, patch clamp, Optogénétique, Imagerie calcique
Pharmacologie des canaux ioniques	Criblage pharmacologique de toxine Immunofluorescence, microscopie confocale, Modèles murins génétiquement modifiés

Principales publications :

1. Francois A, Kerckhove N, Meleine M, Alloui A, Barrere C, Gelot A, Uebele VN, Renger JJ, Eschalier A, Ardid D, Bourinet E State-dependent properties of a new T-type calcium channel blocker enhance Ca(V)3.2 selectivity and support analgesic effects. **Pain** 154: 283-93, 2013.
2. Garcia-Caballero A, Gadotti VM, Stemkowski P, Weiss N, Souza IA, Hodgkinson V, Bladen C, Chen L, Hamid J, Pizzoccaro A, Deage M, Francois A, Bourinet E, Zamponi GW The Deubiquitinating Enzyme USP5 Modulates Neuropathic and Inflammatory Pain by Enhancing Cav3.2 Channel Activity. **Neuron** 83: 1144-58, 2014.
3. Francois A, Schuetter N, Laffray S, Sanguesa J, Pizzoccaro A, Dubel S, Mantilleri A, Nargeot J, Noel J, Wood JN, Moqrich A, Pongs O, Bourinet E The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function. **Cell Rep** 10: 370-382, 2015.
4. Reynders A, Mantilleri A, Malapert P, Rialle S, Nidelet S, Laffray S, Beurrier C, Bourinet E, Moqrich A Transcriptional Profiling of Cutaneous MRGPRD Free Nerve Endings and C-LTMRs. **Cell Rep** 10: 1007-19, 2015.
5. Voisin T, Bourinet E, Lory P Genetic alteration of the metal/redox modulation of Cav3.2 T-type calcium channel reveals its role on neuronal excitability. **J Physiol** 594(13): 3561-74, 2016.

Responsable : **Radhouane DALLEL (PU/PH)**

Intitulé de l'équipe : Neuro-Dol, Inserm/UCA, U1107

Douleur Trigéminale et Migraine

Faculté de Chirurgie Dentaire

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Composition :

Enseignants-Chercheurs/Hospitaliers	17
ITA/Ingénieurs	5
Master/Doctorants/Post-Doctorants	7

Organigramme :

1. Facteurs de risque de chronicisation des douleurs céphaliques
2. Plasticité moléculaires et cellulaires segmentaires des douleurs trigéminales
3. Cortex et migraine

Principaux mots clés :

Thématiques	*Méthodologiques*
Douleur , Nociception, Inflammation	Electrophysiologie extracellulaire multi-unitaires *in vivo*
Migraine et céphalées, Neuropathies	Electrophysiologie intracellulaire *in vitro*
Trijumeau, Hypothalamus, Thalamus, Cortex	Neuroanatomie, Immunocytochimie
Allodynie, hyperalgésie	Biologie moléculaire, cellulaire
Chronicité, émotion, stress	paramètres végétatifs (télémétrie, …)
Momoamines, GABA/glycine, PKC, Glie	Analyse comportementale (Vidéographie,….)
	Epidémiologie, psychophysique, imagerie cérébrale, EEG

Principales publications :

1. Normandin A, Luccarini P, Molat JL, Gendron L, Dallel R. Spinal mu and delta opioids inhibit both thermal and mechanical pain in rats. **J Neurosci** 33:11703–11714, 2013.
2. Moisset X, Ouchchane L, Guy N, Bayle DJ, Dallel R, Clavelou P. Migraine headaches and pain with neuropathic characteristics: comorbid conditions in patients with multiple sclerosis. **Pain** 154:2691-9, 2013.
3. Boyer N, Dallel R, Artola A, Monconduit L. General trigemino-spinal central sensitization and impaired descending pain inhibitory controls contribute to migraine progression. **Pain** 155:1196-205, 2014.
4. Alba-Delgado C, El Khoueiry C, Peirs C, Dallel R, Artola A, Antri M. Subpopulations of PKCγ interneurons within the medullary dorsal horn revealed by electrophysiological and morphological approach. **Pain** 156:1714-28, 2015.
5. Peirs C, Bourgois N, Artola A, Dallel R. PKCγ Interneurons Mediates C-Fiber-Induced orofacial secondary static mechanical allodynia, but not C-fiber induced nociceptive behavior. **Anesthesiology** 24:1136-52, 2016.

Responsable : **Patrick DELMAS (DR1 CNRS)**

Intitulé de l'équipe : Equipe Canaux Ioniques et Transduction Sensorielle

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Composition :

Chercheurs	6 (1 CR2, 2 MCU, 2 DR1 CNRS)
ITA	1 IR, 1IE, 1tech
Doctorants/Post-Doctorants	4

Thèmes abordés:

1. Mécanismes moléculaires et cellulaires de la nociception et de la mécanotransduction
2. Douleurs neuropathiques, inflammatoires, somatiques et viscérales
3. Migraine
4. Mécanismes de l'excitabilité neuronale et de la sensibilité cutanée
5. Système nerveux entérique et douleur intestinale

Principaux mots clés :

Thématiques	*Méthodologiques*
Douleur	Electrophysiologie, *in vitro*, *ex vivo*
Nociception	Patch clamp : in situ, culture primaire
Inflammation	Clonage, expression hétérologue
Sensibilisation périphérique	Transgéniques animaux, siARN,
Mécanismes de transduction	Immunocyto/histochimie
Mécanotransduction	Comportement
Ganglions spinaux (DRG)	Protéomique
Trijumeau	Neuroanatomie
Fibres C et Aδ	Génomique
Keratinocytes, Odontoblastes, Cellules de Merkel, Canaux sodium & potassium, Canaux Piezo	, Canaux TRPs, mécanotransducteurs , Canaux calcium

Principales publications:

1. Delmas P, Hao J, Rodat-Despoix L. Molecular mechanisms of mechanotransduction in mammalian sensory neurons. **Nature Reviews**, 12(3):139-53, 2011.
2. Coste B. The cellular feeling of pressure. **Science** 338:59, 2012.
3. Delmas P, Coste B. Mechano-gated ion channels in sensory systems. **Cell** 155(2):278-84, 2013.
4. Hao J, Padilla F, Dandonneau M, Lavebratt C, Lesage F, Noël J, Delmas P. Kv1.1 channels act as mechanical brake in the senses of touch and pain. **Neuron**, 77(5):899-914, 2013.
5. Coste B, Murthy SE, Mathur J, Schmidt M, Mechioukhi Y, Delmas P, Patapoutian A. Piezo1 ion channel pore properties are dictated by C-terminal region. **Nature Commun**, 6:7223, 2015.
6. Lolignier S, Bonnet C, Gaudioso C, Noël J, Ruel J, Amsalem M, Ferrier J, Rodat-Despoix L, Bouvier V, Aissouni Y, Prival L, Chapuy E, Padilla F, Eschalier A, Delmas P, Busserolles J. The Nav1.9 channel is a key determinant of cold pain sensation and cold allodynia. **Cell Rep**. 11(7):1067-78, 2015.

Responsable : **Claude DUBRAY (PU/PH)**

Intitulé de l'équipe : Centre de Pharmacologie Clinique - Inserm CIC 1405 -

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Composition :

Enseignants-Chercheurs/Hospitaliers	3 (PH, PU-PH)
Infirmier(e)s de Recherche	3
ARC/TEC	3
Ingénieur biomédical	1
Secrétaire	1,5
Master/Doctorants/Post-Doctorants	4

Organigramme :

1. Centre de Pharmacologie Clinique dédié à l'étude clinique des médicaments. Ce Centre est équipé et labellisé par l'ARS pour étudier l'action de nouvelles molécules chez l'homme, dès les premières étapes de leur développement clinique (études de phase I).
2. Plateforme de recherche clinique plurithématique, ouverte à l'ensemble des équipes du CHU de Clermont-Ferrand, de l'Université d'Auvergne et des EPST (Inserm, INRA, CNRS) implantés localement.
3. Structure de recherche clinique sur la douleur et les médicaments antalgiques localisée à proximité immédiate du Centre d'Evaluation et de Traitement de la Douleur (CETD) du CHU. Programmes de recherche translationnelle en partenariat avec les équipes Inserm UMR 1107 Neuro-Dol et collaboration régulière avec les services cliniques particulièrement actifs dans ce domaine (anesthésie-réanimation, neurologie, neurochirurgie, odontologie, gastro-entérologie…). Les thématiques de recherches prioritaires sont axées (1) sur l'identification des caractéristiques sémiologiques, étiologiques, génomiques et physiopathologiques pouvant orienter les stratégies thérapeutiques de soulagement des douleurs neuropathiques (2) sur la compréhension du mécanisme d'action pharmacologique des médicaments antalgiques.

Principaux mots-clés :

Douleur , Antalgiques , Pharmacologie clinique, Etudes de Phase I , Etudes de Phase II , Neurosciences cliniques , Neuropathies périphériques, Douleurs chroniques , Modélisation PK/PD , Antidépresseurs, Antagonistes NMDA, Douleurs post-chirurgie, Génomique , Psychophysique, Electrophysiologie des voies de la nociception, Essais cliniquesModèles cliniques d'hyperalgésie induite, Essais cliniquesModèles cliniques d'hyperalgésie induite

Publications :

1. Richez B, Ouchchane L, Guttmann A, Mirault F, Bonnin M, Noudem Y, Cognet V, Dalmas AF, Brisebrat L, Andant N, Soule-Sonneville S, Dubray C, Dualé C, Schoeffler P. The Role of Psychological Factors in Persistent Pain After Cesarean Delivery. **J Pain** 2015 Nov;16(11):1136-46, 2015.
2. Vaillant-Roussel H, Laporte C, Pereira B, De Rosa M, Eschalier B, Vorilhon C, Eschalier R, Clément G, Pouchain D, Chenot JF, Dubray C, Vorilhon P. Impact of patient education on chronic heart failure in primary care (ETIC): a cluster randomised trial. **BMC Fam Pract.** 19;17:80. 2016.
3. Morel V, Joly D, Villatte C, Dubray C, Durando X, Daulhac L, Coudert C, Roux D, Pereira B, Pickering G Memantine before Mastectomy Prevents Post-Surgery Pain: A Randomized, Blinded Clinical Trial in Surgical Patients. **PLoS One** 6;11(4), 2016.
4. Kerckhove N, Mallet C, Pereira B, Chenaf C, Duale C, Dubray C, Eschalier A. Assessment of the effectiveness and safety of Ethosuximide in the Treatment of non-Diabetic Peripheral Neuropathic Pain: EDONOT-protocol of a randomised, parallel, controlled, double-blinded and multicentre clinical trial. **BMJ Open** 16;6(12):e013530, 2016.
5. Pickering G, Macian N, Dubray C, Pereira B. Paracetamol sharpens reflection and spatial memory: a double-blind randomized controlled study in healthy volunteers**Drug Des Devel Ther**. 5;10:3969-3976, 2016.
6. Azpiroz F, Dubray C, Bernalier-Donadille A, Cardot JM, Accarino A, Serra J, Wagner A, Respondek F, Dapoigny M. Effects of scFOS on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: a randomized, double blind, placebo controlled study. **Neurogastroenterol Moti**l. 29(2), 2017.

Responsable : **André DUFOUR (PU)**

Intitulé de l'équipe : Laboratoire de Neurosciences Cognitives et Adaptatives

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Composition :

Enseignants-Chercheurs	*3* (1 PU, 2 MCU dont 1 HDR)
ITA	1 (IR HDR UNISTRA)
Master/Doctorants/ Post-Doctorants	4

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur aiguë	Electroencéphalographie :
Douleur chronique	Potentiels Evoqués
Vieillissement	Imagerie cérébrale électrique
Déficit cognitif	Exploration sensorielle :
Réseaux frontaux	LASER
Modulation de la douleur	Electrique
	Contact Heat Evoqued Potentials
	Cold/Hot Pressure Test

Principales publications :

1. Kemp J, Després O, Dufour A. Unreliability of the visual analogue scale in experimental pain assessment: a sensitivity and evoked potentials study. **Pain Physician** 15:693-699, 2012.
2. Kemp J, Després O, Dufour A. Age-related decrease electrical somatosensivity is unrelated to skin conductance: an evoked potentials study. **Clin Neurophysiol** 125:602-607, 2014.
3. Kemp J, Després, O, Dufour, A. Differences in age-related effects on myelinated and unmyelinated peripheral fibers: a sensitivity and evoked potentials study. **Eur J Pain** 18:482-488, 2014.
4. Kemp J, Després O, Dufour A. Impaired thermal adaptation in the elderly: an evoked potential study. **Psychophysiology** 51:539-545, 2014.
5. Zhou S, Després O, Pebayle, T, Dufour, A. Age-related decline in cognitive pain modulation induced by distraction: evidence from event-related potentials. **J Pain** 19:669-676, 2015.
6. Zhou S, Després O, Pebayle T, Dufour A. Involvement of prefrontal functions in pain tolerance in aging: Evidence from neuropsychological assessments and EEG source reconstruction. **Neurobiol Aging** (in press) 2016.
7. Després O., Lithfous S., Tromp D., Pebayle T., Dufour A. Gamma oscillatory activity is impaired in episodic memory encoding with age. Neurobiology of aging [Epub ahead of print], 2017.
8. Duval C., Goumon Y., Kemmel V., Kommeier J., Dufour A., Andlauer O., Vidailhet P., Poisbeau P., Salvat E., Muller A., Mensah-Nyagan A.G., Schmidt-Mutter C., Giersch A.Neurophysiological responses to unpleasant stimuli (acute electrical stimulations and emotional pictures) are increased in patients with schizophrenia. Scientific Reports, (in press).

Responsable : **Luis GARCIA-LARREA (DR1 Inserm)**

Intitulé de l'équipe : Intégration centrale de la douleur - ***NeuroPain***

Inserm U1028 – Centre de Neurosciences de Lyon

Hôpital Neurologique — CHU de St Etienne (Hôpital Nord)

Locaux de recherche du rez-de-Jardin — Service de Neurologie

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E-mail :larrea@univ-lyon1.fr

Composition :

Enseignants-Chercheurs/Hospitaliers	7
Chercheurs	2 (1 DR, 1 CR Inserm)
Ingénieurs	2
Master2 / Doctorants / Post-Doctorants	1+5+2

Thèmes :

1. Imagerie de la douleur neuropathique (R. Peyron, I Faillenot, L Garcia-Larrea, B. Laurent)
2. Douleur / émotion / mémoire : M. Frot, A Chapon, L Garcia-Larrea)
3. Stimulation corticale antalgique (E Simon, P. Mertens, R. Peyron, N. André-Obadia, L. Garcia-Larrea,)
4. Electrophysiologie des douleurs neuropathiques (Garcia-Larrea, Perchet, Andre-Obadia, Creac'h, Convers)
5. Electrophysiologie intracrânienne nociceptive (Frot, Bastuji, Garcia-Larrea, Magnin, Mauguière)
6. Sommeil et douleur (H. Bastuji, M Magnin, C Perchet, S Mazza, L Garcia-Larrea)
7. Modèles animaux de neurostimulation (J Maarraawi, S Kobaiter, M Magnin)

Principaux mots clés :

Thématiques	**Méthodes maîtrisées**
Douleur	Neuroimagerie fonctionnelle (TEP, IRM-f)
Douleurs chroniques	Potentiels évoqués somesthésiques (PES)
Douleurs neuropathiques	Potentiels évoqués LASER (PEL)
Allodynie	Réflexes nociceptifs (RIIAllodynie
Neurostimulation antalgique	Electrophysiologie intracrânienne (EEG, PEL, PES)
Accidents Vasculaires	Evaluation Quantifiée de la douleur
Lésions médullaires	Psychophysique (uniquement certaines techniques)
Analgésie	Stimulation corticale magnétique (TMS)
Evaluation clinique, thérapeutique - Outils diagnostiques	

Principales publications :

1. Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: A review. **Pain** 154; Suppl 1:S29-43, 2013.
2. Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans. How symptoms help disclose mechanisms. **Nature Neurol Reviews** 9(10):572-582, 2013.
3. Houzé B, Bradley C, Magnin M, Garcia-Larrea L. Changes in the cortical representation of the hand and in pain perception induced by repetitive magnetic stimulation of the motor cortex. **Cereb Cortex** 23(11):2667-76, 2013.
4. André-Obadia A, Mertens P, Lelekov-Boissard A, Afif A, Magnin M, Garcia-Larrea L. Is life better after motor cortex stimulation for pain control? Results at long-term and their prediction by preoperative rTMS. **Pain Physician** 17:53-62, 2014.
5. Montavont A, Mauguière F, Mazzola L, Garcia-Larrea L, Catenoix H, Ryvlin Ph, Isnard J. On The origin of Painful Somatosensory Seizures. **Neurology** 84:594-601, 2015.
6. Claude L, Chouchou F, Prados G, Castro M, De Blay B, Perchet C, García-Larrea L, Mazza S, Bastuji H. Sleep spindles and human cortical nociception: a surface and intracerebral electrophysiological study. **J Physiol** 593:4995-5008, 2015.
7. Vartiainen N, Perchet C, Magnin M, Creac'h C, Convers P, Nighoghossian N, Mauguière F, Peyron R, Garcia-Larrea L. Thalamic pain: anatomical and physiological indices of prediction. **Brain** 139:708-22, 2016.
8. Bradely C, Joyce N, Garcia-Larrea L. Adaptation in human somatosensory cortex as a model of sensory memory construction: a study using high-density EEG. **Brain Structure & Function** 221:421-31, 2016.

Responsable : **Yann HERAULT (DR Inserm)/Claire GAVERIAUX-RUFF (Université)**

Intitulé de l'équipe : *Département de Médecine Translationnelle et Neurogénétique*

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Composition :		
	Enseignants-Chercheurs	1
	Chercheurs	3
	ITA	2
	Master/Doctorants/Post-Doctorants	2

Organigramme :

1. Rôle des récepteurs mu et delta dans le contrôle de la douleur : approches par knockout conditionnel
2. Rôle des récepteurs opioïdes des cellules gliales dans la tolérance et l'hyperalgie opioïde

Principaux mots clés :

Thématiques	***Méthodologiques***
Récepteurs opioïdes	Ingénierie de la souris
Douleur	Tests comportementaux
Développement médicament	
Gènes	

Principales publications :

1. Nozaki C, Vergnano AM, Filliol D, Ouagazzal AM, Le Goff A, Carvalho S, Reiss D, Gaveriaux-Ruff C, Neyton J, Paoletti P, Kieffer BL Zinc alleviates pain through high-affinity binding to the NMDA receptor NR2A subunit **Nat Neurosci** 14:1017-22, 2011.
2. Nozaki, C., B. Le Bourdonnec, D. Reiss, R.T. Windh, P.J. Little, R.E. Dolle, B.L. Kieffer, and C. Gaveriaux-Ruff. Delta-Opioid mechanisms for ADL5747 and ADL5859 effects in mice: analgesia, locomotion, and receptor internalization. **J Pharmacol Exp Ther** 342:799-807, 2012.
3. Weibel R, Reiss D, Karchewski L, Gardon O, Matifas A, Filliol D, Becker JA, Wood JN, Kieffer BL, Gaveriaux-Ruff C. Mu opioid receptors on primary afferent Nav1.8 neurons contribute to opiate-induced analgesia: insight from conditional knockout mice. **PLoS One**8(9):e74706, 2013.
1. Nozaki, C., B. Nagase H.. Nemoto T., Matifas A. Kieffer, and C. Gaveriaux-Ruff. In vivo properties of KNT-127, a novel delta opioid agonist: receptor internalization, antihyperalgesia and antidepressant effects in mice. **Br J Pharmacol** 171:5376-5386, 2014.
2. Reiss D, Ceredig RA, Secher T, Boué J, Barreau F, Dietrich G, Gavériaux-Ruff C. Mu and delta opioid receptor knockout mice show increased colonic sensitivity. **Eur J Pain.** doi: 10.1002/ejp.965., oct 172016, 2016.

Responsable : **Marc LANDRY**

Intitulé de l'équipe CNRS UMR 5297, Institut Interdisciplinaire des Neurosciences

Mécanismes centraux de sensibilisation à la douleur

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Composition :

Enseignants-Chercheurs/Hospitaliers	4 (1 PR, 3 MCU)
Chercheurs	1 (1 CR1 CNRS)
ITA	1
Master/Doctorants/ Post-Doctorants	6

Organigramme :

1. Intégration spinale des afférences sensorielles (Y. Le Feuvre)
2. Contrôles descendants et propriétés d'amplification des neurones spinaux (P. Fossat)
3. Contrôles descendants et modulation métabotropique des réseaux spinaux (M. Landry)
4. Rôles des miRNAs dans les mécanismes de douleurs chroniques (A. Favereaux)
5. Régulation génique ciblée dans la moelle épinière (C. Baudet)

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Electrophysiologie extracellulaire *in vivo*
Nociception	Imagerie
Moelle épinière	Patch-clamp in vitro
Micro RNA	Patch-clamp in vivo
Modulation	Electromyographie
Neuropathies	Immunohistochimie – hybridation in situ
Cancer	Immunoprécipitation – western blots
Récepteurs (NMDA, GABA, glycine, galanine)	Cultures cellulaires
	Transfections
	Biologie moléculaire : qRT-PCR, mutagenèse

Principales publications :

1. Fossat, P., Dobremez, E., Bouali-Benazzouz, R., Favereaux, A., Bertrand, S.S., Kilk, K., Leger, C., Cazalets, J.R., Langel, U., Landry, M., and Nagy, F. Knockdown of L calcium channel subtypes: differential effects in neuropathic pain. **J Neurosci** 30, 1073-1085, 2010.
2. Favereaux, A., Thoumine, O., Bouali-Benazzouz, R., Roques, V., Papon, M.A., Salam, S.A., Drutel, G., Leger, C., Calas, A., Nagy, F., and Landry, M. Bidirectional integrative regulation of Cav1.2 calcium channel by microRNA miR-103: role in pain. **The EMBO journal** 30, 3830-3841, 2011.

3. Laffray, S., Bouali-Benazzouz, R., Papon, M.A., Favereaux, A., Jiang, Y., Holm, T., Spriet, C., Desbarats, P., Fossat, P., Le Feuvre, Y., Decossas M, Héliot L, Langel U, Nagy F, Landry M. (2012). Impairment of GABAB receptor dimer by endogenous 14-3-3zeta in chronic pain conditions. **The EMBO journal** 31, 3239-3251, 2012.
4. Dolique, T., Favereaux, A., Roca-Lapirot, O., Roques, V., Leger, C., Landry, M., Nagy, F. . Unexpected association of the "inhibitory" neuroligin 2 with excitatory PSD95 in neuropathic pain. **Pain** 154, 2529-2546, 2013.
5. Letellier, M., Elramah, S., Mondin, M., Soula, A., Penn, A., Choquet, D., Landry, M., Thoumine, O., and Favereaux, A. MicroRNA miR-92a regulates translation and synaptic incorporation of GluA1 containing AMPA receptors during homeostatic scaling. **Nat Neurosci** 17(8):1040-1042, 2014.
6. Radwani H, Lopez-Gonzalez M, Dobremez E, Eriksdottir E, Langel Ü, Favereaux A, Landry M[1], Fossat P[2]. Differential effect of L-type calcium channel subunits in pain transmission and pain sensitization. **J. Phyiology** (London), doi: 10.1113/JP272725, 2016.
7. Roca-Lapirot O, Radwani H, Aby F, Nagy F, Landry M, Fossat P. (2017) Calcium signaling through L-type calcium channels: role in pathophysiology of spinal nociceptive transmission. **British J. Pharmacol**. (In press).

Responsable : Michel LANTERI-MINET (PH)

Intitulé de l'équipe : Département d'Evaluation et Traitement de la Douleur (DETD)

Pôle Neurosciences Cliniques

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Composition :

Enseignant-Chercheur/Hospitalier	5 PH
Assistant Spécialiste	1
Infirmier de recherche clinique	2
Assistant de recherche clinique	1
En partenariat sur cet aspect	1 PU-PH

du Service de neurochirurgie dans le cadre du **FHU InovPain**

Organigramme :

1. Observatoire de la stimulation des nerfs grands occipitaux dans le traitement des céphalées chroniques réfractaires (réseau 22 équipes tertiaires médico-chirurgicales françaises et suisses pratiquant cette approche thérapeutique / coordination assurée par le DETD du CHU de Nice)
2. Prise en charge thérapeutiques des céphalées chroniques réfractaires
3. Epidémiologie de la maladie migraineuse
4. Algie vasculaire de la face
5. Névralgie faciale
6. Typologie des douleurs neuropathiques

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Epidémiologie
Céphalées primaires	Quantification des sensibilités
Migraine	Essais thérapeutiques
Névralgie faciale	Neurochirurgie stéréotaxique
Algie vasculaire de la face	
Douleurs neuropathiques	

Principales publications :

1. Fontaine D, Lazorthes Y, Mertens P, Blond S, Géraud G, Fabre N, Navez M, Lucas C, Dubois F, Gonfrier S, Paquis P, Lantéri-Minet M. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. **J Headache Pain** 10:203-206, 2009.
2. Fontaine D, Lanteri-Minet M, Ouchchane L, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, Navez M, Lucas C, Dubois

F, Sol JF , Paquis P, Lemaire JJ. Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache **Brain** 133:1214-23, 2010.

3. Fontaine D, Sol JC, Raoul S, Fabre N, Geraud G, Magne C, Sakarovitch C, Lanteri-Minet M,. Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. **Cephalalgia** 31:1101-5, 2011.
4. Lanteri-Minet M, Valade D, Geraud G, Lucas C, Donnet A. Revised French guidelines for the diagnosis and management of migraine in adults and children. **J Headache Pain** 15:2, 2014.
5. Braunstein D, Donnet A, Pradel V, Sciortino V, Allaria-Lapierre V, Lantéri-Minet M, Micallef J. Triptans use and overuse : A pharmacoepidemiology study from the French health insurance system databse covering 4.1 million people. **Cephalalgia**. Feb 9. pii: 0333102415570497. [Epub ahead of print], 2015.

Responsable : **Eric LINGUEGLIA (DR2 Inserm)**

Intitulé de l'équipe : Canaux Ioniques et Douleur

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Equipe membre du LabEx ICST - Ion Channel Science and Therapeutics

Composition :

Enseignants-Chercheurs/Hospitaliers	1
Chercheurs	4
ITA	2
Doctorants/Post-Doctorants	3+1

Principaux mots clés :

Thématiques	***Méthodologiques***
Canaux ioniques	Electrophysiologie (patch-clamp, nerf-peau, enregistrements *in vivo* dans la moelle épinière, double microélectrode sur ovocytes).
Canaux ASIC	Imagerie calcique.
Canaux K2P	Biochimie.
Ganglion rachidien	Purification de toxines animales.
Moelle épinière	Biologie moléculaire et cellulaire.
Douleur	Neuroanatomie moléculaire et cellulaire.
Nociception	Souris knock-out, knock-down *in vivo*.
Physiopathologie	Analyse comportementale.
Pharmacologie	
Toxines	

Principales publications :

1. Pereira V, Busserolles J, Christin M, Devilliers M, Poupon L, Legha W, Alloui A, Aissouni Y, Bourinet E, Lesage F, Eschalier A, Lazdunski M, Noël J. Role of the TREK2 potassium channel in cold and warm thermosensation and in pain perception.**Pain** 155(12):2534-44, 2014.
2. Deval E, Lingueglia E. Acid-Sensing Ion Channels and nociception in the peripheral and central nervous systems. **Neuropharmacology** 94:49-57, 2015.
3. Marra S, Ferru-Clément R, Breuil V, Delaunay A, Christin M, Friend V, Sebille S, Cognard C, Ferreira T, Roux C, Euller-Ziegler L, Noel J, Lingueglia E, Deval E. Non-acidic activation of pain-related Acid-Sensing Ion Channel 3 by lipids. **EMBO J** 35(4):414-28, 2016.
4. Mourier G, Salinas M, Kessler P, Stura EA, Leblanc M, Tepshi L, Besson T, Diochot S, Baron A, Douguet D, Lingueglia E, Servent D. Mambalgin-1 pain-relieving peptide: stepwise solid-phase synthesis, crystal structure and functional domain for acid-sensing ion channel 1a inhibition. **J Biol Chem** 291(6):2616-29, 2016.
5. Diochot S, Alloui A, Rodrigues P, Dauvois M, Friend V, Aissouni Y, Eschalier A, Lingueglia E, Baron A. Analgesic effects of mambalgin peptide inhibitors of acid-sensing ion channels in inflammatory and neuropathic pain. **Pain** 157(3):552-9, 2016.

Responsable : **Aziz MOQRICH (DR2 CNRS)**

Intitulé de l'équipe : **Equipe ATIPE-CNRS**

Equipe ERC-starting grant (2011 à 2016)

Spécification de l'hétérogénéité du système nerveux somato-sensoriel

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Composition :

Enseignants-Chercheurs/Hospitaliers	1 (MCU)
Chercheurs	3 (1 CR1 et 2 DR2)
ITA	1
Doctorants/Post-Doctorants	2/1

Organigramme :

1. Développement, physiologie et neuroscience
2. Bases moléculaires de l'hétérogénéité du système sensoriel somatique

Principaux mots clés :

Thématiques	***Méthodologies***
Neurones sensoriels somatiques	Clonage de nouveaux gènes codant pour des
Ciblage génique	facteurs de transcriptions, canaux ioniques,
Ablation neuronale	molécules signalétiques
Circuits neuronaux	Bioinformatique, hybridation in situ
	et immunohistochimie, miroarray,
	inactivation génique chez la souris

Principales publications:

1. Gaillard S, Lo Re L, Mantilleri A, Hepp R, Urien L, Malapert P, Alonso S, Deage M, Kambrun C, Landry M, Low SA, Alloui A, Lambolez B, Scherrer G, Le Feuvre Y, Bourinet E, Moqrich A. GINIP, a G□i interacting protein, functions as a key modulator of $GABA_B$ receptors-mediated analgesia. **Neuron** 84:123-36, 2014.
2. Gorokhova S, Gaillard S, Malapert P, Legha L, Baronian G, Desvignes JP, Alonso S and Moqrich A. Uncoupling of molecular maturation from peripheral target innervation in nociceptors expressing a chimeric TrkA/TrkC receptor. **PLoS Genetics** 10, 2014.
3. Reynders A, Mantilleri A, Malapert P, Rial S, Laffrey A, Beurrier C, Bourinet E, Moqrich A. Transcriptional profiling of cutaneous MRGPRD free nerve endings and C-LTMRs. **Cell Rep** pii S2211-1247 (15) 47-9, 2015.
4. Francois A, Shütter A, Sanguesa J, Pizzoccaro A, Dubel S, Nargeot J, Noel J, Wood J, Moqrich A, Pong O, Bourinet E. A low threshold-activated calcium channel for low threshold mechanoreceptors. **Cell Rep, 2**015.
5. Reynders. A, Mantilleri. A, Malapert. P, Rial. S, Laffrey. A, Beurrier. C, Bourinet. E* and **Moqrich. A***. Transcriptional profiling of cutaneous MRGPRD free nerve endings and C-LTMRs. **Cell Rep,** 2015
6. Louise Urien[1,3], Stéphane Gaillard[1,3], Laure Lo Re[1], Pascale Malapert[1], Chiara Salio[2] and **Aziz Moqrich[1,*]**. Genetic ablation of GINIP-expressing neurons reveals a critical role of C-LTMRs in modulation of Chemical and Mechanical pain. ***Scientific Reports*** in press

Responsable : **Stéphane OLIET (DR CNRS)**

Intitulé de l'équipe : Inserm U 1215 Neurocentre Magendie

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Composition :

Enseignants-Chercheurs/Hospitaliers	2/5
Chercheurs	3 (1 DR CNRS, 1 CR Inserm, 1CR CNRS)
ITA	3
Master/Doctorants/ Post-Doctorants	2/3/4

Organigramme :

1. Physiologie
2. Pathologie

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Culture cellulaire
Nociception	Patch-clamp *in vitro*
Cancer	Tests comportementaux
Douleur neuropathique	Immunohistochimie
Récepteur NMDA	Electrochimie
D-sérine	Biochimie
Glie	Modèle de rats cancéreux
Astrocyte	Modèle de rats neuropathiques
	Imagerie cérébrale

Principales publications :

1. Papouin T, Ladépêche L, Ruel J, Sacchi S, Labasque L, Hirawi M, Groc L, Pollegioni L, Mothet JP and Oliet SHR. Synaptic and extrasynaptic NMDA receptors are gated by different co-agonists. **Cell** 150(3):633-646, 2012.
2. Ducourneau VR, Dolique T, Hachem-Delaunay S, Miraucourt LS, Amadio A, Blaszczyk L, Jacquot F, Ly J, Devoize L, Oliet SH, Dallel R, Mothet JP, Nagy F, Fénelon VS, Voisin DL. Cancer pain is not necessarily correlated with spinal overexpression of reactive glia markers. **Pain** 155:275-91, 2014.
3. Israel JM, Cabelguen JM, Le Masson G, Oliet SH, Ciofi P. Neonatal testosterone suppresses a neuroendocrine pulse generator required for reproduction. **Nat Commun** 5:3285, 2014.
4. Murphy-Royal C, Dupuis JP, Varela JA, Panatier A, Pinson B, Baufreton J, Groc, L, Oliet SH. Surface diffusion of astrocytic glutamate transporters shapes synaptic transmission. **Nat Neurosci.** 18:219-226, 2015.
5. Sherwood MW, Arizono M, Hisatsune C, Bannai H, Ebisui E, Sherwood JL, Panatier A, Oliet SH, Mikoshiba K. Astrocytic IP(3)Rs: Contribution to Ca(2+) signalling and hippocampal LTP. **Glia**. 65(3):502-513, 2017.

Responsable : **Jean-Philippe PIN (DRCE CNRS) & Laurent PREZEAU (DR2 CNRS)**

Responsable projets douleur : Cyril GOUDET (DR2 CNRS)

Intitulé de l'équipe : Neurorécepteurs, dynamiques et fonctions

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Composition :

Chercheurs	5 (1 DR1, 3 DR2, 1 CR1 CNRS)
ITA (IE CNRS)	3
Master/Doctorants/ Post-Doctorants	3/2/4

Principaux mots clés :

Thématiques	***Méthodologies***
Etude de l'implication des récepteurs métabotropiques du Glutamate (mGluRs) dans la douleur	Pharmacologie moléculaire, cellulaire (screening moyen débit, mesure de seconds messagers -IP3, AMPc, Ca^{2+}- par des techniques de FRET, de radioimmunomarquage ou de fluorescence, optopharmacologie) et comportementale, qPCR, IF
Couplage fonctionnel des mGluRs dans les neurones sensoriels	Enregistrements électrophysiologiques (patch clamp), culture primaire neurones sensoriels…
Recherche de nouveaux ligands orthostériques ou allostériques des mGluRs	Pharmacologie, biologie moléculaire, mesure d'expression (ELISA)
Nouveaux outils pour l'étude des récepteurs couplés aux protéines G	FRET, BRET, mesure d'expression (ELISA)
Importance fonctionnelle de la dimérisation des récepteurs couplés aux protéines G de classe C	Pharmacologie, biologie moléculaire, mesure d'expression (ELISA), FRET, BRET…
Etude de l'implication des mGluRs dans la maladie de Parkinson	Pharmacologie moléculaire, cellulaire et comportementale
Régulation du récepteur GABAB par des protéines d'interaction	Protéomique, BRET, FRET, IP, mesure d'expression (ELISA)

Principales publications :

1. Kniazeff J, Bessis A-S, Maurel D, Ansanay H, Prezeau L, Pin J-P. Closed state of both binding domains of homodimeric mGlu receptors is required for full activity. **Nat Str Mol Biol** 11:706-713, 2004.
2. Maurel D, Comps-Agrar L, Brock C, Rives M.-L, Bourrier E, Ayoub M. A, Bazin H, Tinel N, Durroux T, Prézeau L, et al. Cell surface protein-protein interaction analysis with combined time-resolved FRET and snap-tag technologies: application to GPCR oligomerization. **Nat Meth** 5:561-567, 2008.
3. Goudet C, Chapuy E, Alloui A, Acher F, Pin J-P, Alain E. Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. **Pain** 137:112-124, 2008.
4. Goudet C, Magnaghi V, Landry M, Nagy F, Gereau RW, Pin JP. Metabotropic receptors for glutamate and GABA in pain. **Brain Res Rev** 60:43-56, 2009.
5. Goudet, C., Vilar, B., Courtiol, T., Deltheil, T., Bessiron, T., Brabet, I., Oueslati, N., Rigault, D., Bertrand, H.O., McLean, H., et al. A novel selective metabotropic glutamate receptor 4 agonist reveals new possibilities for developing subtype selective ligands with therapeutic potential. **Faseb J**. 2012
6. Vilar, B., Busserolles, J., Ling, B., Laffray, S., Ulmann, L., Malhaire, F., Chapuy, E., Aissouni, Y., Etienne, M., Bourinet, E., Acher, F., Pin, J. P., Eschalier, A., and Goudet, C. Alleviating Pain Hypersensitivity through Activation of Type 4 Metabotropic Glutamate Receptor. **J Neurosci** 33, 18951-18965, 2013.
7. Pittolo S, Gomez-Santacana X, Eckelt K, Rovira X, Dalton J, Goudet C, Pin JP, Llobet A, Giraldo J, Llebaria A, Gorostiza P (2014) An allosteric modulator to control endogenous G protein-coupled receptors with light. **Nat Chem Biol** 10: 813-815, 2014.
8. Zussy C, Gomez-Santacana X, Rovira X, De Bundel D, Ferrazzo S, Bosch D, Asede D, Malhaire F, Acher F, Giraldo J, Valjent E, Ehrlich I, Ferraguti F, Pin JP, Llebaria A, Goudet C Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4. **Mol Psychiatry** in press

Responsable: **Pierrick POISBEAU (PU)**

Intitulé de l'équipe: **Molecular Determinants of Pain**

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Composition :

Enseignants-Chercheurs/Hospitaliers	4 (2 PU, 1 PU-PH, 2 MCU, 1 PH)
Chercheurs	2 (CR Inserm, CR CNRS)
ITA	2 (CNRS)
Master/Doctorants/ Post-Doctorants	1/6/1

Organigramme :

1. Ocytocine et émotions (Alexandre Charlet)
2. Système morphinergiques et contrôle de l'expression douloureuse (Yannick Goumon)
3. Rôle du VIP sur le développement et la mise en place des fonctions sensorimotrices (Vincent Lelièvre)
4. Plasticité des contrôles de la douleur (Pierrick Poisbeau)
5. Effet du champ magnétique sur les fonctions sensorielles et motrices (Hervé Cadiou)
6. Ontogenèse de la nociception chez le nouveau-né grand prématuré (Pierre Kuhn)

Principaux mots clés :

Thématiques	***Méthodologiques***
Système nociceptif spinal	Electrophysiologie extracellulaire *in vivo*
Contrôles descendants (ocytocine, opioïdes)	Electrophysiologie *in vitro* (Patch Clamp)
Inhibition nerveuse	Cultures cellulaires
Récepteurs GABA et glycine	Tranches de moelle épinière et d'amygdale
Morphine endogène	Immunocytochimie
Stéroïdes neuroactifs	Tests nociceptifs et comportementaux
Amygdale	Radiotélémétrie
Plasticité synaptique et excitabilité	Dosage ELISA, RIA
Anxiolytiques (benzodiazépines, étifoxine)	Chromatographie
Interactions neurones-glies	Régulations épigénétiques

Principales publications :

1. Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, Abatis M, Magara F, Stoop R. Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. **Science**. 1;333(6038):104-7, 2011.
2. Treiber CD, Salzer MC, Riegler J, Edelman N, Sugar C, Breuss M, Pichler P, Cadiou H, Saunders M, Lythgoe M, Shaw J, Keays DA. Clusters of iron-rich cells in the upper beak of pigeons are macrophages not magnetosensitive neurons. **Nature**. 11;484(7394):367-70, 2012.
3. Laux-Biehlmann A, Mouheiche J, Vérièpe J, Goumon Y. Endogenous morphine and its metabolites in mammals: History, synthesis, localization and perspectives. **Neuroscience** (2013) 233C:95-117, 2013.
4. Juif PE*, Breton JD*, Rajalu M, Charlet A, Goumon Y, Poisbeau P Long-Lasting Spinal Oxytocin Analgesia Is Ensured by the Stimulation of Allopregnanolone Synthesis Which Potentiates GABAA Receptor-Mediated Synaptic Inhibition. **The Journal of Neuroscience**, 33(42): 16617-16626, 2013.
5. Juif PE, Poisbeau P Neurohormonal effects of oxytocin and vasopressin receptor agonists on spinal pain processing in male rats. **Pain** 154(8):1449-56, 2013.

6. Aouad M, Zell V, Juif PE, Lacaud A, Goumon Y, Darbon P, Lelievre V, Poisbeau P Etifoxine analgesia in experimental monoarthritis: A combined action that protects spinal inhibition and limits central inflammatory processes. Pain 155(2):403-12, 2014.
7. Eliava M, Melchior M, Knobloch-Bollmann HS, Wahis J, Tang, Y., Ciobanu AC, Triana del Rio R, Roth LC, Althammer F, Chavant V, Goumon Y, Gruber T, Petit-Demoulière N, Busnelli M, Chini B, Tan L, Mitre M, Froemke RC, Chao MV, Giese G, Sprengel R, Kuner R, Poisbeau P, Seeburg PH, Stoop R*, Charlet A*, Grinevich V*. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. **Neuron**, 2016. (in the press). * equally contributed.

Responsable : **François RASSENDREN (DR2 CNRS)**

Intitulé de l'équipe : CNRS UMR5203, Inserm U1191

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Composition :

Chercheurs 4

Master/Doctorants/Post-Doctorants 2/2/0

Organigramme :

1. Implication des récepteurs P2X dans les douleurs inflammatoires et neuropathiques (L.Ulmann, F. Rassendren)
2. Récepteurs P2X et mécanismes de libération de médiateurs pro-inflammatoires (L. Ulmann,)
3. Biologie cellulaire et biochimie des récepteurs P2X (Vincent Compan)
4. Transcription et signalisation purinergique de la microglie (H. Hirbec, F. Rassendren)

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Biologie moléculaire et cellulaire
Récepteur P2X	Transgénèse
Système immunitaire	Biochimie
Ganglions de la racine dorsale	Comportement
Inflammation	Immunohistochimie
	vidéomicroscopie calcique

Principales publications :

1. Sim JA, Chaumont S, Jo J, Ulmann I, Young MT, Cho K, Buell G, North RA, Rassendren F. Altered hippocampal synaptic potentiation in P2X4 knock-out mice. **J Neurosci** 26:9006-9009, 2006.
2. Avignone E, Ulmann L, Levavasseur F, Rassendren F, Audinat E. Status epilepticus induces a particular microglial activation state characterized by enhanced purinergic signaling. **J Neurosci** 28:9133-9144, 2008.
3. Chaumont S, Compan V, Toulme E, Richler E, Housley GD, Rassendren F, Khakh BS. Regulation of P2X2 receptors by the neuronal calcium sensor VILIP1. **Sci Signal** 1: ra8, 2008.
4. Ulmann L, Hatcher JP, Hughes JP, Chaumont S, Green RJ, Conquet F, Buell GN, Reeve AJ, Chessell IP, Rassendren F. Up-regulation of P2X4 receptors in spinal microglia after peripheral nerve injury mediates BDNF release and neuropathic pain. **J Neurosci** 28:11263-11268, 2008.
5. Ulmann L, Hirbec H, Rassendren F. P2X4 receptors mediate PGE2 release by tissue-resident macrophages and initiate inflammatory pain. **Embo J** 29:2290-2300, 2010.

Responsable : **Rémy SCHLICHTER (PU)**

Intitulé de l'équipe : Signalisation nociceptive dans la moelle épinière

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Composition :

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Chercheurs	3 (CR CNRS)
ITA	1,5 (1 CNRS ; 0,5 Université)
Master/Doctorants/ Post-Doctorants	7 (2 Masters, 4 Doct ; 1 post-doc)

Principaux mots clés :

Thématiques	***Méthodologiques***
Douleur	Electrophysiologie *in vitro* et *in vivo*
Nociception	Cultures dissociées de moelle épinière
Douleurs inflammatoires	Cultures organotypiques de moelle épinière
Neuropathies	Co-cultures de cellules nerveuses (neurones,
Réseaux de neurones spinaux	astrocytes, cellules microgliales)
Interactions couches superficielles et profondes	Co-cultures neurones sensoriels - kératinocytes
Transmission, cotransmission et plasticité synaptiques	Tranches de SNC (jeune et adulte)
Stéroïdes neuroactifs et neurostéroïdes	Imageries calcium et pH
Neuropeptides, cytokines, chemokines	Neuroanatomie (traçage)
Contrôles descendants	Immunocytochimie
	Transfert de gènes
	Techniques optogénétiques

Principales publications :

1. Petitjean H, Rodeau JL, Schlichter R Interactions between superficial and deep dorsal horn spinal cord neurons in the processing of nociceptive information. **Eur J Neurosci** 36:3500-3508, 2012.

2. Pawlowski S, Gaillard S, Ghorayeb I, Ribeiro-da-Silva A, Schlichter R, Cordero-Erausquin M A novel population of cholinergic neurons in the macaque spinal dorsal horn of potential clinical relevance for pain therapy. **J Neurosci** 33:3727-3737, 2013.

3. Seibt F, Schlichter R Noradrenaline-mediated facilitation of inhibitory synaptic transmission in the dorsal horn of the rat spinal cord involves interlaminar communications. **Eur J Neurosci** 42:2654-2665. , 2015.

4. Medrano MC, Dhanasobhon D, Yalcin I, Schlichter R, Cordero-Erausquin M Loss of inhibitory tone on spinal cord dorsal horn spontaneously and non-spontaneously active neurons in a mouse model of neuropathic pain. **Pain** 157:1432-1442, 2016.

5. Kahle KT, Schmouth JF, Lavastre V, Latremoliere A, Zhang J, Andrews N, Omura T, Jlaganière J, Rochefort D, Hince P, Castonguay G, Gaudet R, Mapplebeck JCS, Sotocinal SG, Duan JJ, Ward C, Khanna AR, Mogil JS, Dion PA, Woolf CJ, Inquimbert P, Rouleau GA Inhibition of the kinase WNK1/HSN2 ameliorates neuropathic pain by restoring GABA inhibition. **Sci Signal** 9: DOI:10.1126/scisignal.aad0163, 2016.

6. Cordero-Erausquin M, Inquimbert P, Schlichter R, Hugel S Neuronal networks and nociceptive processing in the dorsal horn of the spinal cord. **Neuroscience** 338:230-247. Review article, 2016.

Responsable : **Frédéric SIMONIN (DR2 CNRS)**

Intitulé de l'équipe : RCPG, douleur et inflammation

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Composition :

Chercheurs :	4 (2 CR, 2 DR)
ITA :	4 (3 CNRS, 1 Université)
Master/Doctorants/Post-doctorants	1/4/4

Organigramme :

1. Rôle des récepteurs RF-amide dans l'hyperalgésie induite par les opiacés et les douleurs persistantes (F. Simonin, B. Ilien, R. Wagner)
2. Rôle de GASP-1 dans la stimulation chronique des RCPG et de la douleur (F. Simonin, S. Lecat, R. Wagner)
3. Rôle des chimiokines dans le développement de l'hyperalgésie induite par les opiacés et les douleurs persistantes (F. Simonin, J.-L. Galzi)

Principaux mots clés :

Thématiques	***Méthodologiques***
Sytème nociceptif spinal	Pharmacologie in vitro
Hyperalgésie	Criblage de ligands de RCPG
Systèmes opioïdes et anti-opïoides	Pharmacologie in vivo (tests nociceptifs)
Adaptations à la stimulation prolongée	Biologie Moléculaire
des RCPG	Biologie cellulaire (voies de transduction
Récepteurs à peptide RF-amide	du signal)
G protein coupled associated protein 1 (GASP-1)	Production, purification de RCPG
Chimiokines	
Interactions neurones-glie	

Principales publications

1. Simonin, F., M. Schmitt, J.P. Laulin, E. Laboureyras, J.H. Jhamandas, D. MacTavish, A. Matifas, C. Mollereau, P. Laurent, M. Parmentier, B.L. Kieffer, J.J. Bourguignon, G. Simonnet. RF9, a potent and selective neuropeptide FF receptor antagonist, prevents opioid-induced tolerance associated with hyperalgesia. **Proc. Natl Acad Sci USA** 103:466-71, 2006.
2. Hachet-Haas M., Balabanian K., Rohmer F., Pons F., Franchet C., Lecat S., Chow KYC, Dagher R., Gizzi P., Didier B., Lagane B., Kellenberger E., Bonnet D., Baleux F., Haiech J., Parmentier M., Frossard N., Arenzana-Seisdedos F., Hibert M,, Galzi J.-L. Small neutralizing molecules to inhibit actions of the chemokine CXCL12. **J Biol Chem** 283:23189-99, 2008.
3 Elhabazi K., Trigo J.-M., Mollereau C., Moulédous L., Zajac J.-M., Bihel F., Schmitt M., Bourguignon J.-J., Meziane H., Petit-demoulière B., Bockel F., Maldonado R., Simonin F. Involvement of neuropeptide FF receptors in neuroadaptative responses to acute and chronic opiates treatments. **British J Pharmacol** 165(2):424-435, 2012.
4 Elhabazi K., Humbert J-P., Bertin I., Schmitt M., Bihel F., Bourguignon J.-J., Bucher B., Becker J.A.J., Sorg T., Meziane H., Petit-Demoulière B., Ilien B., Simonin F. Endogenous mammalian RF-amide peptides, including PrRP, kisspeptin and 26RFa, modulate nociception and morphine analgesia via NPFF receptors, **Neuropharmacol** 75:164-171, 2013.

5 Bihel F., Humbert J.-P., Schneider S., Bertin I., Wagner P., Schmitt M., Laboureyras E., Petit-Demoulière B., Schneider E., Mollereau C., Simonnet G., Simonin F*. and Bourguignon J.-J.* Development of a peptidomimetic antagonist of the neuropeptide FF receptors for the prevention of opioid-induced hyperalgesia. **ACS Chem Neurosci** 6:438-445, 2015.

6 Guillemyn K, Starnowska J, Lagard C, Dyniewicz J, Rojewska E, Mika J, Chung NN, Utard V, Kosson P, Lipkowski AW, Chevillard L, Arranz-Gibert P, Teixidó M, Megarbane B, Tourwé D, Simonin F, Przewlocka B, Schiller PW, Ballet S.Bifunctional Peptide-Based Opioid Agonist-Nociceptin Antagonist Ligands for Dual Treatment of Acute and Neuropathic Pain. **J Med Chem** 59:3777-3792, 2016.

Responsables : **Vassilia THEODOROU (Pr. ESAP)**

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Composition :

Enseignants-Chercheurs/Hospitaliers	2 (ESAP)
Chercheurs	4 (1 DR, 2 CR INRA)
ITA	5
Master/Doctorants/ Post-Doctorants	4

Organigramme :

1. Approche des mécanismes physiopathologiques de l'hypersensibilité viscérale (facteurs locaux et centraux).
2. Mise au point de modèles de douleur abdominale et évaluation des médiateurs impliqués.

3. Recherche clinique des facteurs de l'hypersensibilité associée aux troubles fonctionnels intestinaux chez l'homme en particulier au syndrome de l'intestin irritable (SII).

Principaux mots clés :

Thématiques	*Méthodologiques*
Douleur	Test de distension
Nociception	Enregistrements EMG
Interactions immunes locales	RT-PCR cytokines Th1/Th2
Rôle de la barrière épithéliale	Mesures de perméabilité
	Translocation bactérienne
	Immunohistochimie des médiateurs sensoriels

Principales publications :

2. Annaházi A, Gecse K, Dabek M, Ait-Belgnaoui A, Rosztóczy A, Róka R, Molnár T, Theodorou V, Wittmann T, Bueno L, Eutamene H. Fecal proteases from diarrheic-IBS and ulcerative colitis patients exert opposite effect on visceral sensitivity in mice. **Pain** 144:209-17, 2009.
3. Eutamene H, Bradesi S, Larauche M, Theodorou V, Beaufrand C, Ohning G, Fioramonti J, Cohen M, Bryant AP, Kurtz C, Currie MG, Mayer EA, Bueno L. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. **Neurogastroenterol Motil**. 22(3):312-e84, 2010.
4. Annaházi A, Dabek M, Gecse K, Salvador-Cartier C, Polizzi A, Rosztóczy A, Róka R, Theodorou V, Wittmann T, Bueno L, Eutamene H. Proteinase-activated receptor-4 evoked colorectal analgesia in mice: an endogenously activated feed-back loop in visceral inflammatory pain. **Neurogastroenterol Motil** 24(1):76-85, 2012.
5. Silos-Santiago I, Hannig G, Eutamene H, Ustinova EE, Bernier SG, Ge P, Graul C, Jacobson S, Jin H, Liong E, Kessler MM, Reza T, Rivers S, Shea C, Tchernychev B, Bryant AP, Kurtz CB, Bueno L, Pezzone MA, Currie MG. Gastrointestinal pain: unraveling a novel endogenous pathway through uroguanylin/guanylate cyclase-C/cGMP activation. **Pain** 154:1820-30, 2013.
5. Annaházi A, Ferrier L, Bézirard V, Lévêque M, Eutamène H, Ait-Belgnaoui A, Coëffier M, Ducrotté P, Róka R, Inczefi O, Gecse K, Rosztóczy A, Molnár T, Ringel-Kulka T, Ringel Y, Piche T, Theodorou V, Wittmann T, Bueno L. Luminal cysteine-proteases degrade colonic tight junction structure and are responsible for abdominal pain in constipation-predominant IBS. **Am J Gastroenterol** 108:1322-31, 2013.

Responsables : **Jean VALMIER (PU) / Patrick CAROLL (DR)**

Intitulé de l'équipe : Inserm U 1051

Développement et Physiopathologie du système sensori-moteur

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Composition :

Enseignants-Chercheurs/Hospitaliers	5
Chercheurs	4
ITA/ingénieur	4
Doctorants/Post-Doctorants	2

Organigramme :

1. Spécification neuronale dans le système somato-sensoriel (P. Carroll)
2. Physiopathologie du système somato-sensoriel (J. Valmier)

Principaux mots clés :

Thématiques	*Méthodologiques*
Neurone sensitifs	Electrophysiologie
Ganglion rachidien dorsaux	Imagerie du vivant
Système somato-sensoriel	Immunohistochimie
Somesthésie	Génomique fonctionnelle
Douleurs neuropathiques	Biologie moléculaire
Allodynie	comportement
Axotomie	
Régénération	
Développement	

Principales publications :

1. Bourane S, Garces A, Venteo S, Pattyn A, Hubert T, Fichard A, Puech S, Boukhaddaoui H, Baudet C, Takahashi S, Valmier J, Carroll P. Low-threshold mechanoreceptor subtypes selectively express MafA and are specified by Ret signalling. **Neuron** 64:857-70, 2009.
2. Nouette-Gaulain K, Jose C, Capdevila X, Rossignol R.From analgesia to myopathy: When local anesthetics impair the mitochondrion. **Int J Biochem Cell Biol** 43:14-9, 2011.
3. Ventéo S, Bourane S, Méchaly I, Sar S, Samad O, Puech S, Blostein R, Valmier J, Pattyn A and Carroll P Regulation of the Na,K-ATPase gamma-subunit FXYD2 by Runx1 and Ret signaling in normal and injured non-peptidergic nociceptive sensory neurons. **PlosOne** 7: e29852, 2012.
4. Nouette-Gaulain K, Capdevila X, Rossignol R Local anesthetic 'in-situ' toxicity during peripheral nerve blocks: update on mechanisms and prevention. **Curr Opin Anaesthesiol** 25:589-95, 2012.
5. Rivat C, Sebaihi S, Van Steenwinckel J, Fouquet S, Kitabgi P, Pohl M, Melik Parsadaniantz S, Reaux-Le Goazigo A. Src family kinases involved in CXCL12-induced loss of acute morphine analgesia. **Brain Behav Immun** 38:38-52, 2014.
6. Parsadaniantz SM, Rivat C, Rostène W, Goazigo AR. Opioid and chemokine receptor crosstalk: a promising target for pain therapy? **Nat Rev Neurosci** 16:69-78, 2015.

Responsable : **Nathalie VERGNOLLE (DR1 INSERM)**

Intitulé de l'équipe : Physiopathologie de l'épithélium intestinal

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Chercheurs	8 (1DR, 6 CR INSERM, 1CR CNRS)
ITA	3 (2 INSERM, 1 Université)
Master/Doctorants/Post-Doctorants	12

Principaux mots clés :

Thématiques	**Méthodologiques**
Maladies inflammatoires chroniques de l'intestin	Tests comportementaux (nociception)
Syndrome du colon irritable	Mesure d'hypersensibilité viscérale (colon,
Cystite interstitielle	vessie)
Nociception	Modèles animaux d'inflammation intestinale
Douleur inflammatoire	Imagerie calcium
Inflammation	Activité protéasique/*in situ* zymography
Immunité	Médiateurs lipidiques
Neurones sensitifs	Immunochimie / Immunologie cellulaire
Protéases	Biologie moléculaire/systèmes d'expression
Transient Receptor Potential	Perméabilité intestinale
Canaux calciques	
Pharmacologie	

Principales publications :

1- Cenac N, Bautzova T, Le Faouder P, Veldhuis NA, Poole DP, Rolland C, Bertrand J, Liedtke W, Dubourdeau M, Bertrand-Michel J, Zecchi L, Stanghellini V, Bunnett NW, Barbara G, Vergnolle N. Quantification and Potential Functions of Endogenous Agonists of Transient Receptor Potential Channels in Patients With Irritable Bowel Syndrome. **Gastroenterology**. Aug;149(2):433-44.e7. doi: 10.1053/j.gastro..04.011, 2015.

2- Rolland-Fourcade C, Denadai-Souza A, Cirillo C, Lopez C, Jaramillo JO, Desormeaux C, Cenac N, Motta JP, Larauche M, Taché Y, Berghe PV, Neunlist M, Coron E, Kirzin S, Portier G, Bonnet D, Alric L, Vanner S, Deraison C, Vergnolle N. Epithelial expression and function of trypsin-3 in irritable bowel syndrome. **Gut**. 2017 Jan 17. pii: gutjnl312094. doi: 10.1136/gutjnl-2016-312094. [Epub ahead of print], 2016.

3- Vergnolle N. Protease inhibition as new therapeutic strategy for GI diseases. **Gut**. Jul;65(7):1215-24. doi: 10.1136/gutjnl-2015-309147. Review, 2016.

4- Monjotin N, Gillespie J, Farrié M, Le Grand B, Junquero D, Vergnolle N. F16357, a novel protease-activated receptor 1 antagonist, improves urodynamic parameters in a rat model of interstitial cystitis. **Br J Pharmacol.** Jul;173(14):2224-36. doi: 10.1111/bph.13501, 2016.

5- Cenac N, Castro M, Desormeaux C, Colin P, Sie M, Ranger M, Vergnolle N. A novel orally administered trimebutine compound (GIC-1001) is anti-nociceptive and features peripheral opioid agonistic activity and Hydrogen Sulphide-releasing capacity in mice. **Eur J Pain**. May;20(5):723-30. doi: 10.1002/ejp.798, 2016.

Responsable : **Luis VILLANUEVA (DR2 CNRS)**

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Composition :		
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	Chercheurs	1 (DR)
	ITA	2
	Master/Doctorants/Post-Doctorants	3

Organigramme :

1. Plasticité hypothalamique, nociception / stress (L. Villanueva, L. Bourgeais)
2. Mécanismes dysfonctionnels centraux, céphalées et neuropathies (L. Villanueva, L. Bourgeais, W. Dieb)
3. Activité gliale, unités neurovasculaires et douleurs pathologiques (Y. Boucher, N. Moreau)
4. Douleurs oro-faciales (Y. Boucher, W. Dieb)

Principaux mots clés :

Thématiques	***Méthodologiques***
Réseaux neuronaux	Pharmacologie
Neuroplasticité dysfonctionnelle	Biologie moléculaire & cellulaire
Interaction neuro -gliales, -vasculaires	Comportement animal
Douleur	Electrophysiologie
Inflammation	Voies de signalisation
	Immunohistochimie
	Imagerie Cérébrale Fonctionnelle à ultrasons (fUS)

Principales publications :

1. Constandil L, Goich M, Hernández A, Bourgeais L, Cazorla M, Hamon M, Villanueva L, Pelissier T. Cyclotraxin-B, a new TrkB antagonist, and glial blockade by propentofylline equally prevent and reverse cold allodynia induced by BDNF or partial infraorbital nerve constriction in mice. **J Pain** 13:579-589, 2012.
2. Urtikova N, Berson N, Van Steenwinckel J, Doly S, Truchetto J, Maroteaux L, Pohl M, Conrath M. Antinociceptive effect of peripheral serotonin 5-HT2B receptor activation on neuropathic pain. **J Pain** 153:1320-1331, 2012.
3. Robert C, Bourgeais L, Arreto CD, Condes-Lara M, Noseda R, Jay T, Villanueva L. Paraventricular hypothalamic regulation of trigeminovascular mechanisms involved in headaches. **J Neurosci** 33:8827-4880, 2013.
4. Dauvergne C, Molet J, Réaux-Le Goazigo A, Mauborgne A, Mélik-Parsadaniantz S, Pohl M. Implication of the chemokine CCL2 in trigeminal nociception and traumatic neuropathic orofacial pain. **Eur J Pain** 18:360-75, 2014.
5. Molet J, Mauborgne A, Diallo M, Armand V, Geny D, Villanueva L, Boucher Y, Pohl M. Microglial Janus kinase/signal transduction and activator of transcription 3 pathway activity directly impacts astrocyte and spinal neuron characteristics. **J Neurochem** 136:133-147, 2016.
6. Moreau N, Mauborgne A, Bourgoin S, Couraud PO, Romero IA, Weksler BB, Villanueva L, Pohl M, Boucher Y. Early alterations of Hedgehog signaling pathway in vascular endothelial cells after peripheral nerve injury elicit blood-nerve barrier disruption, nerve inflammation and neuropathic pain development. **Pain** (in press) 2016.