JOB DESCRIPTION

Job Title : Postdoctoral position: **Mu-delta opioid receptor heteromers : towards novel therapeutic strategies ?**

Job Summary :

Mu opioid receptors mediate morphine analgesic and rewarding effects. However, tolerance and dependence develop upon chronic administration, which limits its therapeutic use and can elicit drug addiction. Functional interactions between mu and delta opioid receptors appear essential and may involve heteromerization of the two receptors. Indeed, mu-delta heteromers show specific binding and signaling in heterologous systems and chronic morphine increases mu-dependent delta function *in vivo*. Recently, we showed strong mu-delta co-localization in pathways associated with nociception or withdrawal using double knock-in mice co-expressing fluorescent mu and delta receptors. In order to evaluate mu-delta heteromers as novel therapeutic target, we will use these mice to identify the specific mu-delta interactome by a proteomic approach and to characterize its impact on receptor signaling and trafficking and animal behavior under basal conditions or upon chronic morphine treatment.

Job Description :

Opiates, with morphine as a prototype, are the most potent analgesics to date. However, chronic administration induces tolerance and dependence. At the molecular level, mu opioid receptors are the primary target of opiates and mediate the analgesic and euphoric properties. However, functional interactions between mu and delta receptors play a crucial role in the development of tolerance. Opioid receptors belong to class A G protein-coupled receptors and are functional as monomers. Numerous studies indicate that mu-delta co-expression in heterologous systems can also form a new entity called heteromer with specific binding and signaling properties. However, despite increasing evidence that mu-delta heteromers are present in vivo, molecular mechanisms underlying mu-delta functional interactions remain poorly characterized. These heteromers are thus potential therapeutic targets in drug addiction but also in chronic pain for which opiates represent a large proportion of the current treatment. This project aims at characterizing the signaling and trafficking properties specific to endogenous mu-delta heteromers. Using double fluorescent Knock-in mice co-expressing functional delta-eGFP and mu-mcherry fusions, the impact of heteromerization on receptor trafficking and signaling will be analyzed in primary neuronal cultures, acute brain slices and/or in vivo. Parameters under investigation will include receptor phosphorylation and internalization, G protein activation and beta 2 arrestin-dependent signaling following pharmacological activation. The candidate will also participate to the identification of interacting partners of mu-delta heteromers by a proteomic approach (collaboration Philippe Marin, IGF, Montpellier).

The position is to be held at the Institute for Cellular and Integrative Neuroscience (INCI) UPR 3212, in Strasbourg (http://inci.u-strasbg.fr/fr/index.html) in Dr Michel Barrot's laboratory under the supervision of Dr Dominique Massotte.The candidate should have obtained his (her) PhD less than 4 years ago at 01/01/2016 in any university except the university of Strasbourg. Experience in primary neuronal cultures as well as theoretical and practical experience in cellular biology, biochemistry and/or pharmacology is mandatory. Experience in animal behavior and/or opioid receptors would be an asset.

Massotte D. (2014) « *In vivo opioid receptor heteromerization : where do we stand ?* » British Journal of Pharmacology doi: 10.1111/bph.12702

Erbs E., Faget L., Scherrer G., Matifas A., Filliol D., Vonesch J.-L., Koch M., Kessler P., Hentsch D., Birling M.-C., Koutsourakis M., Vasseur L., Veinante P., Kieffer B.L. and **Massotte D**. (2015) *« A mu-delta opioid receptor brain atlas reveals neuronal co-occurrence in subcortical networks."* Brain Structure and Function 220, 677-702

Ceredig R.A. and **Massotte D**. (2015) *"Fluorescent knock-in mice to decipher the physiopathological role of G protein-coupled receptors"* Frontiers in Pharmacology 5:289

Main research field : Neurosciences

JOB DETAIL

Type of contract : Temporary
Status : Full-time
Company / Institute : Université de Strasbourg
Country : France
City : Strasbourg
Postal Code : 67000
Street : 4 rue Blaise Pascal

APPLICATION DETAILS (mandatory)

Envisaged job starting date : 01/06/2016
Application deadline : 31/03/2016
Application e-mail : d.massotte@unistra.fr