Involvement of NPFF1 and NPFF2 receptors in hyperalgesia and analgesic tolerance associated with chronic morphine, and inflammatory pain in mice

Claire Muller*[1,2], Maud Fischer[1], Claire Gavériaux-Ruff[1], and Frédéric Simonin[1]

[1]Biotechnologie et signalisation cellulaire – université de Strasbourg, Centre National de la Recherche Scientifique – France

[2]Euridol - The Graduate School of Pain – Euridol – France

Résumé

There are two main types of pain: acute pain, which is intense but short-lived, and chronic pain, which is long-lasting and disabling. Worldwide, 30% of adults suffer from chronic pain. 50% of them are unable to relieve their pain causing major social and economic repercussions. During the 1990s, the use of opioids for pain management began to increase, particularly in the United States. Today, opioid abuse remains the leading cause of preventable death in the United States. Opiates analgesia in the clinics is mainly due to the activation of mu-opioid receptor. Their chronic use results in the development of pain hypersensitivity, analgesic tolerance and dependence, the most commonly observed side effects of opioids. In the laboratory, we are particularly interested in studying the involvement of GPCRs of the RFamide family in the modulation of nociception and adaptations associated with chronic opioid administration and inflammatory agents. To this purpose, we first assessed the effect of peripheral morphine administration on nociceptive threshold and/or morphine-induced analgesia, hyperalgesia and analgesic tolerance in wild-type, NPFFR1 and NPFFR2 KO mice. In addition, we evaluated the effect of two inflammatory agents, Freund's Complete Adjuvant (CFA) and carrageenan, on the development of inflammation and hyperalgesia in these same animals.

Our data show that (i) hyperalgesia induced by repeated morphine administration is reduced in NPFFR1 KO animals in the thermal modality, equivalent to the WT group in the mechanical modality, and absent in NPFFR2 KO animals in both thermal and mechanical modalities. (ii) analgesic tolerance is aggravated in NPFFR1 KO animals in the thermal modality, equivalent to the WT group in the mechanical modality and reduced in NPFFR2 KO animals. (iii) hyperalgesia induced by CFA or carrageenan is present in WT and NPFFR1 KO animals and absent in NPFFR2 KO mice in both heat and mechanical modalities. (iv) inflammatory edema appears to be greater in NPFFR1 KO animals than in WT and NPFFR2 KO mice.

In conclusion, our data show that NPFFR2 plays a critical role in the development of hyperalgesia and analgesic tolerance associated with chronic morphine as well as hyperalgesia induced by inflammatory agents. Conversely, NPFFR1 appears to play a limited role in these phenomena.

*Intervenant

Mots-Clés: RF, amide, Receptor, Inflammation, Pain, Hyperalgesia