0026-895X/03/6404-796–797$7.00
MOLECULAR PHARMACOLOGY

Mol Pharmacol 64:796–797, 2003

Vol. 64, No. 4
2826/1099483
Printed in U.S.A.

PERSPECTIVE

Simple Nuclear Factor κB-Mediated μ-Opioid Receptor Induction in Immune Cells

T. J. MURPHY

Department of Pharmacology, Emory University School of Medicine, Atlanta, Georgia

Received July 16, 2003; accepted July 17, 2003

This article is available online at http://molpharm.aspetjournals.org

A small family of G protein-coupled receptors (the μ-, δ- and κ-opioid receptors) mediates the biological effects of opioids, are the mimetics of endogenous neuropeptides, and are best known as analgesics and for their illicit potential. At the very least, this is the central "take-home" message from the typical introductory pharmacology curriculum. A student who has had the misfortune of treatment with morphine and experienced its powerful ability to halt intestinal motility for days on end will quickly appreciate that this is a highly simplified view of opioid pharmacology and biology. More experienced scholars within the field recognize that opioid receptors are expressed in cells outside of the central, peripheral, and enteric nervous systems, where they serve other biological roles.

A substantial body of evidence indicates that modulation of immune system function is among these roles. A decade has passed since Lysle et al. (1993) demonstrated that opioid receptor activation is immunomodulatory by showing that morphine treatment attenuates several indices of immune activation, including lymphocyte proliferation, natural killer cell activity, and cytokine expression. These and other effects are very likely to be mediated via opioid receptors that are expressed upon the surface of immune cells (Sharp et al, 1998; Makarenkova et al., 2001). This paints a very pleasing picture, predicting the existence of a neuroendocrine-immune system axis, one through which the mind possesses an innate capacity to modulate disease processes by tweaking immune surveillance.

In a metaphorical sense, it now seems that the disease can whisper back to the mind in the form of a possible feedback regulatory mechanism. The article in this issue by Kraus et al. (2003) convincingly demonstrates that human immune cell μ-opioid receptor expression is tightly controlled by the tumor necrosis factor receptor (TNF)/NFκB signaling pathway. μ-Opiate receptor mRNA levels are undetectable under basal conditions among a thorough survey of cells, including primary T and CD38+ dendritic cells and also in model B, endothelial, and monocyte cell lines. However, activation of the TNF receptor on each of these strongly induces μ-opioid receptor mRNA expression. Promoter reporter assays convincingly point to NFκB as the necessary transcriptional coactivator that is required for this induction, where it seems to work through one or more of three candidate response elements within the proximal 5′ flanking gene region. These are the types of straightforward and airtight findings most promoter bashers can only dream about.

It is of interest to note that allelic variants exist for one of these candidate NFκB response elements (at −557 base pairs upstream), which the authors speculate may impair μ-opioid receptor regulation in carriers. However, although the artificial promoter reporter assay shows that this site can function as an NFκB response element, left unanswered is whether it or either of the two additional NFκB response elements becomes occupied in the chromatin locus in response to TNF. What points to this concern is the finding that transcriptional induction from constructs containing all three of these elements is no greater than from those in which any of the three is omitted.

In a well controlled series of indirect experiments, the authors were nevertheless able to further build the case for a specific role of NFκB in the control of this gene within its native chromatin context. They took advantage of an approach (Bielinska et al., 1990) wherein transfection with NFκB element decoy oligonucleotides are used to squelch μ-opioid receptor mRNA induction by TNF, whereas additional control decoys, including activator protein 1, have no apparent effect on TNF responsiveness. Shown here, the decoy method is impressively efficacious and worthy of adopting as a pharmacologic approach to functionally assess the roles that various transcription factor families might play in a response to agonists. The method has several conceivable advantages over the alternative, which involves collecting, creating, and expressing with quantitative efficiency various *trans*-dominant transcription factor proteins. That is a difficult bar to hurdle in many model systems.

One important issue this report has raised, but not addressed, is what underlies this apparently cell-specific mech-

ABBREVIATIONS: TNF, tumor necrosis factor; NFκB, nuclear factor κB.

anism for μ-opioid receptor expression. Are 'inflammatory' cytokines, such as TNF, also as significant in the regulation of human μ-opioid receptor gene expression elsewhere in the body? The gene seems to be tightly suppressed in immune cells under basal conditions before its induction through NFκB, not at all atypical in immune cells, which are basically specialized for conducting on-demand gene expression. Does NFκB play any measurable or biological role in regulating human μ-opioid receptor gene in cells such as neurons, where its mRNA can be constitutively expressed? It may prove that the μ-opioid receptor gene is structured to accommodate entirely distinct (constitutive versus highly inducible) assemblies of transcriptional coregulators depending upon its cellular environment. The funny thing about this business; as soon as you think you've settled upon one simple "take-home" message, it turns out to be not so simple after all.

References

Bielinska A, Shivdasani RA, Zhang LQ, and Nabel GJ (1990) Regulation of gene expression with double-stranded phosphorothioate oligonucleotides. *Science (Wash DC)* **250:**997–1000

Kraus J, Borner C, Giannini E, and Hollt V (2003) The role of nuclear factor κB in tumor necrosis factor-regulated transcription of the human μ-opioid gene *Mol Pharmacol* **64:**876–884.

Lysle DT, Coussons ME, Watts VJ, Bennett EH and Dykstra LA (1993) Morphine-induced alterations of immune status: dose dependency, compartment specificity and antagonism by naltrexone. *J Pharmacol Exp Ther* **265:**1071–1078.

Makarenkova VP, Esche C, Kost NV, Shurin GV, Rabin BS, Zozulya AA, and Shurin MR (2001) Identification of delta- and mu-type opioid receptors on human and murine dendritic cells. *J Neuroimmunol* **117:**68–77.

Sharp BM, Roy S, and Bidlack JM (1998) Evidence for opioid receptors on cells involved in host defense and the immune system. *J Neuroimmunol* **83:**45–56.

Address correspondence to: T. J. Murphy, Department of Pharmacology, Emory University School of Medicine, 5031 Rollins Research Bldg., Atlanta, GA 30322. E-mail: medtjm@emory.edu