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The Molecular Basis for Neuroimmune Receptor Signaling

Thomas J. Rogers

Fels Institute for Cancer Research and Molecular Biology, Center for Inflammation, Translational and Clinical Lung Research, Center for Substance Abuse Research, Temple University School of Medicine, 3307 N. Broad Street, Philadelphia, PA 19140, USA

Many of the receptors which are responsible for the responses to the common drugs of abuse belong to the G protein-coupled receptor (GPCR) family. In this special issue of the Journal of Neuroimmune Pharmacology a collection of papers is presented which deals with signaling events that are important for the function of these receptors. These receptors are expressed by neuronal cells at potentially high levels, and the function of these receptors in the CNS is well described. However, these receptors may also be expressed by hematopoietic cells, and the role of these receptors in the function of the immune system is still not fully understood. We are still working to understand fundamental processes which include the biochemical and molecular basis for the regulation of receptor expression. It is also apparent that once these receptors are expressed, the functional activity of these membrane proteins is also an additional important aspect of receptor regulation.

There are related issues that are important for the functional activity of these receptors. For example, once these receptors are activated, a complex series of signaling events are initiated that can have a substantial impact on the function of the immune system. At this time, we only have a limited understanding of these signaling events. With more complete information, we may be able to control the undesirable consequences of receptor activation by drugs of abuse. In this way, information about all of these signaling events may lead to the creation of therapeutics that could be used to block the detrimental influences of drugs of abuse on the immune and nervous systems.

Our understanding of the regulation of opioid receptor expression has been greatly enhanced by studies on the capacity of microRNAs (miRNAs) to influence receptor transcription and/or translation. These small (approximately 22 nucleotide) non-coding RNA molecules bind to complementary mRNA sequences typically within the 3' untranslated region. A single miRNA species may bind multiple mRNA targets, and a single mRNA species may be regulated by multiple miRNAs. The paper by Hwang et al. () describes recent research which shows that the opioid receptors are subjected to significant regulation by miRNAs, and their review describes notable work with miR-23b and miR-339. These miRNA species target sites in the 3' UTR of the mu opioid receptor (MOR), and work with these miRNAs have revealed novel signaling pathways that were not previously understood to be involved

Correspondence: Thomas J. Rogers, Fels Institute for Cancer Research and Molecular Biology, Center for Inflammation, Translational and Clinical Lung Research, Temple University School of Medicine, 3307 N. Broad Street, Philadelphia, PA 19140, USA, Phone: 215-707-3215, rogerst@temple.edu.

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in the regulation of these receptors. Hwang et al. () also review recent studies which show that the activation of MOR alters miRNA expression, including a reduction in the expression of miR-190 in the brain, and miR-28, 125b, 150, and 382 in monocytes. The level of expression of these miRNA species may play an important role in regulating susceptibility to HIV infection.

Additional information regarding the regulation of receptor expression is provided by Zhang et al () who studied the impact of T cell activation on the expression of the mu opioid receptor (MOR). These studies show that activation by either superantigen-treatment, or stimulation with the combination of anti-CD3 and anti-CD28, result in rapid up-regulation of MOR in developing T cells in the thymus. In additional studies, these investigators show that several cytokines known to be present in the thymus gland during T cell maturation induce a substantial elevation of MOR expression. This includes the cytokines transforming growth factor- β , interferon- γ , interleukin-1 β , and interleukin-2. These results confirm earlier published results that have indicated that opioid receptor expression is regulated by both T cell activation as well as cytokine signaling. Moreover, these results are consistent with growing evidence which suggest that opioid receptor expression is expressed early in T cell development in the thymus gland.

The interface between development and receptor expression is particularly relevant to the function of those GPCRs which exhibit homeostatic properties. Mithal, Banisadr and Miller () review a body of literature which shows that the expression of the chemokine receptor CXCR4, and its natural ligand CXCL12, are critical for normal leukocyte and neuronal cell development. These authors review literature which shows that both CXCL12 and CXCR4 are widely expressed in a variety of tissues during ontogeny, and a deficiency of either of these proteins results in severe impairment of neuronal, gastrointestinal, and hematopoietic tissues. In the nervous system, signaling through CXCR4 is required for normal development particularly through the regulation of cell migration and axon guidance. The principal mechanisms that are responsible for the role of this chemokine receptor in neuronal development are still incompletely understood, and are likely to involve activities of the receptor that extend beyond its well documented chemoattractant function.

There are two papers in this special issue which deal with the nature of cannabinoid receptors. In the first of these papers, Karmaus et al. () describe results which show that signaling initiated by delta-9-tetrahydrocannabinol (Δ^9 -THC) results in suppressed cytotoxic T cell activity, and this effect is mediated through a mechanism which is independent of the cannabinoid receptors 1 (CB1) or 2 (CB2). There is now a growing literature which suggests that at least a part of the immunomodulatory activities of the cannabinoids is mediated through either some other receptor, or set of receptors, or is receptor-independent. The work described by Karmous et al. () also extends earlier work by this group showing that the cannabinoids mediate significant immunomodulatory activity for T cells. A second paper in this issue shows that a third receptor, designated GPR55, is also a cannabinoid receptor. In this case, Shanir et al. () show that the endocannabinoids anandamide and virodhamine signal through GPR55 to induce β -arrestin distribution via a lysophosphatidylinositol activation pathway. These effects are reported to be independent of CB1 or CB2, and result in internalization of GPR55. These two papers provide very important information about the

nature of the signaling processes which are induced by the cannabinoids, and specifically illustrate the need for more information about the receptor sets that are involved in responses to these drugs.

Panas et al. () report results in this issue which show that the trace amine associated receptor-1 (TAAR1), a GPCR which responds to endogenous trace amines, as well as to psychostimulant drugs of the amphetamine class (such as methamphetamine), initiates a signaling pathway which leads to lymphocyte activation. The signaling process induced through TAAR1 appears to result, in part, in the activation of two critical transcription factors, CREB and NFAT, and these are well-established lymphocyte-activating factors. Moreover, these authors show that lymphocyte activation leads to an apparent up-regulation of TAAR1 receptor expression. This receptor may serve as an important therapeutic target, given its role in the immunomodulatory response to methamphetamine.

The consequences of receptor-mediated signaling are also addressed in the report by Podhaizer et al. () who show that the morphine-induced activation of MOR, when administered together with HIV gp120, induce significant neurotoxicity. This study demonstrates a significant role for glial cells in the neurotoxicity mediated by morphine with gp120, results which are consistent with earlier findings which showed that the toxicity mediated by HIV tat with morphine is also dependent on glia. However, the degree of toxicity exhibited by the combination of morphine and gp120 is dependent on the specific strain of HIV (e.g., HIV gp120MN was much more toxic in combination with morphine than HIV gp120IIB). The authors point out that these results demonstrate the complexity of the interactions between morphine and the potential neurodegeneration associated with HIV infection.

Taken together, the papers presented in this special issue address the issue of signaling pathways that are important for the regulation of drug-related GPCR expression, and are a part of a growing body of literature on this topic. A more complete understanding of the molecular and biochemical mechanisms that regulate receptor expression have a great deal of potential clinical and therapeutic significance. The papers presented here also deal with signaling events which are an important part of the consequences of receptor activation. These consequences may involve activation of hemopoietic or neuronal cells, or they may contribute to substantial toxicity. Signaling which leads to receptor expression, and signaling which mediates the consequences of receptor activation can be viewed as two sides of the same coin. As our understanding of these signaling pathways improves, we will be able to manipulate these pathways to attenuate undesirable drug effects, or enhance beneficial drug activities.

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