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SCIENCE DIRECT

Pharmacology & Therapeutics 107 (2005) 44–58

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

Associate editor: J. Wess

The clinical potential of chemokine receptor antagonists

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Abstract

Chemokines belong to a family of chemotactic cytokines that direct the migration of immune cells towards sites of inflammation. They mediate their biological effects by binding to cell surface receptors, which belong to the G protein-coupled receptor superfamily. Since chemokines and their receptors have been implicated in the pathophysiology of a number of autoinflammatory diseases, chemokine receptor antagonists could prove to be useful therapeutics to target these diseases. Here, we review the role of chemokines in autoimmunity, concentrating mainly on the chemokine receptors CCR1 and CCR5, and discuss the potential utility of antagonists that target these 2 receptors as they progress through the clinic.

Keywords: Chemokine; G-protein coupled receptor; Receptor antagonists; Autoimmune disease; Multiple sclerosis; Clinical trials

Contents

1. Introduction

Just like a mullah calling the faithful to prayer, chemokines call immune cells into action whenever they sense danger from potentially harmful invading microorganisms. This exquisite system of host defense is present not only in mammals but in a variety of vertebrates, including birds and fish. We know that chemokines accomplish their task by

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0163-7258/$ - see front matter © 2005 Published by Elsevier Inc.
doi:10.1016/j.pharmthera.2005.01.004

binding and activating specific chemokine receptors that belong to the G protein-coupled receptor family (Horn et al., 2003) and are expressed on a wide variety of immune cells (Baggiolini, 1998). This system of chemokine action is under very tight control, and the tight regulation includes different patterns of receptor expression that can be dependent on cytokine stimulation (Loetscher et al., 1996), proteolytic processing of chemokines that can influence both their target cell and their receptor profile (Struyf et al., 1999), function of a particular chemokine as an agonist on one receptor and as an antagonist on another, and the list goes on. It is easy to imagine the consequences of a breakdown in this stringent regulation of immune cell mobilization, and it demonstrates the Jekyll-and-Hyde-like nature of the chemokines. On the one hand, chemokines aid in protecting the host from attack by dangerous pathogens, and on the other hand, they can direct immune cells to target and destroy perfectly healthy cells (Baggiolini, 1998). When this destruction by friendly fire involves the death of cells like pancreatic beta cells or of neurons, it gives rise to autoimmune diseases like diabetes or multiple sclerosis (Horuk, 2001). The realization that chemokines are involved in the pathogenesis of a number of autoimmune diseases and that their receptors belong to one of the most pharmacologically exploited families of proteins (GPCRs) has made them the focus of intense interest by pharmaceutical companies.

However, it is not only their role in autoimmunity that has attracted the attention of the drug industry to the chemokines but also the fact that, because of their part in host defense, these proteins have themselves been exploited by pathogens. The most relevant example of this is the HIV-1 virus that uses the chemokine receptors CXCR4 and CCR5 to gain entry into and set up house in immune cells (Horuk, 1999). The consequences of this for the host are dire because the very cells that form the first line of defense in infection are themselves targeted for destruction by the virus. Eventually, when the immune system is sufficiently impaired by the virus, the host usually succumbs to an opportunistic infection. Thus, small molecule chemokine receptor inhibitors that target these coreceptors could be useful additions to the armory of anti-HIV-1 drugs that are being used to combat AIDS. After many years of research, chemokine receptor antagonists of a broad variety are now at hand, and the most advanced of these is currently in phase III trials as a CCR5 inhibitor for the treatment of AIDS (IDdb, 2004e; Pfizer, 2004). We have come a long way since the first chemokine Gordon Conference in Plymouth, NH, in June of 1994, where the prospect of therapeutic strategies targeting chemokine receptors was merely a twinkle in the eye of the participants. However, the next few years will reveal whether this promise is finally realized, as numerous clinical trials involving chemokine receptor antagonists finally reach their end points and are analyzed.

This review will focus on the rapid advances that have been made in identifying and characterizing chemokine receptor antagonists exemplified by discussing the biology and chemistry of the 2 most advanced classes of chemokine receptor antagonists that are currently in the clinic, those that target the receptors CCR1 and CCR5. For a more detailed discussion of chemokine receptor antagonists, the reader is directed toward several recently published reviews that discuss the importance of this growing family of proteins (Horuk, 2001; Schwarz & Wells, 2002).

2. Chemokines and their receptors

Chemokines are small, chemotactic cytokines characterized by a distinctive pattern of conserved cysteine residues (Horuk, 2001). They are divided into 2 major (CXC and CC) and 2 minor (C and CX3C) groups dependent on the number and spacing of the first 2 conserved cysteine residues (Baggiolini et al., 1997). Although originally identified on the basis of their ability to regulate the trafficking of immune cells, the biological role of chemokines goes well beyond this simple description of their function as chemoattractants, and they have been shown to be involved in a number of biological processes, including growth regulation, hematopoiesis, embryonic development, angiogenesis, and HIV-1 infection (Horuk, 2001).

Chemokines mediate their biological effects by binding to cell surface receptors that belong to the GPCR superfamily (Horn et al., 2003). Receptor binding initiates a cascade of intracellular events mediated by the receptor associated heterotrimeric G proteins. These G protein subunits trigger various effector enzymes, which leads to the activation not only of chemotaxis but also to a wide range of functions in different leukocytes, such as an increase in the respiratory burst, degranulation, phagocytosis, and lipid mediator synthesis (Baggiolini, 1998).

Chemokines have been shown to be associated with a number of autoinflammatory diseases, including multiple sclerosis, rheumatoid arthritis, diabetes, endometriosis, transplant rejection, multiple myeloma, etc. (Gerard & Rollins, 2001). Evidence, reviewed below, is mounting that chemokines may play a major role in the pathophysiology of these diseases and thus chemokine receptor antagonists could prove to be useful therapeutics in treating these and other inflammatory diseases.

3. Chemokines in multiple sclerosis

Multiple sclerosis is an autoimmune disease mediated by T and B lymphocytes and macrophages, which results in extensive inflammation and demyelination of the white matter (Ransohoff & Bacon, 2000). Although the mechanisms responsible for causing this immunologic damage in the CNS are still unknown, they are almost certainly mediated by infiltrating leukocytes. Initial interactions between T cells and monocytes result in the production of cytokines such as TNF and IL-1. These cytokines induce a variety of effects that