

P001 A fine line between agonism and antagonism at chemokine receptor CCR3

Emma Wise, Cécile Duchesnes, Paula Da Fonseca, Rodger Allen, Timothy Williams and James Pease

Leukocyte Biology Section, NHLI, Imperial College London; Institute of Cancer Research, London; UCB-Celltech, Slough.

The GPCR known as CCR3 is highly expressed by eosinophils and signals in response to binding of the chemokine CCL11/eotaxin which is upregulated in asthma. Consequently, CCR3 blockade is of interest as a possible therapeutic approach. We have described previously a bi-specific antagonist of CCR3 and the related receptor CCR1 (UCB35625), which interacts with the transmembrane residues Y41, Y113 and E287 of CCR1. Here, we show that cells expressing the mutant CCR3 constructs Y113A and E287Q are insensitive to UCB35625 and exhibit impaired chemotaxis in response to CCL11 suggesting that these residues are important for both antagonist binding and receptor activation. Surprisingly, mutation of Y113 turned the antagonist UCB35625 into a CCR3 agonist. A novel specific agonist of CCR3 named CH0076989 was also identified which was able to activate both eosinophils and CCR3 transfectants. Mutation of the CCR3 residues Y41, Y113 and E287 resulted in abrogation of agonist activity, suggesting that the compound mimicks the natural ligand CCL11. We conclude that the both agonists and antagonists of CCR3 appear to occupy overlapping sites within the intrahelical bundle, suggesting a fine line between agonism and antagonism of chemokine receptors.