lysozyme and truncated the N-terminal 19 residues. The structure was determined at the 3.1 Å resolution with a first-generation antihistamine, doxepin. The structure allows us to characterize its ligand-binding pocket in detail. Doxepin sits much deeper in the pocket than the antagonists in other aminergenic G protein coupled receptor (GPCR) structures and directly interacts with the highly conserved Trp428, a key residue in GPCR activation. Asp107, a strictly conserved residue in aminergic receptors, forms an anchor salt bridge with the amine moiety of doxepin. The antihistamine is also surrounded by highly conserved residues among aminergenic receptors including Ile115, Phe424 and Phe432. The well-conserved pocket and its mostly hydrophobic nature contribute to low selectivity of doxepin and other first-generation compounds causing considerable side effects. The pocket is associated with an anion-binding region occupied by a phosphate molecule.

Docking of various second-generation antihistamines reveals that the unique carboxyl-group present in this class of compounds interacts with Lys191 and/or Lys179, both of which form part of the anion-binding region and are not conserved in other aminergenic receptors.

The structural details of the antihistamine-binding pocket of H1R will be highly beneficial for guiding rational design of new antihistamines that do not penetrate the BBB while maintaining H1R selectivity.

Keywords: histamine, receptor, structure

MS.85.3

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Towards a structural understanding of drug and peptide transport within the proton dependent oligopeptide transporter (POT) family

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The proton dependent oligopeptide transporters (POTs) are a large family of integral membrane proteins that use the inwardly directed proton electrochemical gradient to transport small peptides, amino acids and nitrate across cellular membranes in both pro- and eukaryotic cells. Evolutionarily the POT family sits within the much larger Major Facilitator Superfamily (MFS), members of which contain a common structural motif of 12 transmembrane-spanning alpha-helical segments. The human genome contains four members of this family, two of which, PepT1 and PepT2 are responsible for the absorption of dietary peptides in the small intestine and peptide re-absorption in the kidney. Peptide transporters also contribute significantly to the oral bioavailability and pharmacokinetic properties of a number of important drug families, such as the beta-lactam antibiotics. To gain further insight into the molecular mechanism of drug and peptide transport, we determined the crystal structure of a prokaryotic member of the POT family, $PepT_{So}$, with similar substrate specificity and a high degree of sequence conservation to the mammalian PepT proteins [1]. The structure of $PepT_{So}$, together with our associated kinetic data, provides valuable new insights into mammalian peptide transport and provides the starting point for further structural and biochemical studies on this pharmaceutically important transporter family.

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Keywords: major facilitator superfamily, occluded state, peptide transport

MS.85.4

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Molecular basis of substrate-induced permeation by an amino acid antiporter

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Transporters of the amino acid, polyamine and organocation (APC) superfamily play essential roles in cell redox balance, cancer and aminoacidurias. The bacterial L-arginine/agmatine antiporter, AdiC, is the main APC structural paradigm and shares the "5+5 inverted repeat" fold found in other families like the Na+-coupled neurotransmitter transporters. The available AdiC crystal structures capture two states of its transport cycle [1-3]: the open-to-out apo and the outward-facing Arg+-bound occluded. However, the role of Arg+ during the transition between these two states remains unknown. Here, we show the crystal structure at 3.0 Å resolution of an Arg+-bound AdiC mutant (N101A) in the open-to-out conformation, completing the picture of the major conformational states during the transport cycle of the "5+5 inverted repeat" fold-transporters [4]. The N101A structure is an intermediate state between the previous known AdiC conformations. The Arg+-guanidinium group in the current structure presents high mobility and delocalization, hampering substrate occlusion and resulting in a low translocation rate. Further analysis supports that proper coordination of this group with residues Asn101 and Trp293 is required to transit to the occluded state, providing the first clues on the molecular mechanism of substrate-induced fit in a "5+5 inverted repeat" fold-transporter. The pseudo-symmetry found between repeats in AdiC, and in all fold-related transporters, restraints the conformational changes, in particular the transmembrane helices rearrangements, which occur during the transport cycle. In AdiC these movements take place away from the dimer interface, explaining the independent functioning of each subunit.

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Key words: AdiC, APC transporter, 5+5 inverted repeat fold

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Crystal structure of the copper pump

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