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Cyclic lactam hybrid α-MSH/Agouti-related protein (AGRP) analogues with nanomolar range binding affinities at the human melanocortin receptors

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ABSTRACT

A novel hybrid melanocortin pharmacophore was designed based on the topographical similarities between the pharmacophores of Agouti related protein (AGRP) an endogenous melanocortin antagonist, and α-melanocyte-stimulating hormone (α-MSH), an endogenous melanocortin agonist. When employed in two different 23-membered macrocyclic lactam peptide templates, the designed hybrid AGRP/MSH pharmacophore yielded non-competitive ligands with nanomolar range binding affinities. The topography-based pharmacophore hybridization strategy will prove useful in development of unique non-competitive melanocortin receptor modulators.

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Proopiomelanocortin (POMC) is a primordial gene found in virtually all vertebrates. The peptide hormones and neurotransmitters derived from POMC by post-translational processing, including α-, β-, and γ-melanocyte stimulating hormones (MSHs) and adrenocorticotropin (ACTH),[1] (Fig. 1) as well as their targets, the melanocortin receptors (MCRs), are responsible for many physiological functions critical for survival.[2,3] These functions include regulation of feeding behavior and energy homeostasis,[3–5] control of the immune system and inflammation,[1,2] skin pigmentation,[1,2] cardiovascular function,[6] sexual function and procreation,[4,7,8] modulation of aggressive/defensive behavior,[9] thermoregulation,[10] and mediation of pain.[11,12] The multitude of biological functions displayed by the melanocortin receptors and their ligands offer attractive opportunities in addressing a variety of medical conditions including obesity,[4] cachexia,[13] inflammatory disorders,[14,15] sexual dysfunction,[4,16] and even infectious diseases.[17]

Significant efforts have been made in development of more potent and selective melanocortin ligands based on the endogenous agonists α-, β-, and γ-MSH,[18–21] while structure–activity relationship studies on the endogenous antagonists Agouti-signaling (ASIP)[22] and Agouti-related (AGRP)[23] proteins (Fig. 1) have received comparatively less attention.[24] The Agouti (-Arg-Phe-Phe-) tripeptide pharmacophore[25] differs significantly from the MSH (-His-Phe-Arg-Trp-) tetrapeptide pharmacophore,[26] and is a part of the central loop within the inhibitor cystine knot (ICK) motif in both Agouti proteins,[27] which suggests that the SAR trends observed for MSH peptides are unlikely to be manifested in the Agouti protein-derived analogues (Fig. 1). Previous literature reports describe truncation of both ASIP and AGRP sequences resulting in substantial loss of both binding affinities and antagonist/inverse agonist potencies,[28,29] while the Ac-mini-AGRP(87–120, C105A)-NH_2 variant has been reported to be equipotent to the full-length AGRP,[30] which points to possible significance of N- and C-terminal sequences of these proteins in receptor–ligand interactions. When the His-D-Phe-Arg-Trp MSH tetrapeptide pharmacophore was used to replace the Arg-Phe-Phe tripeptide sequence, the resulting cyclic peptide was a relatively potent agonist,[31,32] which can be attributed to the well-known propensity of the His-D-Phe-Arg-Trp tetrapeptide sequence to inducing melanocortin agonist activity in a wide variety of linear and cyclic peptide templates.[19,20,26,33–36] In another instance, replacement of the MSH pharmacophoric D-Phe-Arg-Trp tripeptide sequence with the agouti Arg-Phe-Phe sequence in the linear and cyclic α-MSH templates produced nanomolar range mMC1R agonists, which however registered >300 fold lower than the agonist potency of the super-agonist MT-II control as determined by CRE/β-galactosidase assay.[37] Our recent report[38] described a novel MSH/ASIP hybrid pharmacophore Arg-L/D-Phe-Xaa-L/D-Trp (Xaa = Cys or Glu), which, when incorporated into a monomeric cyclic disulfide template, yielded peptides with hMC3R-selective non-competitive binding affinities. In contrast, in a cyclodimeric lactam template this pharmacophore produced

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α-MSH Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

γ-MSH H-Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-Gly-OH

hASIP(92-132) SCVATRDSCKPPAPACCDPCASCQCRFFRSACTCRVLNPNC

hAGRP(86-132) RCVRLHESCLGQQVPCCDPCATCYCRFFNAFCYCRKLGTAMNPCSRT

MT-II Ac-Nle-c[Asp-His-*D*-Phe-Arg-Trp-Lys]-NH_2

SHU9119 Ac-Nle-c[Asp-His-*D*-Nal(2')-Arg-Trp-Lys]-NH_2

Figure 1. Sequences of some endogenous and synthetic melanotropin peptides.

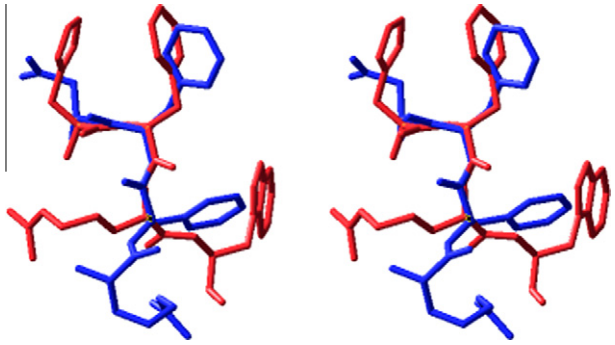

Figure 2. Stereo view of the retro-directed superposition of NMR structures of the pharmacophoric tetrapeptide sequences of endogenous hMC3/4R antagonist AGRP (blue) and of non-selective super agonist MT-II (red) (rmsd = 0.17 Å, C^{α} atoms of His[6], D-Phe[7], and Arg[8] residues of MT-II overlapped with the C^{α} atoms of the Asn[114], Phe[113], and Phe[112] residue of AGRP, respectively). Hydrogens are omitted for clarity.

nanomolar range (25–120 nM) hMC1R-selective full and partial agonists.

Comparison of the NMR structures of AGRP (110–117)[27] and MT-II[39] revealed striking similarities. Both structures feature a β-turn-like motif within the pharmacophore region, which spans over the first two residues in the His-D-Phe-Arg-Trp MSH pharmacophore, and the over the last two residues of the Arg-Phe-Phe-Asn AGRP pharmacophore. Intriguingly, a superposition of these pharmacophoric sequences in a retro-directed fashion (i.e., the C^{α} atoms of His[6], D-Phe[7], and Arg[8] residues of MT-II overlapped with the C^{α} atoms of the Asn[114], Phe[113], and Phe[112] residue of AGRP, respectively) revealed fairly similar overall topographies, matching the loci of the three pharmacophoric elements (two aromatic side chains, and a positively charged Arg side chain) that are believed to be involved in receptor–ligand interactions of both α-MSH analogues and AGRP (Fig. 2). The positions of Trp[9] (MT-II) and Arg[111] (AGRP) showed significant deviation, which was deemed unsubstantial, as much structural flexibility around Trp[9] in MSH analogues is known to be well tolerated by the hMCRs.[40] The hypothesis that the pharmacophores of α-MSH-derived ligands and AGRP are retro-directed in relation to one another suggests that a hybrid pharmacophore can be obtained by (a) replacement of Phe[112] with Trp; (b) D-amino acid substitutions in Phe[113] and Asn[114] positions to stabilize the β-turn motif; (c) Asn[114] position substitutions with other amino acids, in a fashion similar to His[6] position substitutions in α-MSH analogues; specifically, N114Q, N114H and N114R substitutions were planned, since similar modifications were reported previously for MSH-derived templates to affect the potency and receptor selectivity of the resulting peptide analogues (Fig. 3).[41,42] The resulting pharmacophore sequences were incorporated into two different 23-membered macrocyclic lactam templates, which provide global constraints (Table 1).[43–45]

The binding affinities and the agonist activities of the cyclic α-MSH analogues at the hMC1 3, 4 and 5R are summarized in

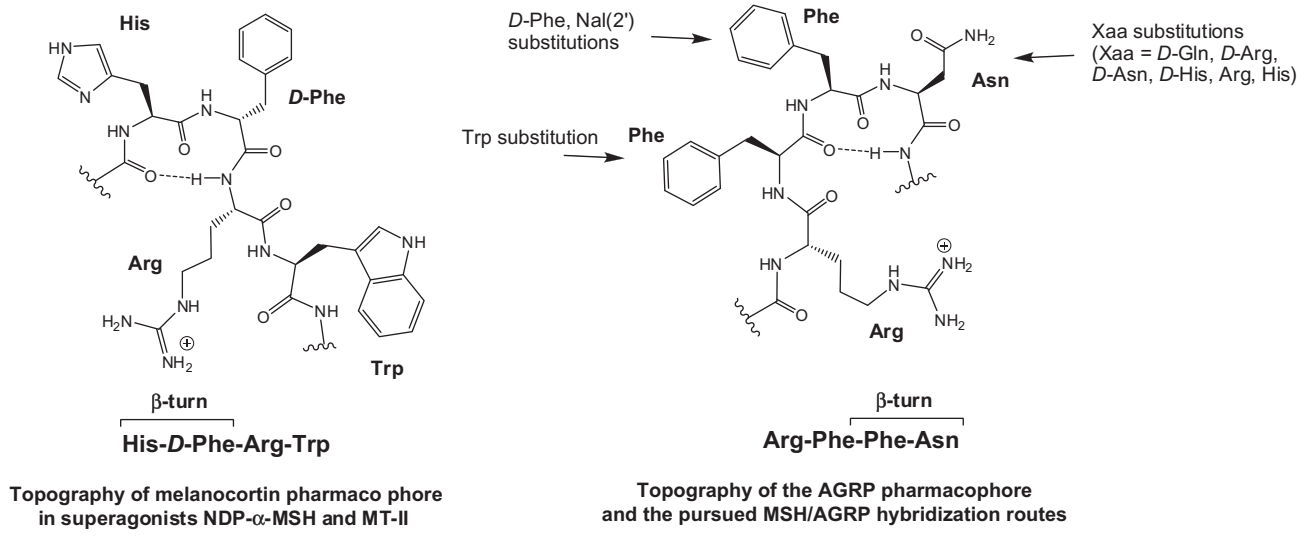

Figure 3. Design of the hybrid α-MSH/Agouti-related protein (AGRP) pharmacophore.

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