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Review Article

Use of the Chemical Structure of Peptides as the Starting Point to Design Nonpeptide Agonists and Antagonists at Peptide Receptors: Examples with Cholecystokinin and Tachykinins

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Introduction

The past 10–15 years has seen an increase in research into the discovery of nonpeptide small molecules that function as antagonists of neuropeptides and regulatory peptides. Several excellent recent reviews summarize strategies and give examples of these endeavours.[1–3] These objectives have been driven by the need to circumvent the perceived major limitations associated with peptides themselves as therapeutic agents. These limitations include poor bioavailability, short half-life, potential for immunogenicity, multiple actions and poorly controlled pharmacokinetics.

Nonpeptides derived from these approaches have been given a variety of names such as peptidomimetics, limetics or peptoids.[1–3] Ariëns and Farmer first coined the word 'peptoid' to describe a *monomeric* nonpeptide species that was able to mimic the three-dimensional display of the side-chains of key amino acids in the parent peptide, i.e. mimic the topographical relationship.[4] The word 'peptoid' has been recently used in the separate context of *N*-alkylglycine *oligomeric* species.[5] The word 'peptoid' in this review is used in the spirit of the Ariëns and Farmer definition as a nonpetide *monomeric* mimetic that has been derived from a peptide.

Mammalian neuropeptides and regulatory peptides are involved in numerous physiological and pathophysiological processes, acting as neurotransmitters, neuromodulators or as hormones. These functions are in common with those of the classical small molecule hormones and neurotransmitters.

The chemical structures of the small molecule hormones have served as starting points for medicinal chemists to design important therapeutic agents. For example, the catecholamines epinephrine and nor-epinephrine have been chemically modified to produce the anti-hypertensive β-adrenergic blockers such as propranolol as well as the anti-asthmatic β-adrenergic agonists such as salbutamol; histamine has been modified to give the anti-ulcer selective H_2 antagonists such as cimetidine; and 5-HT (serotonin) has been modified to give the anti-migraine 5-HT1_D agent sumatriptan (Fig. 1).[6] Hence, both therapeutically important agonists and antagonists have been derived from the chemical lead of the hormone itself.

With these important precedents in the discovery of novel therapeutics, we endeavoured to use polypeptides as our chemical lead. The success of this approach in the area of cholecystokinin (CCK-A and CCK-B receptors) and tachykinin (NK-1 and NK-2 receptors) are illustrated in this review and are outlined in Figure 2.[7]

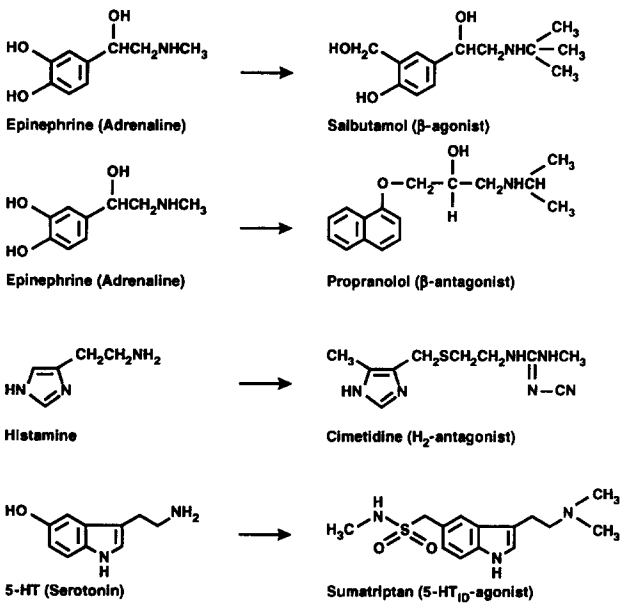

Figure 1. Examples where the chemical structure of small molecule hormones and neurotransmitters serve as the starting point for novel therapeutic agents.

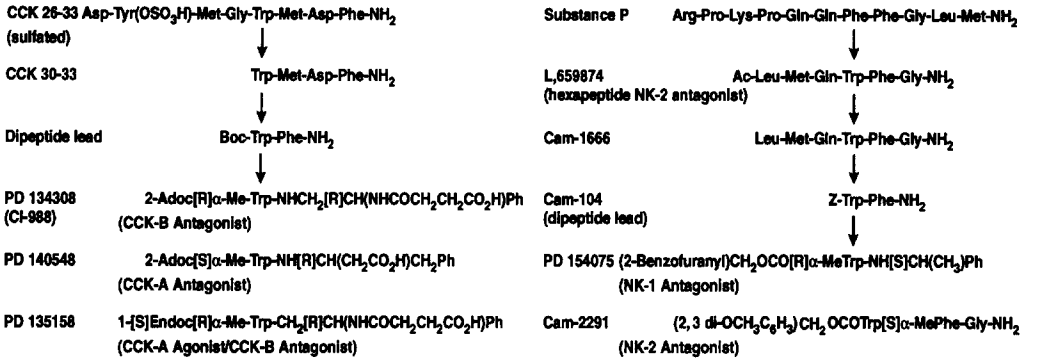

Figure 2. The development of small molecule 'peptoids' for the CCK-A, CCK-B, NK-1, and NK-2 receptors starting from the chemical structures of cholecystokinin (CCK-26–33 (sulfated)) and substance P.

Modifications/Deletions to Cholecystokinin and Tachykinins (Substance P) to give Nonpetide Agonists and antagonists

Amino acid deletion studies on CCK 26–33 (sulfated) identified the dipeptide Boc Trp—Phe—NH_2 as a *noncontinuous* fragment that retained micromolar binding affinity for the CCK-B receptor. In short, introduction of the semi-rigid conformational constraint of an α-MeTrp- moiety to this dipeptide, deletion of the *C*-terminal amide, replacement of the *N*-terminal Boc- by 2-adamantyl-oxycarbonyl (2-Adoc), addition of a carboxylic acid side-chain (to topographically mimic the Asp- side-chain of CCK) and optimal identification of the two chiral centres gave the nanomolar affinity and selective nonpetide ('peptoid') CCK-A antagonists such as PD 140548,[8] the CCK-B antagonist PD 134308 (CI-988)[9] as well as the interesting mixed agonist/antagonist PD 135158 for the CCK-A and CCK-B receptor (Fig. 2).[10] Interestingly, PD 135158 is a weak micromolar potency but *full efficacy* CCK-A agonist. Its chemical structure has been recently been hybridized with a CCK 30–33 CCK-A agonist tetrapeptide derivative to produce a nanomolar potency nonpeptide (**1**) (Fig. 3) as a pure CCK-A agonist.[11] This represents the first highly potent nonpeptide agonist to be derived from a peptide structure.

The tachykinin NK-1[12] and NK-2[13] antagonists PD 154075 and Cam-2291, respectively, were developed from substance-P, via the hexapeptide NK-2 antagonist, L-659,874 (Fig. 2). In short, an alanine scan on L-659,874 revealed the importance of the Trp—Phe *continuous* fragment for both NK-1 and NK-2 receptor binding. Similar to the experience with CCK, modifications to the *C*-terminal (chain shortening for NK-1, glycine extension for NK-2), N-terminal (2-benzofuranyl for NK-1, 2,3-di$OCH_3C_6H_3$ for NK-2), and introduction of methyl groups as semi-rigid conformational constraints ([*R*]αMeTrp for NK-1, [*S*]αMePhe for NK-2) gave the nanomolar potent and highly selective NK-1 and NK-2 antagonists such as PD 154075 and Cam-2291, respectively.

Role of the αMe-Conformational Constraints in the Design Strategy

The importance of the α-methyl groups as conformational constraints is worthy of comment. In the cases above, and other examples in our laboratory, this constraint was instrumental as a low molecular weight 'device' to induce selectivity and high affinity for these ligands. It has been suggested that the resultant geminal substitution of the α-amino acid forces appended amino acids into a β-bend arrangement.[14] Interestingly, an analogy in the study of reaction coordinates has suggested that geminal dimethyl groups placed in the *center* of linear molecules facilitates proximity effects, by allowing preferred population of favored ground state conformations on probability grounds.[15] Hence, such semi-rigid constraints may serve to aid population of 'productive' conformations that are recognized by the receptors.

Therapeutic Potential of the CCK and Tachykinin Ligands

CCK-A antagonists may have therapeutic potential for irritable bowel syndrome (IBS), the treatment of pancreatitis and pancreatic tumors. CCK agonists, such as **1** may find use in the treatment of obesity as this compound was shown to be a potent anorectic agent in rats (ED_{50}=30 nmol/kg ip).[11] The CCK-B antagonist PD 134308 (CI-988) is a highly lipophilic compound and, although it has apparent low bioavailability, is

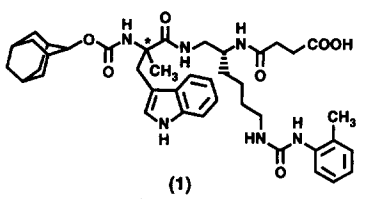

Figure 3. Chemical structure of the CCK-A nonpeptide monomolar potency agonist (**1**).

under clinical development as a novel anti-anxiety agent.[16]

The tachykinin NK-1 antagonists show promise in the treatment of disorders ranging from emesis (e.g. in co-administration with emetic chemotherapeutic agents such as *cis*-platin and streptozocin), schizophrenia and neurogenic inflammation associated with disorders such as rheumatoid arthritis, asthma and migraine.[17] PD 154075 is under clinical development for such conditions. This compound, despite being a secondary amide, has a good pharmacokinetic profile in rats and dogs (e.g. oral bioavailability = 49%; 1/2 life = 3 h po in rats).

Hence, 'peptoids' compounds of this type appear to be able to show both a pharmacodynamic and pharmacokinetic profile compatible with oral administration as therapeutic agents.

Agonist/Antagonist Profile of the Nonpetide CCK Ligands

The agonist/antagonist profile of the CCK ligands is worthy of comment. The CCK Trp—Phe derivatives show a spectrum of properties. At the CCK-A receptor both PD 135158 (Fig. 2) and **1** (Fig. 3) show agonist properties whereas the close analogue PD 140548 is a CCK-A antagonist. PD 134308 (CI-988) behaves as a CCK-B antagonist in its ability to block CCK evoked spontaneous firing of isolated neurons from the ventromedial nucleus of the hypothalamus from rat.[18] However, PD 134308 and its didehydro analogue PD 136450 act as a CCK-B/gastrin partial agonist in a rat gastric acid secretion assay.[19] These results lend support to the notion that both agonist and antagonists can be derived from this drug design strategy. These results therefore parallel the earlier experiences with the catecholamines described above. The classical example from the peptide receptor field where such a spectrum is found with nonpetides is with the opioids, where chemical modification to morphine (a nonpetide agonist at opiate receptors) can lead to either partial agonism such as seen with the benzomorphans, or full antagonists such as naloxone and nalorphine.[20]

Development of Tachykinin NK-3 Antagonists by Utilizing a Dipeptide Library

Inspection of the results summarized in Figure 2 reveals that identification of dipeptide leads was critical in the development of the CCK-A, CCK-B, and tachykinin NK-1 and NK-2 dipeptide and amino acid derivatives. Modified dipeptides and amino acids do constitute important orally bioavailable therapeutic agents. For example, captopril is essentially an *N*-terminally modified Ala—Pro-derivative, methotrexate is an *N*-terminally modified glutamic acid derivative, and α-methyl Dopa is an α-methyl geminally constrained derivative of Dopa. These three important therapeutic agents have an oral bioavailability of 65, 65 and 25%, respectively.[21]

Based on our experience, and these precedences, we elected to construct a dipeptide library consisting of 256 modified dipeptides that, by a principle component analysis, represented a *minimal data set* to use for screening at peptide and other receptors.[22] For example, this approach led to the identification of the hydrophobic biased dipeptide Boc—Phe—Phe—NH_2 as a micromolar hit for the human tachykinin NK-3 receptor. We felt comfortable with this as a novel lead because the continuous Phe—Phe motif is also found in the endogenous mammalian NK-3 agonist, neurokinin-B. The SAR of the conversion of this lead into the dipeptide NK-3 antagonist PD 157672, [23] and its nonpetide analogue PD 161182[24] is outlined in Figure 4. Both compounds were shown to be functional nanomolar potency NK-3 antagonists in the guinea pig habenula and human receptor expressed in CHO cells.[23,24]

Conclusion

It appears from the results presented here that the molecular recognition information embedded in the chemical structure of derivatives of single members of the 20 genetically encoded amino acids can give rise to functional peptide receptor agonists and antagonists. These small molecule nonpetides ('peptoids') have the ability to show pharmacodynamic and pharmacokinetic properties consistent with the expectations for orally active therapeutic agents. We are currently developing these concepts further to create other novel templates that may interact with other peptide receptors and mimic protein–protein interactions.

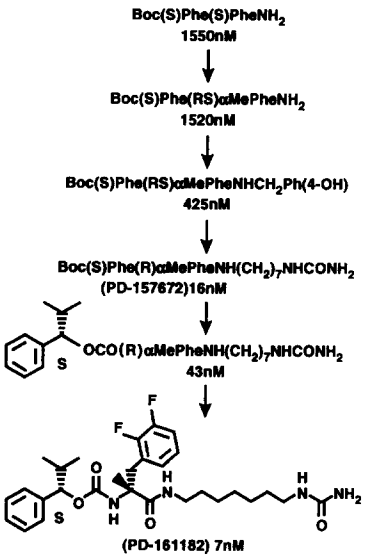

Figure 4. The development of a nonpeptide NK-3 receptor antagonist PD-161182 from the hydrophobic dipeptide Boc—Phe—Phe—NH_2 (nM figures represent binding affinities at human NK-3 receptors).

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References

1. Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed.* **1993**, *32*, 1244.

2. Dutta, A. S. In *Small Peptides, Chemistry, Biology and Clinical Studies, Pharmacochemistry Library*; Timmerman, H., Ed.; Elsevier: Amsterdam, 1993; Vol. 19.

3. Hirschman, R. *Angew. Chem. Int. Ed.* **1991**, *30*, 1278.

4. Farmer, P. S.; Ariëns, E. J. *Trends Pharmacol. Sci.* **1982**, *5*, 362.

5. Kessler, H. *Angew. Chem. Int. Ed.* **1993**, *32*, 543.

6. Ganellin, R. C. In *Medicinal Chemistry Principles and Practice*; King, F. D., Ed.; Royal Society of Chemistry, 1994; pp 185–205.

7. Horwell, D. C. *Trends Biotechnol.* **1995**, *13*, 132.

8. Boden, P.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; Hughes, J.; Rees, D. C.; Roberts, E.; Singh, L.; Suman-Chauhan, N.; Woodruff, G. N. *J. Med. Chem.* **1993**, *36*, 552.

9. Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. *J. Med. Chem.* **1991**, *34*, 404.

10. Höcker, M.; Hughes, J.; Fölsch, U. R.; Schmidt, W. *Eur. J. Pharmacol.* **1993**, *242*, 105.

11. Dezube, M.; Sugg, E. E.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; James, M. K.; Johnson, M. F.; Mosher, J. T.; Queen, K. L.; Rimele, T. J.; Sauls, H. R.; Triantafillou, J. A. *J. Med. Chem.* **1995**, *38*, 3784.

12. Boyle, S.; Guard, S.; Higginbottom, M.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A.; Martin, K.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J.; Woodruff, G. N. *Bioorg. Med. Chem.* **1994**, *2*, 357.

13. Boyle, S.; Guard, S.; Hodgson, J.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A.; Martin, K.; Pritchard, M. C.; Watling, K. J.; Woodruff, G. N. *Bioorg. Med. Chem.* **1994**, *2*, 101.

14. Formaggio, F.; Toniolo, C.; Crisma, M.; Valle, G.; Kaptein, B.; Shoemaker, H. E.; Kamphuis, J.; Di Blasio, B.; Maglio, O.; Fattorusso, R.; Benedetti, E.; Santini, A. *Int. J. Peptide, Protein Res.* **1995**, *45*, 70.

15. Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595.

16. Dethloff, L. A.; De La Iglesia, F. A. *Drug Metab. Rev.* **1992**, *24*, 267.

17. Maggi, C. A.; Patacchini, R.; Rovero, P.; Giachetti, A. *J. Auton. Pharmacol.* **1993**, *13*, 23.

18. Hughes, J.; Boden, P.; Costall, B.; Domeney, A.; Kelly, E.; Horwell, D. C.; Hunter, J. C.; Pinnock, R. D.; Woodruff, G. N. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6728.

19. Schmassmann, A.; Garner, A.; Flogerzi, B.; Hasan, M. Y.; Sanner, M.; Varga, L.; Halter, F. *Gut* **1994**, *35*, 270.

20. Rees, D. C.; Hunter, J. C. *Comprehensive Medicinal Chemistry*; Emmett, J. C., Ed.; Pergamon: New York, 1990; pp 805–846.

21. *The Pharmacological Basis of Therapeutics*; Gilman, A. G.; Goodman, L. S.; Dall, T. W.; Mirad, F., Eds.; Macmillan: New York, 1985; pp 1673, 1695, and 1696.

22. Horwell, D. C.; Howson, W.; Ratcliffe, G. S.; Rees, D. C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 799.

23. Boden, P.; Eden, J. M.; Hodgson, J.; Horwell, D. C.; Howson, W.; Hughes, J.; McKnight, A. T.; Meecham, K.; Pritchard, M. C.; Raphy, J.; Ratcliffe, G. S.; Suman-Chauhan, N.; Woodruff, G. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1679.

24. Boden, P.; Eden, J. M.; Hodgson, J.; Horwell, D. C.; Pritchard, M. C.; Raphy, J.; Suman-Chauhan, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1773.

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