Neuropeptide Y

AND Drug Development

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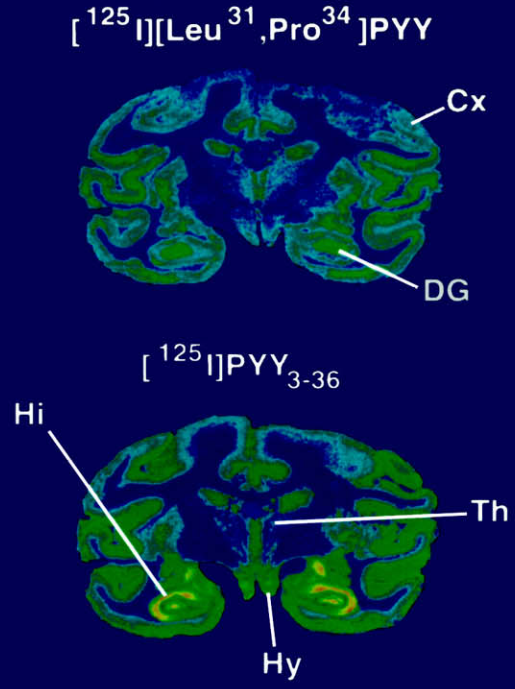

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Front cover: Autoradiography showing the distribution of Y1-binding sites (top) and Y2-binding sites (bottom) at the level of the hippocampal formation of the monkey brain (see Dumont *et al.*, Chapter 4).

Back cover: Serendipity means the faculty of making fortunate discoveries by accident. The word comes from the Persian fairy tale 'The Three Princes of Serendip' (from Persian Sarandip, former name of Sri Lanka), the heroes of which were . . . 'always making discoveries, by accident and sagacity, of things they were not in quest of', and the expression serendipity was coined by the English author Horace Walpole in 1754. Serendipity is sometimes used in the pharmaceutical process of drug development in order to illustrate the random discovery of drugs and the often unpredictable ways they undergo to their final therapeutical niche (see also Preface).

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A colour plate section appears between pages 148 and 149

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Preface: the search for new therapeutic approaches

'New beauty pill – lose pounds on a once-a-day tablet'. Such newspaper headlines announce yet another spurious breakthrough in a field over-ripe with expectation. The first genuinely safe and effective oral therapy that can be taken over decades will be the world's first trillion dollar drug.

Neuropeptide Y (NPY) causes hypertension, increased food intake, inhibits sexual function, inhibits growth and causes sedation, amongst several other actions. The mythical NPY-blocked man would be thin, tall, vivacious and very interested in sex. Certainly a profitable image.

More seriously, many drugs acting on neuro–hormonal targets modulate the transmission in monoamine transmitter systems, like dopamine, noradrenaline and serotonin. These drugs include antiparkinsonism drugs, neuroleptics, antidepressants and antihypertensive drugs and the principles of how these drugs act are well understood. The launch of such therapeutics in the 1950s and 1960s represented breakthrough achievements in the treatment of many disorders. Ironically, several of these drugs were introduced clinically before they were recognized as important neuropharmacological tools with which it was possible to delineate the significance of monoamines as transmitters in various physiological processes and pathological states.

Developments during the last two decades resulted in the discovery of many novel transmitter types, such as the neuropeptides and polypeptide hormones. Although, there are obvious differences between monoamine transmitters and peptide transmitters in molecular size and processing, monoamines and neuropeptides have many features in common. In fact, transmitters from both chemical groups are often co-stored and co-released from nerve terminals, act on the same neurons through activation of distinct and specific receptors, and affect the same ion channels and signal transduction pathways. Vasopressin and oxytocin analogues, ACTH and some other polypeptide agonists have been used clinically in substitution therapy and other conditions for a number of years. However, for clinical use, peptides suffer from poor pharmacokinetic properties, such as low oral bioavailability and rapid degradation.

Most neuropeptides, like many other neurotransmitters, activate G-protein-coupled receptors. Characteristic of this receptor superfamily are the seven transmembraneous spanning domains, which are linked together by extracellular and intracellular loops, of which the third intracellular loop is known to modulate the function of the G-protein.

It has sometimes been argued that neuropeptides act merely as modulators or that they are redundant in mammalian physiology. The rapidly increasing body of knowledge about the various neuro/hormonal peptide systems in the brain and periphery suggests that many of them indeed play a role in controlling important physiological processes and that several of the peptide receptors are promising therapeutic targets. Although the cloning of monoamine receptors has shown that they consist of many

more receptor types than expected, the multitude of neuropeptides and their many receptors offer a large number of additional and attractive drug targets. Much effort has been taken to identify the pharmacophore of several neuropeptides (and other transmitters) and the parts of the receptor that recognize the ligand. This knowledge, in addition to high throughput screening techniques, has been beneficial in the search for non-peptide ligands acting on peptide receptors. Thus, it appears that the obstacle of constructing non-peptide receptor antagonists can be overcome and, for example, the angiotensin II (AT1)-receptor antagonist losartan has recently been approved for use in hypertension in several countries. In many neuropeptide receptor systems there is a search for new therapeutic approaches and they include, for instance, modulation of opioid-, tachykinin-, cholecystokinin-, neurotensin- and NPY receptor systems.

NPY is a member of a family of peptides, which also includes the structurally related gut hormones peptide YY (PYY) and pancreatic polypeptide (PP). Since the isolation and identification of NPY in 1982, several thousand publications have examined various aspects of this neuropeptide. NPY has received much attention because it is ubiquitous in the mammalian nervous system and because numerous physiological functions in the brain and periphery have been attributed to the peptide. Interestingly, the NPY molecule is remarkably well conserved through evolution and appears to be the oldest member in this peptide family, suggestive for an important physiological role of this peptide. For instance, NPY is one of the most potent stimuli of food intake known and it occurs in hypothalamic nuclei known to regulate feeding behaviour. The peptide has been implicated in disorders related to altered energy balance, like obesity and anorexia/bulimia. In the periphery, the peptide occurs in perivascular sympathetic nerve fibres and it is co-released with noradrenaline upon high sympathetic nerve activity. NPY is a potent vasoconstrictor, being several orders of magnitude more potent than noradrenaline and the peptide has been implicated in various cardiovascular disorders.

Very recently Erickson and coworkers presented results on functional consequences of embryonic NPY gene knock out in mice (*Nature* (1996) **381**, 415–418). Such mutated mice appeared to have a normal food intake and body weight, but were more sensitive to weight loss following leptin treatment. Besides an increased susceptability to epileptic seizures, these mice did not show any other gross anomalies and were able to reproduce. These seemingly disappointing results on the importance of NPY in feeding behaviour and other physiological processes should naturally be interpreted with caution. The fundamental system(s) that regulates feeding behaviour consists of many parallel neurotransmitter pathways in a highly complex manner. Conceivably, these results illustrate an embryonic dynamic plasticity, resulting in compensatory mechanisms that are not necessarily apparent in the mature individual. A temporary blockade of NYP effects in the adult animal is probably required to elucidate this issue.

NPY and its congeners act at multiple receptor types, belonging to the family of G-protein-coupled receptors. Several of the NPY-receptor types are promising targets for drug development and many pharmaceutical companies are carrying out research

on this peptide. The rational approach of designing non-peptide receptor antagonists by identifying peptide pharmacophores using minimization of polypeptides, followed by the construction of small non-peptide ligands has generated useful NPY-receptor antagonists. The most promising areas for application of NPY-receptor antagonists appear to be in the treatment of obesity and perhaps cardiovascular disorders.

An irrational but important factor in the drug discovery and development is serendipity. Often it is difficult to predict the clinical value of a drug candidate based solely on recognized pharmacological effects. For instance, who could have foreseen the widespread use of β-adrenoceptor antagonists in the treatment of hypertension and other cardiovascular disorders? The pharmacological history of drug development illustrates the fact that important breakthroughs are often associated with accidental findings, and that many drugs on the market are used today on indications quite distinct from those originally predicted. In the case of NPY, it is important first to elucidate the physiological and pathophysiological significance of the peptide. With the use of newly developed NPY receptor antagonists, such knowledge is about to emerge. This knowledge can then be used to increase our understanding of how these agents can best be used in a clinical context. It is not unlikely that future studies will discover novel clinical applications of NPY-receptor antagonists distinct from those already proposed. However, an area that is not discussed in this book is the possible utility of NPY-receptor agonists, which perhaps may be beneficial in nasal congestion, diarrhoea, anxiety, epilepsia and pain. More studies are required to assess the role of NPY in these conditions and it is generally difficult to construct non-peptide agonists with acceptable pharmacodynamic and kinetic properties compared with non-peptide antagonists.

Previous books about NPY have been either proceedings from symposia and meetings, or have aimed to cover wide aspects of the whole NPY/PYY/PP family. This book discusses why NPY-receptors represent promising therapeutic targets and describes the latest progress in NPY pharmacology, molecular biology of receptors, characteristics of newly developed NPY-receptor antagonists, and focuses on physiological systems where the use of such antagonists might offer new therapeutic approaches. Efforts have been made to link basic experimental knowledge with areas of possible clinical importance.

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