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Erratum

Erratum to: "Receptor chemistry towards the third millennium"☆ [Farmaco 55 (2000) 69–75]

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The publisher sincerely regrets that the above article had incorrect running headlines and accepts full responsibility for this error. The corrected article is published in its entirety on the following pages.

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Meeting Report

Receptor chemistry towards the third millennium[☆,☆☆]

12th Camerino–Noordwijkerhout Symposium held in Camerino (MC), Italy, September 5–9, 1999

The series of Camerino Symposia present the most recent knowledge and discoveries in the growing field of drug–receptor interaction and the design and mechanisms of drug action. "*Receptors in Neurodegenerative Diseases*" was the general subject of this "*End-of-Millennium meeting*" chaired by Mario Giannella (University of Camerino, Italy). Specifically, the meeting focused on the involvement of cholinergic and adrenergic receptors in neurodegenerative and cardiovascular diseases, respectively, and also provided an update on sigma-, imidazoline-, excitatory amino acid-, chemokine-, kappa opiod-, ICAM-1-, and neurotrophin-receptors. Almost 200 participants in an international audience, composed principally of chemists, biochemists and pharmacologists, spent the five days of the conference in the eye-catching medieval setting of the University of Camerino and enjoyed both the scientific and cultural programs. Despite some residual damage from the earthquake of 1997, the town again put its best face forward for a very successful meeting.

1. Introduction

The well-balanced interdisciplinary cooperation among chemists, biochemists, pharmacologists, biophysicists and physiologists continues to be the main feature and the driving force of this symposium which is, in fact, a continuation of a series started in 1978 and from 1987 run jointly as the Camerino–Noordwijkerhout series alternating every 2 years between Camerino and Noordwijkerhout (The Netherlands). The 1999 edition was attended by close to 200 participants, from industry and academia, from 19 countries, who listened to 40 speakers.

2. Cholinergic receptors and neurodegenerative diseases

Fulvio Gualtieri (University of Florence, Italy) chaired this first session dedicated to the cholinergic approach for the treatment of dementias and particularly of Alzheimer's disease (AD). Currently available drugs are not particularly effective — tacrine, donezepil and rivastigmine —when directed against cholinesterase or muscarinic receptors. Amyloid β peptides derive from abnormal proteolytic processing of amyloid precursor protein (APP) and represent highly hydrophobic and self-aggregating molecules suspected of being the main determinant of the disease. Since the stimulation of muscarinic M_1 receptors can accelerate the α-secretase cleavage of APP, the efforts of many researchers have been directed towards developing compounds able to increase the level of cholinergic transmission in the brain directly (nicotinic and M_1 selective muscarinic agonists) or indirectly (acetylcholinesterase inhibitors, M_2 selective muscarinic antagonists, acetylcholine releasers, high-affinity choline uptake inhibitors). The potential of centrally acting nicotinic agonists has been recognized for the treatment of Parkinson's disease (PD) as well, because of their ability to release other neurotransmitters like dopamine.

2.1. Nicotinic receptors

CNS nicotinic mechanisms in normal human cognitive and behavioral functioning as well as their role in disease states, including AD, PD, schizophrenia and Tourette's disorder, were discussed by Paul Newhouse (University of Vermont, College of Medicine, Burlington, VT, USA). Nicotinic receptors are involved in the control of ACh, DA and NE release as well as the control of NGF release — all involved in memory functions and neuronal growth and development, respectively. A positive association has been described

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between smoking and the incidence of AD and the moderation of schizophrenia. The nicotinic receptor is a ligand-gated ion channel and the $\alpha_4\beta_2$-type is of particular importance in the CNS. Recent studies with nicotine and novel nicotinic agonists such as ABT-418 in AD patients suggest that nicotinic stimulation can improve the acquisition and retention of verbal information and decrease errors. Acute administration and stimulation of nicotine and the novel nicotinic agonist SIB-1508 improve some aspects of cognitive and motor performance and may improve the processing speed of more complex tasks.

An overview by Richard Glennon (School of Pharmacy of Virginia Commonwealth University, VA, USA) focused on the structure–activity relationships (SARs) formulated in pharmacophores [Beers and Reich, Nature 225 (1970) 917; Sheridan et al., J. Med. Chem. 29 (1986) 899] for the binding of nicotinic agents at, primarily, $\alpha_4\beta_2$-type nicotinic receptors. The affinity values of many nicotinoids (compounds displaying a structural similarity to nicotine in that they contain a basic nitrogen atom and a pyridine, or equivalent, aromatic ring) and miscellaneous agents, for the $\alpha_4\beta_2$ population of nicotinic acetylcholine receptors (nAChRs), were presented and related to the nicotine structure. Limitations to these early pharmacophore models were presented. Glennon also presented ligands active on α_7 nAChRs, a neuronal population characterized by high affinity for α-bungarotoxin and reduced affinity for nicotine.

Structural aspects of high-affinity ligands for the $\alpha_4\beta_2$ neuronal nicotinic receptor was the subject dealt with by Michael J. Dart (Abbott Laboratories, Abbott Park, IL, USA). On the theme of pharmacophores Dart noted that the compounds having low-energy conformations that achieve the best-fit superposition with the putative pharmacophoric elements of (−)-epibatidine also exhibit the highest binding affinity for the $\alpha_4\beta_2$ receptor. He observed that the receptor exists in multiple allosteric states and that ligand binding assays, reflecting principally the desensitized state may not mirror functional status. He observed that nicotine and epibatidine have served as structural templates for the design of the majority of active compounds and that all potent $\alpha_4\beta_2$ ligands include a basic or quaternized nitrogen atom and a less basic nitrogen or a carbonyl oxygen interacting with electron rich and electron deficient sites on the receptor, respectively. Among the ligand classes retaining potent $\alpha_4\beta_2$ receptor binding affinity, the pyrrolizidine, 2-azabicyclo[2:2:1]heptane and furo[2-3-*b*]pyridine nuclei serve as useful design templates. ABT-594, a member of a novel series of 3-pyridyl ether compounds, possesses broad-spectrum antinociceptive activity in preclinical models and is the first nAChR-mediated analgesic to enter human clinical trials.

Nicholas D.P. Cosford (SIBIA Neurosciences Inc., La Jolla, CA, USA) outlined the SIBIA approach of screening in cell lines with a fluorescence-based assay and discussed altinicline (SIB-1508Y), a selective nAChR agonist that was discovered by employing a medicinal chemistry approach based on modifying the structure of nicotine. This small molecule, designed to selectively activate neuronal nAChRs, is in Phase II clinical trials for PD where it has shown neuroprotective properties in animal models. Biological data for cognitive deficits and antidepressant properties were also presented.

M. Rosini (University of Bologna, Italy) discussed the polymethyleneamine 'universal template' [Bolognesi et al., J. Med. Chem. 41 (1998) 4150], which appears in molecules active at multiple receptor types including muscarinic, adrenergic, opiod and others. Methoctramine is the parent member of the series and this structure was combined with the non-competitive philanthotoxin-343 to obtain new molecules.

2.2. Muscarinic receptors

In an introductory review the session Chair, Piero Angeli (University of Camerino, Italy), discussed the muscarinic receptor classification, m1–m5 and M_1–M_5, and the ligands available and the extent of receptor discrimination provided by them.

William S. Messer (College of Pharmacy, The University of Toledo, Toledo, OH, USA) and Haile Tecle (Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Ann Arbor, MI, USA) presented their results on selective M_1 muscarinic agonists useful for the treatment of AD. Messer presented CDD-0102 (a 1,4,5,6-tetrahydropyrimidine with an oxadiazole substituent) and xanomeline, two agonists that can reverse memory deficits associated with a loss of basal forebrain cholinergic function. CDD-0102 and xanomeline are both functionally selective for M_1 receptors. CDD-0102 is considered a candidate for clinical trial. Messer discussed a bivalent ligand approach for developing more selective muscarinic agonists in which two xanomeline molecules were linked by a flexible chain of varying lengths and maintained activity. Zang and Wess [J. Biol. Chem. 274 (1999) 19487] have reported dimeric muscarinic receptors.

A series of 1-azabicyclo[2.2.1]heptane-3-one oximes are potent muscarinic agonists whose SAR studies were outlined by Tecle. He argued that 'larger' agonists were needed in order to provide better receptor subtype discrimination. CI-1017 improved spatial memory in hippocampal deficient mice and nbM-lesioned rats and markedly increased the soluble form of APP and decreased the production of amyloidogenic Aβ. CI-1017 was found to be well tolerated in Phase I clinical trials and is proceeding into Phase II studies.

The idea that drugs acting at allosteric sites of the muscarinic receptor might achieve the selectivity thus far not realized at the agonist site has long been attractive, although unproven. Ligands for the allosteric site of ACh M_2 receptors are able to retard the dissociation of simultaneously bound ligands for the orthosteric site. Ulrike Holzgrabe (University of Würzburg, Germany) optimized the affinity of the modulators for the common allosteric binding site of muscarinic M_2 receptors, taking the phthalimido substituted alkane–bisammonium compound W 84 as a starting point. With 3D QSAR analysis, Holzgrabe presented highly potent compounds characterized by a rigid hydrophobic moiety in position 3 of the phthalimide and a large aromatic area annellated to the imide. The perspective to find ligands endowed with higher allosteric potency and suitable for therapeutic purposes may be closer. Allosteric modulators of muscarinic M_2 receptors were presented by D.P. Zlotos (University of Würzburg, Germany; poster presentation) as bisquaternary caracurine V derivatives: depending upon the substituents affinities varied from 3 to 1750 nM as allosteric modulators.

New analogues of McN-A-343 were reported by C. Keim (University of Frankfurt, Germany; poster presentation). Very potent compounds were obtained with a phenyl substituent in the side chain and 4-F in place of 3-Cl (pK_I values of 9.40–8.60 against M_1-M_5), but no real evidence of selectivity. The 2,2-diphenyl-1,3-dioxolane-4-trimethylammonium structure was modified to add *N*-alkyl substituents of chain length $n = 2–5$ (P. Angeli et al., University of Camerino, Italy; poster presentation). Varying degrees of receptor selectivity were obtained according to n and the *N*-alkyl substituents: when $n = 1$ and R and $R' = Et$, M_1 and M_2 selective; when $n = 4$ and R and $R' = Me$, M_3 selective.

3. Receptors in cardiovascular diseases

3.1. Adrenergic receptors

Amedeo Leonardi (Pharmaceutical R&D Division, Recordati S.p.A., Milan, Italy), charged Chair of this session, could not be present because of illness.

J. Paul Hieble (SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA) presented a comprehensive analysis of adrenoceptor (AR) classification and of the drugs that interact with these receptors. Emphasis was given to the therapeutic role of each subtype, notably hypertension, benign prostatic hyperplasia (BPH), congestive heart failure, cardiac arrhythmia. Among the α_1 antagonists, prazosin congeners doxazosin and terazosin remain important options in the treatment regimen available for hypertension, while the cardiovascular profile of the selective α_{1B} antagonists (+)cyclazosin and L-765,314 has not been extensively characterized. Selective α_1 antagonists, such as RS 17053, Rec. 15/2739, SL 890591 and the most recently introduced tamsulosin, have been proven to be effective drugs for BPH. Potential targets for an α_2-antagonist include hypertension, obesity, non-insulin-dependent diabetes and erectile dysfunction. BRL 48962 is, at the moment, the only antagonist endowed with significant α_{2A} selectivity. α_1 Agonists may be useful to increase the tone of the urethral sphincter as therapy for stress incontinence, without an associated increase in systemic blood pressure. NS-49, an α_1 agonist having this selectivity profile, is currently in clinical trials for stress incontinence. β_3 Agonists, such as BRL 37144, have been evaluated in man as potential anti-obesity and anti-diabetic drugs. The difficulty in extending useful agents in this area from rodent to human pharmacology was noted: BRL 37344 is selective at β_3 rodent receptors but is not efficacious in man. Most drugs act at a single receptor type, but carvedilol, an antagonist with high affinity for all nine AR subtypes, has found clinical use in the treatment of congestive heart failure. It is possible that α_1 and β AR antagonist actions of carvedilol are synergistic in the therapy of heart failure patients. The existence of a β_4 receptor was speculated upon and may drive a cardiac inotropic response that might be helpful in acute congestive heart failure.

Susanna Cotecchia (University of Lausanne, Switzerland) presented the results of her studies combining 3D model building of the receptor structure with computational simulation of receptor dynamics on the activation process of the α_{1a} and α_{1b} adrenergic receptor subtypes as well as on the mechanisms of action of drugs acting at these receptors. Specific mutations that produced constitutively active mutants were discussed: in the α_{1b} receptor mutation of residue A293 produced a range of active receptors. A model was advanced that suggests that receptor switching maybe similar. A model was presented in which R143 lies in a polar pocket comprising N63, D91, N344, Y348 and T295. Protonation of D142 is linked to receptor activation by triggering the shift of R143 out of its pocket. The use of constitutively active receptors permitted analysis of antagonist ligands. *N*-arylpiperazines as alpha-blockers were identified that display the most striking difference at the two α_1 subtypes, being inverse agonists with negative efficacy at the α_{1b} type but not at the α_{1a} type. In particular, REC 15/3039, REC 15/2739 and REC 15/3011 are the first alpha-blockers identified so far which do not display inverse agonism at one of the α_1 subtypes, namely the α_{1a}. Preliminary SAR studies suggest that the geometry of the protonated nitrogen atom as well as that of the molecular moiety closest to this nitrogen might be responsible for the functional effect of the ligands tested.

Recent developments in the design of new α_1-AR antagonists bearing a quinazoline or a benzodioxane moiety were discussed by Carlo Melchiorre (University of Bologna, Italy). Structural modifications, such as replacement of the piperazine ring with a linear chain and of the furan ring with a phenyl unit, on prazosin-related compounds were summarized. In particular, the presence of a phenyl ring offered the opportunity to study the effect of different substituents in the receptor recognition process. Here a 2-MeO substituent or a 2-CF_3 substituent yielded α_{1a} and α_{1d} selective compounds, respectively [Giardinà et al., J. Med. Chem. 39 (1996) 4602]. Moreover, structural modifications performed on WB 4101-related compounds have been analyzed [Quaglia et al., J. Med. Chem. 42 (1999) 2961]. A *trans*-phenyl ring at C3 of the 1,4-benzodioxan maintained alpha-antagonist activity, but decreased activity at $5HT_{1a}$ and α_2 receptors. It has been shown that the replacement of the carbon chain separating the amine and the phenoxy groups of WB 4101 with a cyclopentane ring afforded stereoisomers that retained good affinity for α_{1D}-ARs or 5-HT_{1A} receptors according to the configuration of the cyclopentane unit.

Positron emission tomography (PET) is an imaging technique that provides the possibility to assess human cardiac ARs directly in vivo with the help of effective radioligands for the targeted ARs. Changes in the numbers of human ARs are associated with diseases, such as myocardial ischemia, congestive heart failure, cardiomyopathy and hypertension. Victor W. Pike (Hammersmith Hospital, London, UK) focussed on the status of AR radioligand development in the context of the imaging capabilities of PET. Several fundamental criteria, such as high affinity and selectivity for the target receptor population, antagonist action, stereoselectivity where enantiomers exist, low or moderate lipophilicity, low metabolism and toxicity, amenability to labeling with a positron-emitter (generally ^{11}C or ^{18}F), must be observed by a prospective radioligand to be effective for PET imaging of receptors in vivo. Among β-AR radioligands, [^{11}C]pindolol, [^{11}C](S)-carazolol and mainly [^{11}C](S)-CGP 12177 and [^{11}C](S)-CGP 12388 would be excellent radioligands for PET imaging, while [^{18}F](S)-1′-fluorocarazolol is a promising radioligand for imaging pulmonary and brain β-ARs. The use of PET to investigate the α-adrenergic system is of great interest, since in vitro evidence suggest that α_1-ARs levels alter because of myocardial ischemia. In this respect, [^{11}C]GB67, a potent and selective α_1-AR antagonist, appears as a promising radioligand for the study of α_1-ARs in human subjects and in normal male volunteers revealed a high and sustained uptake of radioactivity in myocardium giving a clear image of the left ventricular wall and septum.

4. Enigmatic receptors

4.1. Sigma and imidazoline receptors

An overview of the imidazoline (I) and sigma (σ) receptors was presented by Livio Brasili (University of Modena, Italy), focussing on the imidazoline and sigma receptors, sites still awaiting a clear-cut definition of physiological function and selective ligand action. At least three imidazoline-preferring sites exist of which I_1 and I_2 are associated with membrane and mitochondrial locations, respectively, and characterized by high affinity for both clonidine and idazoxan and for idazoxan alone. Endogenous ligands have been proposed, including 'clonidine-displacing substance' and agmatine (decarboxylated arginine). These sites await selective ligands as possible therapeutic agents in the treatment of a variety of disorders such as hypertension, diabetes mellitus, depression and stroke: new agents such as PMS 812, 2-BFI, BU-224, BU-239, tracizoline and benazoline are emerging.

Three sites (σ_1, σ_2 and σ_3) seem to define sigma (σ) receptors that play a modulatory role in the central nervous system. The search for selective σ receptor antagonists, which may be effective antipsychotic drugs, is producing specific compounds, such as NE 100 ($\sigma_1/\sigma_2 = 55$) an antipsychotic drug which is in Phase II clinical trials, and spipethiane, one of the most σ_1-selective ligands ($\sigma_1/\sigma_2 = 832$). The σ_1 receptor has some 30% homology to the C8-C7 isomerase of the sterol biosynthetic pathway.

The involvement of non-ARs in the induction of the hypotensive effect of imidazoline-related drugs was reviewed by Pascal Bousquet (Louis Pasteur University, Strasbourg, France). Recently, a synthetic imidazoline ligand, benazoline, which is 10 421 times more selective for IRs than for α_2-ARs (A_2Rs), has become available. LNP 509 is an imidazoline derivative selective for IRs, while S23515 exhibits high affinity for I_1Rs, with a selectivity ratio (I_1 over A_2Rs) over 4000. Finally, rilmenidine, an imidazoline-like oxazoline, has been defined as the first centrally acting antihypertensive drug selective for IRs. These results provide evidence that a drug highly selective for I_1Rs over A_2Rs can reduce blood pressure, and actions on I_1Rs and A_2Rs may potentiate each other through an interaction between themselves. This seems to account for the marked and rapid hypotensive effect caused by hybrid drugs, such as clonidine.

M. Massi (University of Camerino, Italy) discussed the possible role of I_2 receptors in hyperphagia. There appears to be a peripheral site at which imidazoline I_2 ligands influence feeding, but since idazoxan also induces feeding the role of an alpha-AR is not to be discounted.

Sigma receptors have important functions in brain and outside of the nervous system, and subserve a more general role than a neurotransmitter receptor. Sigma-1 and sigma-2 constitute two subclasses that are differentiable by pharmacological profile, function, and molecular size, both having high to moderate affinity for typical neuroleptics, with haloperidol exhibiting highest affinity for both sites. Wayne D. Bowen (National Institutes of Health, Bethesda, MD, USA) focused his attention particularly on the possible role of sigma-2 receptors in regulation of cell proliferation and maintenance of cell viability. This author presented his results showing that sigma ligands cause damage to cell processes and ultimate death by an apoptotic mechanism with concomitant changes in intracellular calcium and in cell morphology. On the therapeutic point of view sigma-2 receptor antagonists my be useful tools for ameliorating the debilitating effects of tardive dyskinesia resulting from chronic treatment of psychoses; sigma-2 receptor agonists could be useful alone as antineoplastic agents at doses which induce apoptosis or, at subtoxic doses, in combination with common antineoplastic agents to reverse drug resistance. Finally, activation of sigma-2 receptors could have chemosensitizing effects (potentiation of doxorubicin actions) and sigma receptor ligands may be useful for non-invasive tumor imaging.

5. Excitatory aminoacid receptors

Glutamate receptor systems were reviewed by Giovanni Gaviraghi (Glaxo Wellcome SpA, Verona, Italy). They remain a major target for neurodegenerative and related disorders although success has yet to appear clinically. Two main types of glutamate receptors have been identified: three inotropic receptors, that is *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate, and eight metabotropic glutamate G protein-coupled receptors designated as mGluR1–mGluR8. Their structure and functions and their subtypes have been characterized as well as their involvement in human diseases. The ionotropic NMDA receptor subtype has been associated with the neuronal damage induced by acute ischemia in stroke, while AMPA and mGluR2 subtypes to epileptic episodes. The amino acid glycine acts as a coagonist with glutamate of the NMDA receptor.

David G. Trist (Glaxo Wellcome SpA, Verona, Italy) related on the identification of the glutamate receptor subtypes. Changes in glutamate transmission have been associated with a number of CNS pathologies. Competitive glycine antagonists, such as GV150526, are neuroprotective and seem to have less side-effects than other approaches to block the NMDA receptor such as NMDA antagonists (CCP) or NMDA ion channel blockers (MK-801). In the MCAO model it reduced the spread of damage and it was reported to have promising physical and behavioral protective effects in a small ($n = 6$) IIA trial. A Phase III trial is now under way. Moreover, glycine antagonists such as GV196771 block hyperalgesia and allodynia in animal models of pain.

Roberto Pellicciari (University of Perugia, Italy) presented novel metabotropic glutamate receptor ligands able to disrupt the chain of events linked to neurodegeneration without impairing excitatory neurotransmission. Ligands for the glycine co-receptor site continue to be of interest as therapeutic agents. Daniele Donati (Glaxo Wellcome SpA, Verona, Italy) presented glycine antagonists with indole-2-carboxylate and benzazepinone structures. The indole derivative GV 228869 had a K_I value of 2 nM and was used as a pharmacophoric lead to the benzazepinone GV 224029 that had similar in vivo activity to GV 150526 now in Phase III clinical trial.

6. Receptors for neurodegenerative disorders

6.1. Neurotrophic factor receptors

Wolfgang Froestl (Novartis Pharma AG, Basel, Switzerland) discussed the use of trophic factors — NGF, BDNF, CNTF, GDNF — in the treatment of neurodegeneration associated with human diseases which is accounted for by their ability to regulate developmental neuronal survival and adult nervous system plasticity. The findings that nerve growth factor (NGF) prevents cholinergic neuron atrophy and ameliorates spatial memory impairment in rats led to the identification of molecules that induce the synthesis of NGF and potentiate its actions, such as the 5-HT_{1A} receptor agonist SR-57746A (Sanofi) which is in Phase 3 clinical trials, the hypoxanthine AIT-082 (Neotherapeutics), which is in Phase II, and GPI-1046 (Guildford). Froestl also noted the 'death receptors' — TNFR1, Fas/CD95, TRAMP, TRAIL1/2 and p75 NTR — activation of which leads to apoptosis.

Moses V. Chao (New York University School of Medicine, New York, NY, USA) outlined the control of cell survival and death by the NGF family as determined by the Trk receptor tyrosine kinase and the p75 neurotrophin receptor. These may be loosely associated and may function to bidirectionally control survival and death. p75 is upregulated in stress injury (a 'stress' receptor?) and the association of a death regulator with a growth factor may be important for correcting 'wiring when cells are exposed to the wrong factor'.

Mark W. Sleeman (Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) focussed on CNTF and its receptor (CNTFRα). This receptor anchors via glycosyl/PI linkage and with other proteins gp130 and

LIFRbeta homodimerizes. A clinical trial of CNTF against motorneuropathy failed, but a decreased appetite was noted. Axokine, a second-generation CNTF, is in trial for obesity. In ob/ob mice it blocks the weight rise and decreases body fat with little impact on lean body mass. This is a centrally mediated effect, probably mediated in the hypothalamus.

Rémi Quirion (McGill University, Montreal, Quebec, Canada) illustrated the role of insulin-like growth factors I and II (IGF-I and IGF-II), that is their trophic as well as neuromodulatory functions in the brain. The effects of IGF-I on key markers of the AD brains namely cholinergic dysfunction, neuronal amyloid toxicity, tau phosphorylation and glucose metabolism suggest the potential usefulness of this growth factor in the treatment of neurodegenerative diseases. Moreover, the recent development of a small, non-peptidyl mimetic of insulin, L-783,281, able to directly activate the insulin receptor, suggests that a similar strategy could be used for IGF-I and the IGF-I receptor leading to the characterization of IGF-I mimics of potential clinical usefulness.

Death receptors and apoptosis were presented by Pascal Schneider (University of Lausanne, Switzerland). These receptors are members of the TNF family and have a specific intracellular domain that recruits other proteins, notably TRADD, FADD and the protease Caspase-8. Apoptosis, programmed cell death, is a physiologic event that helps to keep the right number of cells in the organism. This process is also a favored response in cells exposed to stress stimuli and damaging conditions, preventing the appearance and proliferation of potentially dangerous cells. Deregulation of the apoptotic process leading to either increased or reduced cell death, in fact, can contribute to various pathologic conditions such as autoimmune diseases, AIDS or cancer. Decoy receptors also exist that are homologs of death receptors, but lack the death domain: these include TRAIL-R3 and FLIP.

7. Hijacked receptors

David J. Triggle (State University of New York, Buffalo, NY, USA), who chaired the hijacked receptor session, gave some examples of receptors recognized by non-related ligands, such as the rabies virus at n-AChR4, the CD4 and chemokine receptors for HIV, the fibroblast growth factor receptor for herpes simplex, ICAM-1 for the rhinovirus, EGF receptors for *Salmonella typhimurim* and *alpha*-dystroglycan for *Mycobacterium leprae*. The use of the CFTR by *S. typhii* and the failure to infect cells expressing a nonfunctional CFTR was noted, together with the resistance to infectivity of individuals expressing mutant chemokine receptors.

Jordi Bella (University of Manchester, UK) discussed the interaction between human rhinoviruses (HRVs) and their receptor, intercellular adhesion molecule-1 (ICAM-1). Molecular models resulting from the combination of crystal structures of HRVs and ICAM-1 fragments with electron microscopy reconstructions of the complexes, have been useful to understand receptor recognition, binding specificity and mechanisms by which ICAM-1 induces virus uncoating.

Viral-encoded GPCRs may play an important role in viral infection and are likely implicated in chronic diseases. Martine J. Smit (Vrije University of Amsterdam, The Netherlands) underlined the role of GPCRs as successful drug targets in the past and as emerging targets for the development of drug research. A number of viruses, including HCMV, HHV6-8, pappiloma virus etc., contain 'hijacked' genes for GPCRs. HHV-8 GPCR is likely related to the Kaposi sarcoma, is linked to angiogenesis and is constitutively active. CMV contains four GPCRs and may be linked to atherogenesis. The challenge is the design of small molecule drugs.

Silvano Sozzani (Mario Negri Institute, Milano, Italy) continued the discussion of viral-encoded chemokines and discussed the therapeutic potential of anti-chemokines. He observed that mammalian viruses could avoid immune surveillance by expressing chemokines and chemokine receptors [Sozzani et al., Blood 92 (1998) 4036]. HSV 8 encodes chemokines homologous to the MIP CC chemokines that may serve as endogenous antagonists.

8. General topics and discussion

Henk Timmerman (Vrije University of Amsterdam, The Netherlands) provided an overview of current concepts in understanding.

Roberto Maggio (University of Pisa, Italy) introduced the concept of (hetero/homo)dimers in GPCR. Although receptors are generally considered as closely packed structures, actually they can behave structurally in a fashion analogous to multiple subunit receptors. New functional structures, as a dimer, are formed from the combination of truncated muscarinic receptors. The combination of m_2 'truncated' + m_3 'tail' to give receptors that both bind ligands and express functional activity was discussed. Additionally, hybrids of adrenergic and muscarinic receptors exist, which can be formed by these subunit receptor interactions. When different subtypes of muscarinic receptors are co-expressed in the same cells, they might interact to form heterodimers with new pharmacological properties. Although the molecular mechanism that underlies dimerization is not known, a domain swapping in GPCR dimerization has been recently proposed. This may be the mechanism by which M_2 and M_3 muscarinic receptors interact in their heterodimerization acquiring novel functions.

Rob Leurs (Vrije University of Amsterdam, The Netherlands) discussed constitutively active GPCRs starting from original observations on the opiate receptor [Costa and Herz, Proc. Natl. Acad. Sci. USA 86 (1989) 7321] and the concept of agonists, inverse agonist and antagonists. Using examples from the H_1 and H_2 receptor systems, he argued that most 'conventional' antagonists might, in fact, be inverse agonists. A number of disease states are likely to involve constitutively active GPCRs and inverse agonists should have a therapeutic role in treating such disorders resulting from increased expression, mutations or autoantibodies).

A novel G protein, Gβ5 isoform, has been presented by William F. Simonds (NIDDKD, Bethesda, MD, USA). This subunit exhibits novel properties in its activation of effector pathways such as MAPK, phospholipase C-β, and adenylyl cyclase type II when compared with $G\beta_1$. A highly specialized role for Gβ5 in G protein signal transduction is indicated.

John L. Neumeyer (Harvard Medical School, McLean Hospital, Belmont, MA, USA) showed a series of morphinans, structural analogs of cyclorphan, keto morphinans and a keto benzomorphan, structurally related to ketocyclazocine, as kappa opioid agonists useful in the treatment of cocaine dependence. In fact, activation of kappa opioid receptors may functionally antagonize some effects of cocaine, possibly by inhibiting the release of dopamine from dopaminergic neurons, and may provide a new approach to the continuing search for effective treatment medications. The binding results showed that two morphinans, namely MCL-101 and (−)cyclorphan, had a high affinity for μ, δ and κ opioid receptors. In particular, while both are κ agonists, only (−)cyclorphan produces some antinociception mediated by the δ opioid receptor. While having similar affinity for the μ opioid receptor, (−)cyclorphan and MCL-101 display opposing effects at the μ receptor, the former behaving as a μ antagonist, the latter as a μ agonist.

The symposium concluded with an overview by David J. Triggle (State University of New York at Buffalo, Buffalo, NY) on the future of medicinal chemistry. He argued that medicinal chemistry, and the pharmaceutical sciences in general, would be shaped by both scientific and economic factors. The paradigms of molecular biology applied to molecules — diversity, reproduction, evolution, targeting and delivery — would become components of synthetic chemistry and, in a flight of fancy, it was proposed that 'circulating nanofactories' might be envisaged that contained the synthetic machinery and targeting processes necessary to maintain pharmaceutical vigilance over the body. It was noted that science alone would not be the only factor determining the future of the pharmaceutical sciences. Economic, political and social issues would also be of critical importance. Notably, the cost of drug development would necessitate the adoption of new cost-reducing measures, as would the social demands for increased access to healthcare and the political demands for cost-reduction.

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