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RECEPTOR CHEMISTRY
TOWARDS THE THIRD MILLENNIUM
Proceedings of the 12th Camerino-Noordwijkerhout Symposium
Camerino, Italy, 5-9 September 1999

Edited by
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Preface

Despite Langley’s brilliant intuition way back in 1878, it was still a long time before the receptor could be called a reality; in fact, even in the early 1960s De Jongh described this molecule as a woman whose lovely seductive image could be deduced only from the type of answer received to the many “messages” sent to her. Thus, when we met together for the first time in Camerino back in 1978, we were rightly inspired by that enthusiasm typical of pioneers attracted by the fascination of a discipline still all to be discovered.

Over the last twenty years our joints may well have begun to creak due to increasing age, but our enthusiasm has by no whit been dulled; indeed, even if we now know almost all there is to be known about the way ligands “mate” with receptors, which have by now been isolated, characterized, and cloned, many other secrets still remain to tease our curiosity. In particular, differentiation into distinct subpopulations and the multiplicity of transduction processes seem to offer us unhoped for, and even more specific targets in our search for new drugs. And so, that dream of Ehrlich in 1908 to design for each individual pathology a highly selective “charmed bullet”, and thus one with reduced toxicity, now appears increasingly less utopistic.

It is with these ideas that the 12th Camerino-Noordwijkerhout Symposium has seen us into the third millennium with an awareness that the only success for converting our hopes into reality is a multidisciplinary study based on a wakeful and critical comparison between experiences that have been reaching maturity through different approaches to the problematic - as has always been the case in our Symposia.

Ugo Gulini
Mario Giannella
Gabriella Marucci
Wilma Quaglia

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Pharmacological receptors: a century of discovery — and more

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Abstract

A brief survey of the history of the development of the concept of the pharmacological receptor is presented. From the pioneering concepts of Paul Ehrlich, John Langley and others, receptors are described in terms of their recognition properties, their structures, transducing abilities and the impact of genomics and their role in contributing to genetic diseases. The receptor concept has firmly underpinned our advances in drug development and molecular medicine of the latter half of this century and it is clear that it will continue to drive pharmaceutical developments in the 21st century. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Receptors; Receptor history; Paul Ehrlich; John Newton Langley; Emil Fischer; Louis Pasteur; Drug–receptor interactions; Stereoselectivity; Receptor diseases; Receptor regulation; Receptor structure

1. Introduction

Separate, but complementary, lines of evidence led in the late 19th century to the establishment of the concept of “the receptor” as the cellular site at which drugs, toxins and antibodies mediated their physiological or pathological effects. These lines of evidence are particularly associated with Paul Ehrlich in Germany and John Newton Langley in England. However, their work built upon many centuries of work that attempted to define the action of naturally occurring materials on the body. These earlier contributions have been expertly summarized in the books, “Murder, Magic and Medicine” by John Mann (1992) and “In Search of a Cure” by M. Weatherall (1990).

From his extensive work on immunology and the chemotherapy of parasitic infections, Ehrlich argued that cells must possess specific and defined protoplasmic side chains that, because of their unique chemistry and steric architecture, could interact specifically with the complementary groups of a chemotherapeutic agent, toxin or antibody (Parascondola, 1981; Ehrlich, 1900):

“For the sake of brevity in what follows we shall in general designate as receptor that binding group of the protoplasmic molecule to which a foreign, newly introduced group binds.” P. Ehrlich, 1900

Even prior to these speculations, Langley (1878) had observed:

“We may, I think, without much rashness assume that there is some substance or substances in the nerve endings or gland cells with which both atropine and pilocarpine are capable of forming compounds. On this assumption, then, the atropine or pilocarpine compounds are formed according to some law of which their relative mass and chemical affinity for the substance are factors.” J.N. Langley, 1878

But Langley (1906) also recognized the receptor as a transducing engine that:

“...receives the stimulus and, by transmitting it causes contraction.” J.N. Langley, 1906

Langley, contemporaneously with the work of Ehrlich, used the term “receptive substance” for these specific entities and speculated that specific receptors must exist for curare, atropine, pilocarpine and the other autonomic drugs with which his research had been principally concerned. Certainly, the specificity of such drug–receptor interactions had been anticipated by Emil Fischer who wrote:

“...I will say that enzyme and glucoside must fit together like lock and key in order to be able to exercise a chemical action on each other.” Emil Fischer, 1894
Thus, by the beginning of this century, the conceptual foundation had been laid for the existence of pharmacological receptors, albeit as "black boxes", that received input and translated it into a physiological, pharmacological or pathological output. The present century has been largely devoted to opening this box and defining its contents. It has been a spectacularly successful century that has culminated with the classification, isolation, characterization and cloning of pharmacological receptors, with the identification of receptors — "orphan receptors" — for which ligands may not have been identified and with the determination of the detailed three-dimensional structure of a membrane receptor — a bacterial potassium channel.

2. Receptors as recognition entities

The specificity of the drug–receptor recognition process has long been regarded as a critical feature of the receptor concept, even when the nature of receptors was entirely unknown. Indeed, the absence of such specificity, including stereoselectivity, is often a component of arguments that a receptor event is not involved in the action of a particular drug. These structure–activity relationships were originally qualitative in character, but were transformed first by the application of regression techniques that permitted the elucidation of one-dimensional quantitative structure–activity relationships (QSARs) and then by protein sequence determination and the determination of three-dimensional protein structures and the mapping of receptor sites (Greer et al., 1994).

With these approaches, it is increasingly possible to interpret the actions of drugs at their receptors and to facilitate the design of drugs for new receptor sites. Thus, the design of the HIV-protease inhibitors, a critically available class of drugs for the treatment of this lethal disease, was greatly facilitated by the resolution of the structure of the enzyme. The dimeric, essentially symmetric, structure composed of two identical aspartate protease-like domains, was critical to the development of the first protease inhibitors.

Sterechemistry of interaction has long been recognized in drug–receptor interactions and Pasteur very explicitly recognized that different stereoisomers could have very different physiological properties:

"There cannot be the slightest doubt that the only and exclusive cause of this difference in the fermentation of the two tartaric acids is caused by the opposite molecular arrangements of the tartaric acids. In this way, the idea of the influence of the molecular asymmetry of natural organic products is introduced into physiological studies, this important characteristic being perhaps the only distinct line of demarcation which we can draw today between dead and living matter. I have in fact set up a theory of molecular asymmetry, one of the most important and wholly surprising chapters of the science, which opens up a new, distant but definite horizon for physiology." Louis Pasteur, 1860

The stereochemical basis of drug actions was early investigated by Arthur Cushny at the beginning of this century (Cushny, 1926). These pioneering investigations on atropine and related compounds revealed the quantitative differences that can occur between drug enantiomers. Today, the issue of the chirality of drug–receptor interactions has assumed both scientific and regulatory significance. Scientific and clinical significance derives from consideration of the efficacy of a single enantiomer versus a racemate, from considerations of stereoselective metabolism and disposition, and from the impact of the route of administration and patient variability. Regulatory issues derive from considerations that racemic drugs may represent separate agents in fixed combinations: development issues derive from considerations of the costs, including those for chemical synthesis, of pursuing a single enantiomer or a racemic mixture.

Recent developments in stereochemistry have focused upon the gaseous general anesthetics, long a topic of discussion concerning their potential interactions with receptors. The long-standing assumption that these agents interacted non-specifically through partitioning into lipid membranes has been challenged from a variety of sources, including the stereospecificity of interaction of isoflurane and halothane (Moody et al., 1994; Sedensky et al., 1994). The differences, though small, are potentially significant from the perspective of clinical safety.

3. Receptors as transduction machines

As realized by Langley, recognition is a necessary, but not sufficient, characteristic of a receptor. Receptors are also biological machines translating the information of the interaction with the ligand into the cellular response. And with this translation comes the necessary amplification of the input information by several orders of magnitude. Several types of physical and biochemical process are involved in this biological transduction. Of particular significance, because of their widespread occurrence are the transduction events mediated by G protein-coupled receptors and by ion channels. The G proteins are a large group or superfamily of GTP hydrolases and the interaction of an activated receptor with the heteromeric G protein releases bound GDP and replaces it with GTP with concomitant liberation of the activated GTP-associated Go subunit. This activated subunit then interacts with a number of effector systems, including phospholipase C, adenyl cyclase and ion channels.

Similar amplification events occur during the opening or closing of ion channels mediated by chemical (ligand-gated channels) or physical (potential-dependent channels).
To a first approximation, ion channel opening is an all-or-none stochastic event and the effect of a stimulus, chemical or physical, is to alter the probability of channel opening. Patch clamp techniques make it possible to observe the opening or closing of single channels and thus to measure single molecular events. This ability, coupled with recent structural information on the K⁺ channel, makes possible to a first approximation a molecular description of ion channel function.

4. Receptor classification

Receptor structure, the linear and ultimately the three-dimensional representation of the sequence, provides a definitive classification and basis for the classification of receptors. This permits the identification of “families” and of “super-families” of receptors and, in recent years, has made possible the isolation and characterization of so-called “orphan receptors”, for which physiological ligands or physiological function may not have been identified. Earlier classification schemes that used the identity of the physiological ligand that interacts with the receptor, the nature of the physiological or pharmacological response induced by receptor activation or the nature of the antagonist drug all have significant limitations. Multiple systems and receptors control blood pressure and similarly many receptors share a common biochemical cascade — adenylyl cyclase or phospholipase C activation or the opening and closing of K⁺ channels. To further complicate matters, many receptors are pleiotropic, initiating multiple consequences that may differ according to cell type and even agonist quality. Similarly, many physiological ligands may interact with multiple receptors that are of fundamentally different classes: acetylcholine interacts with both muscarinic and nicotinic receptors, the former being members of the G protein-coupled family (Bikker et al., 1998) and the latter a member of the ligand-gated ion channel family (Holladay et al., 1997). Finally, many receptors are heteromeric assemblies of multiple types of subunits: the pharmacological specificity and the actions induced can be very dependent upon subunit composition. Despite this complexity, it is convenient to recognize four principal families of chemically sensitive pharmacological receptors (Table 1).

5. Receptor structure

The majority of receptors under discussion are integral membrane proteins and have not, until recently, yielded to three-dimensional structural determination. However, progress is now being made in three principal areas — the structure of rhodopsin as a model for the very large G protein-coupled receptor family, the role of the nicotinic acetylcholine receptor as a model for ligand-gated ion channels and a bacterial K⁺ channel from Streptomyces lividans that will materially define the ionic conductivity, selectivity and gating processes of ion channels. Additionally, powerful molecular biological approaches including selective mutagenesis and the use of chimeric constructs have served to define the roles of particular sequences or residues in receptor recognition and activation processes.

The very large G protein-coupled receptor family has provided many examples of the definition of residue roles in drug interactions. Thus, for the beta-adrenoceptor, critical interacting residues have been determined to be aspartate-113 on helix III, serine-204 and -207 on helix V and phenylalanine-290 on helix VI. Such studies have defined a “homologous” binding pocket on this receptor family that is shared by the cationic neurotransmitters, acetylcholine, histamine, norepinephrine etc., and related small ligands.

Perhaps the most recent dramatic advance has been the determination of the three-dimensional structure of a bacterial K⁺ channel from S. lividans (Doyle et al., 1998). This channel is composed of four identical subunits, each with two trans-membrane sequences and a “pore” region, that associate in “tepee” shape to form the functional ion channel containing within it the selectivity filter that discriminates K⁺ from other ions. The selectivity filter contains a so-called “signature” sequence, highly conserved residues that characterize K⁺ ion channels and the Gly–Tyr–Gly components of this sequence in the four subunits bind K⁺ through their carbonyl residues and are responsible for the ionic selectivity of the channel.

These structural studies have also revealed the importance that very minor changes, frequently a single residue, can have on the drug–receptor interaction. Thus, the 5-HT₁B receptor in the rodent and man is pharmacologically quite distinct, a differentiation that is provided by residue 355, threonine in the human and asparagine in the rat (Oksenberg et al., 1992). Similarly, the interaction of barbiturates and other anesthetics with the GABAₐ receptor depends upon the presence of a single isoleucine residue: replacement of this residue by serine confers

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<th>Characteristics</th>
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<td>Ion channels</td>
<td>Integral membrane; subunit composition; each subunit has two or more membrane inserts as a pore region and four or more form the central pore of the channel</td>
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<tr>
<td>G protein-coupled</td>
<td>Seven-transmembrane integral proteins that couple to the G protein family of proteins</td>
</tr>
<tr>
<td>Enzyme-associated</td>
<td>One-transmembrane integral proteins that have kinase activity; may dimerize during receptor activation</td>
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<td>Nuclear receptors</td>
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anesthetic sensitivity (Beelli et al., 1999). Such changes are of extreme importance in the determination of individual human sensitivity to drugs where single nucleotide polymorphisms (SNPs) may determine clinically significant drug responses and interactions (Kleyn and Vessell, 1998). Thus, there are a number of polymorphisms in the human beta-adrenoceptors and these have been associated with bronchodilation in response to beta2-agonists and with the development of hypertension (Buscher et al., 1999). The P450-mediated drug metabolism process is highly polymorphic leading to extensive inter-individual variation in drug metabolism (Ingelman-Sundberg et al., 1999). Exploitation of this knowledge, now possible through gene-array technologies, will increasingly alter both drug development and drug prescribing.

6. Orphan receptors

The classical route to the receptor concept has always been the existence first of a drug and an associated family structure with defined physiological and pharmacological effects. A classic example is morphine and the opiates and the subsequent discovery of the endogenous ligands and subsequently the G protein-coupled opiate receptor. The isolated and expressed receptor could then be used as a screen for novel structures that might have more desirable therapeutic properties. Advances in molecular biology now permit the reverse of this process. DNA sequences are identified that are analogs of known receptors. These sequences can be expressed to yield novel or "orphan" receptors for which the endogenous ligand can now be hunted (Soontjens et al., 1996; Robertson and Willy, 1997; Civelli et al., 1998; Wilson et al., 1998).

Both the G protein family and the steroid hormone family have yielded many orphan receptors. At least 140 G protein receptors have been identified from the human genome and since this class has generated major drugs for many therapeutic targets, the status of orphan receptors here has attracted much attention. The identification of the opioid receptor ORL1 is but one example, interacting with a specific endogenous ligand nociceptin that appears to have widespread roles in the mediation of nociception and stress reduction. Over 70 orphan receptors have thus far been identified in the steroid receptor family and for most of these, neither endogenous ligand nor physiological action has yet been defined.

7. Receptors and genetic diseases

Defects in the structure and expression of receptor proteins are increasingly known to be associated with specific disease states. As one of the largest families of receptors, the G protein-coupled receptors exhibit a variety of mutations and associated functional changes, including both "loss of function" and "gain of function" (Spiegel, 1995; Farfel et al., 1999). These defects can lie in the actual receptors or in the associated G proteins. Similarly, mutations in ion channels are being associated with a variety of diseases from cardiac abnormalities to cystic fibrosis.

Loss-of-function mutations in G protein-coupled receptors are quite common, with approximately 100 having been described, and include nephrogenic diabetes insipidus (V2 vasopressin receptor), familial hypothyroidism (TSH receptor), Hirschsprung disease (endothelin B receptor) hypercalcemia and neonatal hyperparathyroidism (Ca2+ sensing receptor). These loss of function mutations may prevent protein expression, folding or insertion in the membrane or may impair agonist binding or interaction of the receptor with G proteins. Loss-of-function defects may also arise in the associated G proteins. Pseudohypoparathyroidism, resistance to parathyroid hormone with a subnormal urinary cAMP response to the hormone, provides one example. Individuals with the type 1a form of the disease also show resistance to a variety of other hormones that stimulate cAMP formation and this is associated with a defect in the Gs-α subunit. A number of gain-of-function mutations have also been described in which there is constitutive receptor activation. These include McCune–Albright syndrome characterized by excessive cell proliferation, including hyperpigmented skin, precocious puberty, hyperthyroidism, acromegaly and polyostotic fibrous dysplasia and results from persistent activation of the G protein from an inability to hydrolyze GTP and thus to terminate the receptor-G protein cycle. A defect in the beta-subunit of a G protein has been shown to be associated with an increased incidence of hypertension, being found in 53% of patients with essential hypertension and 44% of normotensive patients (Siffert et al., 1998).

Defects associated with ion channels underlie a variety of diseases, including cystic fibrosis, cardiac arrhythmias, episodic ataxia, heritable myasthenia and nocturnal frontal lobe epilepsy (Keating and Sanguinetti, 1996; Ackerman and Clapham, 1997; Cooper and Jan, 1999). Cystic fibrosis arises from a defect in a chloride channel — the cystic fibrosis transmembrane regulator — that blocks chloride transport in epithelial cells. It is a remarkably common defect amongst Caucasians — some 3.5% of the population carrying a defective gene. The most common defect is the deletion of phenylalanine 508, which results in a protein that does not insert properly into the membrane. In long QT syndrome, there is a lengthening of the QT interval of the electrocardiogram, a delay that may initiate cardiac arrhythmias, fibrillation and death. The defect has several origins associated primarily with K+ channels: one of these channels associated with the HERG gene and accounting for some 30% of LQTS cases is of particular importance since it is a target for a number of clinically available drugs, including some antibiotics, antihistamines and antifungal agents that increase the chance of arrhythmias and sudden death.
8. Genetically modified animals

Techniques, targeted mutations and transgenes, that permit the creation of animals — transgenic animals — that have been genetically modified in their receptor function provide a powerful tool with which to dissect the specific sites of action of drugs (Rudolph and Mohler, 1999). Gene inactivation — receptor knockout — provides a valuable technique for determining the action of subtype-selective drugs. Thus, mice lacking the $A_{2A}$ receptor fail to show a stimulant effect to caffeine, both confirming the receptor subtype at which adenosine acts and suggesting that antagonists at this receptor may be cognition enhancers. Receptor knockouts may also yield unanticipated targets: mice lacking the $G_{oq}$ subunit had a prolonged bleeding time and were not responsive to platelet activators, thus identifying this subunit as a potential target for antithrombotic therapy. Finally, animals with receptors bearing specific mutations can be very useful to dissect the spectrum of pharmacological actions that a given drug may produce. An interesting example is provided by the $GABA_{A}$ receptor, which, like many other ligand-gated channel receptors, is a heteromeric collection of subunits making many distinct subtypes. In a system where the $\alpha_1$ subunit has been mutated to produce a diazepam-insensitive $\alpha_1$-receptor, the major actions of diazepam are unaltered mediated by the $\alpha_2$, $\alpha_3$ and $\alpha_5$ subunits while other actions are lost (Rudolph et al., 1998).

9. Conclusions

It has been a remarkable century for receptors! Still a hypothetical entity in 1900, receptors come to the year 2000 as known and defined entities and more. We can now synthesize receptors of defined character and properties and we can produce genetically modified animals that display our own human receptors. And our concept of receptors has expanded enormously: from their beginning and Ehrlich might today be strangers in a strange land were they to return, but they would surely recognize the magnificent fruits of their toil in the vineyards.

References


Cholinergic receptors and neurodegenerative diseases

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Keywords: Neurodegenerative diseases; Alzheimer’s disease; Parkinson’s disease; Cholinergic hypothesis; Muscarinic agonists; Muscarinic antagonists; Nicotinic agonists; Acetylcholine releasers; Acetylcholinesterase inhibitors; High affinity choline uptake enhancers

1. Introduction

The severe disturbance of cholinergic function in dementias and particularly in Alzheimer’s disease (AD) was discovered nearly simultaneously by several researchers in the mid-seventies (Bowen et al., 1976; Davies and Maloney, 1976; Perry et al., 1977). As a consequence, some 20 years ago several scientists (McGeeer, 1981; Coyle et al., 1983), among whom Bartus et al. (1982) are the most cited, suggested that at least some of the symptoms of dementias were due to impaired cholinergic transmission in the brain and proposed that drugs able to restore CNS cholinergic tone would be able to revert the symptoms of the disease and to slow down its progress.

Known as the Cholinergic Hypothesis of Alzheimer’s disease, this hypothesis has served as the main rationale for the development of anti-AD drugs, even if alternative approaches, such as the use of neurotrophic agents, nootropics, glutamate antagonists, benzodiazepine receptor ligands, calcium antagonists, anti-inflammatory agents, radical scavengers and compounds interfering with amyloid precursor protein (APP) processing have been proposed and evaluated (Gualtieri et al., 1995). In the past 20 years, the popularity of the cholinergic hypothesis has experienced some ups and downs, mainly due to the fact that central cholinergic impairment appears as a consequence more than the cause of AD. However, the finding that cholinergic drugs can control correct processing of APP has boosted a recent revival of the approach.

Familial AD is indeed associated with increased formation of a specific APP derivative, the 42 residue variant (Aβ1-42) of the amyloid β-peptides. Amyloid β peptides derive from abnormal proteolytic processing of APP (referred to as β and γ secretase cleavage) and represent highly hydrophobic and self-aggregating molecules suspected of being the main determinant of the disease. It is becoming clearer and clearer that correct processing of APP (referred to as α-secretase cleavage) can be accelerated by the stimulation of muscarinic M2 receptors within minutes of receptor activation, while the formation of Aβ peptides is decreased by approximately 50% (Schenk et al., 1995).

Despite the drawbacks of the cholinergic hypothesis, this idea has guided most of the researchers involved with AD and enormous resources have been invested in developing compounds that would directly (nicotinic and M1 selective muscarinic agonists) or indirectly (acetylcholinesterase inhibitors, M2 selective muscarinic antagonists, acetylcholine releasers, high affinity choline uptake inhibitors) increase the level of cholinergic transmission in the brain.

2. Cholinesterase inhibitors

Tacrine, donepezil and rivastigmine (Francis et al., 1999) (Fig. 1), all belonging to the acetylcholinesterase inhibitors class, represent, at the moment, the result of these intensive efforts. They produce a measurable, albeit modest improvement in cognition, with effects equivalent to a 6- to 12-month delay in the symptomatic progression of the disease. A few other compounds are presently in
clinical trials or await approval; in Fig. 2, some selected compounds that have reached advanced developing phases are shown.

3. Muscarinic agonists

In addition to acetylcholinesterase inhibitors, \(M_1\) selective muscarinic agonists are among the most studied compounds (Fig. 3). At the moment, their future does not appear particularly brilliant as their efficacy is low and the usually modest selectivity is causing side effect problems. The uncertainty in the efficacy and usefulness of \(M_1\) muscarinic agonists is hampering the development of most of the compounds of this class. Forest Laboratories are reported to have abandoned their development of the \(M_1\) muscarinic agonist \(M_3\) antagonist LU25109 and the same seems the fate of milameline, discovered by Hoechst Mar-
4. Muscarinic antagonists

The approach based on M₂ antagonists has not produced, so far, compounds of practical interest, mainly because of poor brain penetration of known selective M₂ antagonists. The prototype BIBN-99 (Doods et al., 1993), which is M₂ selective and seems able to cross the blood brain barrier (BBB), is still in an early stage of development while, as regards the recently disclosed SCH 57790 (Lachowicz et al., 1999), available pharmacological data are insufficient to evaluate its interest (Fig. 4).

5. Acetylcholine releasers

Acetylcholine releasers, which can be viewed as muscarino-mimetics, are experiencing similar difficulties. Linopirdine, that blocks a variety of K⁺ channels including I₅, has been withdrawn from clinical trials (Kelly, 1999), while SM21 (Ghelardini et al., 1997) is still at the pre-clinical stage (Fig. 5).

6. High affinity choline uptake enhancers

Increasing the uptake of choline is another possible way to improve central cholinergic tone. Two compounds of this class are in preclinical evaluation: MKC-231 from Mitsubishi (Chaki et al., 1995) and Z-4105 from Zambon (Anonymous, 1995) (Fig. 6).

7. Nicotinic agonists

Apparently, the expectations deriving from the cholinergic hypothesis, based on muscarinic agonists, have been transferred to nicotinic agonists, as one can hardly pick up a pre-clinical journal without reading about nicotinic ago-
nists and their highly selective presynaptic action on a variety of neurotransmitters release in the brain.

Although nicotine has been reported to be beneficial for memory in human and animal tests, the cardiovascular, gastrointestinal and endocrine side effects of nicotine, as well as the negative connotation associated with tobacco smoking, have apparently delayed intensive research efforts to develop nicotinic agonists which would restore central cholinergic tone. In the past few years, however, thanks also to progress in molecular biology, physiology and pharmacology of central nicotinic receptors (Boyd, 1997; Chavez-Noriega et al., 1997), the potential of nicotinic agonists for the treatment of neurodegenerative disorders has been recognised. Indeed, besides their utility in AD, centrally acting nicotinic agonists have potentials for the treatment of Parkinson’s disease (PD) due to their ability to release other neurotransmitters like dopamine. As a consequence, intensive research has been performed on the synthesis and pharmacological evaluation of several classes of drugs that possess nicotinic properties without the undesirable side effects of nicotine (Decker et al., 1994; Holladay et al., 1995, 1997; Brioni et al., 1996; Glennon and Dukat, 1996). Most of the work in this field has been performed in the Abbott and SIBIA research laboratories; in Fig. 7 are reported some of the molecules that seem promising and are in clinical trial.

It is interesting that in addition to potential anti-Alzheimer and anti-Parkinson drugs, the research on cholinergic agonists has identified compounds (both nicotinic and muscarinic) that are potent analgesics and that could be developed as non-classical painkillers (Fig. 8).

Fig. 7. Selected nicotinic agonists in development for AD/PD treatment.

Fig. 8. Anti-nociceptive cholinergic agents.

References


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Nicotinic systems in central nervous systems disease: degenerative disorders and beyond

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Abstract

Advances in the understanding of the structure, function, and distribution of central nervous system (CNS) nicotinic receptors has provided the impetus for new studies examining the role(s) that these receptors and associated processes may play in CNS functions. Further motivation has come from the realization that such receptors are changed in degenerative neurologic diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD). Ongoing investigations of the molecular substructure of CNS nicotinic receptors and their pharmacology have begun to open up new possibilities for novel CNS therapeutics with nicotinic agents. Exploiting these possibilities will require understanding of the role(s) that these receptor systems play in human cognitive, behavioral, motor, and sensory functioning. Clues from careful studies of human cognition and behavior are beginning to emerge and will provide direction for studies of potentially therapeutic novel nicotinic agents. Modulation of these receptors with the ultimate goal of producing therapeutic benefits is the goal of these investigations and drug development. This paper will review studies from our laboratory and others that point to the importance of CNS nicotinic mechanisms in normal human cognitive and behavioral functioning as well as their role in disease states. In addition, this paper will examine potential clinical applications of nicotine and/or nicotinic agonists in a variety of CNS disorders with particular emphasis on structural brain disease including: movement disorders such as Parkinson’s disease and Tourette’s syndrome, cognitive/behavioral disorders such as Alzheimer’s disease, attention deficit/hyperactivity disorder, and schizophrenia, and other more speculative applications. Important results from early therapeutic studies of nicotine and/or nicotinic agonists in these disease states are presented. For example, recent studies with nicotine and novel nicotinic agonists such as ABT-418 by our group in AD patients suggest that nicotinic stimulation can improve the acquisition and retention of verbal information and decrease errors. Preliminary results from a series of studies examining the acute and subchronic quantitative effects of nicotine on cognitive and motor functioning in Parkinson’s disease suggest that acute nicotine administration and stimulation improves some aspects of cognitive and motor performance and may improve the processing speed of more complex tasks. The most likely near-term applications of novel nicotinic agonists in CNS disorders are likely to be in those disorders that are degenerative in nature, e.g. Parkinson’s disease and Alzheimer’s disease, or other movement disorders such as Tourette’s syndrome. The most likely direct therapeutic role for nicotinic agonists is as augmentation therapy in combination with other agents rather than as monotherapy, except early in disease states or as a prophylactic or preventative treatment.

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1. Introduction:

Interest in the possibility of utilizing agents that directly interact with nicotinic receptors for the treatment of central nervous system (CNS) disease has followed as understanding of the structure, function, and distribution of CNS nicotinic receptors has increased. Ongoing investigations of the molecular substructure of CNS nicotinic receptors and their pharmacology have begun to open up new possibilities for novel CNS therapeutics with nicotinic agents (Arneric et al., 1995). There is considerable evidence from both animal and human studies for the involvement of CNS nicotinic cholinergic receptors in a variety of cognitive, motor and behavioral systems. Modulation of these receptors with the ultimate goal of producing therapeutic benefits is the goal of these investigations and drug development.

This chapter will briefly examine potential clinical applications of nicotine and/or nicotinic agonists in a variety of CNS disorders with particular emphasis on structural brain disease. For further details, the reader is referred to a more comprehensive review (Newhouse and Kelton, 1999). Clinical areas covered include: cognitive disorders, move-
ment disorders, analgesia, smoking cessation, cytoprotection, and other more speculative applications. Important results from early therapeutic studies of nicotine and/or nicotinic agonists in these disease states are presented. As clinical therapeutic research in this field is still in its infancy, few long-term controlled clinical trials have been conducted except for smoking cessation.

2. Cognitive disorders

2.1. Alzheimer’s diseases

Nicotinic mechanisms may be important in explaining the pathophysiology and in designing treatments for AD (James and Nordberg, 1995). Patients suffering from AD have a marked reduction in cortical nicotinic cholinergic receptor binding compared to age-matched controls (Flynn and Mash, 1986; Whitehouse et al., 1986; Aubert et al., 1992). Normal aged subjects show an age-related decline in cortical nicotinic binding (Flynn and Mash, 1986). Warpmann and Nordberg (1995) used epibatidine and ABT-418 to show selective losses of α4β2 nicotinic receptors in the brains of patients with AD. Perry et al. (1996) showed that the entorhinal cortex (important in memory formation) rich in nicotinic binding, appears particularly vulnerable to amyloid plaque-induced loss of receptors. More generally, Perry et al. (1995) have shown that nicotinic receptor loss seems tightly linked to the primary pathology in the dementias, e.g., linked to dopaminergic cell loss in PD and Lewy Body dementia, and linked to amyloid plaques and tangles in hippocampal and parahippocampal areas in AD.

In humans, nicotine is reported to increase arousal and attention as well as decrease reaction time and prevent decline in efficiency over time (Wesnes and Warburton, 1983, 1985). In both animals and humans nicotine improves the subject’s ability to withhold responses to inappropriate stimuli (Myrsten et al., 1972; Wesnes and Warburton, 1983; Newhouse et al., 1988). This may be relevant to AD because a cardinal feature of the cognitive disorder of AD and a possible marker of cholinergic dysfunction (Fuld et al., 1982) is the difficulty demented patients have in inhibiting inappropriate responses or in responding to inappropriate stimuli. This difficulty in response selection and/or suppression is one explanation of the liberal response bias seen in AD. Gray et al. (1996) have shown that nicotine enhances hippocampal synaptic transmission which may be critical for new learning to take place.

AD is associated with a marked cerebral blood flow (CBF) perfusion deficit in parietotemporal cortex in addition to the global decrease in cerebral perfusion. It is of interest that the nicotinic antagonist mecamylamine reliably reproduces this abnormal CBF pattern in normal volunteers, (Gitelman and Prohovnik, 1992). Nicotine reliably augments the enhancement in CBF produced by electrically stimulating basal forebrain cholinergic neurons (Arneric, 1989). As the basal forebrain cholinergic neurons are heavily damaged in AD, changes in observed CBF may be secondary to damage to nicotinic systems. Presumably, the inability to autoregulate CBF impairs cognitive functioning.

Neuroimaging studies also support the involvement of nicotinic cholinergic systems in AD. Nordberg (1993) showed a significant correlation change between the change in temporal cortex labeling of 11C-nicotine and cognitive function scores in AD patients using positron emission tomography (PET). This result was bolstered by further work from these investigators (Nordberg et al., 1995) in which a kinetic model was developed to quantify the loss of nicotinic receptor binding in vivo in AD patients. Significant correlations were shown between cognitive dysfunction and the loss of nicotinic receptor binding in temporal and frontal cortices and hippocampus in these patients using PET. Nordberg (1993) also examined the effects of treatment with the anticholinesterase tacrine on AD patients using PET and showed that brain nicotinic receptor binding of 11C-nicotine increased along with CBF after 3 weeks of treatment.

Epidemiologic studies of AD that assess risk factors show that, like Parkinson’s disease, smokers are at a lower risk of developing AD than nonsmokers, even when other factors are controlled for (Tysas, 1996). Lee (1994) has done a meta-analysis of these studies and has calculated a relative risk of 0.64 for smokers to develop AD. In a retrospective case-control autopsy study, Ulrich et al. (1997) analyzed 72 age- and sex-matched smoker–non-smoker pairs and showed that an apparent protective action against senile plaque formation could be demonstrated in 28 age matched pairs of smoking–nonsmoking women, although a positive correlation between the amount of smoking and neurofibrillary changes in smokers of both sexes was also seen. Whether potential protective effects of smoking are secondary to nicotine is unclear but in vitro data suggesting a neuroprotective effect of nicotine are consistent with this possibility (Arneric et al., 1995).

2.2. Studies of nicotinic antagonists and agonists in Alzheimer’s disease

2.2.1. Antagonist studies

Studies utilizing antagonists are useful for establishing the cognitive relevance of neuro-receptor changes in brain as they produce a temporary chemical “lesion”. Newhouse et al. (1992; 1993; 1994) have studied the effects of the centrally-active non-competitive nicotinic antagonist and peripheral ganglionic blocker mecamylamine on cognitive functioning in young and elderly normals and Alzheimer’s and Parkinson’s disease patients. These studies attempted to establish that nicotinic blockade produced cognitive impairment in humans, and examined whether
there were age- or disease-related changes in sensitivity to nicotinic blockade, which would be indicated by shifts in dose–response curves between groups.

Mecamylamine administration produced dose-related impairment of the acquisition of new information with group differences in sensitivity. Young normals showed significant cognitive impairment errors after the highest dose. By contrast, the elderly normals showed significant impairment after the middle and high doses, and the Alzheimer’s disease subjects showed impairment after all three active doses. This pattern was seen in both verbal and nonverbal learning tasks.

In the AD patients, the learning rate actually became negative at 10 and 20 mg of mecamylamine, i.e., they were actually getting worse with increasing trials. Interestingly, in the old normals, mecamylamine produced a dose-related change in response bias with a significant liberal shift after the high dose, which has been seen in AD patients. This did not occur with the young normals. Regarding psychomotor speed, mecamylamine produced dose-related slowing in a number of tasks that measured reaction time. These included increases in reaction time for the CPT and manikin tasks. Older subjects tended to show proportionately greater increases in reaction time than the younger subjects did. By contrast, there were minimal behavioral effects.

Pickworth (1997) examined the effects of mecamylamine in smoking and non-smoking volunteers on electrophysiological and performance measures. In both groups, mecamylamine cause dose-related decreases in alpha EEG frequency and increases in delta frequency. In addition, response time slowed in both vigilance and distractibility tasks and delayed recall was impaired. These results confirm prior studies concerning the cognitive-impairing effects of blocking central nicotinic receptors and provide support for an important role for nicotinic receptor loss in the pathogenesis of the cognitive impairment in Alzheimer’s disease.

These results suggest that the deficits produced by mecamylamine resemble in several respects those seen in AD. Deficits in short- and long-term memory, impaired attention, liberal response bias, and decreases in reaction time are hallmarks of the dementing picture seen in these disorders. The age-related nature of some of the findings suggest that the decline in nicotinic receptors with age produces increased vulnerability to the effects of nicotinic blockade.

2.2.2. Agonist studies

Newhouse et al. (1988; 1993; 1996) have examined the effects of intravenous nicotine in AD with particular attention on tasks that are affected by mecamylamine. Analysis of the cognitive effects of nicotine in the AD group showed that there was a significant dose-related decrease in verbal learning errors, with a “U”-shaped dose–response curve. A similar improvement pattern was seen in long-term verbal recall. Neuroendocrine measures (Newhouse et al., 1990) tended to confirm that the doses used were active at CNS nicotinic receptors. Results show that nicotine produces improvements in attentionally driven tasks with improved reaction time, hits and false alarms on a continuous performance task. Throughput (speed–accuracy product) was improved as well. These findings of the beneficial results of acute nicotinic stimulation in AD have been supported by the studies of Sahakian et al. (Jones et al., 1992; Sahakian and Coull, 1994) who have shown that subcutaneous nicotine administration in AD patients produced improvements in attentional functioning. This group found that nicotine produced a highly significant improvement in accuracy on a sustained visual attention task (which involved the detection of number sequences). Importantly, there was no speed–accuracy tradeoff, i.e., patients do not become slower, even though they become more accurate. Further, they showed that the AD subjects improved in a dose-dependant matter on attentional aspects of a visual short-term memory and attention task. Katayama et al. (1995) showed that nicotine improved performance in dementia patients using event-related potentials. More chronic administration of nicotine to AD has also shown promise. Wilson et al. (1995) administered nicotine by patch to six AD patients for 8 days. Compared to the placebo patch condition, there were significantly fewer errors on a non-verbal learning task while subjects were on nicotine. This effect persisted for at least a week after withdrawal. However, Snaedal et al. (1996) were unable to find a significant effect of 4 weeks of transdermal nicotine administration on memory in 18 AD patients, possibly due to a significant placebo effect as patients on both nicotine and placebo showed improvements in short-term memory.

Potter et al. (1999) have recently examined the acute effects of the novel nicotinic agonist ABT-418 on cognitive functioning in Alzheimer’s disease. Subjects showed significant linear dose-related improvements in verbal learning and memory on the Selective Reminding Task as reflected by improved total recall and a decline in recall failure. Qualitatively similar improvements were seen in nonverbal learning tasks such as spatial learning and memory and repeated acquisition. Positive dose-related effects on reaction time were also seen. Interestingly, subjects also showed a dose-related decline in anxiety and fear, confirming prior animal studies suggesting that this agent may also have anxiolytic effects. These positive results echo studies of this agent in aged monkeys by Buccafusco et al. (1995) who showed dose-related improvements in a delayed matching-to-sample task performance following administration of ABT-418.

These studies represent significant evidence that stimulation of nicotinic receptors can improve the acquisition and retention of verbal (declarative) and non-verbal information in humans. The role of attentional effects of nicotinic stimulation has been stressed by Sahakian and Coull (1994). However, as has been suggested by Warburton and
Rusted (1993), nicotine's effects are most often seen in tasks that have a large attentional load. Preclinical studies of other novel nicotinic agonists also show promise. Aged rats show improved learning when treated with GTS-21 (Arendash et al., 1995). SIB-1553A is an α4β2 subtype-selective nicotinic agonist and appears to be efficacious in acute and chronically stimulating hippocampal acetylcholine release (Lloyd et al., 1998). This compound appears to produce enhanced performance in a variety of models of cognitive dysfunction (e.g., aged rats, rhesus monkeys, rats with cholinergic lesions) in areas such as spatial and non-spatial working and reference memory (Lloyd et al., 1998). A profile such as this suggests that this compound may have activity in disorders of cortical and subcortical cholinergic dysfunction such as AD. RJR-2403 (Lipiello et al., 1996) appears to be a highly selective ligand for the α4β2 subtype of nicotinic receptor and may be a useful agent for investigating the clinical and cognitive effects of stimulating this receptor subtype in degenerative neurologic disease.

3. Schizophrenia

The very high rates of cigarette smoking in schizophrenia (as high as 93% in male schizophrenic patients; Kirch, 1999) do not appear to be explained by gender, age or socioeconomic status (Dalack et al., 1998) and appear to reflect either disease- or treatment-related processes that encourage cigarette use. A major hypothesis for this high rate of use is that nicotine may have salutary effects on cognitive and/or behavioral functioning in this disorder (reviewed in detail in Dalack et al., 1998).

Cigarette smoking appears to improve abnormal smooth pursuit eye movements that are commonly found in schizophrenic subjects (Olinney et al., 1998). The P50 auditory evoked response to repeated stimuli appears to be abnormal in many schizophrenic patients (Freedman et al., 1994) and their first-degree relatives (Waldo et al., 1991). Studies of this wave are designed to examine inhibitory control of sensory processing and involve examining the ratio of the two P50 waves evoked after auditory stimuli 500 ms apart. In schizophrenic subjects Adler et al. (1992; 1993) have shown that nicotine administration, via smoking or nicotine gum appears to transiently normalize this impaired response and restore sensory gating. The neurobiological mechanism responsible for this response has been traced to pyramidal neurons of the hippocampus as a major source (Bickford-Wimer et al., 1990). The normal response is blocked by the α7-nicotinic receptor antagonist α-bungarotoxin (Lutz-Leyman et al., 1992). Autoradiography has shown that these α7 receptors appear to occur on non-pyramidal hippocampal GABA-containing inhibitory neurons (Freedman et al., 1993). An extension of this work (Freedman et al., 1997) has linked this abnormality in schizophrenics and their first-degree relatives to a dinucleotide polymorphism at chromosome 15q13–14, the site of the α7-nicotinic receptor.

In addition other studies performed in schizophrenic patients support salutary effects of nicotine on cognitive performance and attention in this disorder. Levin et al. (1996a; b) found that nicotine administered via skin patch reversed some of the haloperidol-related impairments in a variety of cognitive tests assessing memory and reaction time. As with normal volunteers, nicotine also improved attentive performance during a continuous performance task in these subjects. Haloperidol administration has also been found to increase smoking behavior (McEvoy et al., 1995a), and the atypical neuroleptic clozapine appears to decrease smoking in schizophrenic subjects (McEvoy et al., 1995b). Clozapine, unlike most neuroleptics, appears to improve P50 gating in schizophrenic patients (Nagamoto et al., 1996) in a similar manner to nicotine. Dalack et al. (1998) have suggested that the high rate of nicotine use in schizophrenia may be associated with a partial correction of a putative cortical–subcortical dissociation of dopamine activity and that nicotine use is associated with increased glutamatergic activity in limbic regions implicated in schizophrenia, particularly the frontal cortex and hippocampus.

An optimal nicotinic agonist for use in this patient population may have to have mixed properties to improve both dopaminergic and glutamatergic functioning as this may require stimulation of several different subtypes, including α7 homomeric receptors as well as α5- and α6-containing receptors. An important concern in any clinical trial of a potential nicotinic agonist for schizophrenia would be the identification of appropriate clinical endpoints. In addition to the highly specific attentional/sensory abnormalities heretofore demonstrated in schizophrenic patients, negative and deficit symptomatology may well be an appropriate target for such trials as there is little convincing evidence thus far that the florid psychotic symptoms are likely to be responsive to nicotinic stimulation. Nonetheless, improvements in cognitive symptoms may produce significant long-term clinical benefit. The development of effective nicotinic agonists could be an important contribution to progress in this challenging disorder.

4. Attention deficit hyperactivity disorder

Given the attentional improvement that has been demonstrated with nicotinic receptor stimulation, there are implications for nicotine or novel nicotinic agonists as a possible treatment strategy in attention deficit–hyperactivity disorder (ADHD). This is a disorder primarily of children, but affects adults as well. ADHD afflicts as many as 3–5% of American children (American Psychological Association, 1994) and is characterized by inattention, restlessness, impulsiveness and hyperactivity. There is sig-
significant co-morbidity of smoking in teens and adults with ADHD. It has been reported that 40% of adults with ADHD smoke cigarettes compared to 26% of the general population (Pomerleau et al., 1995). As the symptomatology of ADHD often leads to difficulty in school and other behavioral problems, there is some debate as to whether cigarette smoking is an act of self-medication, or a manifestation of the behavioral problems related to the symptomatology.

Several studies have examined the effects of nicotine administered via patch on the attentional processes in adults with ADHD. Conners et al. (1996) administered placebo or low and high dose nicotine patches to non-smoking and smoking adults with ADHD, respectively. Nicotine significantly improved attentional performance on the Continuous Performance Task and increased attentional self-ratings of smokers on the Profile of Mood States. All subjects were rated as having a decrease in ADHD symptoms in the Clinical Global Impressions scale. These findings were replicated in a separate study by Levin et al. (1996a; b). In this study, nicotine administration also reduced the standard error of reaction time over blocks of trials, suggesting improved consistency in attentional performance. Novel nicotinic agonists such as ABT-418 have also been found to improve some aspects of attention in aged primates (Prendergrast et al., 1998). In the primate study, Prendergrast et al. found that ABT-418 and ABT-089 prevented distractibility and increased delayed recall accuracy in trials where a distractor was present.

It has been suggested that the central disorder of ADHD is an impairment of behavioral inhibition of responding to inappropriate external stimuli or distractors (Barkley, 1997). Children with ADHD showed excessive errors of commission and a stronger tendency to respond correctly and in error during a Continuous Performance Task (Iaboni et al., 1995). If nicotinic stimulation improves attention and allows for more effective inhibition of attention to inappropriate stimuli, then perhaps ADHD may be treatable by stimulating the nicotinic system both in adults and children. This may also potentially prevent cigarette smoking in some subjects. As the abuse liability of nicotine separate from tobacco products is extremely low (Hughes, 1998), such treatment may be acceptable for adolescents.

5. Movement disorders

5.1. Parkinson’s disease

A number of studies have shown that smokers have a lower than expected incidence of PD, suggesting a protective effect of nicotine (Baumann et al., 1980; Baron, 1986, 1994). These studies have been carefully reviewed by Morens et al. (1995) who conclude that the association is not artifactual. While epidemiologic studies do not confirm that nicotine is the protective agent, the only other possible protective aspect of cigarette smoke identified thus far is a reduction in monoamine oxidase-B (MAO-B) activity after long-term smoking (Fowler et al., 1996). Nicotine has also been shown to counteract the locomotor effects of MPTP-induced lesions in mice, a putative model for PD (Sershen et al., 1987). A similar loss of cholinergic cells in the basal forebrain nuclei as occurs in AD has been described in PD (Whitehouse et al., 1983). The loss of cholinergic markers in the cortex (Perry et al., 1995) that occur in PD may be related to lesions in these nuclei and other cholinergic projections to the cortex (Whitehouse et al., 1988). In demented PD patients, the loss of cortical cholinergic markers has been shown to be of greater magnitude and more extensive than that of nondemented PD patients (Perry et al., 1985). Studies have shown a marked reduction in cortical nicotinic receptor binding that parallels the degree of dementia in PD and increasing age (Whitehouse et al., 1988; Aubert et al., 1992). There is similarity between the cortical nicotinic binding site loss in PD and AD as well as similar changes in other cholinergic markers.

Nicotine was examined as a treatment for PD as early as the 1920s (Moll, 1926) in patients with a form of secondary parkinsonism due to encephalitis lethargica. Marshall and Schniden (1966) examined the effects of nicotine on tremor, including that secondary to Parkinson’s disease and showed mildly positive effects in several patients. More recently Fagerström et al. (1994) reported a detailed study of two patients who had nicotine gum and patch added to their Parkinson’s disease therapy. Using a single subject, placebo-control reversal design, improvement was associated with nicotine dosing and involved diminished tremor and disorganized thinking in one patient and lessened bradykinesia and increased energy in the other.

Newhouse et al. (1998) have preliminarily examined the quantitative effects of nicotine in PD patients. Subjects with mild to moderate PD received dose-ranging infusions of intravenous nicotine up to 1.25 μg/kg/min, followed by chronic administration of nicotine by transdermal patch with doses ranging up to 14 mg/day for 2 weeks. Testing occurred both during drug administration and up to 2 weeks after drug cessation to look for prolonged effects. Nicotine appeared to acutely improve attention/arousal in PD patients as measured by the Critical Flicker Fusion (CFF) and the Choice Reaction Time test. Mecamylamine pre-administration antagonized the improvement, suggesting a specific effect on nicotinic receptors. During the chronic phase of administration by transdermal patch, nicotine appeared to improve performance speed in standard clinical motor performance tasks. In most cases, improvement appeared to persist after drug withdrawal, although there was some evidence for the beginning of a return towards baseline values at the session 2 weeks after drug withdrawal. For the computerized performance tasks, subjects showed improvement on the motor portions of certain
tasks at day 14, but by 2 weeks post drug, they had returned almost to baseline values. These effects are consistent with the possibility that a sustained evoked increase in the release of dopamine in nigrostriatal pathways may be occurring as a result of presynaptic nicotinic receptor stimulation. Studies such as these provide optimism that nicotinic stimulation may be a fruitful strategy for PD treatment, either by utilizing nicotinic agonists as monotherapy in early cases or as a dopa-augmenter or dopa-sparing drug in later stage disease.

In addition to nicotine, other novel nicotinic agonists are being developed specifically focused on Parkinson’s disease. SIB-1508 and its racemate SIB-1765F are subtype selective nicotinic agonists particularly for α4β2-containing nicotinic receptors (Sacaan et al., 1997). These compounds appear to have greater efficacy than nicotine at releasing dopamine from striatal slices. SIB-1765F potentiated the positive locomotor effects of L-dopa in a reserpine model of PD in rats (Menzaghi et al., 1997) with a rapid onset of action. The compound produced a small improvement in locomotion when administered alone, however the effect was much greater when combined with L-dopa. SIB-1508Y, an isomer of SIB-1765F, is even more potent in this model and has also shown positive activity in the MPTP-treated monkey model of PD (Schneider et al., 1998).

6. Tourette’s syndrome

Tourette’s syndrome (TS) is a hyperkinetic movement disorder with symptoms of sudden, rapid and brief, recurrent, stereotyped motor movements or sounds (tics) and can range from mild to severe. TS is commonly treated with dopamine antagonists such as haloperidol, which may be effective but has significant adverse side effects and is ineffective in up to 30% of cases. While the etiology is not known it is proposed that, unlike PD, TS represents a disorder of excess dopamine transmission in the striatum (Shapiro et al., 1989; Wolf et al., 1996), either through dopamine excess or receptor hypersensitivity.

Following laboratory studies showing that acute nicotine administration could potentiate haloperidol-induced catalepsy and locomotor activity in rodents (Emerich et al., 1991), an intuitive leap was made and clinical trials were begun in TS patients (Sanberg et al., 1989). Initial open trials with nicotine gum showed reductions in both tic severity and frequency particularly when used to augment the effects of haloperidol (McConville et al., 1992). More recent studies (Silver and Sanberg, 1995) using transdermal nicotine have confirmed the positive effects of nicotine when added to haloperidol therapy in TS patients and have also shown that in some patients the positive effects persist for several weeks after patch removal. Long-term positive effects of transdermal nicotine were also found by Dursan et al. (1994) who found that two consecutive nicotine patches reduced tic severity scores for up to 4 weeks after patch removal.

The potential efficacy of nicotine and/or nicotinic agonists in both hypodopaminergic (PD) and hyperdopaminergic disorders (TS) may reflect the mixed agonist/antagonist activities of nicotine. In the case of TS, available evidence from animal studies suggests that a prolonged desensitization and inactivation of nicotinic receptors following exposure to nicotine may be producing the therapeutic response (Shytle et al., 1999). This theory has been tested by the use of the nicotinic antagonist mecamylamine to augment the effect of antidiopaminergic agents in TS with positive results (Sanberg et al., 1998). Whether novel agonists which do not produce as rapid or as long-term a desensitization of nicotinic receptors would be helpful in TS remains untested.

7. Other potential clinical applications

7.1. Analgesia

The possible analgesic effects of nicotine have been a subject of dispute. Decreased sensitivity to pain has been demonstrated in studies involving men but the effect has been difficult demonstrate in women (Jamner et al., 1998). The discovery of the potent antinociceptive effects of the frog-derived nicotinic neurotoxin epibatidine has activated the search for analogs that might provide significant analgesia without unacceptable toxicity. Epibatidine itself appears to have antinociceptive activity 200-fold more potent than that of morphine (Brioni et al., 1997), but has significant toxicity due to potent activity at the ganglionic and neuromuscular junction. There is evidence for both central and peripheral sources of nicotine-induced analgesia (Caggiula et al., 1995), as well as activity at the level of the primary sensory neuron (Puttfarcken et al., 1997) and dorsal root ganglia (Roberts et al., 1995).

A major goal, therefore, is to develop novel nicotinic analogs with both a large therapeutic index and significant analgesic activity. The potent novel nicotinic agonist ABT-594 (a potent α4β2 agonist) appears to exhibit antinociceptive properties equal in efficacy to those of morphine across a series of animal models of acute thermal, chemical and neuropathic pain (Bannon et al., 1998; Donnelly-Roberts et al., 1998). The analgesic effects are blockable by mecamylamine and repeated treatment did not appear to elicit opioid-like withdrawal or physical dependence. Such a compound appears to be a promising agent for clinical development as a non-opiate analgesic agent if toxicity is low.

8. Cytoprotection

Intriguing evidence has been developed that suggests that nicotine and nicotinic drugs may have cytoprotective
Risk groups, such as individuals with a strong family history of AD and/or who are positive for the APOE4 allele, or individuals who appear, based on cognitive or clinical assessment, to be either questionably impaired or in very earliest stages of dementia.

9. Smoking cessation

Smoking cessation is the only currently approved indication for nicotinic therapy. Several meta-analyses of randomized controlled trials using nicotine for smoking cessation have concluded that nicotine replacement therapy is an effective treatment for smoking cessation, although 6-month quit rates do not appear to be much better than approximately 20% for any type of nicotine replacement device (Fiore et al., 1996; Westman and Rose, 1999), especially if given in the absence of a behavioral program. A more promising approach may be to utilize a combined agonist/antagonist approach. In a series of studies, Rose et al. (1994; 1996) have shown that combining low-dose mecamylamine administration with nicotine in smokers produces dramatic improvements in smoking 6-month quit rates over nicotine alone (40% versus 20%). In addition to this novel approach, the development of orally available novel nicotinic agonists may provide additional therapeutic options with reduced side effects and improved patient acceptability. Lobeline, a mixed nicotinic agonist/antagonist, is being examined for efficacy in smoking cessation clinical trials, for further information on the use of nicotine in smoking cessation, the reader is referred to several recent reviews for coverage of this topic (Balfour and Fagerstrom, 1996; Westman and Rose, 1999).

10. Anxiety / depression

The anxiety relieving effect of nicotine appears to be independent of the subject’s smoking status (Gilbert, 1979), but may be quite dependent on the baseline anxiety state of the individual. Novel nicotinic agonists such as ABT-418 show a non-benzodiazepine anxiolytic profile in animal tests (Brioni et al., 1994) and studies in AD patients show fear and anxiety reducing characteristics without cognitive impairment (Potter et al., 1999). The possibility therefore exists that nicotinic agonists could be developed specifically for their anti-anxiety properties which would offer the potential benefit of decreasing anxiety without cognitive impairment, a combination that is hard to achieve with today’s agents.

Studies have shown that individuals who smoke heavily are at high risk of depressive illness, either first onset or recurrent, if they cease smoking, especially without nicotine replacement therapy (Glassman et al., 1990). Although direct antidepressive effects of nicotine remain to be demonstrated, there is no question that nicotine can have significant salutary effects on mood, at least in deprived smokers (Foulds et al., 1997). As nicotine has significant effects on the release of monoamine neurotransmitters.
which are important in depression, such as serotonin, the possibility exists that novel nicotinic agonists without the adverse side effects seen with nicotine could be developed specifically for their antidepressive effects, either as monotherapy or as an augmentative therapy.

11. Epilepsy

Autosomal dominant nocturnal frontal-lobe epilepsy (ADNFLE) is a form of partial epilepsy which is characterized by frontal-lobe motor seizures occurring during sleep (Philips et al., 1998). This disorder has been linked to a mutation in the channel-lining domain (M2) of the α4 nicotinic receptor subunit with “use-dependent potentiation” of the electrophysiological response to nicotinic agonists (Lena and Changeux, 1998). If the symptoms of ADNFLE are secondary to overactivity of this receptor or unusual potentiation, then nicotinic antagonists such as mecamylamine may be helpful.

12. Further directions

The most likely near-term applications of novel nicotinic agonists in CNS disorders are likely to be in those disorders that are degenerative in nature, e.g., Parkinson’s disease and Alzheimer’s disease, or other movement disorders such as Tourette’s syndrome. The most likely direct therapeutic role for nicotinic agonists is as augmentation treatment in combination with other agents rather than as monotherapy, except early in disease states or as a prophylactic or preventative treatment. A major problem remains as to whether compounds can be developed which are selective in producing improvement in cognition, motoric behavior, attention or pain without significant side-effects. Therapeutic trials of nicotine and novel nicotinic agonists will be important to assess the realistic likelihood of long-term improvements in functioning as heretofore virtually all studies have been short-term or acute. Future clinical studies should carefully focus on cognitive and behavioral measures that are likely to be positively affected by nicotinic stimulation based on preliminary acute studies.

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