Special Feature

The contribution of drugs and toxins to understanding of cholinergic function

THE USE OF DRUGS and toxins for the analysis of nervous system function is over 100 years old. It considerably predates the general acceptance of the theory of chemical transmission at synapses, and indeed provided much of the evidence that led to the formulation of the theory. Studies with drugs and toxins have since helped to elucidate the detailed mechanisms of neurotransmission, and to classify receptor types and subtypes. The first terminal to be examined in detail in this way was the cholinergic nerve terminal.

The cholinergic nerve terminal

Figure 1 shows the currently accepted view of the organization of the cholinergic neurone[1]. Briefly, acetylcholine is synthesized from choline and acetyl-coenzyme A in the terminal cytoplasm by the soluble cytoplasmic enzyme choline acetyltransferase; it leaks out in a non-quantized fashion at a rate that at rest greatly exceeds the spontaneous quantized release from vesicles but does not increase significantly on stimulation. By contrast, stimulation greatly increases quantized (vesicular) release and generates, from the reserve vesicle population, an actively recycling pool which replenishes itself from the cytoplasmic pool.

Acetylcholine released in either quantized or non-quantized form after interaction with receptors is rapidly hydrolysed by acetyl-cholinesterase to acetate and choline. Choline, and probably acetate are reutilized. Choline is taken up by a high affinity transport system and reacetylated to acetylcholine which then again becomes available for vesicular uptake. At rest, after stimulation, recycling vesicles become fully charged with transmitter and join the reserve pool. Transmitter release is highly regulated by negative-feedback loops (Fig. 1).

Evidence for this model has been amassed in two ways: by subcellular fractionation[2,3]; and by the use of drugs and toxins that selectively interact, as agonists, antagonists or blocking agents at various points in the process (Fig. 1; Table I). Such substances have been of great importance in dissecting out the various steps in the synthesis, storage and release of acetylcholine, and this in turn has led to a better understanding of the mode of action of drugs and toxins on the cholinergic system and the development of rational therapies and antidotes.

Receptor agonists and antagonists

The first drugs used to investigate neurotransmission were naturally occurring toxins that interact with the acetylcholine receptor.

Curare

The great French physiologist Claude Bernard carried out the first physiological investigation of the South American arrow poison curare, the main active principle of which is D-tubocurarine. Bernard showed that curare blocked neuromuscular transmission in the frog without affecting the excitability of either the motor nerve or the muscle and thereby correctly concluded that the site of action was the junction between them.

Claude Bernard (1813–1878) was one of the most remarkable men of his day. Of humble origins, he managed to qualify in medicine but never practised: he devoted himself to physiological research at considerable personal and financial sacrifice at a time when scientific research was not regarded as a full-time profession. He was a pupil of Magendie who discovered the 'law of the spinal roots' which stated that afferent nerve fibres entered the spinal cord through the dorsal roots, whereas the efferent fibres left through the ventral. Bernard eventually obtained the Professorship in Physiology at the Sorbonne and membership of the Academy. He made important contributions to our knowledge of digestion and liver function and introduced the concept of the constancy of the *'milieu intérieur'* (interior environment) which was later developed by the American physiologist W. B. Cannon in his concept of homeostasis.

His personal life was less successful. He married a well-to-do widow who sympathized more with the animals he operated on than with her husband's scientific achievements – perhaps with some justification, since curarization was used by Bernard and others as a form of anaesthesia. The realization by British physiologists that this was unjustified led to the world's first legal regulation of animal experimentation by the British parliament (*Cruelty to Animals Act*, 1876).

The discovery of the action of curare on the neuromuscular junction did not lead immediately

TABLE I. Sites of action of drugs and toxins that affect cholinergic neurotransmission

Cellular location	Functional component	Specific inhibitors
Presynaptic plasma membrane	choline transporter	hemicholinium; choline mustard aziridinium
Presynaptic terminal cytosol	choline acetyl transferase	naphthylmethylpyridinium
Recycling synaptic vesicles	acetylcholine transporter	vesamicol
Postsynaptic plasma membrane	nicotinic acetylcholine receptor	α-bungarotoxin; D-tubocurarine; succinylcholine
	muscarinic acetylcholine receptor	muscarine; atropine; quinuclidines
Synaptic cleft	acetylcholinesterase	carbamates; organo-phosphates; acetylcholine analogues

to the concept of chemical transmission – 60 or more years would pass before scientific opinion was ready for that – but it is worth mentioning that it was the discovery of the analogous action of strychnine in specifically blocking inhibitory synaptic action in the spinal cord that so impressed Eccles and led him to accept the concept of chemical transmission in the CNS.

Nicotine and the nicotinic acetylcholine receptor

The alkaloid nicotine is responsible for much of the physiological response to smoking – particularly the hyperglycaemia with its attendant sense of well-being. Tobacco (Fig. 2) was first grown in France as the result of the initiative of the French ambassador to Portugal, Jean Nicot, who sent seeds to France in 1550. The plant received the systematic name *Nicotiana tabacum* after Nicot; nicotine was first isolated in pure form in 1828 and was synthesized in 1904.

The Cambridge (UK) physiologist Langley found that, when painted on autonomic ganglia, nicotine first stimulated, then blocked them. This property enabled him to work out the anatomy of the autonomic nervous system, and led to the recognition of one large class of acetylcholine receptors as nicotinic. These resolve into a number of subclasses: decamethonium is an excellent blocking agent at the type of nicotinic receptor at the neuromuscular junction; hexamethonium is not effective at this junction but blocks transmission in autonomic ganglia.

For many decades the nicotinic acetylcholine receptor was a pharmacological and physiological hypothesis: a ligand-gated channel with permeability to univalent cations. The isolation of α-bungarotoxin from the venom of the banded krait, *Bungarus multicinctus* (Fig. 2) by the Taiwanese biologist Lee[4] and his demonstration that it specifically blocked nicotinic receptors with a very high affinity gave neurochemists for the first time a handle with which to isolate and characterize the receptor.

α-Bungarotoxin itself has too high an affinity to be useful, but Edith Heilbronn and her colleagues[5] in Uppsala found that a
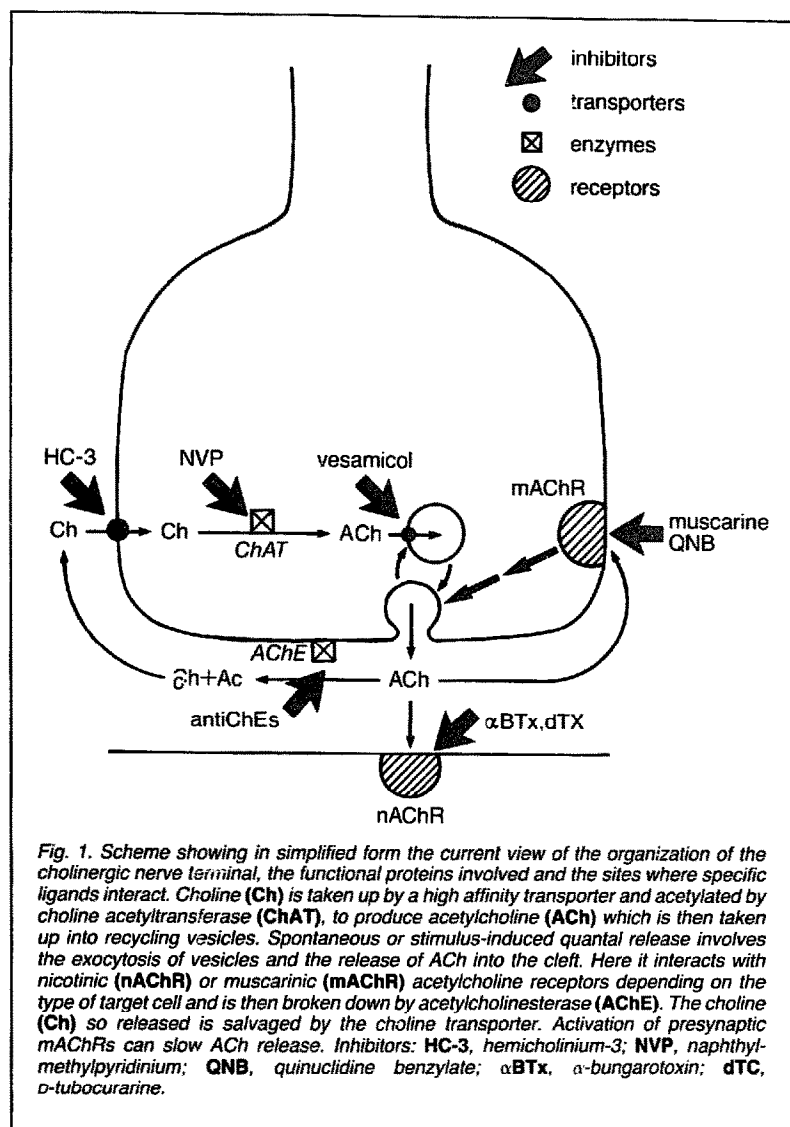

Fig. 1. Scheme showing in simplified form the current view of the organization of the cholinergic nerve terminal, the functional proteins involved and the sites where specific ligands interact. Choline (Ch) is taken up by a high affinity transporter and acetylated by choline acetyltransferase (ChAT), to produce acetylcholine (ACh) which is then taken up into recycling vesicles. Spontaneous or stimulus-induced quantal release involves the exocytosis of vesicles and the release of ACh into the cleft. Here it interacts with nicotinic (nAChR) or muscarinic (mAChR) acetylcholine receptors depending on the type of target cell and is then broken down by acetylcholinesterase (AChE). The choline (Ch) so released is salvaged by the choline transporter. Activation of presynaptic mAChRs can slow ACh release. Inhibitors: HC-3, hemicholinium-3; NVP, naphthylmethylpyridinium; QNB, quinuclidine benzylate; αBTx, α-bungarotoxin; dTC, D-tubocurarine.
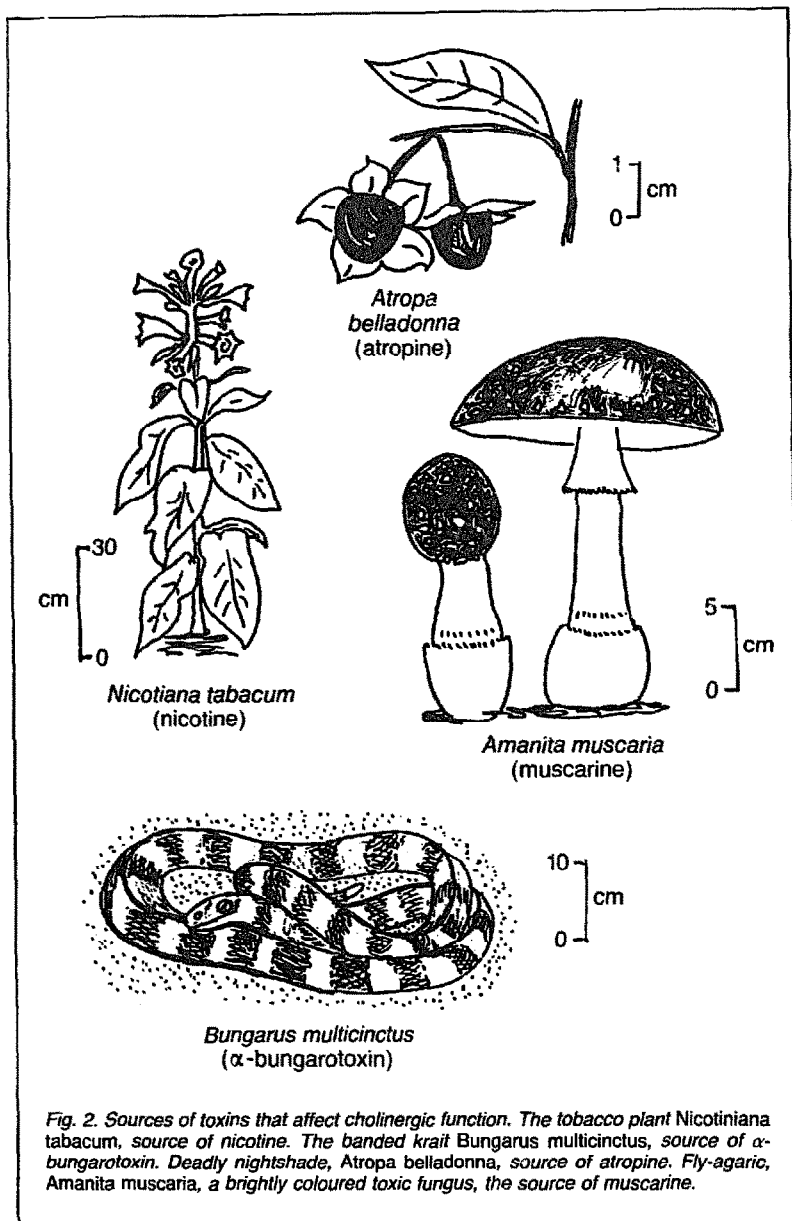
similar venom from the cobra, *Naja naja*, especially when acetylated, had the right affinity to provide the basis for the purification of the receptor by affinity chromatography. In an attempt to raise an antibody to the newly isolated receptor protein, Heilbronn and Mattsson[6] observed – as Patrick and Lindstrom[7] independently observed at about the same time – the hind-limb paralysis now designated experimental autoimmune myasthenia gravis.

Subsequent work by many groups has led to a detailed knowledge of the structure of the receptor. A notable contribution has been the cloning and sequencing of cDNA encoding its four constituent polypeptides by the Numa group[8].

Muscarine and the muscarinic acetylcholine receptor

Another historically important alkaloid is muscarine, the toxic principle of the intensely poisonous mushroom *Amanita muscaria* or fly-agaric (Fig. 2). This alkaloid excites, and then blocks a different type of cholinergic synapse: that of the parasympathetic endings in smooth muscle and glands. All its effects are reversed by atropine, the toxic alkaloid of *Atropa belladonna* or deadly nightshade (Fig. 2). Urged on by a Swedish professor of pharmacology who assured me I would not exceed the threshold dose, I once ate several berries and found them sweet and delicious; this may explain the tendency of children to eat them and to be poisoned by them.

More recently, muscarinic

Fig. 2. Sources of toxins that affect cholinergic function. The tobacco plant Nicotiniana tabacum, *source of nicotine. The banded krait* Bungarus multicinctus, *source of α-bungarotoxin. Deadly nightshade,* Atropa belladonna, *source of atropine. Fly-agaric,* Amanita muscaria, *a brightly coloured toxic fungus, the source of muscarine.*

receptors have been found in the CNS and, presynaptically, in some types of cholinergic terminal where they form part of a negative-feedback loop regulating the release of the transmitter (Fig. 1). Three subtypes can be distinguished pharmacologically. A vast number of muscarinic ligands are now known; more than 90 are listed in the 10th edition of the *Merck Index*, among them the quinuclidines. Molecular geneticists have recently succeeded in uncovering several more subtypes hitherto unknown to pharmacologists and these offer the possibility of very precise targeting of muscarinic drugs.

The concept of chemical transmission

The ability of muscarine to mimic parasympathetic stimulation parallels that of adrenaline to mimic sympathetic stimulation. These resemblances led Elliot in 1904[9] and Dixon in 1906[10] to postulate that endogenous ligands identical or similar to these compounds could act as chemical transmitters at parasympathetic and sympathetic synapses respectively. These prescient ideas attracted little support at the time, but were subsequently energetically taken up by Dale. Impressed by Hunt and Taveau's demonstration[11] (in 1911) that the acetyl-

ation of choline enormously potentiated its ability to lower blood pressure in the cat, Dale demonstrated, with Dudley, the presence of acetylcholine in a mammalian tissue[12].

However, the identification of acetylcholine as the parasympathetic transmitter, 'vagusstoff', eluded Dale, and was achieved by Otto Loewi (see Ref. 13). Dale and Loewi shared the Nobel Prize, and Dale and his co-workers identified acetylcholine as the transmitter at a variety of sites, including the electromotor terminals of *Torpedo*, during the 1930s.

New words often have an important slogan value in science. Who would now remember Funk if it were not for 'vitamins' or Benda if it were not for 'mitochondria'? Dale's terms adrenergic and cholinergic, while not completely accurate, neatly enshrine the concept of chemical transmission and have led to an extended and progressively less euphonious terminology: 'GABA-ergic', 'glutamergic', 'substance P-ergic', and so on.

The anticholinesterases

An important contribution of Otto Loewi was his discovery that released acetylcholine is unstable in contact with tissues owing to the action of a specific enzyme. This enzyme, cholinesterase, was purified by a husband and wife team of Edinburgh biochemists, E. and E. Stedman.

Physostigmine

Cholinesterase is inhibited by the naturally occurring alkaloid physostigmine or eserine, a carbamate ester of a nitrogenous base. Many synthetic analogues are known.

Loewi's realization that the basic effects of eserine were explicable on the basis of its specific inhibition of cholinesterase and the ensuing accumulation of acetylcholine is perhaps the first example of what Sir Rudolph Peters termed a 'biochemical lesion' – the explanation of a toxic action in terms of a specific interference with a biochemical mechanism rather than a non-specific, generalized effect on the cell.

The organophosphates

An even more potent class of anticholinesterases is the highly

toxic organophosphorus compounds[14]. These have given perhaps the biggest boost of any drug or toxin to cholinergic research because of their potential as chemical warfare agents and later as insecticides. During World War II it became an urgent matter of national security for governments to know as much as possible about the action of these substances and how they could be combated, and this in turn made it essential to understand as fully as possible the biochemistry of the cholinergic system. The continued use of some of these compounds as insecticides after the war created a record in terms of industrial toxicology, surpassing even the problems that arose when tetraethyl lead was introduced as an anti-knock agent into petrol by the American petroleum chemist Kettering in the 1920s.

The potential of the organophosphorus anticholinesterases was first appreciated in Germany between the wars. The first compound of this type (tetraethylpyrophosphate, TEPP) was synthesized as far back as 1854 by De Clermont. Several other chemists worked with this or similar compounds but failed to appreciate their highly toxic nature. Willy Lange and his graduate student Gerda von Krueger synthesized dimethyl- and diethylphosphorofluoridate – the first fluorine compounds in the series – in 1932. They immediately appreciated the toxicity of these compounds (perhaps because they were more volatile than TEPP) and noticed the effect of the vapour on respiration and the eyes. Lange was interested in synthetic insecticides and thought his compounds might be useful there. It is now known that all these effects are due to the powerful action of the compounds on the cholinergic synapse, and that insects use cholinergic transmission intensively in their nervous system.

Some years later IG Farbenindustrie put the chemist Gerhard Schrader on to making Lange's compounds and many others in the same series – about 2000 between 1938 and 1944. Their high toxicity interested the German Army and a security veil fell on the work. About 10000 tons of tabun, a cyanide analogue, were manufactured in Dühernfurt

north of Breslau (now Wrocław) in Silesia, then part of the German Reich. This factory was captured by the Russians and may well have been the starting point for their interest in chemical warfare.

The general formula of organophosphorus compounds is given in Table II. The group Y is always oxygen or sulphur; group X is a leaving group which can exist as a stable anion. R_1 and R_2 are alkyl, alkoxy, or alkylamino groups. The whole molecule acts as a 'pseudo-substrate' for cholinesterases, whose active centre catalyses the splitting off of the leaving group and the transfer of the rest of the molecule to the active site forming a stable complex (Fig. 3, Eqn 3).

Meanwhile, a team of chemists and pharmacologists in Britain were investigating the literature for potential war gases. Prominent members were B. C. Saunders[15], a Cambridge organic chemist, and the Kilbys[16], also working in Cambridge as a husband and wife team, a biochemist and pharmacologist, respectively. In 1940 they came across Lange and Krueger's compounds and synthesized and tested numerous analogues of which the most potent was di-

isopropylfluorophosphate (DFP; diisopropylphosphorofluoridate). This team quickly discovered that these compounds worked by blocking cholinesterase irreversibly at very low concentrations. The more volatile ones were easily absorbed by inhalation.

When the USA entered the war, information was passed by the British to them and they set up their own teams, one of which was headed by David Nachmansohn who was one of the few biochemists in the USA at that time who knew much about cholinesterases.

After the war, the insecticidal aspect of the organophosphorus compounds began to be worked on. The goal was non-volatile compounds that could be more safely handled by farm workers. These include mipafox and parathion (Table II).

The combination of continuing military and agricultural interest in these compounds meant good funding for basic research in the cholinesterase field and the mode of action was fairly quickly discovered. Kinetic and specificity studies by Zeller and Bissegger[17] and by myself and David Adams[18],
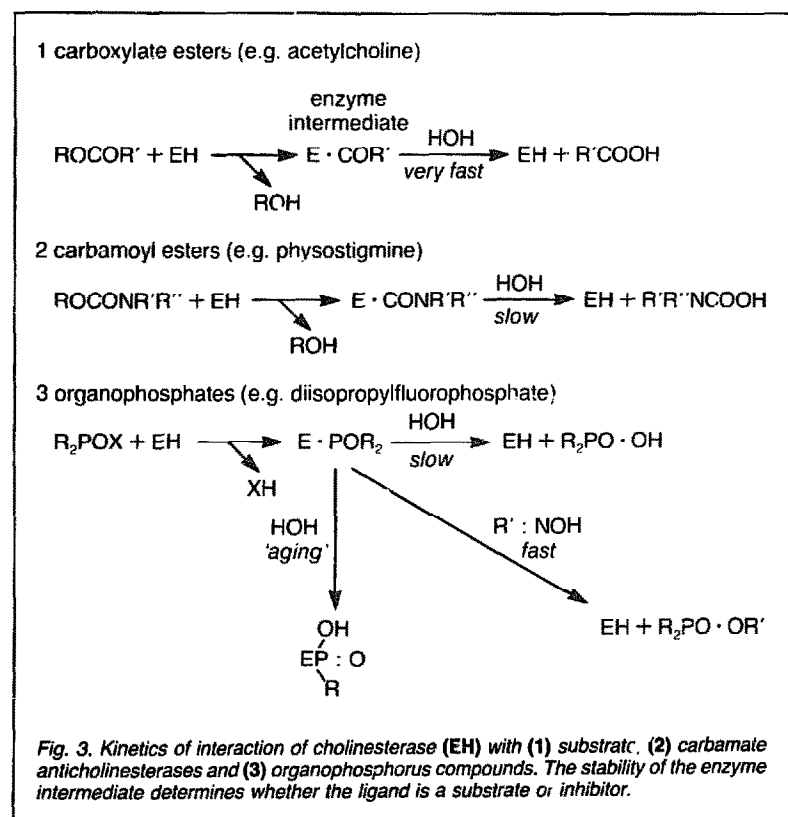
1 carboxylate esters (e.g. acetylcholine)

$$ROCOR' + EH \xrightarrow{\quad} E \cdot COR' \xrightarrow[very\ fast]{HOH} EH + R'COOH$$
$$\searrow ROH$$

2 carbamoyl esters (e.g. physostigmine)

$$ROCONR'R'' + EH \xrightarrow{\quad} E \cdot CONR'R'' \xrightarrow[slow]{HOH} EH + R'R''NCOOH$$
$$\searrow ROH$$

3 organophosphates (e.g. diisopropylfluorophosphate)

$$R_2POX + EH \xrightarrow{\quad} E \cdot POR_2 \xrightarrow[slow]{HOH} EH + R_2PO \cdot OH$$

XH

HOH 'aging'

R' : NOH fast

$$EH + R_2PO \cdot OR'$$

$$\begin{array}{c} OH \\ | \\ EP : O \\ \backslash \\ R \end{array}$$

Fig. 3. Kinetics of interaction of cholinesterase (EH) with (1) substrate, (2) carbamate anticholinesterases and (3) organophosphorus compounds. The stability of the enzyme intermediate determines whether the ligand is a substrate or inhibitor.

TABLE II. Structure of organophosphorus compounds

R\P(X)(Y)R	R₁	R₂	X	Y
Nerve gases				
Sarin	$isoC_3H_7O$	Me	F	O
Tabun	Me_2N	EtO	CN	O
Diisopropylfluoro-phosphate	$isoC_3H_7O$	$isoC_3H_7O$	F	O
Insecticides				
Mipafox	$isoC_3H_7NH$	$isoC_3H_7O$	F	O
Paraoxon	EtO	EtO	$p\text{-}HOC_6H_4NO_2$	O

and studies of the effect of pH on the binding of reversible anti-cholinesterases in the enzyme by Wilson in Nachmansohn's group independently led both us and Wilson[19] to the conclusion that the active centre of cholinesterase consisted of two parts: the acyl binding centre, and the 'negative nitrogen attracting group' or anionic centre which binds the choline group of acetylcholine. Work by Wilson *et al.* and several other groups showed that the substrate reacted with the acyl active centre of the enzyme as an acetylating agent to form an acetylated enzyme that was then extremely rapidly hydrolysed (Fig. 3, Eqn 1). The organophosphates are pseudo-substrates which transfer a dialkylphosphate instead of an acetate group to the enzyme (see above); this is only very slowly regenerated by water but can be much more rapidly activated by substituted hydroxylamines (Fig. 3, Eqn 3).

A serious problem in providing an effective chemical antidote for organophosphorus anticholin-esterases is the 'aging' reaction in which the dialkylphosphoryl- or dialkylphosphonyl-esterase is slowly converted into a mono-alkylphosphoryl- or monoalkyl-phosphonyl-esterase. Such linkages are much more difficult to reverse (hence the term 'aging'),
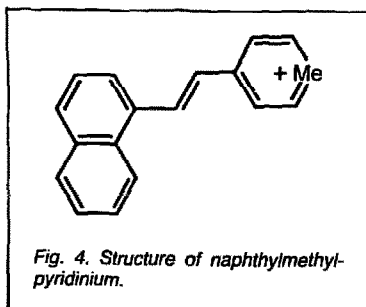

Fig. 4. Structure of naphthylmethyl-pyridinium.

and with some organophosphorus anticholinesterases the 'aged' state is reached in minutes, giving little time for chemical therapy.

In the case of the carbamate anti-cholinesterases, such as physostig-mine (eserine) (Fig. 4, Eqn 2), the carbamylated enzyme inter-mediate is hydrolysed much more rapidly by water than the corres-ponding phosphorylated enzyme. Thus spontaneous reactivation occurs in a few hours.

Blockers of acetylcholine synthesis and storage

Aziridinium compounds

The choline transporter is very sensitive to nitrogen mustard ana-logues of choline. These contain the three-membered aziridinium ring and are alkylating agents. They are formed spontaneously in solution from the corresponding N-chloromethyl tertiary bases. Choline analogues of this type have a selective affinity for high affinity choline binding sites which they can be induced to alkyl-ate; this blocks the function of the choline transporter, eventually bringing acetylcholine synthesis to a standstill and blocking trans-mission. If the aziridinium com-pound is labelled, this also pro-vides a handle for isolating the transporter protein. The first such compound, hemicholinium-3, was discovered by Schueler[20] in 1955. Radioactive hemicholinium and a simpler compound, choline mustard aziridinium, have been used by Breer[21] and by Rylett[22], respectively, to isolate the choline transporter from insect brain and *Torpedo* electromotor terminals. The insect carrier appears to be a single peptide of relative mol-ecular mass 86 000, and the *Torpedo* carrier a complex of two peptides of 43 000 and 57 000.

Choline acetyltransferase inhibitors

The anti-ChAT compound naphthylmethylpyridinium (Fig. 4) was introduced by Cavallito[23] in 1962. Its lack of specificity has, however, limited its use.

Vesamicol

This inhibitor of vesicular acetylcholine uptake (also known as AH-5183) was discovered by Marshall[24], but its mode of action was defined by Stanley Parsons[25] who has shown that it blocks the uptake of acetylcholine into the recycling vesicles which are in-volved in transmitter release (Fig. 1). Such vesicles are recruited on stimulation from the reserve pool and their discovery has gone far to resolve some of the paradoxes of the vesicular theory of transmitter storage and release[26,27].

□   □   □

There is little doubt that new drugs and toxins will continue to provide a powerful tool for dissect-ing and understanding cholin-ergic and other types of synaptic function.

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COMMENT

Pharmacological receptors: the need for a compendium of classification, nomenclature and structure

Jack Peter Green

In an attempt to contain the chaos of receptor nomenclature, the supplement distributed with this issue of TiPS catalogues cell surface receptors and their subtypes according to the most commonly used nomenclature and describes them in pharmacological, biochemical and molecular terms. This reporting of the status quo will be an invaluable aid to communication, but all scientists (not just pharmacologists) working on receptors would agree that a radical and rational classification of receptors also needs to be initiated. In this article, Jack Peter Green proposes a system of (and mechanism for) classification that should satisfy both the 'taxonomic realists' and the 'taxonomic skeptics'.

In considering receptor classification and nomenclature, it is advantageous to learn from the taxonomies that have evolved for other entities. There is no shortage of examples, some of which go back at least to the time of Aristotle[1,2]. Classification has been a preoccupation throughout history and is perhaps an expression of the human eagerness to divide things into specific categories and to give them names – an essential for communication. Few things have avoided classification and naming[3,4]. Systems have been developed for organisms (including viruses), antigens, enzymes, organic chemicals according to their structures, diseases, personality variants, the physical status of patients (e.g.

after surgery, or rankings of the severity of a disease, as in Parkinson's disease), languages, stars, and so on. Official classifications are almost always established under the aegis of the appropriate professional societies.

Classifications that evolve haphazardly tend to be far less orderly, producing classes that may be unparallel and unrelated. For example, the classification system for drugs is not logical or consistent, as is demonstrated by a list of the chapter headings in any textbook of pharmacology.

In a randomly selected typical textbook, drugs are classified according to the sites and types of action (e.g. Cholinergic agonists), the gross effects (e.g. Sedatives and hypnotics), the diseases they are used to treat (e.g. Drugs used in gout), a discipline (Toxicology), the signs, symptoms, or syndromes they are used for (e.g. Antihypertensive agents, Antiarrhythmic agents), the processes

they are used to alter (e.g. Anticoagulants, Diuretics), and combinations of qualities (e.g. Cardiac glycosides, an imprecisely defined chemical grouping used for an effect on a specific organ). Subdivisions of a chapter on drugs acting on the CNS might include: General anesthetics (a title based on use); Aliphatic alcohols (a title based on chemical structure); and Drug addiction and drug abuse (a title based on a special response).

However inconsistent this classification, it serves because the reader knows what information is encompassed in a discussion of each class of drug. Sometimes, however, classifications and names offered by individuals can so vary that confusion results, a circumstance that provoked publication of *Enzyme Nomenclature*[5] and that now fosters the need for an official classification and naming of receptors[4,6]. As research on receptors continues, it is likely that different names of receptors and different schemes of classification will continue to increase, reflecting the different interests and research goals of scientists. The confusion could exceed that which engendered *Enzyme Nomenclature* since scientists working on receptors come from disparate disciplines using different techniques, whereas enzymologists comprise a comparatively cohesive group.

Realists and skeptics

Classifiers have been divided into two groups[7]: the taxonomic realists and taxonomic skeptics. The realists assume that a particular taxonomy is correct or incorrect, that objects are ordered into natural groups. The taxonomic skeptics judge a taxonomy by its usefulness, which depends on the purposes of the classification. The skeptics would be less disturbed than the realists by the view that classification schemes

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