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Past approaches to discovering new medicines

Aproximaciones históricas al descubrimiento de nuevos fármacos

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RESUMEN

Se hace una breve historia de las principales aproximaciones al descubrimiento de nuevos fármacos. Se describen cuatro de las principales aproximaciones: productos naturales, uso de prototipos existentes, screening farmacológico y transmisores fisiológicos.
Palabras clave: Nuevos fármacos.

ABSTRACT

A brief account is given of the main approaches to new drug discovery which have been taken during the twentieth century. Four main sources for new drugs are described and each of these is discussed in turn; they are: natural products, existing drugs, screens and physiological transmitters.
Key words: New medicines.

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INTRODUCTION

Nowadays the development of new medicines takes place in pharmaceutical companies and most of the new drugs are also discovered in their research laboratories.

New drug discovery depends on a complex collaboration and interaction between various scientific disciplines drawn mainly from the chemical, biological and medical sciences. It has reached an extraordinary level of sophistication which is why most of the advances now come from the laboratories of the developed industrial nations.

To gain a historical perspective it is of interest to consider the main approaches to drug discovery which have been taken during the twentieth century with the rise of the modern pharmaceutical industry.

There have been four main sources for new drugs. These are:

— Natural products
— Existing drugs
— Screens
— Physiological transmitters and mechanisms involving them

NATURAL PRODUCTS AS A SOURCE FOR NEW DRUGS

Natural products provide the oldest source for new medicines. Natural selection during evolution, and competition between the species, has produced powerful biologically active natural products which can serve as chemical leads. Thus, moulds and bacteria produce substances that prevent other organisms from growing in their vicinity. Extensive soil screening research programmes have led to a wide range of antibiotics which have given rise to very potent life-saving drugs.

A recent example of the use of microbial fermentation as a source for a drug lead was the discovery of a novel cholecystokinin (CCK) antagonist, asperlicin, from *Aspergillus alliaceus* (1) which served as the starting point for Merck scientists to develop the very specific and potent nonpeptide antagonists at CCK-A and CCK-B receptors respectively. Such fermentation broths are also a potentially rich source of novel enzyme inhibitors.

Venoms and toxins are used by animals as protection or to paralyse their prey; some are extremely potent, requiring only minute doses, e.g., bungarotoxin (from snake venom) which combines with acetylcholine receptors. Currently, toxins from scorpions and snakes are providing important leads for the pharmacological exploration of potassium ion channels.

Folk law medicines have provided another very important source of pharmacologically active natural products, e.g., alkaloids such as morphine, atropine, reserpine and ergotamine.

EXISTING DRUGS AS A BASIS FOR NEW DRUG DISCOVERY

Probably the most productive approach to the discovery of a new drug has been to start with an old drug. Obviously one can aim to improve existing drugs to improve dosage form or to avoid side effects. Less obvious is the approach which has exploited side effects arising from astute observation during studies in animals or in patients.

The discovery of sulphonamide diuretics such as chlorothiazide in the 1950s followed from the observation that the antibacterial drug sulphanilamide

in patients rendered the urine alkaline through inhibition of the enzyme carbonic anhydrase. The phenothiazine tranquilisers, which revolutionized the treatment of psychiatric patients, resulted from astute observation of the effects of an antihistamine. More recently, metoclopramide (a dopamine antagonist) which was found to be antiemetic in some patients led to the development of the new 5-HT_3 antagonists as potent antiemetics, such as granisetron and ondansetron (2).

SCREENS FOR NEW DRUGS

As already mentioned, natural products can be screened to provide leads for antibiotics, receptor blockers, enzyme inhibitors and ion channel blockers. This can be supplemented with the screening of synthetic chemicals, obtained from chemical suppliers such as Aldrich or from company files (libraries) of compounds.

In the past, the most successful screens provided drugs for use in chemotherapy but screens were also established for non-infectious diseases, e.g., anti-convulsants (useful in epilepsy), analgesics (in the hope of being non-addictive), anti-cancer, anti-hypertensives, anti-inflammatory, etc.

There is an important distinction however between the anti-infective screens, and the screens which seek a treatment for a metabolically-based disease. In the anti-infective screens the drug has to be lethal to the pathogen, but leave the host unharmed, i.e., it is a search for selective toxicity between species. In the metabolically-based diseases, by contrast, it is a tissue selectivity which is sought within the same being.

In the past, an animal model was used as a screening test, in which a clinical condition was induced in a laboratory animal such as a rabbit or rat, and compounds were tested to see whether they alleviate it. The model often simulated the disease by presenting similar symptoms, but it was often misleading if the underlying causes were quite different. The modern approach to screening is to combine it with an understanding of physiological mechanisms (see below).

PHYSIOLOGICAL MECHANISMS; THE MODERN "RATIONAL APPROACH" TO DRUG DESIGN

As our understanding of physiological mechanisms has increased it has become possible to take a more mechanistic approach to research and start from a rationally argued hypothesis to design drugs. There are five main sites for drug action:

— Enzymes
— Receptors

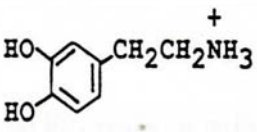
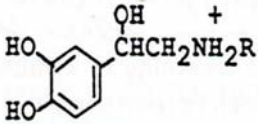
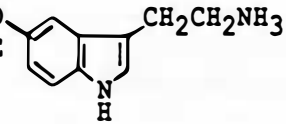
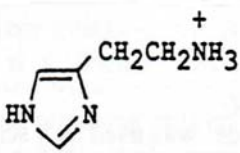
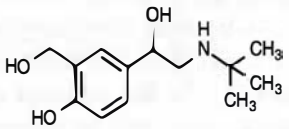
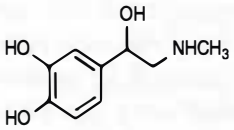
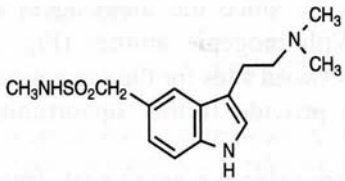
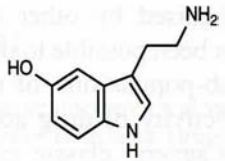
AMINE	STRUCTURE	RECEPTORS
ACETYL CHOLINE	$CH_3CO.O.CH_2CH_2\overset{+}{N}Me_3$	Nicotinic: muscle, neuronal; M_1, M_2, M_3, M_4, M_5
DOPAMINE		D_1, D_2, D_3, D_4, D_5
NORADRENALINE, R=H ADRENALINE, R=CH_3		α_{1A-1D} α_{2A-2C} β_1, β_2, β_3
SEROTONIN (5-HYDROXYTRYPTAMINE		$5\text{-}HT_{1A-1F}$, $5\text{-}HT_{2A-2C}$ $5\text{-}HT_3$, $5\text{-}HT_4$, $5HT_{5A-5B}$ $5\text{-}HT_6$, $5\text{-}HT_7$
HISTAMINE		H_1, H_2, H_3

Fig. 1.—Chemical structures of the biogenic amines (shown as the most prevalent ionic species at pH 7.4) and receptor subtypes (see reference (5) for additional information on receptor subtypes).

— Transport systems
— Cell replication and protein synthesis
— Storage sites

Enzymes and receptors are highly specialised sites which recognise their appropriate substrates or chemical messengers and they possess a very high degree of selectivity. Hence they provide very good chemical starting points for drug design. Since the key to a successful drug lies in its selectivity of action, the rational approach has been especially effective in modern drug discovery when based on enzymes or hormone receptors, and the past three decades have seen some notable drug design successes based on the approach of using as leads, enzymes and their substrates, or receptors for biogenic amines.

AGONISTS

Drugs	*Biogenic Amine*
	
Salbutamol (β_2–stimulant)	Adrenaline
	
Sumatriptan (5-HT_{1D}-agonist)	5-Hydroxytryptamine (5-HT)

ANTAGONISTS

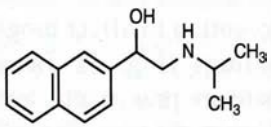
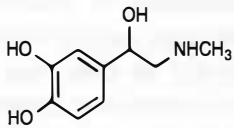
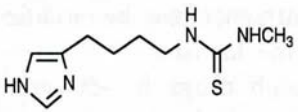
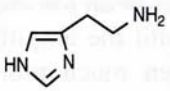
	
Pronethalol (β–blocker)	Adrenaline
	
Burimamide (H_2-antagonist)	Histamine

Fig. 2.—Chemical structures of some agonists and antagonists at biogenic amine receptors where the design was based on the amine structure as a template.

Enzymes have active sites which specifically recognise the substrates which they act upon and one can interrupt this process with enzyme inhibitors which may be designed using the chemistry of the substrate as a starting point. Alternatively, it may be possible to characterise the enzyme active site. For example, angiotensin converting enzyme (ACE) was characterised as a metalloenzyme containing zinc at the active site, and this led to the design of the inhibitor captopril for treatment of hypertension (3). Or, the substrate specificity may be studied using dipeptides as probes which may then be converted into potent inhibitors, as was effected in the design of the enkephalinase inhibitor, thiorphan (4).

Many substances circulate as chemical messengers and combine with their own receptors, e.g., amino-acids, biogenic amines, peptides, prostaglandins, purines, steroids; they are remarkably specific since the messengers are not normally recognised by other receptors. With biogenic amines (Fig. 1), for example, it has been possible to differentiate between sites for the same messenger, suggesting sub-populations of receptors to provide further opportunities for achieving selectivity of drug action.

There are several classic examples where selective antagonist drugs have been designed to block a particular receptor population using the chemistry of the natural messenger as a lead (6-9). Well known drugs (Fig. 2) such as propranolol (adrenergic β-blocker), cimetidine (H_2-receptor histamine antagonist), salbutamol (adrenergic β_2-stimulant) and sumatriptan (5-HT_{1D} agonist) have been derived from compounds whose design was based on the natural biogenic amine transmitter. Thus, modification of the biogenic amine structure and addition of appropriate chemical groups have given rise to compounds which may either selectively stimulate, or selectively block, a sub-population of receptors.

There are many potential sites for drug intervention to affect biogenic amine action especially in their role as neurotransmitters (Fig. 3). In addition to blocking post-synaptic receptors (R_1, R_2 etc.), there are presynaptic autoreceptors which may modulate transmitter release or synthesis, storage sites and reuptake mechanisms which modulate free transmitter concentration, and enzymes which can be blocked to alter the rate of transmitter turnover, e.g., inhibit biosynthesis to deplete the transmitter or inhibit metabolism to prolong its existence. Furthermore, the amine receptor is coupled to a second messenger system, e.g., an enzyme (protein kinase) or an ion channel, so that its influence may be modified by drug interference with the amplifying transducing mechanism.

It has been much more difficult to design drugs to act on transporter proteins or ion channels, or on storage sites, mainly because too little was known about the nature of these specialised units in cells. With the advent of molecular biology, and the future prospect of isolating many of the protein units involved in these functions, it is likely that progress will greatly accelerate for drug design based on these mechanisms. A current example is the considerable

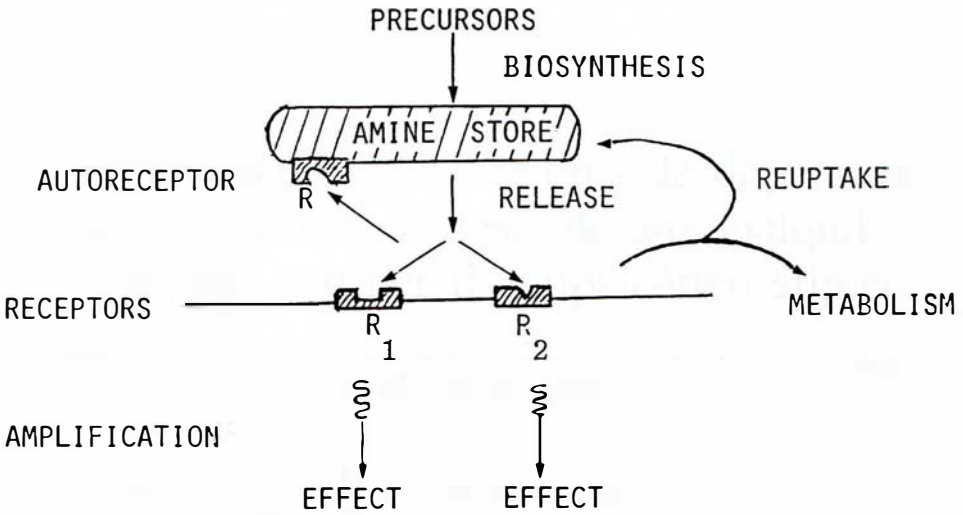


Fig. 3.—Biogenic amine transmission can be modified by drug intervention at various stages and sites using enzyme inhibitors, or selective receptor blockers or stimulants. Drugs may also affect release or uptake.

interest being shown in designing compounds that bind selectively to the dopamine transporter in the hope of finding a treatment for cocaine dependence (10).

For a more detailed discussion of the above topics see reference (11).

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