Reviews

The discovery of antidepressants: A winding path

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Summary. Modern treatment of mental depression started with the availability of monoamine oxidase (MAO) inhibitors and tricyclic antidepressants. These drugs also contributed to the early development of psychopharmacology. Attempts to improve the anti-tuberculous action of the hydrazine derivative isoniazid by developing derivatives thereof led to the synthesis of iproniazid. Its introduction as the first modern antidepressant was based on three unexpected actions of the drug: MAO-inhibition, 'reversal' of reserpine-induced sedation, and the presence of psychostimulation as a clinical side effect in man. However, the initial success of iproniazid and other MAO inhibitors, hydrazides and non-hydrazides, was curtailed by the occurrence of undesirable side effects such as potentiation of the blood-pressure elevating action of food amines. The tricyclic antidepressants were a development of the class of antihistamines, one of which, chlorpromazine, showed neuroleptic activity. A congener of this compound, imipramine, was discovered by clinical observation to have unexpected antidepressant effects. The clinical success of this drug (which is still in use) led to the development of a successful series of other tricyclic and non-tricyclic antidepressants. Progress in the elucidation of possible mechanisms of the action of the tricyclic compounds has helped this development. Recent advances in basic research have also induced a revival of MAO-inhibitors since, due to the discovery of MAO-subtypes, inhibitors with higher specificity and fewer undesirable side effects are now available.

Key words. Depression; antidepressants; psychopharmacology; tricyclic antidepressants; monoamine oxidase inhibition; iproniazid.

Introduction

Mental disorders such as schizophrenia and depression were not accessible to effective drug treatment until the middle of this century. With the advent of modern psychotropic agents, especially neuroleptics and antidepressants, the situation has improved dramatically. The advent of these new agents not only promoted clinical psychiatry, but also advanced our knowledge of the biochemical mechanisms underlying brain function. The mutual feedback between basic research and imaginative clinical observation opened up a new discipline: psychopharmacology.

This article concentrates on the discovery of antidepressant drugs. Two classes of compounds, monoamine oxidase inhibitors and tricyclic antidepressants, will be considered. Several reviews on the history of these classes of psychotropic agents are already available[1, 19, 25, 27], but nevertheless, a further report dealing with this topic was thought to be justified since history has an individual note, and the author has been fortunate enough to have witnessed psychopharmacology in its infancy and to have known many of its creators personally. An attempt will be made to discuss the original observations which led to the break-throughs in antidepressant therapy. However, lithium, which is of great value for the control of manic disorders, has been omitted from this review for two reasons. Firstly, its possible mode of action (e.g. interference with the phosphoinositide cycle) has only recently been clarified, and therefore the substance played no major role in the early development of modern psychopharmacology. Secondly, the serendipitous discovery of the antimanic action of lithium has been comprehensively described by its discoverer, John Cade, himself[6].

Monoamine oxidase inhibitors

The conquest of tuberculosis

The middle of our century brought good news for millions of patients suffering from an incapacitating, life-threatening disease: tuberculosis. Drugs started to appear which showed a marked tuberculostatic effect in vivo and eventually led to an efficient chemotherapeutic treatment for this scourge of humanity. One of these drugs, isoniazid, was discovered by 'serendipity'. In their endeavour to prepare pyridine-4-aldehyde, which was needed for the synthesis of semicarbazones (known to exert some tuberculostatic action in experimental conditions), chemists of F. Hoffmann-La Roche Ltd USA isolated an intermediate, isonicotinyl hydrazide (isoniazid). This substance had already been described in the literature in 1912, without anyone knowing that it had biological activity. In a newly developed biological screening system, Grunberg and Schnitzer of Roche discovered the marked tuberculostatic action of isoniazid in vivo[13]. A few weeks later this effect was also described by Bernstein et al.[3] and Otte et al.[22]. Subsequently the substance was developed as a drug against tuberculosis and has been widely used in medical practice.

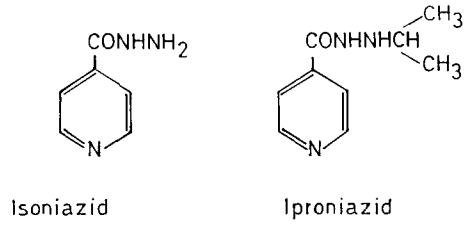


Figure 1.

In attempts to improve the tuberculostatic effect of isoniazid, Fox and Gibas of Roche [12] synthesized some of its monoalkyl derivatives including isopropyl-isonicotinyl hydrazide (iproniazid) (fig. 1). This compound later proved, quite unexpectedly, to be the key which opened up the field of the chemotherapy of mental depression.

Iproniazid: breakthrough in antidepressant therapy

The development of iproniazid as an antidepressant has been along three main lines, which will be briefly described in the following.

Inhibition of monoamine oxidase (MAO). In the early 1950s, E. A. Zeller and colleagues at Northwestern University, Chicago, discovered that iproniazid was a potent inhibitor of the enzyme monoamine oxidase (MAO). The drug was active in vitro and in vivo and it also acted on brain MAO. The parent compound, isoniazid, had a weaker effect [29, 30]. MAO catalyses the oxidative deamination of biogenic monoamines and could therefore be assumed to have a role in their biological inactivation in vivo. At the time of Zeller's discovery, ideas about a possible functional role of biogenic monoamines had already appeared on the scientific horizon. Of special interest were the findings that the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5HT) occurred normally in the brain and that the potent hallucinogen lysergic acid diethylamide (LSD) (which had been synthesized somewhat earlier by A. Hoffmann [14]) interacted with 5HT. However, it was still premature to build the bridge between MAO-inhibition and treatment of depression, although an important foundation for this concept had been laid.

Reserpine reversal. A second important discovery originated in the laboratory of B. B. Brodie at the National Institutes of Health (NIH), Bethesda, Maryland, USA, where Pletscher, Shore and Brodie found that reserpine, an indole alkaloid previously isolated from the Indian plant *Rauwolfia serpentina*, caused a marked, long-lasting depletion of 5HT in the brains of animals [23]. Two factors were essential for this discovery – previous work on the biochemistry of 5HT by Sidney Udenfried's group, and the availability of a prototype of the first spectrophotofluorimeter, constructed at the NIH by R. L. Bowman. They allowed the development of a sensitive, specific method for the detection of 5HT in tissues, including brain extracts [4].

At the time of these developments, reserpine, following the discovery of its pharmacological action by H. J. Bein and collaborators [2], was clinically used to lower elevated blood pressure and as a tranquilizing agent, e.g. in schizophrenia. The drug also decreased locomotor activity and induced autonomic symptoms (e.g. miosis and diarrhoea) in animals. The biochemical and clinical 'ends' were then tied together, leading to the hypothesis that the tranquilizing effects of reserpine were due to its action on brain 5HT. This stimulating hypothesis led to another important discovery made simultaneously by two independent groups [5, 9], namely the reversal of the action of reserpine by iproniazid. Thus, after pretreatment with the MAO-inhibitor, reserpine no longer caused sedation and miosis, but rather excitation and mydriasis, and the reserpine-induced decrease of brain 5HT was attenuated (fig. 2). Iproniazid alone had no overt behavioural effect, and when given after reserpine (when the cerebral monoamine depots had been depleted) did not influence the reserpine-induced behaviour. These findings suggested to the researchers that interference with 5HT metabolism, e.g. by inhibition of the degradation of released (synaptic) 5HT, might be connected with psychotropic action. Later on, this hypothesis had to be modified due to additional findings. For instance reserpine was shown also to deplete the brain of catecholamines, another group of functionally important amines.

Clinical observations. A third and essential group of findings pointing to a psychostimulant effect of iproniazid stemmed from clinical observations. In the early fifties

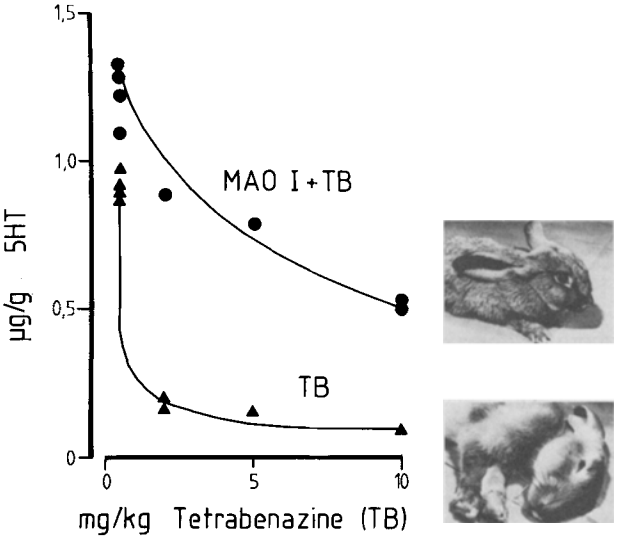


Figure 2. Curves: 5-Hydroxytryptamine (5HT)-content in µg/g of rabbit brain 1 h after i.p. injection of various doses of tetrabenazine (TB; a compound with reserpine-like action) before (below) and after (above) i.p. treatment with the MAO-inhibitor (MAO I) iproniazid. In the pretreated animals the decline of cerebral 5HT is attenuated. Rabbit pictures: 1 h after injection of TB before (below) and after (above) pretreatment with iproniazid.

numerous clinicians[24] reported unexpected side effects of hydrazine derivatives, especially of iproniazid. In patients treated for tuberculosis with iproniazid, the drug not only showed tuberculostatic action, but also caused euphoria and psychostimulation, leading in some cases to psychomotor excitation, psychotic states, insomnia, increase of appetite, changes in sexual behaviour etc. Patients severely affected with tuberculosis have been described as 'dancing in the hall' under treatment with iproniazid. Later on, the drug was intentionally used to improve the depressed mood of chronically ill patients with tuberculosis, and psychostimulant effects of iproniazid were also seen in patients with other chronic affections such as cancer and rheumatoid arthritis. However, trials of iproniazid in hospitalized psychiatric patients with various diagnoses did not reveal any therapeutic effects worth following up[15,26]. This failure was probably due to defects in the study design, for example the wrong choice of patients (e.g. schizophrenics) and an insufficient duration of treatment. When iproniazid-induced psychostimulation was eventually observed it was looked upon as an amphetamine-like effect rather than a true antidepressant action.

The rise and fall of MAO-inhibitors. The final breakthrough in the development of MAO-inhibitors was made by N. S. Kline and his colleagues J. C. Saunders and M. Loomer[20,21,24]. They were intrigued by the biochemical and pharmacological actions of iproniazid in animals and its clinical side effects in man and suspected that they might be interrelated. This led them to start an open clinical trial with the drug. Patients with stable depression, institutionalized for an average of 20 years, were chosen without regard for the underlying diagnoses. After treatment for several weeks with iproniazid about 70% of the patients were reported to show a remarkable improvement of their depressed state, and similar observations were made in ambulatory patients with depression. Later, numerous investigations confirmed these findings and the drug was introduced under the trade name Marsilid® as the first modern antidepressant in clinical practice.

This new approach to treating mental depression proved to be very successful. The sales figures of Marsilid® mounted massively during the next few years. Also, successors of Marsilid®, MAO-inhibitors of both the hydrazine and the non-hydrazine type, were developed and introduced by several drug companies. However, the initial enthusiasm for MAO-inhibitors then suffered a heavy blow; the occurrence of serious side effects. The drugs were shown to enhance the blood pressure-elevating action of food amines such as tyramine, leading to dangerous hypertensive crises, e.g. the 'cheese reaction'. Also, cases of acute hepatic necrosis during treatment with MAO-inhibitors were reported. These findings heavily curtailed the use of MAO-inhibitors and led to the withdrawal of several of these drugs from the market. Nevertheless, some classical MAO-inhibitors are still in medical use today as antidepressants, although on a rather limited scale.

Tricyclic antidepressants

In spite of the disappointment with MAO-inhibitors these drugs had opened new vistas for psychiatry. At a time when biological psychiatry was still in its infancy, the idea of treating mental disturbances, such as psychic depression, by interfering with biochemical processes in the brain, was quite sensational. The use of MAO-inhibitors helped to overcome the negative attitude of many psychiatrists towards chemotherapy of mental illness and, as already mentioned, contributed to the development of the new discipline psychopharmacology. The ground for the breakthrough to another discovery was prepared; the 'victory march' of the tricyclic antidepressants became possible.

Whereas in the development of MAO-inhibitors as antidepressants the 'marriage' between basic research and clinical findings played an important role from the beginning, the discovery of the first tricyclic antidepressant was primarily based on clinical observation. This breakthrough was made possible by a chain of developments, starting with the antihistamines, which were then followed by the neuroleptics and ultimately by the tricyclic antidepressants[27].

Antihistamines

In 1949 the French navy surgeon Henri Laborit was concerned with surgical shock. He tried to prevent the drastic fall in blood pressure occurring in this condition using antihistamines. A combination of these compounds (e.g. the phenothiazine derivative promethazine of Specia Laboratories of Rhône Poulenc) with other drugs became known as 'lytic cocktail'. It caused hypothermia and sedation and proved to be useful as a hibernating agent in major surgery[18]. It then became evident that the anti-shock action of promethazine was due to the unexpected effects of this compound on the central nervous system and not to its antihistaminic activity. This knowledge revived the interest of Specia Laboratories in phenothiazines.

Neuroleptics

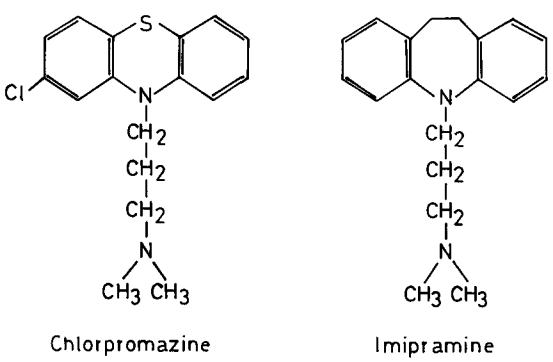
Phenothiazines had been synthesized by Paul Charpentier in the mid-1940s in an attempt to find new antihistamines[8]. These compounds were now subjected to a pharmacological screening for centrally depressant rather than antihistaminic effects. Simone Courvoisier and collaborators[10] discovered that a ring-chlorinated derivative, chlorpromazine, showed pronounced sedative action with low toxicity. Laborit found this compound very useful as a lytic agent. His clinical observations led him to believe that the drug had additional effects. In fact, the patients treated perioperatively with chlorpromazine were unusually relaxed and showed amazingly little concern. Laborit persuaded a group of psychiatrists

to treat mental patients with the drug. They found a remarkable calming activity in agitated states[27]. Other psychiatrists, especially Jean Delay and Paul Deniker[11] elaborated the psychiatric indications for the treatment with chlorpromazine. This drug was classified as a neuroleptic and became the prototype of a new class of compounds, which has been progressively extended. Due to its antipsychotic and sedative (not hypnotic) action, chlorpromazine found a wide use in the treatment of mental disorders, especially in schizophrenia, years before investigations of its mode of action (e.g. blockade of dopamine receptors[7]) began.

Imipramine, the pioneer of tricyclic antidepressants

The discovery that a tricyclic compound had an antidepressant effect was first made in a Swiss psychiatric hospital on Lake Constance. In 1950, the then head physician, Roland Kuhn, tested an antihistaminic, the iminodibenzyl derivative G22150, sent to him by the J. R. Geigy company Basel for investigation of its hypnotic activity. This compound exhibited the same ring system as chlorpromazine except that the S-bridge of the middle ring of chlorpromazine was replaced by a CH-CH group (by analogy with benzene and thiophene, S- and CH-CH-bridges were thought to be exchangeable without major influence on the properties of the molecule). Although Kuhn became interested in the drug and suggested further studies, it was abandoned by Geigy. Later, when chlorpromazine started to be of interest for psychiatry, the effects of this drug reminded Kuhn of those he had earlier noticed in the abandoned antihistaminic. He insisted on a reinvestigation of G 22150 and Geigy, already aware of the possibilities because of the experience with chlorpromazine, sent further material to him.

G 22150 did indeed show psychopharmacological properties, but had to be given up because of side effects. In the course of further trials with iminodibenzyl derivatives an analogue, G 22355, was sent to Kuhn. In this compound the N side-chain had been replaced by that of chlorpromazine following a suggestion of Kuhn (fig. 3). He administered this drug to his psychiatric patients and concluded that it could not replace chlorpromazine. However, he observed a beneficial effect of G 22355 in patients with mental depression which was not seen with chlorpromazine. Kuhn reported his first observations to the Geigy company in February 1956, and in September of the following year on the occasion of the second international congress of psychiatry in Zürich, he gave a paper on the antidepressant action of G 22355 to an audience with only a handful of participants. This report is not even part of the voluminous proceedings of the psychopharmacology symposium held at this congress. At the same time Kuhn published his results in a Swiss medical journal, describing the antidepressant effect of G 22355 in detail[16,17].



Chlorpromazine Imipramine

Figure 3.

The victory march of imipramine

The claim that a tricyclic compound (related to phenothiazines) without MAO-inhibitory activity showed an antidepressant effect, was not easily accepted by the medical community, especially in the USA. However, ultimately the antidepressant effect of G 22355 observed by Kuhn was generally recognized and the compound was gradually introduced worldwide under the name imipramine. Four elements were probably responsible for the final breakthrough of imipramine and similar drugs. Firstly, the clinical observations of Kuhn were widely confirmed by other investigators. Secondly, several psychiatrists were already sensitized by the experience with MAO-inhibitors to the possibility that mental depression was a condition accessible to chemotherapy. Thirdly, imipramine did not exhibit the severe side effects (e.g. potentiation of hypertension caused by food amines) of MAO-inhibitors.

Finally, findings by the groups of Fridolin Sulser and Julius Axelrod in the early 1960s on the mode of action of tricyclic antidepressants hinted that these drugs and MAO-inhibitors could have a 'common denominator'. In fact, imipramine and derivatives, like MAO-inhibitors, reversed the depressant effects of reserpine and compounds with similar effect (e.g. benzoquinolizines; for review see Sulser and Mishra[28]). Also, tricyclic antidepressants and MAO-inhibitors both seemed to increase the cerebral content of free neurotransmitters such as catecholamines and 5 HT in the synaptic clefts, though by different mechanisms (inhibition of reuptake into storage sites and breakdown respectively). Therefore both types of drugs were thought to affect brain function by ultimately causing similar changes in neurotransmitter dynamics. This hypothesis provided a rational explanation for the unexpected action of imipramine-like compounds and thereby increased the 'credibility' of these drugs. In fact, imipramine became the drug of choice for the pharmacological treatment of mental depression and has held this position for many years. It is still being widely used for this purpose.

The post-pioneer period

The success of imipramine challenged research workers both in industry and in academia to enter the field of

antidepressants. Numerous successors of imipramine, tricyclic and non-tricyclic compounds, have been successfully introduced. In contrast, the field of MAO-inhibitors has remained silent for many years. This silence is now being broken by new basic findings. It is known that MAO exists in two subforms, MAO-A and MAO-B, with different substrate specificities and localizations in the brain. Relatively specific, reversible inhibitors for these subforms are being developed. Compounds interfering preferentially with MAO-A (which is involved in the deamination of neuronal 5HT and noradrenaline) probably have advantages over the old, unspecific and irreversible inhibitors (e.g. iproniazid) which also inhibit MAO-B and thus the degradation of food amines, e.g. tyramine. By the use of the new inhibitors dangerous side effects, e.g. hypertensive crises, seem to be avoided and a revival of MAO-inhibitors for the treatment of mental depression may be the consequence.

In spite of the availability of modern psychotropic agents, drug treatment of psychoses, including mental depression, has remained symptomatic. Nevertheless antidepressants, together with other psychoactive compounds, e.g. neuroleptics, have helped to turn previously closed, prison-like psychiatric institutions into open hospitals, and to enable many patients who were formerly kept on closed wards to live a relatively normal social life. Also, the elucidation of the mechanism of action of the anti-depressants has made considerable progress, though it is not yet fully complete. The initial hypotheses have had to be modified and extended. Not only changes of neurotransmitters, but also of other components in neurotransmission, e.g. receptors and postreceptor events, have had to be taken into account. Furthermore, it can be anticipated that the modern psychotropic drugs, possibly combined with new non-invasive techniques (e.g. positron emission tomography of the human brain in situ), will lead to a better understanding of the pathophysiological disturbances underlying mental depression, about which our knowledge is, at present, still rather scant.

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