CHAPTER 1

The Discovery of The SSRIs: A Milestone In Neuropsychopharmacology and Rational Drug Design

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Besides being a major therapeutic advance, the selective serotonin reuptake inhibitors (SSRIs) have become important tools in basic and clinical brain research. They were the first drugs to establish beyond doubt a pathophysiological role for serotonin (5-HT) in affective illnesses and in the broad spectrum of anxiety disorders. Likewise, the SSRIs were the first to confirm the inhibition of neurotransmitter reuptake as an important therapeutic principle. As a result, the discovery of these agents marks a milestone in neuropsychopharmacology and rational drug design. Below is an account of the fascinating, winding path of research leading to the SSRIs.

The antidepressant action of imipramine was discovered in 1957 by Kuhn.[1] At first pharmacologists were taken aback because this action was entirely unpredicted. In 1959 Sigg[2] demonstrated that imipramine can potentiate the effects of noradrenaline as well as the response to sympathetic nerve stimulation. This was the first clue to the elucidation of the mode of action of imipramine. In 1960 Burn and Rand[3] described the uptake of noradrenaline by adrenergic nerves. Cocaine was reported to block this uptake. In the same year, Marshall et al[4] reported that the uptake of 5-HT by platelets could be blocked by imipramine and, in 1961, Axelrod et al[5] described the uptake of labeled noradrenaline by adrenergic nerves. This uptake could be blocked by imipramine, cocaine and reserpine. At the same time Dengler et al[6] reported similar data regarding noradrenaline uptake by brain tissue.

Disentangling the Riddle of Dual Amine Transport

These observations were of course interesting but did not lend themselves easily to interpretation. Particularly confusing was Axelrod's finding[5] that drugs with entirely different pharmacological profiles, i.e., imipramine and reserpine, seemed to have the same effect on the uptake of noradrenaline. This enigma was resolved by the discovery that amine-storing cells are equipped with two distinct amine-concentrating mechanisms. One of these is localized on the cell membrane and is sensitive to imipramine while the other is found on the membranes of intracellular vesicles (or granules) and blocked by reserpine. Blockade of the cell membrane pump leads to enhanced neurotransmission, whereas blockade of the

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intracellular mechanism causes failure of neurotransmission via depletion of neurotransmitter. As briefly summarized below, some of the early work leading to this discovery dealt partly with the storage of 5-HT by platelets and partly with the corresponding mechanisms in catecholamine-storing cells.

An early important discovery was that adrenal medullary cells are capable of storing catecholamines in special organelles, called granules or vesicles.[7,8] Subsequently, similar organelles were found to exist in adrenergic neurons, especially in their nerve terminals. The first observation of a specific drug effect on amine storage was reported by Brodie and his colleagues[9] who showed that reserpine is capable of depleting the tissue store of 5-HT: this effect was shown to be exerted directly on the platelet 5-HT stores by low concentrations of reserpine added in vitro.[10] Soon afterwards a similar action of reserpine on the storage of catecholamines was discovered.[11,12]

The first clue that the site of action of reserpine was at the subcellular level came from experiments on isolated adrenal medullary granules. These were found to take up labeled monoamines in vitro provided that adenosine triphosphate (ATP) was present.[13,14,15] This uptake could be blocked by low concentrations of reserpine but not by imipramine. Subsequent experiments using histochemical techniques demonstrated the imipramine-sensitive, reserpine-resistant amine uptake by the cell membranes of adrenergic nerves[16] (see also: ref. 17). Initially there was some controversy regarding this dual mechanism. For example, Brodie and his colleagues[18] maintained an opposite view, namely that reserpine acted on the amine uptake located on the cell membrane whereas imipramine acted on vesicular uptake. It was not long, however, until the former alternative was generally accepted. Recently, the different types of transporter protein have been cloned (Chapter 10).

The Tricyclic Antidepressants and the Amine Uptake Theory

As early as the 1960s, a sufficient body of evidence seemed to exist to formulate the hypothesis that the antidepressant action of imipramine and related tricyclic antidepressants was due to blockade of amine reuptake, leading to an increased aminergic neurotransmission. However, there were some caveats. In fact, several kinds of objections were raised but, in my opinion, some of these did not carry much weight. For example, concern was raised about the slow onset of antidepressant effect compared with the almost immediate blockade of amine uptake. However, given the powerful adaptive capacity of the brain, it is not hard to envisage that an originally distinct change, induced by a drug or a pathological process, could lead to a complex cascade of secondary changes in various neurocircuits. These changes could take weeks or even months to evolve and outlast considerably the presence of the drug or initial disturbance.

More serious was the objection dealing with the complex pharmacology of the tricyclic antidepressant drugs. Besides blocking amine reuptake they have affinity for a large number of receptors (e.g., cholinergic, adrenergic, histaminergic) and in addition they have a relatively strong so-called membrane-stabilizing action which leads to cardiotoxicity, lowering of seizure threshold etc. To exclude a role for these various mechanisms in the antidepressant action proved difficult. In fact, the general opinion in the scientific community was probably adequately expressed in Goodman and Gilman's textbook, as late as 1980 (Sixth edition),[19] when they commented that there is increasing doubt that the monoamine uptake theory is "either a necessary or sufficient explanation of the antidepressant action of these drugs." In subsequent editions, this comment has been deleted and opinion has shifted in favor of the amine uptake theory. Below an account will be given of the developments leading to this shift.

5-HT Enters the Scene

In the late 1960s, those who believed in the monoamine-uptake theory focused on the reuptake of noradrenaline. In fact, before 1968 there was no evidence that any other amine was involved in the action of the tricyclic antidepressants insofar as uptake inhibition is concerned. The early report referred to above on the action of imipramine on 5-HT uptake by platelets[4] seemed to have been completely forgotten.

However, in 1968 Carlsson, Fuxe and Ungerstedt[20] reported that the reuptake of 5-HT by central serotonergic neurons was blocked by imipramine. Subsequent work on a large number of tricyclic antidepressants showed that they are able to block the amine-uptake mechanism both in noradrenergic and serotonergic neurons but that there are considerable differences in potency among these agents with respect to their effects on these two types of neuron. Thus, among the tricyclics, the secondary amines were generally more potent than tertiary amines in terms of inhibiting noradrenaline uptake, whereas the reverse was true for inhibition of 5-HT uptake.[21,22]

Clomipramine was an especially potent inhibitor of 5-HT reuptake but, at this time, had not yet been tested in clinical trials. We were impressed by the marked differences in profile among the tricyclic antidepressants and so I visited Geigy in 1968 to report on our findings and urged Geigy to test this agent in the clinic. Unfortunately, Geigy had already decided in favor of another tricyclic agent. However, that agent turned out to possess some (probably toxicological) problems. As a result, clomipramine was then selected for clinical trials and the peculiar clinical profile of this compound was thus discovered.

Development of the First SSRI: Zimelidine

Even before the introduction of clomipramine into the clinic, our research group had proceeded with attempts to develop a 5-HT-selective reuptake inhibitor. We discovered a number of non-tricyclic agents with amine-uptake inhibitory properties, acting on both noradrenergic and serotonergic neurons. Some of these agents were found among the addictive analgesics, e.g., pethidine, while others were antihistamines.[23] Especially potent among the latter were pheniramine and its bromine- and chlorine-substituted derivatives as well as diphenhydramine.

Together with the skillful Swiss organic chemist Dr. Hans Corrodi, who at that time was employed by Hässle (a subsidiary of Astra) but later was promoted to Director of Research at Astra, I decided to start out from brompheniramine in an attempt to develop a selective serotonin (5-HT) reuptake inhibitor. We made and tested zimelidine which proved to be the first SSRI and was patented[24] with the priority date April 28, 1971; the publication date of the first (Belgian) patent was March 23, 1972.

Corrodi was eager to delay the publication of our data except, of course, for patents. In fact, these data were extensively published only in the patents because Corrodi prematurely died of a fulminant leukemia early in 1974. The subsequent publication by Astra scientists on the preclinical properties of zimelidine[25] referred to these patents and provided additional data to support the contention that zimelidine is an SSRI.

Regarding the clinical development of zimelidine, a phase I study was completed in 1971 at Hässle. Thereafter, the project was transferred to Astra Läkemedel at Södertälje, Sweden. The first open study of zimelidine in patients suffering from depression was published in 1976.[26] In April 1980, a symposium entitled 'Recent Advances in the Treatment of Depression' was held in Corfu, Greece.[27] In his concluding remarks Dr. Linford Rees, referring to several well-controlled clinical trials, concluded that zimelidine "is as effective as existing antidepressants in treating depression and in reducing anxiety, yet having a much lower incidence of those side-effects which are known to be particularly troublesome with the conventional tricyclic antidepressants." Zimelidine was approved in Sweden and several

other countries as an antidepressant agent in 1982 and soon became extensively used in those markets where it was available.

After more than 200,000 patients had been treated with zimelidine, in most cases with satisfactory or even excellent results, it became apparent that this SSRI could induce a serious, though generally not lethal, side-effect (Guillain-Barré syndrome) in a few patients. After treatment of at most 80,000 patients with zimelidine in Sweden, 8 cases of this syndrome were identified. It was estimated that at least 1 out of 10,000 patients treated with zimelidine would exhibit this syndrome, compared to the apparently spontaneous occurrence of this syndrome in 1 out of 50,000 individuals. This difference was statistically significant and the drug was withdrawn from the market in all countries on September 17, 1983. However, because of its outstanding therapeutic properties, zimelidine continued to be used 'on license' in Sweden for several years by thousands of patients. In fact, according to Dr. Jan Wålinder, who has considerable experience with zimelidine treatment, there is no risk of serious side-effects provided that the doctor watches for signs of supersensitivity to this drug. Wålinder maintains that the withdrawal of zimelidine was a mistake (for a detailed account, see ref. 28, authored by Dr. Ivan Östholm, at that time Director of Research at Hässle).

Fluoxetine and Other SSRIs

The development of fluoxetine has been described in a minireview in *Life Science*s,[29] entitled 'Prozac (Fluoxetine, Lilly 110140), the First Selective 5-HT Uptake Inhibitor and an Antidepressant Drug.' As detailed below, however, fluoxetine was clearly preceded by zimelidine. Moreover, as acknowledged by the Lilly scientists,[30] the development of fluoxetine was based on concepts developed by our research group and started from our discovery that diphenhydramine has 5-HT- and noradrenaline-reuptake inhibitory properties. Fluoxetine has a chemical structure closely related to diphenhydramine. This was analogous to the development of zimelidine, starting out from the pheniramines. In addition, the in vivo and in vitro methodology used in the development of fluoxetine was similar to that developed by our research group.

The first experiment with fluoxetine, demonstrating 5-HT reuptake inhibitory properties, was performed in Dr. David Wong's laboratory on May 8, 1972. On July 24 of the same year, fluoxetine was recognized as the most potent and selective inhibitor of 5-HT reuptake among its congeners. These events thus took place more than a year after the priority date of the zimelidine patent and more than one month after the first zimelidine patent was published. The first patent application including fluoxetine was filed in late 1973, i.e., more than two years after the priority date of the zimelidine patent. The first publication on fluoxetine, demonstrating its SSRI profile, appeared in 1974,[30] more than two years after the first patent on zimelidine became public. It is hard to believe that the zimelidine patents did not become known shortly after their publication to drug-company scientists working in the same area. In any event these patents were noted in reference 25, which was quoted by Wong et al.[29]

Regarding the clinical development of fluoxetine, an Investigational New Drug Application was filed with the FDA in 1976, i.e., the same year as the first open phase II study with zimelidine was published.[26] After successful clinical studies with the drug, a New Drug Application for fluoxetine was filed with the Federal Drug Administration (FDA) in 1983. It was approved for marketing in 1987, i.e., 5 years after the approval of zimelidine in several European countries. It was introduced for clinical use in January 1988 so the clinical phase of the development of fluoxetine was slower than that of zimelidine. In retrospect, a somewhat slower and more careful clinical development of zimelidine might have changed the fate of this drug; the recommended doses were probably too high, as suggested by two early studies,[31,32] and there were indications that the risk of developing Guillain-Barré

syndrome was dose-dependent. As will appear from a note jointly authored by Dr. Wong and myself[33] there is at present no disagreement between us concerning the essential aspects of the early history of the SSRIs.

Zimelidine and fluoxetine were later followed by several SSRIs which are now on the market. As will be apparent from the following chapters of this book, this novel group of agents has had a great impact on both basic brain research and clinical psychiatry. Concerning one of these subsequent SSRIs, citalopram, our research group has been somewhat involved at an early stage. We studied a series of bicyclic compounds developed by Lundbeck and were able to confirm a finding of the Lundbeck scientists: that these agents are potent inhibitors of noradrenaline reuptake but we found that these agents had no significant effect on 5-HT reuptake.[34] We then reported to the Lundbeck scientists that a noradrenaline-selective drug can be converted into a drug with a greater affinity for 5-HT reuptake by increasing the lipophilicity of the molecule through appropriate substitutions. Citalopram appears to be a modification of the bicyclic compounds studied by us in this direction.

Conclusion

It should be noted that zimelidine, fluoxetine and several other SSRIs are selective not only in regard to inhibition of 5-HT reuptake compared with that of catecholamines but also in that, unlike tricyclic antidepressants, they lack affinity for a number of receptors and have no 'membrane-stabilizing' action leading to cardiotoxicity and lowered seizure thresholds. Thus, for the first time, inhibition of monoamine uptake was confirmed as an important therapeutic principle.

Looking back, it is fair to say that the research leading to the therapeutic principle of selective 5-HT reuptake inhibition marks a milestone in the history of neuropsychopharmacology and rational drug development. Sadly, the premature death of Dr. Hans Corrodi, one of the foremost pioneers in this endeavor, deprived him of the satisfaction of witnessing how his achievements contributed to a major scientific and therapeutic advance which has benefited millions of patients.

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