# A Decade of Collaboration with Nils-Åke Hillarp: Recollections from 1956 to 1965

**ARVID CARLSSON**

*Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden*

Nils-Åke Hillarp and I received our basic education in biomedical research in the Departments of Histology and Pharmacology, respectively, of the University of Lund, Sweden. Hillarp was born in 1916, that is, 7 years before me. Our collaboration started in 1956. The background was the following.

In 1955 I spent a post-doctoral 6 months working in the Laboratory of Chemical Pharmacology of the National Heart Institute, headed by the late Dr Bernard B. Brodie. In the spring of 1955, only a few months before my arrival there, Brodie, Shore and their colleagues had made one of the major discoveries in the history of neuroscience, that is the depletion of serotonin stores in the brain and other tissues by reserpine, a drug recently introduced in the treatment of hypertension and schizophrenia (see Pletscher *et al.*, 1955). Brodie and his colleagues generously introduced me into the field of chemical pharmacology. His laboratory was at that time one of the most important research centres in this discipline and can, in fact, be said to be the cradle of modern biochemical pharmacology. An intense research was on-going not only in psychopharmacology, but also in drug metabolism. The prototype of the spectrophotofluorimeter had just been constructed in this laboratory by Robert Bowman, who was an M.D. but above all an ingenious inventor. This instrument, later manufactured and marketed as Aminco-Bowman spectrophotofluorimeter, is in my opinion one of this century's major breakthroughs in the analysis of drugs and endogenous chemical substances. It became widely used and was to become my main research tool for more than two decades but was thereafter largely superseded by even more powerful methodology.

Brodie was a remarkable person, who managed to stir up emotions wherever he went. He gained much sympathy but also made many enemies. He met with mixed feelings even among his collaborators. He was always full of new ideas and was impatient to have them experimentally tested, which was often disturbing for the continuity of the work in his laboratory. But most of his students became strongly devoted to him and looked upon him as a father. He seemed to have no ambition to be a true mentor but was mainly driven by his enormous scientific curiosity and ambition. Nonetheless he managed to transmit to his collaborators something apparently very important, because an amazing number of these people later became prominent scientists in the USA and in several other countries. To describe what he actually transmitted is not easy. He had an intensely searching mind and little respect for textbook knowledge. He courageously entered research fields that he did not know much about. Sometimes he managed to formulate basic questions that had previously been ignored. Perhaps this was the secret behind his remarkably successful career.

In Brodie's laboratory I worked on the effect of reserpine on the storage of serotonin in platelets, studied *in vitro*. I suggested to Brodie that we should also examine the action of reserpine on some closely related amines, especially the catecholamines. But Brodie considered this waste of time. He was convinced that serotonin was the important agonist in this context. While still in Brodie's laboratory I read an article by Hillarp *et al.* (1955), that had just appeared in *Nature* and described the storage of adrenaline together with adenosine-5′-triphosphate (ATP) in particular intracellular organelles in the adrenal medulla. In preliminary work I had found fairly large amounts of ATP in platelets, and this, in conjunction with Hillarp's report, strengthened my suspicion of a common storage mechanism for serotonin and catecholamines. I then wrote to Hillarp and suggested that we collaborate on the action of reserpine on the catecholamines, and he agreed.

## Monoamines and Brain Function: A Controversial Issue

Hillarp was, at that time, Associate Professor of Histology at the University of Lund. He had already made a number of remarkable contributions in neuroscience and endocrinology. Especially important for our collaboration was his above-mentioned recent discovery of special organelles in the adrenal medulla, responsible for the storage of catecholamines. As we later found (Carlsson *et al.*, 1963), it was specifically these organelles and their counterpart in monoaminergic nerves, i.e. the so-called synaptic vesicles or granules, that reserpine acted on. Hillarp and I started to work together in 1956, and our collaboration lasted until his untimely death in 1965. We (Carlsson and Hillarp, 1956) soon found that

motor functions. This suggestion was further supported by the fact that the motor disturbances in Huntington's chorea can be alleviated by reserpine and similar drugs (Carlsson, 1959).

Thus, for the first time evidence was forthcoming for a role of endogenous agonists, present in brain tissue, in animal behaviour. At first serotonin had come into focus, but the subsequent experiments pointed to a role of the catecholamines, and especially dopamine, for the sedative and akinetic actions of reserpine, and the reversal of these actions by L-DOPA. We were very excited by these findings but were disappointed to meet with considerable resistance by some prominent investigators. In particular, a meeting in London in the spring of 1960 on Adrenergic Mechanisms (Vane *et al.*, 1960) was a rather surprising experience to me. At this meeting practically all prominent workers and pioneers in the catecholamine field were present. It was dominated by the strong group of British pharmacologists, headed by Sir Henry Dale. I was impressed to see how the British pharmacologists, as well as many other former Dale associates, behaved towards Sir Henry, like school children to their teacher, although some of them had indeed reached a mature age. It was also remarkable to find how little disagreement was expressed among these people, who behaved more or less like a football team. At this meeting I reported on our data indicating a role of the catecholamines in motor functions and alertness. No doubts were expressed about our observations as such. In fact Drs Blaschko and Chrusciel presented observations that confirmed our findings on some essential points.

I have re-read the discussions recorded in the Symposium volume, and I am still puzzled by them. To start with Sir John Gaddum's Summary of the session on Central Adrenergic Mechanisms, he concluded (p. 584): "The meeting was in a critical mood, and no-one ventured to speculate on the relation between catecholamines and the function of the brain". As mentioned, my paper, which was entitled "On the Biochemistry and Possible Functions of Dopamine and Noradrenaline in Brain", as well as a considerable number of remarks that I made during the discussion sessions, dealt precisely with this issue. Obviously, in Gaddum's mind I was nobody! Why did he and the other British pharmacologists so completely ignore us? At first there was some concern about L-DOPA being a 'poison'. This appeared to be mainly based on the observation by Weil-Malherbe, that large doses of L-DOPA, given together with a monoamine oxidase inhibitor, could be lethal. This discussion ended by a concluding remark by Sir Henry Dale (p. 551) that L-DOPA is, in fact, a poison, which he found very remarkable for an amino acid. Then Paton referred to unpublished data by Edith Bülbring, suggesting the presence of catecholamines in glia rather than nerve cells. Responding to a question of Dale, Marthe Vogt concluded (p. 551) that there was absolutely no evidence that the catecholamines in the brain act as synaptic transmitters

reserpine caused depletion of the adrenal medullary hormones, and this was soon followed by the discovery that similar depletion took place in other tissues, including brain. These findings offered a possible explanation of the hypotensive action of reserpine, and we could confirm this by experiments where stimulation of sympathetic nerves no longer caused release of their neurotransmitter noradrenaline following reserpine treatment (for review and references, see Carlsson 1987a).

These discoveries made us very excited but placed me in an awkward position in relation to my highly esteemed mentors, Drs Brodie and Shore. Our results challenged their interpretations in two respects. First, they indicated that the action of reserpine should not necessarily be interpreted as due solely to its effect on serotonin, and second, they argued against our mentors' proposal that continuous release of the putative neurotransmitter serotonin onto its receptors is responsible for the action of the drug. Rather, our results suggested that at least the hypotensive action was due to an effect on catecholamines and that this effect was caused by depletion rather than release. Unfortunately, this divergence of opinion was to place my mentors and myself in different 'camps' for many years to come and led to a large number of sometimes vivid debates in writing as well as at various meetings. This was unfortunate, because we, despite these divergences, were much more on common ground than a great number of other workers in this field, as will be apparent from the following.

To resolve the issue concerning the mode of action of reserpine my colleagues and I administered DOPA to reserpine-treated rabbits and mice and discovered the central stimulant action of this amino acid as well as its ability to reverse the akinetic and sedative action of reserpine. Since the serotonin precursor 5-hydroxytryptophan was not capable of reversing the action of reserpine we suggested that depletion of catecholamines rather than serotonin was responsible for some important behavioural effects of reserpine (Carlsson *et al.*, 1957).

However, when we analysed the brains of the animals treated with reserpine and DOPA, we found them still fully depleted of noradrenaline. Further analysis revealed that the behavioural action of DOPA could be explained by the accumulation of dopamine in the brain. Moreover, our studies disclosed that dopamine is a normal brain constituent and is released by reserpine, like noradrenaline and serotonin. The data suggested to us that dopamine is not just a precursor to noradrenaline, as previously assumed, but is an endogenous agonist in its own right (Carlsson *et al.*, 1958). This received further support when my students Bertler and Rosengren (1959) shortly afterwards discovered the marked difference in regional distribution between dopamine and noradrenaline, the former being largely accumulated in the basal ganglia. We could thus suggest that the parkinsonism induced by reserpine is due to dopamine depletion and that dopamine is involved in the control of extrapyramidal

or serve a general hormonal function. The proposal that this may be the case was said to depend on the particular pharmacological agents used. A critical survey of all the available evidence led, according to Marthe Vogt, to the conclusion that any of the theories on a relation between catecholamines or serotonin and behaviour is "a construction which some day will be amended" (p. 579).

Today this reluctance to accept a role for the monoamines in brain function may seem strange, especially since the doubts were expressed by some important pioneers in the theory of chemical transmission. It must be recalled, however, that at this time the predominating mechanism of neurotransmission in the brain, in contrast to the peripheral nervous system, was believed to be electrical. Moreover, the idea that the loss of a nerve function could be replaced by a drug and, thus, Parkinsonian symptoms be alleviated by L-DOPA, was hard to reconcile with the concepts of classical neurophysiology. It should be recollected, on the other hand, that several years earlier Gaddum (1953) had proposed that serotonin may serve to keep us sane, and that Marthe Vogt (1954) had pointed out that the 'sympathin' of the hypothalamus was probably not entirely derived from the peripheral sympathetic nervous system. It would seem that their original thinking had been followed by some 'pale cast of thought'.

Hillarp also attended this meeting, and we had good reasons to be grateful for this scepticism because it prompted us to increase our efforts to strengthen our views. I had just been appointed Professor and Chairman at the Department of Pharmacology, University of Gothenburg. Immediately following this meeting Hillarp and I agreed that he should join me to work on catecholamines in my new department, provided that he could be set free from his associate professorship in histology in Lund. We applied for the necessary funds at the Swedish Medical Research Council, and our grant was approved. We decided to focus on two problems: (1) to investigate a possible active amine-uptake mechanism by the adrenal medullary granules and its inhibition by reserpine; and (2) to try to develop a histochemical fluorescence method to visualize the catecholamines in tissues. Both these projects turned out to be successful. (Concerning the first point, see Carlsson *et al.*, 1963 and below.) Since detailed accounts of the histochemical fluorescence method and the subsequent mapping of monoaminergic pathways have been given elsewhere (Carlsson, 1987a; Dahlström and Carlsson, 1986; Dahlström, this volume), they will not be repeated here.

## A Paradigm Shift—Emerging Synaptology

During the early part of the 1960s a large number of observations were made in Sweden by Hillarp, myself and our respective collaborators,

based on the combination of histochemical, biochemical and functional studies and using a number of pharmacological tools, which had an impact on the scientific community's view concerning the role of biogenic amines as neurotransmitters, not least in the central nervous system. That we can speak here of a true paradigm shift is evident from the proceedings of an international symposium held in Stockholm in February, 1965 and entitled "Mechanisms of Release of Biogenic Amines" (editors, von Euler *et al.*, 1966). In his introductory remarks Uvnäs stated that "these amines play an important role as chemical mediators in the peripheral and central system". None of the distinguished participants in this symposium expressed any doubts on this point.

While the scepticism had thus faded, it was followed by an intensive debate on the function of various synaptic structures and mechanisms. A few early recollections of this debate will be reviewed below.

A major issue dealt with the role of the synaptic vesicles in the transmission mechanism. In the mid-1960s opinions still differed concerning the subcellular distribution of the monoaminergic transmitters. In the fluorescence microscope the accumulation of monoamines in the so-called varicosities of nerve terminals was obvious. This corresponded to the distribution of synaptic vesicles, as observed in the electron microscope. In fact, Hökfelt (1968) was able to demonstrate the localization of central as well as peripheral monoamines to synaptic vesicles in the electron microscope. However, there was controversy about the nature and size of the extravesicular (or extragranular) pool of neurotransmitter. This is evident from the recorded discussions of the above-mentioned symposium "Mechanisms of Release of Biogenic Amines". For example, Drs Axelrod and von Euler (p. 471) maintained that a considerable part of the transmitter was located outside the granules, mainly in a bound form. This fraction was proposed to be more important than the granular fraction, since it was thought to be more readily available for release. Indeed, the granules were facetiously referred to as 'garbage cans'. Our group had arrived at a different model of the synapse, based on combined biochemical, histochemical and pharmacological data (Carlsson, 1966). We were convinced that the granules were essential in transmission, and that the transmitter had to be taken up by them in order to become available for release by the nerve impulse. In favour of this contention was our finding that reserpine's site of action is the amine uptake mechanism of the granules. The failure of adrenergic transmission as well as the behavioural actions of reserpine were correlated to the blockade of granular uptake induced by the drug, rather than to the size of the transmitter stores (Lundborg, 1963). Moreover, extragranular noradrenaline [accumulated in adrenergic nerves by pre-treatment with reserpine, followed by an inhibitor of monoamine oxidase (MAO) and systemically administered noradrenaline], was unavailable for release by the nerve

impulse, as observed histochemically (Malmfors, 1965). We proposed that under normal conditions the extragranular fraction of monoaminergic transmitters was very small, owing to the presence of MAO intracellularly, and that the evidence presented to the contrary was, in fact, an artifact. Subsequent work in numerous laboratories has lent support to these views. Already at the Symposium, Douglas presented evidence suggesting a $Ca^{2+}$-triggered fusion between the granule and cell membranes, preceding the release. The release is now generally assumed to take place as 'exocytosis', even though the complete extrusion of the granule content may still be debatable.

An important issue in the early debate dealt with the site of action of major psychotropic drugs. In their first studies on reserpine Brodie and his colleagues had proposed that this agent was capable of releasing serotonin on to receptors, which would suggest the cell membrane to be its site of action. However, our observations, quoted above, demonstrated that reserpine acted on the storage mechanism of the synaptic vesicles. As to the tricyclic antidepressants, Brodie *et al.* suggested their site of action to be on the synaptic vesicles. In their original studies reported in 1960 Axelrod *et al.* (see Axelrod, 1964) observed that the uptake of circulating catecholamines by adrenergic nerves could be blocked by a variety of drugs, for example, reserpine, chlorpromazine, cocaine and imipramine. These studies obviously did not distinguish between a number of different pharmacological mechanisms. In our own combined biochemical (Carlsson *et al.*, 1963; see also the independent, simultaneous work of Kirshner, 1962) and histochemical studies (Malmfors, 1965) two different amine-concentrating mechanisms could be distinguished, i.e. uptake at the level of the cell membrane, sensitive, for example, to cocaine and imipramine, and uptake by the storage granules or synaptic vesicles, sensitive, for example, to reserpine. These two mechanisms have of course different, essentially opposite functional consequences, implying enhancement and inhibition, respectively, of monoaminergic neurotransmission.

## Receptor Research

In the early 1960s we were puzzled by the fact that the major antipsychotic agents, such as chlorpromazine and haloperidol, have a reserpine-like pharmacological and clinical profile and yet lack the monoamine-depleting properties of the latter drug. We found that chlorpromazine and haloperidol accelerated the formation of the dopamine metabolite 3-methoxytyramine and of the noradrenaline metabolite normetanephrine, while leaving the neurotransmitter levels unchanged. In support of the specificity, promethazine, a sedative phenothiazine lacking antipsychotic and neuroleptic properties, did not change the

turnover of the catecholamines (Carlsson and Lindqvist, 1963). It did not seem far-fetched, then, to propose that rather than reducing the availability of monoamines, as does reserpine, the major antipsychotic drugs block the receptors involved in dopamine and noradrenaline neurotransmission. This would explain their reserpine-like pharmacological profile. To account for the enhanced catecholamine turnover we proposed that neurons can increase their physiological activity in response to receptor blockade. This, I believe, was the first time that a receptor-mediated feedback control of neuronal activity was proposed. These findings and interpretations have been amply confirmed and extended by numerous workers, using a variety of techniques. In the following year our research group discovered the neuroleptic-induced increase in the concentrations of deaminated dopamine metabolites (Andén *et al.*, 1964). Later papers by Andén *et al.* (1970) from our own laboratory and by Nybäck and Sedvall (1970), emphasized the effect of neuroleptics on dopamine, and the work of Aghajanian and Bunney (1974) described the effect of dopaminergic agonists and antagonists on the firing of dopaminergic neurons. Other important, subsequent discoveries were the dopamine-sensitive adenylate cyclase by Greengard and his colleagues (Kebabian and Greengard, 1971) and the binding of dopamine to specific cell-membrane sites, from which it could be displaced by neuroleptics (Seeman *et al.*, 1976; Creese *et al.*, 1976).

The further analysis of receptor-mediated feedback control of neuronal activity revealed that this control was largely, if not entirely, mediated by a special population of receptors, apparently located on the monoaminergic neuron itself. These receptors have been called presynaptic receptors or, perhaps preferably, autoreceptors, since they have various locations on the neuron but share the property of being sensitive to the neuron's own neurotransmitter (Carlsson 1975a, b, 1987b). The first suggestion of the existence of such receptors came from studies by Hillarp's pupils Farnebo and Hamberger (1971) on brain tissue slices, demonstrating inhibition and stimulation of nerve-impulse induced dopamine release by dopamine agonists and antagonists, respectively. Subsequent *in vivo* studies in our laboratory demonstrated inhibition of striatal dopamine synthesis by the dopamine-receptor agonist apomorphine and blockade of this action by the neuroleptic agent haloperidol; moreover, this effect persisted after cutting the dopaminergic axons, thus demonstrating that this feedback control was not loop mediated but was restricted to the nerve-terminal area (Kehr *et al.*, 1972). Aghajanian and Bunney (1974) demonstrated a similar control in the somatodendritic part of dopamine neurons, leading to a decreased firing by dopamine-receptor agonists and a blockade of this action by dopamine-receptor antagonists. Further work along this line has led to the discovery of selective dopamine-autoreceptor agonists and antagonists with interest-

ing pharmacological properties and potential clinical utility (see Clark *et al.*, 1985a, b; Svensson *et al.*, 1986).

## The Ups and Downs of Serotonin

While dopamine, like Cinderella, had to dwell in obscurity for a long time until it came into glory, serotonin took another path. Very soon after the discovery of serotonin as a normal brain constituent it started to attract a great deal of interest, as soon as a link between serotonin and LSD was discovered and brain serotonin was proposed to serve a role to keep us sane (see Gaddum, 1953). This culminated with the discovery of reserpine's serotonin-depleting action already referred to. However, when subsequent work disclosed the catecholamine-depleting action of reserpine, noradrenaline and later dopamine came into focus, and serotonin lost its dominating place. But serotonin made a splendid comeback in a different context.

The tricyclic antidepressants were first shown to block the re-uptake of noradrenaline, and thus this neurotransmitter was proposed to play a major role in the control of mood and drive. Later it was discovered, however, that the tricyclic antidepressants also have powerful actions on the re-uptake of serotonin and that this applied especially to some of the most widely used antidepressants (Carlsson *et al.*, 1968; for further references, see Carlsson, 1976, 1982, 1986). Together with the late Dr Hans Corrodi, a highly talented Swiss chemist, we then developed the first selective 5-HT uptake inhibitor zimelidine (Berndtsson *et al.*, 1972), which turned out to be an active antidepressant agent (see Carlsson *et al.*, 1981) but was withdrawn because of certain rare but serious side-effects (Bengtsson, 1992). Subsequently a number of other selective serotonin uptake inhibitors were developed and likewise found to be efficacious antidepressants. This in conjunction with the discovery of an antidepressant action of L-tryptophan (Coppen *et al.*, 1963) and of reduced concentrations of 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressed and suicidal patients (Träskman *et al.*, 1981) led to a marked increase in the visibility of serotonin, which is now generally recognized as an important neurotransmitter in the control of mood.

Recently serotonin has also started to attract a great deal of attention in the control of anxiety. Panic disorders appear to respond especially well to serotonin uptake inhibitors. Most remarkably, obsessive–compulsive conditions appear to respond specifically to serotonergic drugs (see Eriksson and Humble, 1990). The ability of these agents to influence personality aberrations, also within the range of normal variation, has attracted considerable interest, as evident from the book *Listening to Prozac* (Kramer, 1993).

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