J Neural Transm (2002) 109: 777–787

Journal of Neural Transmission

Treatment of Parkinson's with L-DOPA. The early discovery phase, and a comment on current problems

A. Carlsson

Department of Pharmacology, University of Gothenburg, Gothenburg, Sweden

Received January 7, 2002; accepted January 24, 2002

Beginnings

My encounter with dopamine followed upon an incredible sequence of fortunate events. Thanks to a letter of introduction by Prof. Sune Bergström, who was at that time head of the Department of Physiological Chemistry of the University of Lund, Sweden, I had the opportunity to work for 5 months in 1955–56 under Dr. Bernard B. Brodie, head of the famous Laboratory of Chemical Pharmacology of the National Heart Institute. The timing of my arrival there was extremely fortunate. Brodie and his colleagues had just a few months before made a breakthrough discovery, namely that the administration of reserpine, a recently introduced antipsychotic and antihypertensive drug, caused the virtually complete disappearance of serotonin from the brain and other tissues (Pletscher et al., 1955, 1956).

Brodie was a remarkably charismatic and intensive person. He had gained a tremendous reputation as a pioneer in the area of drug metabolism and should perhaps rightly be called the father of modern biochemical pharmacology. In the 1950s, after hearing about the sensational clinical actions of the new antipsychotic drugs and the ability of the hallucinogenic LSD to block serotonin effects on various peripheral organs, he and his colleagues decided to enter the field of psychopharmacology. While knowing very little about the brain they had a tremendous trump card in being able to determine for the first time serotonin and similar molecules in the brain, using the prototype of a new instrument developed together with Sidney Udenfriend and Dr. Robert Bowman. This instrument, the spectrophotofluorimeter, was to replace previous bioassays and to revolutionize drug research and neurotransmitter pharmacology for several decades.

This research soon led to the breakthrough discovery just mentioned, that is, the depletion of serotonin stores by reserpine treatment. For the first time a bridge seemed to have been built between the biochemistry of the brain and some important brain functions, with some obvious neuropsychiatric implications.

Brodie and his colleagues, especially Dr. Parkhurst Shore, generously introduced me into the new analytical methods and the use of the new instrument. I proposed to Brodie that we investigate the effect of reserpine on the catecholamines, given their chemical similarity to serotonin. But Brodie thought this would be waste of time. He was so sure that serotonin was the target to focus upon.

A "Rosetta Stone"?

But I felt that a look at the catecholamines might be worth while. To get started quickly I would then need a partner specialized in the catecholamine field. Again I was incredibly lucky. Of all the people working in that field at the time the most clever partner in such a project was located in my home University, the University of Lund: Prof. Nils-Åke Hillarp. I wrote to him from Bethesda and proposed a collaboration, and he agreed. Thus a most fruitful collaboration started, lasting until his untimely death in 1965. Hillarp's personality was different from that of Brodie in many respects, but they were similar in terms of brilliance, charisma and intensity. His background was histology and histochemistry, but his knowledge extended far into physiology and biochemistry.

In the spring of the following year Hillarp and I got the first results. We demonstrated the depletion of catecholamines from the adrenal medulla of rabbits following treatment with reserpine (Carlsson and Hillarp, 1956). This was before I had acquired my own miracle instrument, the so-called Aminco-Bowman Spectrophotofluorimeter. The only instrument we had for the determination of catecholamines was a colorimeter, using the method of von Euler and Hamberg (1949). But we did not need any instrument because be absence of a colour development in the samples from reserpine-treated rabbits could be seen with the naked eye.

The same results were obtained when we analyzed heart and brain, in the latter case using our new instrument. We also found that sympathetic nerves no longer responded to nerve stimulation following reserpine treatment, apparently due to depletion of transmitter (Carlsson et al., 1957a). Thus depletion of catecholamines could be the cause of the behavioral inhibition induced by reserpine. To investigate this we gave DOPA (3,4-dihydroxyphenylalanine) to reserpine-treated animals and thus discovered the dramatic reversal of the reserpine-induced syndrome by this catecholamine precursor (Carlsson et al., 1957b). The reason we used the precursor was that the catecholamines are unable to penetrate from the blood into the brain, because of the blood-brain barrier.

We then analyzed the brains of DOPA-treated animals and much to our disappointment we were unable to detect any restoration of noradrenaline levels. Experiments with monoamine oxidase inhibitors clearly showed that a monoamine rather than DOPA itself was responsible for the behavioral response, and thus we were forced to look for the intermediate in the conversion of DOPA to noradrenaline: dopamine.

At that time dopamine was considered to be without any interest because of its low physiological activity, when tested on various smooth-muscle prepa-

rations. We had to develop a method for determining dopamine because no such method was available at the time (Carlsson and Waldeck, 1958). We could then show that dopamine occurs normally in the brain in an amount somewhat higher than that of noradrenaline, that it is brought to disappear by reserpine treatment, and that the antireserpine action of DOPA is closely correlated to the restoration of dopamine levels in the brain. We also showed that the restoration of serotonin levels by treatment with its precursor 5-hydroxytryptophan did not lead to any reversal of the reserpine syndrome (Carlsson et al., 1958).

The classical method in physiology to prove a function of a natural constituent, is to remove the constituent in question and demonstrate a loss of function, and then to reintroduce the constituent, and demonstrate a restoration of the same function. We thought we had done this in the case of dopamine. We could easily exclude possible alternative explanations, such as a role of noradrenaline and serotonin and a direct action of L-DOPA.

In fact, our enthusiasm made us think that now we had found the Rosetta stone that would give us access to the chemical language of the brain.

Later we found the unique distribution of dopamine in the brain, with an accumulation in the basal ganglia, that is structures known to be involved in motor functions. This, taken together with the fact that a characteristic side effect of reserpine is to mimic very faithfully the syndrome of Parkinsonism and to induce a similar symptomatology in animals, led us to conclude that depletion of dopamine will induce the Parkinson syndrome and that treatment with L-DOPA will alleviate that syndrome by restoring the dopamine level. All this I presented at the First International Catecholamine Symposium in October, 1958 (Carlsson, 1959; Bertler and Rosengren, 1959).

A battle in London

A year and a half later, in March 1960, a Ciba Foundation Symposium on Adrenergic Mechanisms was held in London (Vane et al., 1960). I then presented the same data and some additional support obtained from studies on the action of monoamine oxidase inhibitors. At this meeting practically all of the most eminent experts in this area participated. The central figure was Sir Henry Dale, a Nobel Laureate aged 85 but still remarkably vital. He dominated the scene, and the participants, many of whom were his former students, treated him with enormous respect, like school children their headmaster, although many of them had indeed reached a mature age.

To better understand how our dopamine story was received at this meeting it may be useful to recapitulate briefly the development following Otto Loewi's discovery of chemical transmission in the frog heart (Loewi, 1921). During the following decades evidence accumulated, supporting the existence of chemical transmission in various parts of the peripheral nervous system. Dale and his collaborators played an important role here. They had, however, been fiercely attacked by a number of neurophysiologists, who argued in favour of an electrical transmission across the synapses. The most eminent proponent of this view was Sir John Eccles. The debates between Dale and

Eccles had been quite vivid, as witnessed by several attendants of these debates between what was called "the sparks" and "the soup". Despite the sometimes harsh wordings the debates between Dale and Eccles over the years ended in mutual respect and admiration (see Katz, 1996). Doubts about a chemical transmission were particularly strongly expressed concerning the central nervous system. In the mid 1950s, however, Eccles had placed one foot in the "soup" camp, based on his own observation that a recurrent collateral of the motor neurone, impinging on the so-called Renshaw cells, seemed to operate by cholinergic transmission. This was, however, a very special case, given the fact that motor neurons are cholinergic. Apart from this finding, as pointed out by McLennan (1963) in his monograph "Synaptic Transmission", there was no evidence in favour of chemical transmission in the central nervous system.

At this meeting in London the debate that followed upon our paper entitled "On the biochemistry and possible functions of dopamine and noradrenaline in the brain" and a subsequent special discussion session, revealed a profound and nearly unanimous skepticism regarding our points of view.

In retrospect I believe almost everybody would agree that our story and its implications were straight forward and obvious. How come that these eminent experts rejected the whole thing? I have no definite answer. Clearly the pharmacologists had great difficulty in accepting that dopamine could be an agonist in its own right, given its poor physiological effect on smooth-muscle preparations. The idea expressed by Dale about DOPA being a mysterious poison probably came out of some experiments reported at the meeting where large doses of this amino acid, given to experimental animals together with a monoamine oxidase inhibitor, could cause paralysis, convulsions and death. In addition, I believe that the previous "sparks-and-soup" debates still had some impact. In these debates some elaborate criteria for a neurotransmitter had been formulated. Our data were of a different kind and these criteria were not applicable.

A paradigm shift

But it wouldn't be long until the scene would change dramatically. Hillarp also attended the London meeting. On our trip back to Sweden we agreed we should increase our efforts to convince the world that chemical transmission does indeed exist in the brain. Our idea was that Hillarp join me to work full time on research in our new and well-equipped department of pharmacology of the University of Göteborg, where I had been appointed professor and chairman the year before. We managed to obtain a grant from the Swedish Medical Research Council to set Hillarp free from his teaching duties in Lund. He could start full-time research in Göteborg already in the autumn of 1960.

We felt that the ability of catecholamines to yield fluorescent conversion products might be useful for their visualization in the microscope. We first tried a modifcation of the classical trihydroxyindole method (Carlsson et al., 1961). It worked beautifully for the adrenal medulla but not in other tissues.

Hillarp then turned to another reaction that had been used for the quantitative assay of indoleamines, using formaldehyde as a reagent. Together with his skillful research assistant, the late George Thieme, he worked out a model system, in which they managed to optimize the reaction conditions (these experiments were reported by Falck et al., 1962). Subsequently, together with his former student Bengt Falck, Hillarp used air-dried preparations of iris and mesenterium, and discovered that the reaction worked beautifully, thus permitting the visualization of noradrenaline in adrenergic nerves and serotonin in mast cells in the fluorescence microscope. This led to an intense collaboration between our Department of Pharmacology in Göteborg and Hillarp's original Department of Histlogy in Lund, and finally, after Hillarp's move to take over the Chair of Histology at the Karolinska Institute in 1963, with an enthusiastic group of young students in his new Department. Thus within a few years the neuronal localization of dopamine, noradrenaline and serotonin in the central and peripheral nervous system was clearly established. Moreover, the major monoaminergic pathways could be mapped, and the site of action of the major psychotropic drugs clarified (see Dahlström and Carlsson, 1986; Carlsson, 1966).

As mentioned, a large number of people were engaged in this effort. Sadly, many of these people have passed away, in many cases prematurely. Among these Georg Thieme has already been mentioned. Margit Lindqvist, a very skilful laboratrory assistant, who matured to become a qualified research worker, played an enormous role already from the outset of my scientific career. Nils-Erik Andén and Jan Häggendal were originally students of mine who became outstanding pharmacologists and largely contributed to characterize both central and peripheral monoaminergic transmission (for some of their early work, see Andén et al., 1969). Hans Corrodi, a very skilful organic chemist, who moved to Sweden because of his love for the mountains in Northern Sweden, contributed much to clarify the chemistry of the formaldehyde histofluorescence method and to many other projects.

In February 1965 an international symposium entitled "Mechanisms of Release of Biogenic Amines" was held in Stockholm (v. Euler et al., 1966), with most of the major figures of that research field participating. In his Introductory Remarks Prof. Uvnäs mentioned that ". . . these amines play an important role as chemical mediators in the peripheral and central nervous system . . .". None of the participants of this symposium expressed any doubt on this point. It looks as though a paradigm shift had taken place between 1960 and 1965.

It goes without saying that the concept of chemical transmission has had a profound impact on practically every aspect of brain research. In so far as neurology and psychiatry are concerned, a couple of examples are summarized below.

Clinical Parkinson research

Following our above-mentioned proposal of a role of dopamine in Parkinsonism some important parallel and apparently independent developments

that took place in Austria, Canada and Japan. These will now be briefly commented upon, starting out with Austria.

Later in the same year as the Symposium on Adrenergic Mechanisms, there appeared in Klinische Wochenschrift a paper in German, describing a marked reduction of dopamine in the brains of deceased patients who had suffered from Parkinson's disease and postencephalitic Parkinsonism (Ehringer and Hornykiewicz, 1960). This was soon followed by a paper by Birkmayer and Hornykiewicz (1961), in which a temporary improvement of akinesia was reported following a single intravenous dose of L-DOPA to Parkinson patients.

As far as I can gather from an autobiography of Hornykiewicz (1992) as well as a personal communication from him, the following had happened. I wish to mention this in some detail, because it illustrates how the interaction of different minds can lead to important progress. In 1958 Hornykiewicz was approached by his mentor Prof. Lindner or, according to a different version, by his Chief Prof. Brücke, who tried to persuade him to analyze the brain of a Parkinson patient, which the neurologist Walter Birkmayer wanted to be analyzed for serotonin. Presumably Birkmayer had been impressed by Brodie's already mentioned discovery in 1955 of the depletion of this compound by reserpine, and in contrast to many neurologists at that time he was aware of its possible implications. Shortly afterwards, in 1959, Hornykiewicz read about our work on dopamine and its role in the Parkinson syndrome. He then decided to include dopamine and noradrenaline in the study. In fact, in the subsequent work serotonin had to be left out initially because of some technical problems.

Hornykiewicz and his postdoctoral fellow Ehringer were now facing a challenge, because they had no adequate equipment to measure dopamine. But they managed to overcome this problem by using the purification of the brain extracts by ion exchange chromatography that our research group had worked out. The subsequent measurement was performed using the colorimetric method of Euler and Hamberg. Although this method by itself is highly unspecific, specificity could be obtained by using our purification step together with our finding that dopamine is by far the dominating catecholamine in the basal ganglia, where it occurred in high concentrations. They had to work up several grams of tissue and to concentrate the extracts by evacuation to dryness. Following this heroic procedure they were richly rewarded, because the samples from the Parkinsonian brains, in contrast to the controls, turned out to be colourless, as revealed by the naked eye!

The corresponding development of Parkinson research in Canada is summarized in a paper by Barbeau et al. (1962), presented at a meeting in Geneva in September the previous year. The main findings of the Canadian workers was a reduction of the urinary excretion of dopamine in Parkinson patients and an alleviation of the rigidity of such patients following oral treatment with L-DOPA.

In Japan some remarkable progress was made, which has not been adequately paid attention to in the Western countries (see reviews by Nakajima, 1991, and Foley, 2000). In a lecture on the 5th of August, 1959, less than a year

after my lecture at the International Catecholamine Symposium mentioned above, the basic concept regarding the role of dopamine in the basal ganglia in Parkinson's disease was presented by I. Sano (1959). In this lecture data on the distribution of dopamine in the human brain were presented for the first time. In a lecture in Tokyo on the 6th of February, 1960, Sano reported on reduced amounts of dopamine in the basal ganglia of a Parkinson patient, analyzed post mortem, and in the same year he published a paper describing alleviation of rigidity in a Parkinson patient following intravenous administration of DL-DOPA (Sano, 1960).

Thus treatment of Parkinson patients with DOPA was initiated simultaneously in three different countries only a few years after the discovery of the anti-reserpine action of this agent and the subsequent formulation of the concept of a role of dopamine in extrapyramidal functions. While this treatment led to results of great scientific interest, it took several years until it could be implemented as routine treatment of Parkinson patients. The reason was that the treatment regimens used initially were inadequate and led to but marginal improvement of questionable therapeutic value (Hornykiewicz, 1966). It remained for George Cotzias (1967) to develop an adequate dose regimen. After that L-DOPA treatment rapidly became the golden standard for the treatment of Parkinson's disease.

When I had seen Cotzias' impressive film demonstrating the effect of escalating oral doses of L-DOPA at a meeting in Canada I hastened back to Göteborg to initiate studies together with colleagues there. The question was whom to contact.

In this context I wish to mention a couple of previous contacts I took with clinicians, aiming at starting a collaboration in Parkinson research, based on our animal studies on L-DOPA and dopamine. When still in Lund I got in touch with Prof. Lars Leksell, a well-known neurosurgeon with a special interest in Parkinson's disease. He turned out to be very skeptical. He mentioned, however, that Parkinsonian tremor could be worsened by adrenaline, and thus he was willing to supply us with samples of urine from Parkinson patients in order to analyze them for adrenaline. No collaboration came out of this. Immediately after moving to Gothenburg I contacted the professor of neurology there, Tore Broman, and proposed a collaboration in Parkinson's disease. He replied that the only area in which he could agree to a collaboration would have to deal with his research field, that is the blood-brain barrier. However, I was not interested, so again no collaboration was initiated.

The attitudes of Drs. Leksell and Broman were, in fact, typical of specialists in neurology and neurosurgery at that time. The idea that a neurodegenerative disease could be treated by substitution with a drug apparently seemed to a neurologist too fantastic to be seriously considered. Against this background one must appreciate the remarkable creativity shown by the pioneers Sano, Birkmayer, Barbeau and Cotzias. In fact, among them only Dr. Barbeau was a neurologist in the strict sense.

My conclusion was that it would probably be fruitless to try to persuade a neurologist to initiate a trial attempting to replicate Cotzias' results. A geriatrician like Birkmayer would be more open-minded. So my pharmacological

colleagues and I agreed that the obvious person to contact would be Prof. Alvar Svanborg. It very soon became evident that our choice was correct. Alvar immediately started the necessary preparations to initiate the requested study. I still remember seeing the Parkinson patients, many of whom were in wheel-chairs, coming to Alvar's clinic. When seeing them. I felt very doubtful of a successful outcome of the L-DOPA treatment. But sure enough, in full agreement with Cotzias' observations, a most dramatic result of this treatment soon became apparent in these patients (Andén et al., 1970), just as in several other clinics throughout the world.

Dopaminergic stabilizers – a novel pharmacologic principle

In 1963 Margit Lindqvist and I presented the first evidence supporting the view that the most important group of antipsychotic agents, represented by agents such as chlorpromazine and haloperidol, act by blocking receptors for dopamine, and to some extent also receptors for noradrenaline (Carlsson and Lindqvist, 1963). This conclusion has later been confirmed and extended in numerous laboratories, and techniques have been developed to screen for such agents in test tube experiments. One might have expected then that this should have led to the development of drugs with stronger efficacy and less side effects. Unfortunately, this has not happened.

We have hypothesized that the cause of this failure is that treatment with dopamine receptor antagonists can hardly avoid the serious and unpleasant side effects induced by dopamine hypofunction. Even though there is evidence of elevated dopaminergic activity in schizophrenia, this may be limited to psychotic episodes. In fact, we may be dealing with an instability of the dopamine release rather than a continuously elevated baseline. Thus, between psychotic episodes, the patient would then suffer from a dopaminergic hypofunction, especially during treatment with the currently used antipsychotic agents, showing up as a severe disturbance of the reward system and of cognition, and also as motor disturbances. This may make it impossible to attain an adequate dose level (for discussion and references, see Carlsson et al., 2001).

It is interesting to note that a similar problem exists in the case of L-DOPA treatment of Parkinson's disease. In this case the problem arises from the fact that dopamine is a full agonist and that its level is poorly controlled during L-DOPA treatment. The resulting instability, leading to an increased risk of dopamine-receptor over-stimulation, is probably a major cause of the problems arising during long-term L-DOPA treatment, with dyskinesias, the on-off-phenomenon etc.

We believe that we can now get around these problems arising from over- and understimulation of dopamine receptors by using a new principle of intervention that we call dopaminergic stabilization. The underlying mechanism is complicated, but in principle it rests on the existence of mutually antagonistic subpopulations of dopamine D2 receptors, as regards the final functional outcome. For example, the presynaptically located dopaminergic autoreceptors are inhibitory on the overall dopaminergic activity. Dopamin-

ergic stabilizers are dopamine D2 antagonists or partial D2 agonists capable of occupying mutually opposing receptor subpopulations in such proportions as to leave the normal baseline dopaminergic activity level essentially unchanged. This leads to stabilization by dampening fluctuations of dopamine release, simply because fewer dopamine receptors are unoccupied and thus available for the dopamine formed from endogenous or exogenous L-DOPA.

Using the dopaminergic stabilizer (-)-OSU6162, developed by our research group, partly in collaboration with Upjohn (now merged into Pharmacia Corporation), we have demonstrated the stabilization phenomenon in experimental animals and, in preliminary clinical studies, its pharmacotheraputic potential in L-DOPA-induced dyskinesias in Parkinson patients, in Huntington's disease and in schizophrenia (Tedroff et al., 1999; Ekesbo, 1999; Gefvert et al., 2000).

The partial dopamine receptor agonist preclamol ((-)-3-PPP) has likewise a dopaminergic stabilizer profile. This agent was discovered by our research group and is in development in collaboration with Dr. Tamminga and her colleagues at the Maryland Psychiatric Research Center (Lahti et al., 1988).

Our experience with dopaminergic stabilizers suggests that research into neurotransmitter pathophysiology has until now focussed too much on the hyper- versus hypofunction dichotomy. Although the instability concept is by no means new, there has not been much of a goal-directed strategy aiming to stabilize neurocircuits involved in neuropsychiatric disorders. Our preliminary data suggest that such an approach can lead to enormous gains in the treatment of a great variety neurological and psychiatric disorders.

References

Andén N-E, Carlsson A, Häggendal J (1969) Adrenergic mechanisms. Ann Rev Pharmacol 9: 119–134

Andén N-E, Carlsson A, Kerstell J, Magnusson T, Olsson R, Roos B-E, Steen B, Steg G, Svanborg A, Thieme G, Werdinius B (1970) Oral L-DOPA treatment of Parkinsonism. Acta Med Scand 187: 247–255

Barbeau A, Sourkes TL, Murphy GF (1962) Les catecholamines dans la maladie de Parkinson. In: Monoamines et Système nedrveux central. Georg et C^{ie} S.A., Génève, pp 247–262

Bertler Å, Rosengren E (1959) Occurrence and distribution of dopamine in brain and other tissues. Experientia 15: 10

Birkmayer W, Hornykiewicz O (1961) Der L-3,4-Dioxyphenylalanin (=L-DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wochenschr 73: 787–788

Carlsson A (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacol Rev 11: 490–493

Carlsson A (1966) Physiological and pharmacological release of monoamines in the central nervous system. In: von Euler US, Rosell S, Uvnäs B (eds) Mechanisms of release of biogenic amines. Pergamon Press, Oxford, pp 331–346

Carlsson A (1998) Autobiography. In: Squire LR (ed) The history of neuroscience in autobiography, vol 2. Academic Press, San Diego, pp 28–66

Carlsson A, Hillarp N-Å (1956) Release of adrenaline from the adrenal medulla of rabbits produced by reserpine. Kungl Fysiogr Sällsk i Lund Förhandl 26: 8

Carlsson A, Waldeck B (1958) A fluorimetric method for the determination of dopamine (3-hydroxytyramine). Acta Physiol Scand 44: 293–298

Carlsson A, Lindqvist M (1963) Effect of chlorpromazine or haloperidol on the formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol (Kbh) 20: 140–144

Carlsson A, Rosengren E, Bertler Å, Nilsson J (1957a) Effect of reserpine on the metabolism of catecholamines. In: Garattini S, Ghetti V (eds) Psychotropic drugs. Elsevier, Amsterdam, pp 363–372

Carlsson A, Lindqvist M, Magnusson T (1957b) 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature (Lond) 180: 1200 (only)

Carlsson A, Lindqvist M, Magnusson T, Waldeck B (1958) On the presence of 3-hydroxytyramine in brain. Science 127: 471 (only)

Carlsson A, Falck B, Hillarp N-Å, Thieme G, Torp A (1961) A new histochemical method for visualization of tissue catecholamines. Med Exp 4: 123–125

Carlsson A, Waters N, Waters S, Carlsson ML (2000) Network interactions in schizophrenia – therapeutic implications. Brain Res Revs 31: 342–349

Cotzias GC, Van Woert MH, Schiffer LM (1967) Aromatic amino acids and modification of parkinsonism. N Engl J Med 276: 374–379

Dahlström A, Carlsson A (1986) Making visible the invisible (Recollections of the first experiences with the histochemical fluorescence method for visualization of tissue monoamines). In: Parnham MJ, Bruinvels J (eds) Discoveries in pharmacology, vol 3. Elsevier, Amsterdam New York Oxford, pp 97–128

Ehringer H, Hornykiewicz O (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wochenschr 38: 1236–1239

Ekesbo A (1999) Functional consequences of dopaminergic degeneration. Thesis, Uppsala University, pp 1–59

Euler US von, Hamberg U (1949) Colorimetric determination of noradrenaline and adrenaline. Acta Physiol Scand 19: 74–84

Euler US von, Rosell S, Uvnäs B (eds) (1966) Mechanisms of release of biogenic amines. Pergamon Press, Oxford, pp 331–346

Falck B, Hillarp N-Å, Thieme G, Torp A (1962) Fluorescence of catecholamines and related compounds condensed with formaldehyde. J Histochem Cytochem 10: 348–354

Foley P (2000) The L-DOPA story revisited. Further surprises to be expected? The contribution of Isamo Sano to the investigation of Parkinson's disease. In: Riederer P, Calne DB, Horowski R, Mizuno Y, Olanow CV, Poewe W, Youdim MBH (eds) Advances in research on neurodegeneration, vol 8. Springer, Wien New York, pp 1–20

Gefvert O, Lindström LH, Dahlbäck O, Sonesson C et al (2000) (-)-OSU6162 induces a rapid onset of antipsychotic effect after a single dose. A double-blind placebo-controlled study. Abstract. Nordic J Psychiat 54/2: 93–94

Hornykiewicz O (1966) Metabolism of brain dopamine in human Parkisonism: neurochemical and clinical aspects. In: Costa E, Côté LKJ, Yahr MD (eds) Biochemistry and pharmacology of the basal ganglia. Raven Press, New York, pp 171–186

Hornykiewicz O (1992) From dopamine to Parkinson's disease: a personal research record. In: Samson F, Adelman G (eds) The neurosciences: paths of discovery II. Birkhäuser, Boston, pp 125–148

Katz B (1996) In: Squire LR (ed) The history of neuroscience in autobiography, vol 1. Soc Neurosci, Washington, pp 348–381

Lahti AC, Weiler MA, Corey PK, Lahti RA, Carlsson A, Tamminga CA (1998) Antipsychotic properties of the partial dopamine agonist(-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine (preclamol) in schizophrenia. Biol Psychiat 43: 2–11

Loewi O (1921) Über humorale Übertragbarkeit der Herznervenwirkung (I. Mitteilung). Pflüg Arch ges Physiol 189: 239–242

McLennan H (1963) Synaptic transmission. WB Saunders, Philadelphia, pp 1–134

Nakajima T (1991) Discovery of dopamine deficiency and the possibility of dopa therapy in Parkinsonism. In: Nagatsu T, Narabayashi H, Yoshida M (eds) Parkinson's disease. From clinical aspects to molecular basis. Springer, Wien New York, pp 13–18

Pletscher A, Shore PA, Brodie BB (1955) Serotonin release as a possible mechanism of reserpine action. Science 122: 374–375

Pletscher A, Shore PA, Brodie BB (1956) Serotonin as a mediator of reserpine action in brain. J Pharmacol Exp Ther 116: 84–89

Sano I (1959) Biochemical studies of aromatic monoamines in the brain. In: Japanese Medicine in 1959. The report on scientific meetings in the 15th General Assembly of the Japan Medical Congress, vol V, pp 607–615

Sano I (1960) Biochemistry of extrapyramidal motor system. Shinkey Kenkyu no Shinpo (Adv Neurol Sci) 5: 42–48 [English translation in: Parkinsonism and Related Disorders (2000)6: 3–6]

Tedroff J, Ekesbo A, Sonesson C, Waters N, Carlsson A (1999) Long-lasting improvement following (-)-OSU6162 in a patient with Huntington's disease. Neurology 53: 1605–1606

Vane JR, Wolstenholme GEW, O'Connor M (eds) (1960) Ciba Foundation Symposium on Adrenergic Mechanisms. J & A Churchill, London, pp 1–632

Author's address: Prof. Dr. A. Carlsson, Department of Pharmacology, University of Göteborg, P.O. Box 431, SE-40530 Göteborg, Sweden, e-mail: arvid.carlsson@pharm.gu.se