The Neurobiology of Dopamine

edited by
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Preface

This book is an attempt to bring together in one volume as many important facets of dopamine research as possible. By the very nature of the subject and its explosive growth in recent years, however, it is inevitable that certain areas have not been covered.

The order of the chapters was very loosely based on the concept of increasing complexity of the system dealt with in the chapter. Thus in simple terms the two ends of the spectrum of complexity are the chemistry of the dopamine molecule itself and the functional role of dopamine-containing neuronal systems in man.

We would like to take this opportunity to thank sincerely all of our authors (both the fast and the slow writers!) for making this book possible.

Alan Horn
Jakob Korf
Ben Westerink

Contents

Dopamine Receptors

Release, Uptake and Metabolism of Dopamine

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Neurophysiology of Dopamine Systems

CHAPTER 1

Historical Introduction

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The interest in dopamine (DA) has been great in the past decade, partly due the spectacular results of the L-DOPA treatment of Parkinson's disease and also to the demonstration of the probable connection between the antischizophrenic effect and the DA receptor blockade of neuroleptic drugs. Dopamine was first synthesized by Mannich and Jacobsohn (1910). It was, however, long neglected in comparison to the closely related biogenic catecholamines adrenaline and noradrenaline. One reason for this obscurity was in all likelihood that DA has but small sympathomimetic properties (Barger and Dale, 1910).

The history of DA is linked to that of its immediate precursor L-DOPA. DOPA was first synthesized in its racemic form by Funk (1911), who also coined the term "vitamin" because he considered all compounds of that kind as amines. He had the correct idea that adrenaline is formed *in vivo* from this amino acid. Soon afterwards, the L-form of DOPA was isolated from the bean *Vicia faba* and chemically characterized by Guggenheim (1913). He experienced nausea and vomiting when he administered 2.5 g of this compound orally to himself. Unfortunately, he gave rather small oral doses to animals and, therefore, he did not succeed in observing any remarkable effects.

After these early discoveries, it took more than 20 years before the next important step was taken. It was the demonstration of L-DOPA decarboxylase in animal tissues (Holtz *et al.*, 1938). The same group also found that DA is a normal constituent of the human urine and that L-DOPA is decarboxylated *in vivo* with subsequent changes in the blood

pressure (Holtz *et al.*, 1942). Soon after the discovery of L-DOPA decarboxylase, L-DOPA and DA were proposed as intermediates in the biosynthesis of noradrenaline and adrenaline from L-tyrosine (Blaschko, 1939).

Most of our present knowledge of DA has been obtained in the last 25 years with the rapid development of the field of neuropsychopharmacology. Soon after the introduction of the antipsychotic drugs at the beginning of the fifties, it was realized that they produce two peculiar side-effects in humans. Firstly, the patients often developed parkinsonism, i.e., motor disturbances indistinguishable from those seen in Parkinson's disease. Secondly, it was not unusual that the psychosis was converted to an indifferent and sedated condition but with intact intellectual abilities, a so-called neuroleptic syndrome (Delay *et al.*, 1952). These changes could be observed also in animals, e.g., as catalepsy and decreased motor activity in rodents (Courvoisier *et al.*, 1953). A further development that was of great importance was that one of the clinically active neuroleptic drugs, reserpine, was found to interfere with the storage of two monoamines, 5-hydroxytryptamine and noradrenaline. These compounds had previously been demonstrated to occur in the brain (Twarog and Page, 1953; Amin *et al.*, 1954; Vogt, 1954). Initially, the depletion of the body stores of 5-hydroxytryptamine by reserpine was reported (Plestcher *et al.*, 1955). Somewhat later, it was detected that reserpine similarly influences the peripheral and central stores of noradrenaline (Bertler *et al.*, 1956; Holzbauer and Vogt, 1956).

It was tempting to connect the observed changes in the concentrations of 5-hydroxytryptamine and noradrenaline following treatment with reserpine to the pharmacological effects. It was not known, however, if reserpine caused an excess or lack of monoamines at the receptors of the effector cells and if 5-hydroxytryptamine or noradrenaline or both were involved. In order to investigate these problems, Carlsson *et al.* (1957) gave the 5-hydroxytryptamine precursor 5-hydroxytryptophan and the noradrenaline precursor DOPA to reserpine-treated mice and rabbits. They observed that the reserpine-induced sedation was readily counteracted by DOPA, but not by 5-hydroxytryptophan. These data indicated that the reserpine-induced sedation is due to a lack of noradrenaline rather than 5-hydroxytryptamine but, surprisingly, the DOPA treatment did not induce any noticeable increase in the noradrenaline concentration of the reserpine-treated animals. Therefore, interest was directed to DA, the intermediate in the formation of noradrenaline from DOPA. At that time, there was no good method to determine DA so Carlsson and Waldeck (1958) had to develop a sensitive and specific fluorimetric method. By means of this method it was discovered that not only do large amounts of DA accumulate in the brain following

treatment with DOPA, but also that DA is normally present in the brain at a concentration of about the same magnitude as that of noradrenaline (Carlsson *et al.*, 1958). The normal occurrence of DA in the brain was independently discussed by Montagu (1957) and Weil-Malherbe and Bone (1957).

The fact that the concentration of DA in the normal brain is at least as high as that of noradrenaline suggested that DA does not serve only as a precursor of noradrenaline, but that it might have an action of its own. Further evidence for this view was obtained when it was demonstrated that DA has a remarkable distribution in the brain. The caudate nucleus and putamen, i.e. the neostriatum, contains 70–80% of the brain's DA (Bertler and Rosengren, 1959, Sano *et al.*, 1959). Significant amounts of DA were also detected in the substantia nigra (Bertler, 1961).

These findings indicated that DA is involved in the extrapyramidal motor functions and in disorders such as Parkinson's disease and Huntington's chorea. The arguments supporting these hypotheses were summarized as follows (Carlsson, 1959):

1. The presence of large amounts of dopamine in the corpus striatum, which forms an important part of the extrapyramidal system.
2. The extrapyramidal actions of reserpine, which depletes dopamine from the corpus striatum.
3. The ability of DOPA to counteract the hypokinetic action of reserpine. Whether this action of DOPA is entirely due to formation of dopamine, or whether formation of noradrenaline contributes to the effect, remains an open question.

Carlsson's theories soon received substantial support by important clinical observations in Vienna, Austria. First, it was found that DA is more or less completely depleted from the corpus striatum in patients with Parkinson's disease (Ehringer and Hornykiewicz, 1960). The noradrenaline and the 5-hydroxytryptamine in the brain were also lowered, but to a much less marked degree (Bernheimer *et al.*, 1963). The disappearance of DA from the brains of parkinsonian patients prompted trials with intravenous administration of small doses of L-DOPA (Birkmayer and Hornykiewicz, 1961). At about the same time, small oral doses of L-DOPA were given in Canada (Barbeau *et al.*, 1962). Some beneficial effects on the parkinsonian signs and symptoms, particularly the hypokinesia and the rigidity, were obtained but side-effects such as nausea and vomiting were troublesome. Therefore, the clinically useful treatment of Parkinson's disease with DOPA was accomplished only by using large oral doses following slow increases in the dosage (Cotzias *et al.*, 1967. Cotzias *et al.*, 1969).

The understanding of the function of DA in the brain has been facilitated

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