

CHAPTER 1

Brain Dopamine: A Historical Perspective

O. HORNYKIEWICZ

A. Introduction

To the student of the history of brain dopamine (DA), the amine offers an excellent example of an endogenous compound that right from the start has presented aspects of both scientific and clinical importance. Although on several points DA shares this characteristic with the other two catecholamines, adrenaline and noradrenaline (NA), what sets DA apart is the tightness of the interdigitation between its basic research and the clinical implications – for brain DA, there has never been a dividing line between the two; each has served as the driving force for the other. To bring out this interconnection has been the primary object of the following “Historical Perspective”. The decidedly human relevance of brain DA research also has been the ultimate vindication of the pleasure we take in our work as DA researchers. The writer has tried to convey in this essay some of the excitement of this work.

The reader of this chapter will soon notice that it has been written not by a detached historian, drawing his knowledge from the printed word, but by someone who from the very beginning has been an active party to the events that now, with the passage of many years, have become historically significant. The personal involvement has undoubtedly lent a distinctive colouring to the picture of those historical events, still so freshly remembered. However, the writer has made a special effort to leave intact the period’s atmosphere of ideas and to bear witness to those who had been instrumental in translating these ideas into scientific knowledge.

For the most part, the text was written from memory. Therefore, it cannot claim completeness or balance. The limitation on space alone forbade completeness; and in order for the text to be balanced, in depth scrutiny of the literature would have required more time than the writer could allow himself between the pleasures of remembering and the frustrations of forgetting. Thus, for lack of space many important developments had to remain unmentioned; many other events could not, within the given limit on time, be referenced with greater precision. For all these defects, the writer asks his colleagues’ indulgence. To the extent that in the last decades the DA literature has taken such dimensions that it would be in fact difficult to include even a fraction of it, the defects of the present article may be excused, if not forgiven.

B. The First Half-Century: 1910–1959

DA is the youngest of the three catecholamines found to occur naturally in the mammalian organism. Although synthesized in the early years of the last century (BARGER and EWINS 1910; MANNICH and JACOBSON 1910), DA joined the circle of substances of biological interest proper not before 1951. In that year, GOODALL detected, for the first time, DA in mammalian tissues, specifically sheep heart and adrenal medulla (GOODALL 1951). Also in 1951, DALE (SIR HENRY) coined the name “dopamine” for the, as he felt, confusing term 3-hydroxytyramine, short for the full chemical name β -3,4-dihydroxyphenylethylamine (see footnote in BLASCHKO 1952). Much earlier, in 1910, DALE was also the first to study DA’s pharmacological actions, especially on the arterial blood pressure in the cat, declaring the amine to be a weak sympathomimetic substance (BARGER and DALE 1910). In this modest role DA remained for nearly half a century (cf. HORNYKIEWICZ 1986). When GOODALL, in 1951, found DA in mammalian tissues, this discovery was not too surprising. Already earlier, in 1939, BLASCHKO as well as HOLTZ – who, the year before, had discovered the DA-forming enzyme dopa decarboxylase (HOLTZ et al. 1938) – had postulated that DA was the metabolic intermediate, formed from L-dopa, in the biosynthesis of NA and adrenaline (BLASCHKO 1939; HOLTZ 1939). Hence, small amounts of DA and L-dopa could be expected to occur in NA and adrenaline-containing tissues. As for L-dopa, this naturally occurring amino acid precursor of DA had been isolated, in 1913, from *Vicia faba* beans and tested by GUGGENHEIM who found it to be devoid of biological activity (in the rabbit), except for causing nausea and vomiting in a self-experiment (GUGGENHEIM 1913) – unaware that this unpleasant effect was due to the DA formed in his body from the swallowed L-dopa. It is also worth mentioning that FUNK, the inventor of the term “vitamin”, in his early search for a “parent substance” of adrenaline, was the first to synthesize the racemic (D,L) form of dopa (FUNK 1911).

Following up his discovery of dopa decarboxylase, HOLTZ soon showed that after administration of L-dopa to animals and humans, DA was excreted in the urine, thereby proving that also in the body was DA the product of L-dopa decarboxylation (HOLTZ and CREDNER 1942). As a matter of historical fact, a year earlier BING had already shown that the in vivo and in vitro artificially perfused ischemic kidney of the cat formed DA from exogenous L-dopa (BING 1941; BING and ZUCKER 1941). HOLTZ, in the course of his studies, also made the intriguing observation that in the rabbit and the guinea-pig, DA had an action on the arterial blood pressure (vasodepression) opposite to the (vasopressor) action of adrenaline (HOLTZ and CREDNER 1942). It is of interest that considerably earlier HASAMA (1930) had observed the corresponding vasodepressor effect of L-dopa in the rabbit, already then wondering about the qualitative difference to the opposite (vasopressor) effect of adrenaline.

The logical idea that should have immediately suggested itself from HOLTZ’s observations was that DA might have biological actions of its own,

different from those of the other catecholamines. However, HOLTZ gave his discovery a trivial interpretation, suggesting a non-specific vasodepressor action of the DA-derived aldehyde which he assumed to be formed in especially large amounts (through the action of monoamine oxidase) in rabbit and guinea-pig organism. It was not until 15 years later that BLASCHKO, in 1956, for the first time expressed the view that DA may have own physiological actions in the body (BLASCHKO 1957). In the same year, HORNYKIEWICZ, upon BLASCHKO's suggestion, re-examined the vasodepressor action of DA and L-DOPA in the guinea-pig, conclusively showing that it was an intrinsic property of the amine (HORNYKIEWICZ 1958), consistent with BLASCHKO's suggestion of DA having biological activity in its own right.

The study of HORNYKIEWICZ coincided in time with several other crucial observations about DA. First, CARLSSON demonstrated that D,L-dopa (but not D,L-5-hydroxytryptophan) antagonized the reserpine catalepsy in mice and rabbits (CARLSSON et al. 1957); this observation was soon confirmed and enlarged by EVERETT and TOMAN (1959) and BLASCHKO and CHRUSCIEL (1960), and extended to the reserpine "sedation" in humans (DEGKWITZ et al. 1960); second, DA's occurrence in the mammalian brain was discovered (MONTAGU 1957; CARLSSON et al. 1958); third, D,L-dopa was found to restore the brain levels, reduced by reserpine, of DA (and to a much smaller extent of NA) (CARLSSON et al. 1958; EVERETT 1961; EVERETT and WIEGAND 1962). Taken together, these studies laid the groundwork for all future research into the role of DA in normal and abnormal brain function. The final step was taken, again in CARLSSON's laboratory, by BERTLER and ROSENGREN (1959) who found that the bulk of brain DA (in the dog) was concentrated in the corpus striatum, an observation soon confirmed for the human brain (SANO et al. 1959; EHRINGER and HORNYKIEWICZ 1960; BERTLER 1961). Based on their discovery, the Swedish workers suggested that the parkinsonism-like condition produced by reserpine in laboratory animals and humans may be due to lack of DA in the extrapyramidal-motor centres of the corpus striatum (BERTLER and ROSENGREN 1959; CARLSSON 1959).

C. "The Great Brain Serotonin–Catecholamine Debate"

At the time of the brain DA discoveries, a fierce controversy about how best to explain reserpine's central "sedative" actions was raging between two opposing camps. On the one side stood the adherents of the brain serotonin hypothesis of reserpine's central actions; on the other side were the adherents of the brain catecholamine hypothesis. The auspicious arrival, in 1958, of brain DA on the reserpine scene would have been expected to put an end to this dispute. However, the controversy continued unabatedly well into the mid-1960s, forcing the cause of DA into the background. The literature of that time is replete with great debates – which generated much heat but gave little light (see discussion, pp 548–587, in VANE et al. 1960; BRODIE and COSTA 1962;

CARLSSON and LINDQVIST 1962; CARLSSON 1964; general discussion, pp 67–71, in HIMWICH and HIMWICH 1964; CARLSSON 1965). If at all mentioned, DA mostly played the role of a satellite of NA. In the heat of the debates, even the distinction between the specific NA and DA receptors was sometimes forgotten. DA's crucial and so plainly evident role in reserpine parkinsonism and Parkinson's disease (see below) was for some time diminished by claims that the central actions of L-DOPA and the direct (non-natural) NA precursor amino acid 3,4-dihydroxyphenylserine (DOPS) were similar (Carlsson 1964; 1965).

The situation, hardly encouraging for DA, is well illustrated by the fact that at the "Second Symposium on Catecholamines" held in Milan in 1965 (see ACHESON 1966), of a total of 90 contributions, only a single presentation (from CARLSSON's former laboratory), was devoted to brain DA (BERTLER and ROSENGREN 1966). Even in this contribution, the authors – who 7 years earlier had been the first to suggest the connection between striatal DA depletion and (reserpine) parkinsonism – found it safer to say that "relevant to Parkinson's syndrome" was "a decreased catecholamine [!] concentration in the brain". Lamentable as this state of affairs was, three notable exceptions should be mentioned (cf. HORNYKIEWICZ 1992). Two years before the meeting in Milan, at the "Second International Pharmacological Meeting" held in Prague in 1963, a symposium on "Drugs interfering with the extrapyramidal system" included four papers on brain DA (by SOURKES, BERTLER, VAN ROSSUM and HORNYKIEWICZ; cf. TRABUCCHI et al. 1964). Strong experimental support for the cause of brain DA also kept coming from GUY EVERETT, who convincingly defended brain DA against NA, DOPS and serotonin (see EVERETT and WIEGAND 1962; EVERETT 1970). Lastly, GEORGE H. ACHESON, editor of *Pharmacological Reviews* had the right idea at the right time, and, in the summer of 1964, requested "a review of the interesting aspects of dopamine and the brain". The resulting article (HORNYKIEWICZ 1966) finally brought DA to the attention of the scientific community at large, placing the amine permanently on the agenda of modern neuroscience research. However, in the end it was the unprecedented success of the DA replacement therapy with L-dopa that brought the catecholamine-serotonin controversy to an end – simply by making it irrelevant.

D. Striatal Dopamine, Parkinson's Disease and Dopamine Replacement

In retrospect, it appears fortunate that despite the absolute priority claimed by "The Great Brain Serotonin-Catecholamine Debate", research on DA was being carried on, quietly but persistently, by a handful of "DA believers" (cf. HORNYKIEWICZ 1992). Thus, immediately after BERTLER and ROSENGREN had suggested a possible role of striatal DA in reserpine-induced parkinsonism, HORNYKIEWICZ, in Vienna, took up this idea and applied it within a few months to diseases of the human basal ganglia. A study, done in autopsied brains of six patients with Parkinson's disease (PD), two Huntington's disease patients,

seventeen controls, and six cases with extrapyramidal symptoms of unknown aetiology, already showed what now is common textbook knowledge: a severe loss of DA in the caudate nucleus and putamen, confined to the patients with PD (EHRINGER and HORNYKIEWICZ 1960). In the same year, Sano (1960) reported on low putamen DA in one case of PD. DA levels in the substantia nigra were also found to be markedly reduced (HORNYKIEWICZ 1963). Independently, SOURKES, MURPHY and BARBEAU in Montreal measured DA in the urine of patients with extrapyramidal disorders and found reduced amounts of the excreted amine in the parkinsonian group (BARBEAU et al. 1961).

In Vienna and Montreal, these studies were immediately followed up independently by the involved researchers who successfully treated PD patients by replacing the missing brain DA with intravenous or oral doses of L-dopa (BIRKMAYER and HORNYKIEWICZ 1961, 1962; BARBEAU et al. 1962; see also GERSTENBRAND et al. 1963). Although for some time there was considerable reluctance, especially among neurologists, to accept L-dopa's anti-Parkinson's effect (cf. BARBEAU 1969; HORNYKIEWICZ 1994), 5 years later COTZIAS definitely established L-dopa by introducing the high-dose oral regimen presently in use (COTZIAS et al. 1967). This was followed, in 1969, by the combination with peripheral (extracerebral) dopa decarboxylase inhibitors (cf. PLETSCHER and DAPRADA 1993). (Interestingly, also Sano tried D,L-DOPA i.v. in (two) PD patients, but dismissed it as of no therapeutic value [SANO 1960; cf. HORNYKIEWICZ 2001].) The high anti-Parkinson's efficacy of L-dopa demonstrated, for the first time, that neurotransmitter replacement was possible even in chronic, progressive, degenerative brain disorders such as PD. Two recent developments have logically grown out of the DA replacement concept, i.e. grafting of DA-producing fetal (nigral) cells into the PD striatum (BJÖRKLUND and STENEVI 1979) and intrastriatal transfer of somatic cells genetically modified (by means of viral vectors) to express DA synthetic enzymes (GAGE et al. 1991).

E. Dopamine Pathways

At the time of DA's discovery in the brain, its place in brain function was unknown. To illustrate the situation, when in 1954 MARTHE VOGT found an uneven regional distribution of brain NA, she suspected, but could not prove, that the amine might be contained in neurons (VOGT 1954). Even 6 years later this uncertainty remained, applying also to DA's (and serotonin's) brain localization. A new approach to the problem of cellular localization soon removed all uncertainty. Studies using the new Falck-Hillarp method for the histochemical visualization of monoamines in brain-tissue slices demonstrated that in the rat, DA was localized to the neuronal cell bodies of the compact zone of the substantia nigra and the nerve terminals in the striatum (ANDÉN et al. 1964a; DAHLSTRÖM and FUXE 1964; FUXE 1965). Thus, in PD the nigral cell loss typical for this disorder (HASSLER 1938), offered, together with the nigral DA loss (HORNYKIEWICZ 1964), a simple explanation for the marked DA loss in the stri-



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Dopamine in the CNS I

Di Chiara, G. (Ed.)

2002, XX, 344 p., Hardcover

ISBN: 978-3-540-42719-3