Effect of Chronically Administered L-Dopa on Dopa/5HTP Decarboxylase and Tyrosine and Tryptophan Hydroxylases in Cat Brain

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Summary — Résumé

The activity of tyrosine and tryptophan hydroxylases and of Dopa/5-HTP decarboxylase was measured in different structures of the brain of cats administered L-Dopa (100 mg/kg/day, per os) during several consecutive days. The activity of tyrosine hydroxylase which is unchanged after 4 and 7 days of treatment, respectively, is significantly decreased after 21 days of L-Dopa. The activity of tryptophan hydroxylase is normal after 4 days of L-Dopa but it is significantly decreased after 7 and 21 days of L-Dopa, respectively. The activity of decarboxylase is normal after 4 days of L-Dopa but it is significantly increased after 7 and 21 days of L-Dopa, respectively.

Introduction

3, 4-Dihydroxy-phenylethylamine (dopamine, DA) is formed from 3, 4-dihydroxy-L-phenylalanine (L-Dopa) through decarboxyla-
The activity of the aromatic-L-aminoacid decarboxylase determines the rate of dopamine synthesis from L-Dopa and of serotonin (5-HT) from 5-hydroxy-L-tryptophan (5-HTTP). In fact Dopa decarboxylase (EC 4.1.1.26, 3,4-dihydroxy-L-phenylalanine carboxylase) and 5-hydroxytryptophan decarboxylase (EC 4.1.1.28, 5-hydroxy-L-tryptophan carboxylase) are not considered to be specific in regard to their respective substrate and, particularly, the activity of either enzyme is associated with a single protein in mammalian tissues (Sourkes, 1966; Christenson et al., 1972; Lancaster and Sourkes, 1972). On the other hand, the synthesis of L-Dopa involves a highly specific enzyme, tyrosine hydroxylase [EC 1.14.3.1., L-tyrosine, tetrahydropteridine: O2 oxido-reductase (3-hydroxylating)], which catalyses the conversion of L-tyrosine to L-Dopa. In the same way, the hydroxylation of L-tryptophan to 5-hydroxy-L-tryptophan is dependent on tryptophan-5-hydroxylase (EC 1.14.3.2), also a specific enzyme. The last two named enzymes known to be present in different tissues of a variety of animal species (Freedland et al., 1961; Nagatsu et al., 1964; Grahaime-Smith, 1967; McGeer et al., 1967; Peters et al., 1968) are considered to be rate-limiting in catecholamines and 5-hydroxyindole synthesis (Lewitt et al., 1965; Udenfriend, 1966; Ashcroft et al., 1965; McGeer et al., 1967), respectively. At the present time L-Dopa is chronically administered to patients with Parkinson's Disease and it is well known that DA is formed (Davidson et al., 1971) but the longterm effects of L-Dopa on the enzymatic mechanisms of the CNS have to be elucidated. In an attempt to determine the effects of a chronic treatment with L-Dopa on enzymic activity, tyrosine hydroxylase, tryptophan-5-hydroxylase and Dopa/5-HTP decarboxylase were assayed in different brain structures of cats.

Materials and Methods

Thirty-six cats of both sexes, weighing 2—3 kg were used. L-Dopa Larodopa, Hoffmann-La Roche) was administered per os, once a day as a single dose of 100 mg/kg. Eleven cats were used as controls and groups of 6, 12 and 7 cats received L-Dopa during 4, 7 and 21 days, respectively. All cats were sacrificed 18 hours after the last dose of L-Dopa without anaesthesia using a guillotine especially designed for this purpose. The brains were quickly removed and the two striata, the thalamus, hypothalamus and midbrain were immediately dissected out on ice, weighed and homogenized within 45 minutes in 2 volumes of ice-cold 0.32 M sucrose using a Potter-Elveljem homogenizer with a Teflon pestle.

Tyrosine Hydroxylase. The enzymatic activity was measured according to the methods initially described by Nagatsu et al. (1964) and later by