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Positron emission tomographic studies on aromatic L-amino acid decarboxylase activity in vivo for L-dopa and 5-hydroxy-L-tryptophan in the monkey brain

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Summary. The regional brain kinetics following 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA intravenous injection was measured in twelve Rhesus monkeys using positron emission tomography (PET). The radiolabelled compounds were also injected together with various doses of unlabelled 5-hydroxy-L-tryptophan or L-DOPA. The radioactivity accumulated in the striatal region and the rate of increased utilization with time was calculated using a graphical method with back of the brain as a reference region. The rate constants for decarboxylation were 0.0070 ± 0.0007 (S. D) and $0.0121 \pm 0.0010\,min^{-1}$ for 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA, respectively. After concomitant injection with unlabelled 5-hydroxy-L-tryptophan, the rate constant of 5-hydroxy-L-(β-11 C)tryptophan decreased dose-dependently and a 50 percent reduction was seen with a dose of about 4 mg/kg of unlabelled compound. A decreased utilization rate of L-(β-11 C)DOPA was seen only after simultaneous injection of 30 mg/kg of either L-DOPA or 5-hydroxy-L-tryptophan. This capacity limitation was most likely interpreted as different affinity of the striatal aromatic amino acid decarboxylase for L-DOPA and 5-hydroxy-L-tryptophan, respectively.

Keywords: 5-Hydroxy-L-(β-11 C)tryptophan, L-(β-11 C)DOPA, positron emission tomography, aromatic amino acid decarboxylase, monkeys

Introduction

Aromatic amino acid decarboxylase (AADC) catalyzes the decarboxylation of a wide range of aromatic amino acids, including 5-hydroxy-L-tryptophan and

L-DOPA (Lovenberg et al., 1962; Christenson et al., 1970). In the serotonin synthesis, AADC catalyzes the transformation of 5-hydroxy-L-tryptophan to serotonin by removing carbon dioxide, a reaction first reported by Holtz (1939). The enzyme is widely distributed in mammalian tissues, and in the brain AADC seems to be localized in neuronal as well as in non-neuronal cells (Lovenberg et al., 1962; Christenson et al., 1970).

AADC is present in the brain in far greater excess than tryptophan hydroxylase (Ichiyama, 1970). The enzyme is supposed not to be rate-limiting for monoamine synthesis and is not assumed to be modulated by the neuronal activity. The Michaelis-Menten constant of the enzyme has been measured several orders of magnitude higher than the concentration of endogenous precursors (Sourkes, 1977). Recent studies, however, have disputed this statement and a much lower value was recently reported for 5-hydroxy-L-tryptophan (Siow and Dakshinamurti, 1990).

Positron emission tomography, PET, has made possible the quantitation of selective cumulation of 5-hydroxy-L-tryptophan and L-DOPA radiolabelled with 11 C in the β-position in the striatum of Rhesus monkeys (Tedroff et al., 1992 a; Hartvig et al., 1991). The rate of radioactivity accumulation shown with PET mainly represents the formation rate of (11 C)-serotonin or (11 C)-dopamine, respectively. This statement was supported by no striatal cumulation of radioactivity when the precursor radiolabelled in the carboxylic group was administered (Korf et al., 1977; Tedroff et al.,1992; Hartvig et al., 1991). Furthermore, pretreatment of monkeys with a centrally active decarboxylase inhibitor before 5-hydroxy-L-(β-11 C)-tryptophan (Hartvig et al.,1991) or L-(β-11 C)-DOPA (Tedroff et al., 1992 a) had been administered, did not yield any striatal accumulation of radioactivity. The fractional decarboxylation rate of 5-hydroxy-L-tryptophan and L-DOPA radiolabelled with 11 C was calculated using a brain reference region. This directly gives the fractional decarboxylation rate in the striatum, as previous studies have shown that radiolabelled metabolites did not significantly influence the calculated rate constants (Tedroff et al., 1992 a; Hartvig et al., 1991; Miwa et al., 1992). The decarboxylation rate measured in vitro has also been shown similar to the decarboxylation rate of the L-DOPA analogue 6-(18 F)fluoro-L-DOPA measured with PET (Gjedde et al., 1991). A positive identification of formed 11 C-neurotransmitter has also been achieved in the rat brain using microdialysis and brain homogenates (Miwa et al., 1992).

The aims of the present study were to assess by positron emission tomography the in vivo regulation of the decarboxylation of the two neurotransmitter precursors, i.e., 5-hydroxy-L-tryptophan and L-DOPA, radiolabelled with 11 C and to measure differences in enzyme activity for the two substrates. A mass effect on enzyme activity was also studied using various concentrations of the substrates.

Methods

Animals

Twelve female Rhesus monkeys (Macaca mulatta) aged 20 to 30 years and weighing 7–10 kg from the Primate Research Laboratory, Uppsala University, were used. After an overnight fast they were anesthetized with ketamine (Ketalar, Parke-Davis, Morris Plains, U.S.A),which was supplemented with diazepam (Stesolid, Dumex, Copenhagen, Denmark) and ketamine when required. In experiments 6, 7, 11, and 12, (Table 1 and 2), a constant rate infusion of ketamine (3 mg/kg × h) were used to get a more stable anesthesia. Muscle relaxation in these monkeys was achieved with atracurium (Tracrium, Wellcome, London, England) and mechanical ventilation was done with 40% oxygen in air. The study was approved by the Animal Ethics Committee of the University of Uppsala.

Radiochemistry

The radionuclide 11 C was produced as 11 C-carbon dioxide in the accelerator at The Svedberg Laboratory, University of Uppsala, or in the MC 17 cyclotron (Scanditronix AB, Uppsala, Sweden) at the Uppsala University PET center. The synthesis of 5-hydroxy-L-(β-11 C)tryptophan (Bjurling et al., 1990 a) and L-(β-11 C)DOPA (Bjurling et al., 1990 b) was carried out using a combination of organic synthetic methods and a multi-enzymatic procedure. After analysis for identity, radiochemical and chemical purity, the solution was passed through a 0.22 μm filter before intravenous administration to the monkey. The radioactive dose injected to the monkey varied 50–200 MBq. The injected amount corresponded to a dose of 20 to 80μg of L-DOPA or 5-hydroxy-L-tryptophan, except in studies 6, 7, 11, and 12 when the amount injected was ten times lower.

Table 1. Striatal decarboxylation rate and uptake in the brain of 5-hydroxy-L-(β-11 C) tryptophan, 5-HTP

No	Pretreatment	Dose	k 3	Uptake*	F	% of baseline
1.	–		0.0070	0.56	1.08	
	5-HTP	0.5 mg/kg	0.0066	0.58	0.92	94
2.	–		0.0056	0.68	1.16	
	5-HTP	3.0 mg/kg	0.0036	0.65	0.90	64
3.	–		0.0070	0.63	0.97	
	5-HTP	5.0 mg/kg	0.0022	0.50	1.18	32
4.	–		0.0078	0.64	1.08	
	5-HTP	10.0 mg/kg	0.0010	0.35	1.08	13
5.	–		0.0062	0.48	1.17	
	L-DOPA	4.0 mg/kg	0.0061	0.33	1.00	99
6.	–		0.0078	0.90	1.08	
	L-DOPA	15 mg/kg	0.0066	0.80	1.11	88
7.	–		0.0069	0.90	1.12	
	L-DOPA	30 mg/kg	0.0043	0.80	0.98	61

* Mean radioactivity uptake in surrounding brain 10–45 min after dose

Table 2. Striatal decarboxylation rate and uptake in the brain of L-(β-11 C)DOPA

No	Pretreatment	Dose	k 3	Uptake*	F	% of baseline
8.	–		0.0101	0.35	1.03	
	L-DOPA	4 mg/kg	0.0110	0.30	1.08	109
9.	–		0.0145	1.10	1.19	
	L-DOPA	30 mg/kg	0.0100	0.90	1.23	69
10.	–		0.0115	0.30	1.15	
	5-HTP	5 mg/kg	0.0102	0.28	0.97	89
11.	–		0.0105	0.37	1.13	
	5-HTP	5 mg/kg	0.0098	0.36	1.07	94
12.	–		0.0140	1.30	1.03	
	5-HTP	30 mg/kg	0.0126	1.13	1.03	90

* Mean uptake in surrounding brain 10–45 min after injection of dose

In a second experiment in each monkey, 0.5 to 30 mg/kg of unlabelled 5-hydroxy-L-tryptophan (Sigma Chemicals, St. Louis, U.S.A) or 4 to 30 mg/kg of L-DOPA (Janssen Chimica, Geel, Belgium) were injected immediately before the radioactive tracer.

Positron emission tomography

Positron emission tomography was performed with the monkey lying with the head fixed in a two ring PET camera system (Scanditronix PC 384-3 B, Uppsala, Sweden) in experiments 1–5 and 8–10. This PET scanner allows simultaneous acquisition of the radioactivity from three slices interspaced by about 14 mm and with an in-plane resolution of 7.6 mm full width half maximum (Litton et al., 1984). Studies 7 and 12 were performed in a PC 2048-15B Plus and studies 6 and 11 in a PC 4096-15WB Plus positron emission tomograph, respectively, and both from General Electrics Medical Systems, Uppsala, Sweden. These tomographs measure the radioactivity in fifteen slices interspaced with about 6.8 mm. The in-plane resolution at full width half-maximum was 5 mm and 6 mm in the PC 2048 15B Plus (Holte et al., 1989) and PC 4096-15WB Plus (Rota Kops et al., 1990) camera systems, respectively.

The radioactivity was given intravenously to the monkey when a series of scans comprising 30 consecutive measurements was started to measure the regional radioactive distribution. The investigation lasted 45–55 min. Images were reconstructed for each sequential measurement. The two striata and back of the brain were delineated from the images after comparison with an Rhesus monkey brain atlas made after cryosectioning. The radioactivity was corrected for physical decay to the time of administration and was normalized to the injected radioactivity per gram body weight of the monkey. This gives a dimensionless value called 'uptake'. An uptake of 1.0 means an equal distribution of the radioactivity in the monkey body, assuming the density of tissue to be 1 g/cm^3.

Calculations

A compartment model with one compartment for radioactivity in the extracellular space, non-specifically bound in the brain and another for specific utilization of the radioactivity for synthesis was used to mathematically describe the change of radioactivity over time.

Both compartments have arterial blood as input function and this compartment was therefore reduced. The rate constant was then calculated with back-of-the-brain slice as reference region (Tedroff et al.,1992 a). Striatal radioactivity (Ct) and radioactivity in the reference region (Cb) were obtained using the following equation:

$$Ct/Cb = F + F \times k_3 \int_0^t Cb(t)dt/Cb(t)$$

where F is a term proportional to differences in distribution volume and blood flow to the striatal region and reference region, respectively. The rate constant k3 is assumed to represent the fractional rate constant for the decarboxylation of L-(β-11 C)DOPA and 5-hydroxy-L-(β-11 C)tryptophan, respectivley. Linear regression analysis was determined by the least square fit from 7 minutes and onwards.

Results

5-Hydroxy-L-(β-11 C)tryptophan derived radioactivity increased selectively in the striatal area of the Rhesus monkey brain. The rate constant for specific utilization was estimated to be 0.0070 ± 0.0007 min^{-1} in this area, using back-of-the-brain as a reference region (Table 1). A similar brain disposition of L-(β-11 C)DOPA radioactivity was shown although the rate constant was higher, 0.0120 ± 0.0010 min^{-1} (Table 2).

The rate constant was decreased by 50% for 5-hydroxy-L-(β-11 C)tryptophan when administered together with unlabelled 5-hydroxy-L-tryptophan in a dose of 4 mg/kg (Table 1). The rate constant remained unchanged when the 5-hydroxy-L-(β-11 C)tryptophan radioactivity was given together with 4 mg/kg of L-DOPA but decreased slightly with 15 mg/kg of L-DOPA. Administration together with a L-DOPA dose of 30 mg/kg resulted in a 39 percent reduction of the rate constant of 5-hydroxy-L-(β-11 C)tryptophan utilization (Table 1 and Fig. 1).

A decrease in the rate constant for striatal utilization of L-(β-11 C)-DOPA derived radioactivity as compared with the baseline study was only observed when the radioactivity was given together with 30 mg/kg of unlabelled 5-hydroxy-L-tryptophan and L-DOPA. The rate constants decreased by 10 and 31%, respectively (Table 2).

Discussion

The enzymes decarboxylating 5-hydroxy-L-tryptophan and L-DOPA to serotonin and dopamine, respectively, were argued to be identical 20 years ago (Christensen et al., 1972) and thus collectively named L-aromatic amino acid decarboxylase (AADC). The decarboxylases in rat brain exhibited a sevenfold divergence in relative specific activity when their distribution in subcellular fractions were compared. The regional distribution of the two decarboxylases did not parallel each other. The ratio of L-DOPA-decarboxylase activity over 5-hydroxy-L-tryptophan decarboxylase activity was 8 in the striatum; 7 in hypothalamus, hippocampus and frontal grey; and only two in cerebellum (Sims

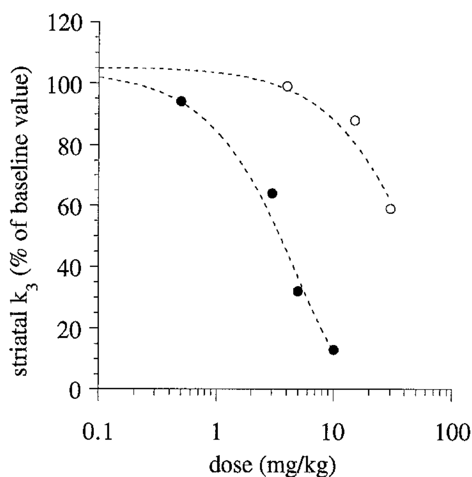

Fig. 1. Diagram showing the striatal rate constant for decarboxylation of 5-hydroxy-L-(β-11 C)tryptophan after pretreatment with various doses of 5-hydroxy-L-tryptophan (filled symbols) and L-DOPA (circles). Values are expressed as percentage of the corresponding baseline investigation

et al., 1973). Additional considerations are required in order to compare these in vitro information with the results of the present and previous investigations performed in vivo with PET (Hartvig et al., 1992; Tedroff et al., 1992 a). According to Michaelis-Menten kinetics, a constant fraction of available tracer is turned over for each time unit when the concentration of tracer available for conversion is well below the affinity constant, Km. In the case of low masses of 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA being administered, the selective striatal radioactivity increase, i.e., k 3 will be directly proportional to the maximal velocity of what is assumed to be the activity of AADC.Using tracer conditions, only a small difference in the rate constants for striatal radioactivity increase was measured for 5-hydroxy-L-(β-11 C)-tryptophan and L-(β-11 C)DOPA, respectively. Therefore, the present results do not confirm the large differences in decarboxylase activity found in vitro for the two substrates.

On the other hand, the present study with PET in the Rhesus monkey brain showed a capacity-limited utilization in striatum as seen as a lower decarboxylation rate for both substrates when administered together with unlabelled amino acid. The capacity limitation was more pronounced for 5-hydroxy-L-tryptophan, with a lower rate constant seen with an amino acid load in the range 8 to 10 ten times lower than that of L-DOPA. The resolution of the used PET camera systems, the small volume of the monkey brain and relatively much lower radioactivities measured did not allow quantitation of decarboxylation rate in other brain areas except striatum. It must be pointed out that PET only measured total changes in radioactivity including events occurring both intra- and extra-neuronally. It is also plausible that utilization of 5-hydroxy-L-(β-

11 C)tryptophan in striatum as measured with PET does not occur specifically in serotonergic neurons but merely in all AADC containing neurons that express specific transport systems for the amino acid. This was supported by the finding of a reduced utilization of both 5-hydroxy-L-(β-11 C)tryptophan and L-(β-11 C)DOPA on the lesioned side in a monkey with an unilateral MPTP-lesion of the striatum (Hartvig et al., 1992).

It has generally been stated that the decarboxylation cannot be modulated by neuronal activity. This statement probably requires re-evaluation since recent investigations have shown the AADC activity in rat retina to be modulated by various factors such as light and dark, or by dopaminergic or alpha-adrenergic drugs (Rosetti et al., 1989, 1990). An upregulation of AADC has also been shown following the administration of dopaminergic receptorantagonists (Zhu et al., 1992). Higher dopamine synthetic rate was measured in Parkinsonian patients with fluctuating symptoms as compared to non-fluctuating disease (Tedroff et al., 1992 b). Another possible coupling between dopamine release and modulation of AADC activity has also been demonstrated with PET as 6 R-L-erythro-5,6,7,8-tetrahydrobiopterin, a co-factor for tyrosinehydroxylase as well as inducer of dopamine release (Koshimura et al., 1990), elevated the rate constant for striatal decarboxylation of L-DOPA (Watanabe et al., 1991). This modulation of decarboxylation rate is of substantial interest in diseases characterized by transmitter deficiencies and for the development of pharmacological tools to bring about this modulation.

The present study demonstrated a mass effect on 5-hydroxy-L-tryptophan utilization at fairly low concentrations. The rate constant for striatal utilization of 5-hydroxy-L-(β-11 C)tryptophan was halved at a 5-hydroxy-L-tryptophan dose of about 4 mg/kg. On the other hand, the striatal utilization of 5-hydroxy-L-(β-11 C)tryptophan or L-DOPA was unchanged at simultaneous L-DOPA doses up to 30 mg/kg. This difference must be interpreted in terms of different affinity for transport, for AADC or the availability for enzymes. One possible explanation might be a difference between the striatal pool sizes of 5-hydroxy-L-tryptophan and L-DOPA, respectively. However, in the steady state the concentrations of endogenous 5-hydroxy-L-tryptophan and L-DOPA (Miwa et al., 1985) were negligable compared with the concentrations reached with the used doses. Most likely, the substrates compete in both serotonergic and dopaminergic neurons for a similar enzyme which has a difference in affinity for the two substrates. A competition for neuronal transport cannot be excluded and a transport competition over the blood brain barrier was also measured as lower brain uptake when the tracer was given together with high doses of precursor amino acid (cf. Tedroff et al., 1992 a). On the other hand, low doses in the µg/kg range of unlabelled amino acid together with tracer elevated tracer uptake somewhat although significantly in humans (Reibring et al., 1992). The effect was tentatively explained by a saturation of the enzymatic blood brain barrier.

The observation of a mass effect on decarboxylation of 5-hydroxy-L-tryp-

tophan may have therapeutic implications. In order to increase serotonergic activity in the brain, large doses of tryptophan or 5-hydroxy-L-tryptophan have been tried (van Praag and de Haan, 1980). Due to the mass effect the decarboxylase may then only give a limited yield of serotonin. Furthermore, 5-hydroxy-L-tryptophan is also an inhibitor of tryptophan hydroxylase (Kaufman, 1982). This may give a biochemical background for the very mixed therapeutic outcomes occurring in patients with affective disorders given high doses of 5-hydroxy-L-tryptophan (van Praag and de Haan, 1980).

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