Mechanism-based Inactivation of Dopa Decarboxylase by Serotonin*

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Mariarita Bertoldi, Patrick S. Moore, Bruno Maras, Paola Dominici, and Carla Borri Voltattorni

From the Istituto di Chimica Biologica, Facoltà di Medicina e Chirurgia, Università di Verona, Strada Le Grazie, 37134 Verona, Italy, 3Dipartimento di Scienze Biochimiche and Consiglio Nazionale delle Richerche Center of Molecular Biology, Università di Roma “La Sapienza,” 00100 Rome, Italy, and 5Facoltà di Scienze Matematiche, Fisiche e Naturali, Università di Verona, 37134 Verona, Italy

Pig kidney dopa decarboxylase (DDC) expressed in Escherichia coli is a homodimeric enzyme containing one catalytically active pyridoxal 5'-phosphate active site per subunit. In addition to catalyzing the decarboxylation of L-phenylalanine, DDC also reacts with 5-hydroxytryptamine (5-HT), converting it to 5-hydroxyindolacetaldehyde and ammonia. These products have been identified by means of the enzymes alcohol dehydrogenase and glutamate dehydrogenase, together with high performance liquid chromatographic and mass spectrometric analysis. The $K_{cat}$ and $V_{max}$ values of this reaction were determined to be 0.48 mM$^{-1}$ and 0.47 mM, respectively. The NaBH$_4$-reduced enzyme does not catalyze this reaction. Concurrent with this reaction, 5-HT inactivates DDC in both a time- and concentration-dependent manner and exhibits saturation of the rate of inactivation at high concentrations, with $K_c$ and $K_{baet}$ values of 0.40 mM and 0.023 min$^{-1}$, respectively. Protection from inactivation by 5-HT was observed in the presence of the active site-directed inhibitor 3,4-dihydroxyphenylalanine (L-Dopa) and d-a-mino acids and production of their corresponding amines. However, like many other pyridoxal phosphate enzymes, the enzyme also catalyzes a "minor" reaction, referred to as decarboxylation-dependent transamination, which in fact was first observed by studying the effects of pig kidney DDC on a-methyl Dopa (1). A speculative mechanism for the reaction and inactivation consistent with the experimental findings is presented.

The major catalytic activity of the pyridoxal 5'-phosphate (PLP)$^1$-dependent enzyme dopa decarboxylase (DDC; EC 4.1.1.28) consists of the decarboxylation of aromatic amino acids and production of their corresponding amines. However, like many other pyridoxal phosphate enzymes, the enzyme also catalyzes a "minor" reaction, referred to as decarboxylation-dependent transamination, which in fact was first observed by studying the effects of pig kidney DDC on a-methyl Dopa (1). A similar phenomena has been described for DDC when it acts on 1,3,4-dihydroxyphenylalanine (L-Dopa) and m-tyrosine and their a-methyl derivatives (2, 3), L-5-hydroxytryptophan and L-5-hydroxytryptophan (4), and 5-hydroxytryptamine (5-HT, serotonin) (5); with all of the above substrates a progressive loss of decarboxylase activity is observed as a consequence of their interaction with the enzyme. The occurrence of abortive decarboxylation-transamination reactions is not uncommon among PLP-dependent a-decarboxylases (6-9). Mechanistically, 0-Leary and Baughn (2, 3) explained this minor pathway by proposing that the carbanion-quinonoid intermediate formed after elimination of the carboxyl group may be protonated either at the a-carbon atom (from which the carboxy group was eliminated) to give the amine or at the 4-carbon of the coenzyme to give the corresponding aldehyde or ketone and pyridoxamine 5'-phosphate (PMP). Nevertheless, when this abortive reaction was more closely investigated, it was found that it cannot be solely explained by the simple model that was proposed. In fact, the reaction of pig kidney DDC with a-methyl Dopa or 5-HT leads to the production of dihydroxyphenylacetone or 5-hydroxyindolacetaldehyde (5-HIA), respectively, in amounts far exceeding on molar basis that of the coenzyme PLP (10).

The above described abortive reaction has been examined in greater detail using 5-HT as the substrate. Being devoid of decarboxylation events, 5-HT yields a simple model and may also provide some physiological significance, as it is an important neurotransmitter. For these studies, recombinant pig kidney DDC was used, which has been recently cloned and expressed in Escherichia coli (11). This protein possesses two catalytically active coenzyme binding sites per enzyme dimer in contrast to the enzyme purified from tissue, which has 1 mol of PLP/dimer (12). In the latter, the remaining coenzyme is found as an inactive, covalently bound adduct.

In this report, an extensive characterization of the reaction and concomitant inactivation of DDC by 5-HT is presented. These results indicate that a mechanism-based inactivation is responsible for the observed loss of decarboxylase activity in the presence of 5-HT. A putative mechanism to explain these events is described herein.

**EXPERIMENTAL PROCEDURES**

Materials—L-Dopa, L-5-hydroxytryptophan, 5-HT chlorohydrate, 5-hydroxyindole ethyl alcohol (5-HIP, 5-hydroxytryptophol), Hepes, a-ketoglutarate, horse liver alcohol dehydrogenase (EC 1.1.1.1), yeast aldehyde dehydrogenase (EC 1.2.1.5), bovine liver o-glutamic dehydrogenase (EC 1.4.1.3), NAD$^+$ and NADH, protease inhibitors, dithiothreitol, octanesulfonic acid, and PLP were obtained from Sigma. [2-14C]5-HT oxalate was a product of DuPont. All other chemicals were the highest grade commercially available. Data for the determination of $K_{cat}$, $V_{max}$, $K_{aet}$, and $K_c$ were fit to lines with the program Enzfitter.

Enzyme Preparation—Recombinant DDC was purified to homogeneity as described previously (11), except that DEAE-Biogel chromatography was substituted with DEAE-Sephrose FF fast protein liquid
chromatography. Briefly, at room temperature crude extract was loaded on a Mono Q 5/5 column previously equilibrated with 10 mM potassium phosphate buffer, pH 7.4, 0.01 mM EDTA, and 0.1 mM dithiothreitol at a flow rate of 6 ml/min and washed with the same buffer. A linear gradient was then inserted (0–100%, 120 min) with the same buffer containing 150 mM potassium phosphate. Active fractions were pooled and further processed as described.

**Determination of Decarboxylase Activity—**Dopa decarboxylase activity was measured as described by Sherald et al. (12), using the modification of Charteris and John (14). One unit of enzymatic activity is defined as the amount of protein that catalyzes the production of 1 nmol amine/min. The enzyme concentration was determined using an $E_	ext{280}$ of 1.3 $\times$ 10 $^{-3}$ m$^{-1}$ cm$^{-1}$ (15).

**Inactivation Experiments—**DDC (10 $\mu$M) was incubated with various concentrations of 5-HT in 50 mM Hepes, pH 7.5, at 25°C. At various times, aliquots were removed and diluted (usually 100-fold) into a normal assay mixture containing 2.2 mM L-Dopa, and residual enzymatic activity was determined as described above. In protection experiments, the indicated substrate analog was included prior to the addition of 5-HT.

**Determination of Aldehyde—**Aldehyde formation during the reaction of DDC with 5-HT was assayed by coupling the aldehyde produced to the NADH-dependent alcohol dehydrogenase-catalyzed reaction. Routinely, a 0.3-ml reaction mixture contained 10 $\mu$M DDC, 96 $\mu$M of alcohol dehydrogenase, and 300 $\mu$M NADH in 50 mM Hepes, pH 7.5. The reaction was initiated by the addition of 24 $\mu$M of 50 mM 5-HT. The amount of aldehyde produced during the course of the reaction was measured by the decrease in absorbance at 340 nm due to the conversion of NADH to NAD$^+$.

Assays with aldehyde dehydrogenase were also performed. In these experiments, the reaction mixture contained 10 $\mu$M DDC, 8 $\mu$g of aldehyde dehydrogenase, and 200 $\mu$M NAD$^+$ in 50 mM Hepes, pH 7.5, in a final volume of 0.3 ml. The reaction was initiated by the addition of 24 $\mu$M of 50 mM 5-HT, and the increase in absorbance at 340 nm due to NAD$^+$ reduction was monitored. All measurements were made at 25°C.

**Assay for Ammonia—**Production of ammonia by the reaction of DDC with 5-HT was determined by a spectroscopic assay using glutamate dehydrogenase, which forms glutamate from $\alpha$-ketoglutarate and ammonia with the concomitant conversion of NADH to NAD$^+$. A 0.3-ml reaction mixture contained 10 $\mu$M DDC, 140 $\mu$g glutamate dehydrogenase, 1 $\mu$M $\alpha$-ketoglutarate, and 300 $\mu$M NADH in 50 mM Hepes, pH 7.5, at 25°C. The reaction was initiated with 24 $\mu$M of 50 mM 5-HT and monitored at 340 nm. Calibration was performed with standard ammonia solutions from Sigma.

**Assay for $\text{H}_2\text{O}_2—$**H$_2$O$_2$ was assayed by measuring the oxidation of 2,2′-azino-bis-(3-ethylbenzthiazoline)sulfonate (Abs$	ext{max}$: 385 nm; $\epsilon$ 18,000) in the presence of horseradish peroxidase (16). Calibration was performed with a standard solution of H$_2$O$_2$.

**Detection of PMP with Apospartate Aminotransferase—**Determination of PMP after reaction with 5-HT was performed according to the method of Bossa and Barra (17). Samples were prepared by reduction with NaBH$_4$, followed by heat denaturation.

**Enzyme Radiolabeling—**DDC (10 $\mu$M) was incubated with 4 nmol [2-14C]5-HT (1.95 $\times$ 10$^6$ cpm/mmol) in 50 mM Hepes, pH 7.5, at 25°C in a final volume of 1.4 ml. At intervals, 350-$\mu$l aliquots were withdrawn; after removal of excess reagents by PD-10 gel filtration followed by extensive conventional dialysis, the samples were counted for residual radioactivity in 2 ml of Beckman Instruments Ready Gel liquid scintillation mixture in a Beckman Instruments LS 1801 liquid scintillator counter.

**High Performance Liquid Chromatographic Separation of the Products of the Reaction of DDC with 5-HT—**All separations were done isocratically on an LKB instrument equipped with a 5-$\mu$m Lichrospher 100 RP-18 column. Two different solvent conditions were used: H$_2$O/ methanol/acetic acid (75:2.4:1) (v/v/v) containing 6 mM octanesulfonyl acid or 5% acetonitrile and 1% acetic acid with 1 mM tetrabutyl ammonium phosphate. For both systems, the flow rate was 1 ml/min, and detection was at 280 nm. After incubation of 10 $\mu$M DDC with 4 mM 5-HT for 5–180 min in 50 mM Hepes at 25°C in the absence or presence of alcohol dehydrogenase and NADH, the reaction was stopped by heating for 2 min at 100°C and then centrifuged to remove the precipitated protein. The supernatants and appropriate blanks were run.

**Mass Spectrometry—**Analysis of 5-HIP and the unknown sample were made by combined liquid chromatography/mass spectrometry with direct liquid introduction. The mass spectrometer (HP 5988; Hewlett-Packard Co., Palo Alto, CA) was coupled with a Particle-Beam introduction system (electron energy 70, eV; ion source, 250°).

**Spectroscopy—**Absorption measurements were carried out using a Jasco V-550 spectrophotometer. Fluorescence spectra were taken with a Kontron SFM 25 spectrofluorometer using 5-nm bandwidths on both sides at a protein concentration of 0.6 $\mu$M. CD spectra were obtained with a Jasco 710 spectropolarimeter at a protein concentration of 0.8–1 mg/ml using a cuvette with a 1-cm path length. Routinely, five spectra were recorded at a scan speed of 50 nm/min using a bandwidth of 2 nm and averaged automatically.

**RESULTS**

**Changes in Absorption Spectrum—**Fig. 1 shows the change in the visible spectrum of DDC versus time during its interaction with 5-HT. Addition of 5-HT to DDC at pH 7.5 causes the immediate appearance of an absorption band at 385 nm and a decrease of the absorbance at 335 nm. The 385-nm peak then decreases in a time-dependent fashion, concomitant with the increase in absorption in the region around 340 nm. A more precise description of the spectral events occurring in the region below 350 nm is hampered by the large absorbance of the indolic compound at 280 nm.

Addition of 4 mM 1,5-hydroxytryptophan to DDC results in the immediate appearance of the absorption at 420 nm and a slight decrease at 335 nm. After the time required for complete decarboxylation, the 420-nm band disappears, and a 385-nm absorption peak appears, which decreases in time-dependent fashion similar to that described for 5-HT (data not shown).

**Product Formation—**Reaction of pig kidney holo-DDC with 5-HT causes the concomitant production of aldehyde and ammonia, as revealed by coupled assay systems using alcohol dehydrogenase and glutamate dehydrogenase, respectively (Fig. 2). The initial velocity is directly dependent on DDC concentration and dependent on 5-HT concentration according to saturation kinetics (data not shown). The $K_m$ for 5-HT was determined to be 0.47 $\pm$ 0.01 mM, with a $V_{max}$ of 0.48 $\pm$ 0.02 nmol of aldehyde or ammonia/min/nmol of dimeric enzyme; thus, the calculated $K_{cat}/K_m$ was found to be 1.02 min$^{-1}$ $\times$ 1 mmol. No aldehyde formation is observed when reaction of DDC with 5-HT is coupled with aldehyde dehydrogenase in the presence of NAD$^+$, suggesting that the aldehyde formed is not acetaldehyde or an aliphatic aldehyde but an aromatic aldehyde, possibly 5-HIA.

The production of 5-HIA from 5-HT by DDC was corroborated by high performance liquid chromatographic and mass spectrometric analysis. DDC was incubated with 5-HT in the presence of alcohol dehydrogenase and NADH; under these conditions, the unstable 5-HIA was converted in situ into the more stable compound 5-HIP. Aliquots were removed at time intervals and heat inactivated. Fractionation of the superna-

![FIG. 1. Time-dependent spectral changes occurring on addition of 5-HT to DDC. 4 mM 5-HT was added to a mixture containing 10 $\mu$M DDC in 50 mM Hepes, pH 7.5. Spectra were then recorded after 3, 7, 12, 20, 33, 50, and 120 min. The spectra of the enzyme is included for reference (---).](http://www.jbc.org/content/23955/1/23955/F1)
tion of H₂O₂ was observed during the reaction of DDC with 5-HT. After a 2-h incubation of DDC with 5-HT, less than 5% of the product undergoes a further reaction in a subsequent step, consistent with a mechanism in which the decarboxylation of the normal product of decarboxylation, 5-HT. This finding is not prevented if 5-HIA or ammonia is continuously removed from the incubation mixture by addition of NADH and alcohol dehydrogenase or glutamate dehydrogenase, respectively. Protection from inactivation by 5-HT, however, was observed when the reaction is carried out in the presence of the active site-directed inhibitor n-Dopa (Ref. 4 and Fig. 3).

After 3 h the enzyme is completely (>95%) and irreversibly inactivated. There is no observable return of activity when 5-HT is removed by either dialysis or gel filtration. Incubation of the inactivated enzyme with PLP after the removal of 5-HT does not result in a return of decarboxylase activity, indicating that loss of the coenzyme is not responsible for the inactivation. There is no discernible change in the observed apparent subunit molecular weight, as determined by SDS-polyacrylamide gel electrophoresis; thus, gross modification of the enzyme due to covalent cross-linking of subunits can be excluded.

**Stoichiometry of Radiolabeling and Stability of the Label—** During inactivation of DDC by 5-HT, there is a progressive incorporation of [2-¹⁴C]5-HT into the protein that parallels the loss of enzymatic activity. After almost complete inactivation by a 3-h reaction of DDC with [2-¹⁴C]5-HT and passage on a desalting column, 3.6 nmol of the label was incorporated per nmol of dimeric enzyme. This material was then divided in two portions. One was diazylated against 50 mM Hepes, pH 7.5, or 5 mM guanidine hydrochloride. The other was first reduced with NaBH₄ and then dialyzed against 50 mM Hepes, pH 7.5, or 5 mM guanidine hydrochloride. In all cases, the same result was obtained; i.e. about 45% of radioactivity was released. The remaining bound label was found to be 1.94 mol/mol of dimeric enzyme. In a separate experiment, a 50% inactivated enzyme shows 1.09 mol of [¹³C]dopa covalently bound per dimer. Thus, inactivation of DDC by 5-HT involves the incorporation of one molecule of inhibitor per enzyme subunit. This stoichiometry is consistent with the presence of one PLP active site per monomer for recombinant DDC, a point recently ascertained (11).

**Properties of the Inactive Enzyme—** After gel filtration, the 5-HT inactivated enzyme is characterized by an absorption band at 340 nm (Fig. 4A) associated with a positive dichroic signal at the same wavelength (Fig. 4B). The positive signals in the aromatic region remain unaltered with respect to the native protein (Ref. 11 and Fig. 4B). This adduct absorbing at 340 nm does not appear to be related to compounds previously described for other PLP-dependent enzymes (18, 19), since treatment at pH 5 or 11 did not restore either the native spectral properties or enzymatic activity. The 340-nm absorb-
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Fig. 4. Spectroscopic properties of 5-HT inactivated DDC. A, absorbance spectra; B, CD spectra; C, emission fluorescence spectra (excitation at 340 nm). The native enzyme shows a fluorescence of about 10 relative units when carried out under the same conditions. All spectra were carried out in 50 mM Hepes, pH 7.5, as described under "Experimental Procedures."

**DISCUSSION**

The first notable finding of these studies is that 5-HT, produced by decarboxylation of L-5-HTP by pig kidney DDC, undergoes a PLP-assisted reaction catalyzed by the same enzyme, which results in the loss of decarboxylase activity. 5-HT, directly added to DDC or formed at the active site of the enzyme following decarboxylation of L-5-HTP, immediately induces a spectral modification of the enzyme-bound coenzyme, which is followed by further time-dependent changes. This behavior strongly suggests an active site-directed event and the occurrence of a reaction between 5-HT and DDC. By means of the enzymes alcohol dehydrogenase and glutamate dehydrogenase, together with high performance liquid chromatographic and mass spectroscopic analysis, the products of this reaction have been identified as 5-HIA and ammonia. Kinetic data of the reaction of DDC with 5-HT show that: 1) 5-HT inactivates in a time- and concentration-dependent manner and saturates at high concentrations of amine; 2) protection of inactivation by 5-HT is exerted by d-Dopa; 3) inactivation occurs at a rate no faster than the rate of 5-HT consumption; 4) there is irreversible covalent bond formation, with no return of activity after removal of 5-HT and addition of coenzyme; and 5) since no lag time is observed during the inactivation reaction, it seems unlikely that there is release of an activated species prior to enzyme inactivation. Taken together, these results indicate that 5-HT is both a substrate and a mechanism-based inactivator of DDC.

Studies have been undertaken to identify and characterize a peptide containing the modified residue. Although elucidation of the precise pathway of mechanism-based inactivation of DDC by 5-HT will require structural characterization of the 340-nm adduct, all the observations reported here are consistent with the mechanism shown in Scheme I. 5-HT is accepted by the active site of DDC, where it forms an external Schif's base with PLP (I). Subsequent deprotonation at α-C generates a quinonoid intermediate (II). The α,β-unsaturated intermediate (II) may be formed by transfer of a proton from β-C of 5-HT to 4-C of the coenzyme (intramolecular process) or by a protonation and deprotonation at 4-C of the coenzyme and at β-C of 5-HT, respectively (intermolecular process, as shown in Scheme I), assisted by amino acid residues of the enzyme. The next step in the pathway, III → IV, requires an oxidation, which could be carried out by molecular oxygen, a yet unidentified oxidizing group of the enzyme, or some other oxidizing species generated during the course of the reaction. Addition of the active site lysyl ε-NH₂ group, K303 (20), to the pyridoxaldehyde carbon of structure IV and protonation of 5-HT β-C by a general acid produces the imine complex (V). The 5-HT imine (VI) eliminated from complex V by decomposition of the tetra-hedral adduct at the C-4’ of PLP, then undergoes hydrolysis to 5-HIA and ammonia. It can be hypothesized that inactivation occurs by attack of a nucleophile in the enzyme on V to yield Va. This structure is consistent with our observation that 5-HT-inactivated DDC contains both the coenzyme spectroscopic (absorbance, fluorescence, and circular dichroism) features and the radiolabel.

The mechanism proposed here does not appear to proceed by any of the known pathways for the principal types of PLP-catalyzed reactions. The oxidative step introduced in this mechanism requires a more detailed investigation. In this regard, it must be kept in mind that although the presence of a second cofactor, pyrroloquinoline quinone, has been claimed (21), no such cofactor could be detected during determination of the complete primary structure of the tissue-purified enzyme by Edman degradation (20). Nevertheless, it cannot be excluded that a modified (or reactive) aromatic amino acid residue behaving as a cofactor (22) and therefore responsible for the oxidation step escaped detection during protein sequence analysis.

Although the small percentage of PMP found after reaction with 5-HT may in fact be due to a half-transamination reaction, this pathway can be ruled out as the major route of inactivation on the basis of the molar ratio of product/coenzyme and the lack...
of reactivation on the addition of PLP. Although it is possible that transaminating events do occur, they would appear to be quite infrequent. The finding that 5-HT behaves as a mechanism-based inactivator of DDC may be useful in the design of DDC-directed inhibitors that demonstrate exclusive selectivity of their target. This could be relevant for therapy of diseases such as Parkinson’s disease and schizophrenia, which are characterized by an aberrant production of catecholamines. For a productive structural guide to design new DDC enzyme-activated inhibitors, detailed knowledge of this minor catalytic function of DDC may be required. In particular, since this “minor” reaction may not have the same substrate specificity as the major catalytic activity of the enzyme, studies using other catecholic and indolic compounds have been undertaken.

Moreover, inactivation events of the type described here may have some physiological relevance. As has been already described for inactivation of d-amino acid transaminase by substrates (19, 23), inactivation of DDC by 5-HT could not be detected under conditions usually used for kinetic assays of decarboxylase activity, i.e., a short incubation time with dilute enzyme concentrations. However, DDC slowly loses activity when relatively high concentrations of the enzyme are exposed to 5-HT for relatively long periods of time. Since DDC in the cell may be at a concentration of the same order of magnitude as that used in the present study and may exist together with 5-HT and/or other decarboxylation products for an extended period, the possible 5-HT-induced loss in the catalytic efficiency of DDC in the cell could provide the basis of a control mechanism.

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