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Pharmacokinetics of L-dopa

Special reference to food and aging

Abstract According to our data in rats, peripheral 3.4-dihydroxyphenylalanine (DOPA) kinetics are similar to striatal DOPA and dopamine kinetics. The measurement of plasma l-3.4-dihydroxyphenylalanine (L-dopa) concentration is thus useful to predict dopamine kinetics in the striatum and to treat the motor fluctuations of parkinsonian patients. In patients with Parkinson's disease (PD), long-term L-dopa therapy accelerated DOPA absorption and steepened features of L-dopa pharmacokinetics. In the senile-onset group, the pharmacokinetic pattern did not change even after long-term L-dopa therapy. The frequency of motor fluctuations is much lower in senile-onset patients with PD than in middle-onset patients. Differences in the pattern of L-dopa pharmacokinetics in the two groups may explain why the senile-onset group rarely develops 'wearing-off', even after long-term L-dopa therapy. L-dopa is transported by a saturable active transporter system, called the LNAA (large neutral amino acid) system, in the gut and blood brain barrier. L-dopa absorption is thus affected by food intake, especially a protein-rich diet. The slope of the time-concentration curve for L-dopa administered before a meal is steeper than if it is administered after a meal. Considering that pulsative stimulation of L-dopa may cause motor fluctuations, L-dopa should be given after meals whenever possible, even if it necessitates a higher L-dopa dose.

Key words Parkinson's disease · absorption · LNAA system · L-dopa · aging

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Introduction

L-dopa is the gold standard of antiparkinsonian pharmacotherapy; however, motor fluctuations, such as 'wearing-off', often develop during long-term L-dopa therapy. The definition of wearing-off is fluctuation of parkinsonian symptoms in line with L-dopa pharmacokinetics [1]. Therefore, the pharmacokinetics of L-dopa are very important in treating patients with Parkinson's disease (PD). The half-life ($T_{1/2}$) of L-dopa is short (1 h) and its absorption is greatly influenced by food intake and aging. Thus, these factors make PD therapy complicated.

Because L-dopa is used with a DOPA decarboxylase inhibitor (DCI), catechol-O- methyltransferase (COMT) is an important enzyme influencing peripheral L-dopa metabolism and L-dopa effects on parkinsonian symptoms. Therefore, nowadays, knowledge about L-dopa pharmacokinetics is increasingly important in treating PD.

In the present review, DOPA and dopamine kinetics in blood and brain, and food and aging effects on the pharmacokinetics of L-dopa are discussed. The correlation between DOPA and 3-O-methyl DOPA is also featured.

L-dopa and dopamine kinetics in peripheral blood and striatum

L-dopa pharmacokinetics are very important when treating PD, and the L-dopa concentration can be measured in blood. Dopamine kinetics in the brain are more

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critical than peripheral DOPA kinetics; however, it is very difficult to measure dopamine in the brain of PD patients in vivo. Therefore, it is important to know how closely peripheral L-dopa kinetics reflect dopamine kinetics in the brain, especially in the striatum.

We measured DOPA and dopamine concentrations in the blood and striatum of normal rats after single and repeated L-dopa administration (Fig. 1) [2]. DOPA and dopamine kinetics in the striatum were well correlated with peripheral DOPA kinetics. We also showed that repeated L-dopa (L-dopa 50 mg/kg + benserazide 12.5 mg/kg) administration for 28 days increased the area under the concentration-time curve (AUC) and shortened $T_{1/2}$ and time to maximum plasma concentration (T_{max}) for both peripheral DOPA and central DOPA and dopamine in normal rats.

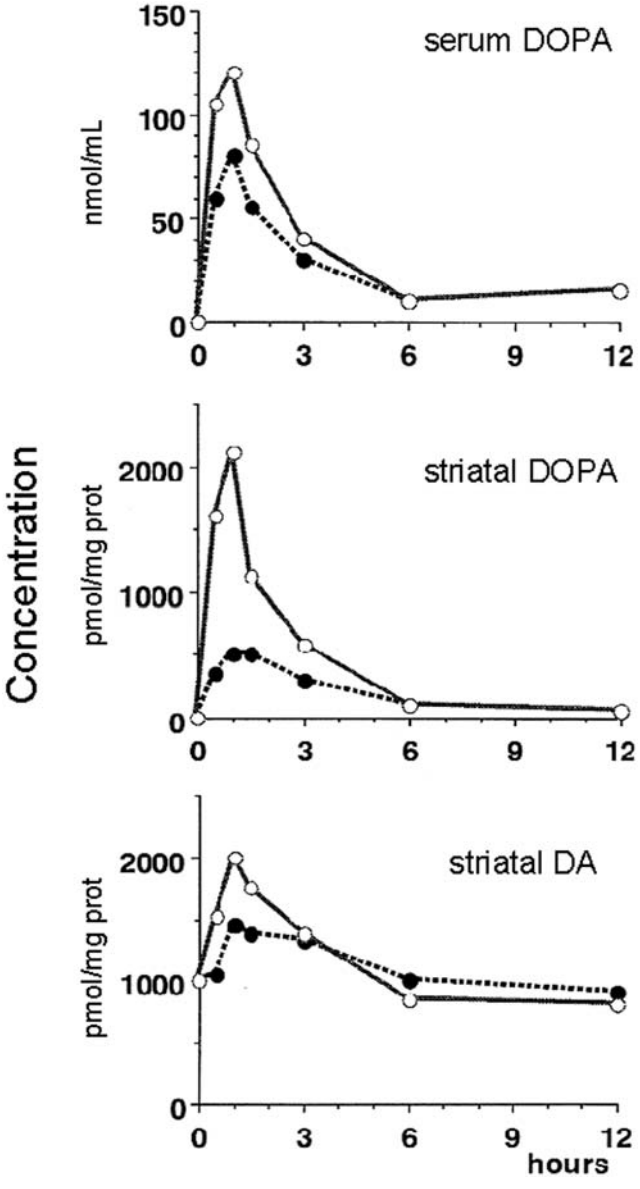

Fig. 1 Time course of serum L-dopa and striatal DOPA and dopamine (DA) after single and repeated administration of L-dopa in rats (-----●----- single administration, ——○—— repeated administration). Time course of serum L-dopa concentration is similar to that of striatal DOPA and dopamine. Repeated L-dopa administration increases C_{max} and AUC and shortens $T_{1/2}$

L-dopa pharmacokinetics in PD patients

PD patients were given L-dopa 100 mg plus benserazide 25 mg orally at 8:00 am after an overnight fast. Plasma DOPA concentrations were measured prior to treatment (baseline) and at 15 min, 30 min, 1 h, 2 h, 3 h and 4 h after medication using HPLC-ECD (L-DOPA test) [3]. In PD patients (onset age < 60 years old) who had received L-dopa therapy for longer than 5 years, the $T_{1/2}$ and T_{max} of L-dopa were much shorter than those measured in PD patients with a duration of L-dopa therapy of less than 5 years (Fig. 2a). In addition, the AUC was greater in the longer therapy duration group (Fig. 2a). These changes in the pharmacokinetics of L-dopa were significantly correlated with duration of L-dopa therapy and dose of L-dopa. A 4-year longitudinal study showed that four of five patients displayed an increased AUC and shortened $T_{1/2}$ and T_{max} at the second assessment [4]. Patients who demonstrated the wearing-off phenomenon had a significantly higher maximum plasma concentration (C_{max}) and greater AUC, and significantly shorter $T_{1/2}$ and T_{max} than those who did not display wearing-off. The pattern of L-dopa kinetics in those with wearing-off was obviously steeper than that of patients without wearing-off.

It is reasonable to suppose that these changes in pharmacokinetic features are due to changes in absorption or metabolism of L-dopa. Decreased metabolism of L-dopa can explain the increase in AUC and C_{max}, but cannot explain the shortening of T_{max} and $T_{1/2}$. Increased absorption, however, can explain the increase in AUC and C_{max} and the shortening of T_{max}. If the absorption system is saturable, increased absorption can also explain the shortening of $T_{1/2}$. L-dopa is transported by the saturable active transport system called the LNAA (large neutral amino acid) system in the gut and blood brain barrier (BBB) [5]. Furthermore, intravenous administration has demonstrated that the distribution and elimination of L-dopa was not changed after long-term L-dopa therapy [6]. Both monoamine oxidase (MAO) activity and COMT activity in the brain are unaffected by long-term L-dopa administration [2, 7]. Therefore, our results show that long-term L-dopa therapy alters its own kinetics by increasing the absorption of L-dopa. As early as 1971, Abrams et al. reported that long-term L-dopa therapy increases its own absorption [8]. At that time, L-dopa therapy involved L-dopa administered without a DCI, and liver DOPA decarboxylase (DDC) ac-

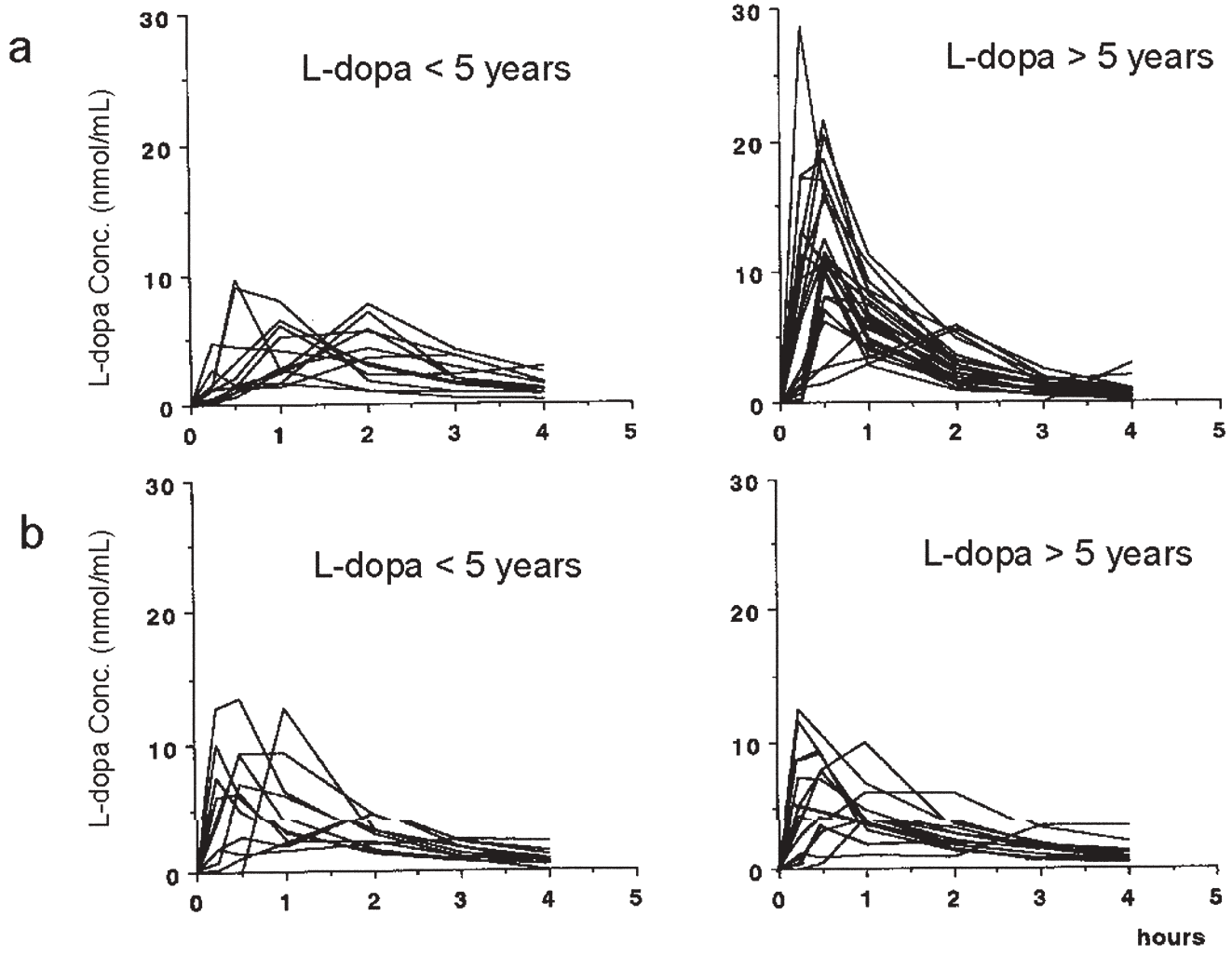

Fig. 2 L-dopa pharmacokinetics in parkinsonian patients with disease onset at < 60 years of age (**a**) and > 60 years of age (**b**) according to duration of L-dopa therapy. Long-term L-dopa therapy (> 5 years' duration) increases C_{max} and AUC and shortens $T^1/_2$. Pharmacokinetic changes after long-term L-dopa therapy are not seen in the senile-onset group

tivation was suggested as a cause of this phenomenon [9]. In fact, long-term L-dopa administration activates DDC in the liver but not in the brain, and no data has been published in the gut [10]. Our data was obtained using L-dopa with a DCI. It has been reported that plasma DDC is induced by administration of L-dopa with a DCI [11]. Therefore, the DDC activation theory cannot explain our results. We propose that long-term L-dopa therapy may induce the LNAA transporter system.

Aging and L-dopa pharmacokinetics

Although long-term L-dopa therapy steepened L-dopa kinetics, this change was less marked in senile-onset patients (onset age > 60 years old) than in younger onset patients (Fig. 2b). The frequency of wearing-off is much lower in senile-onset patients than in younger onset patients [12]. This suggests that changes in peripheral L-dopa pharmacokinetics after long-term therapy certainly contribute to the clinical expression of wearing-off.

Food and acidity effects on L-dopa absorption

L-dopa shares a saturable transporter system with other LNAA such as phenylalanine. Therefore, competitive inhibition of L-dopa absorption occurs with rising concentrations of neutral amino acids derived from food (Fig. 3). The L-dopa pharmacokinetic profile is steeper when intake occurs before a meal than after a meal. Considering that pulsative stimulation of L-dopa may cause motor fluctuations, L-dopa should be given after meals

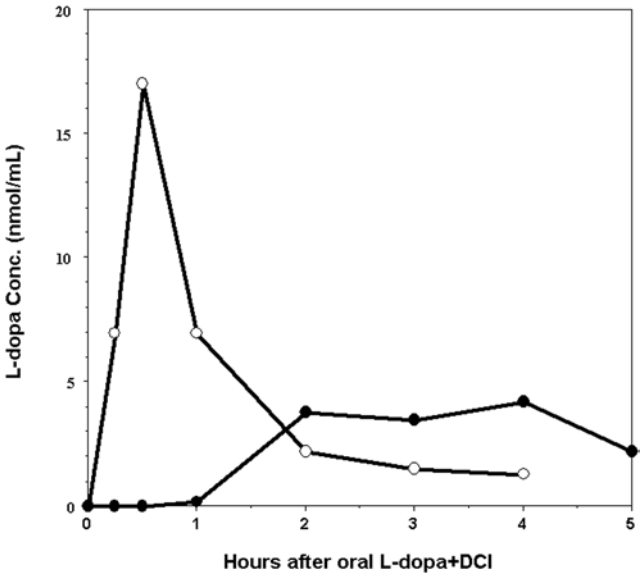

Fig. 3 Effects of a meal on L-dopa kinetics in a 55-year-old female patient with Parkinson's disease (○ L-dopa administration before meal, ● L-dopa administration after meal). C_{max} and AUC were markedly decreased and T_{max} was increased by L-dopa administration after a meal

whenever possible, even if it necessitates a higher L-dopa dose.

L-dopa is known to be easily soluble in acid environments and the pH of gastric juices affects the absorption of L-dopa. Fig. 4 shows the results of an L-DOPA test from a 65-year-old male patient with PD. The first test was performed using the ordinary method and, 1 year later, the second test was performed using duodenal infusion of L-dopa. Although the pH of duodenal juice is high, absorption was not impaired because L-dopa was administered dissolved in water. When it is dissolved in water, L-dopa is absorbed rapidly and adequately, even in alkaline duodenal juice.

L-dopa and 3-O-methyl DOPA

The main metabolite of DOPA is dopamine, formed by decarboxylation, and the COMT pathway is usually a rather minor pathway in the metabolism of DOPA. However, when L-dopa is used with a DCI, the COMT pathway is activated and a large amount of 3-O-methyl DOPA (3OMD) is synthesized. The $T_{1/2}$ of 3OMD (16 h) is much longer than that of DOPA; thus, the plasma concentration of 3OMD increases according to long-term L-dopa therapy (Fig. 5). Although the plasma concentration of 3OMD is usually closely correlated to daily L-dopa dose (Fig. 6), some patients show very low 3OMD concentrations relative to the L-dopa dose and plasma L-dopa concentration. These patients may obtain a good response with a COMT inhibitor. As COMT inhibitors will be approved for PD therapy in Japan this year, it will be important to assess this hypothesis soon.

3OMD also uses the LNAA transporter system in the gut and BBB. After protein-rich meals, competition between L-dopa, dietary LNAA and 3OMD for gut and BBB transport may further contribute to motor fluctuations.

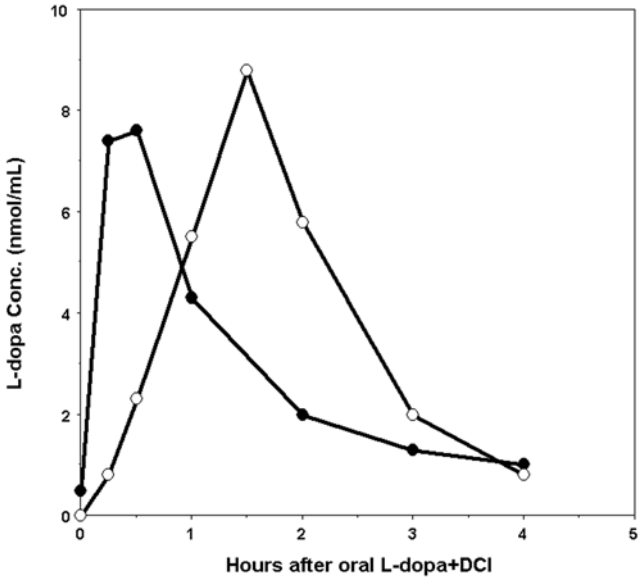

Fig. 4 Effects of duodenal infusion of L-dopa in a 65-year-old male patient with Parkinson's disease (○ L-dopa administration by tablet orally, ● L-dopa administration by duodenal infusion in water suspension). L-dopa concentration is rapidly and adequately increased by duodenal infusion

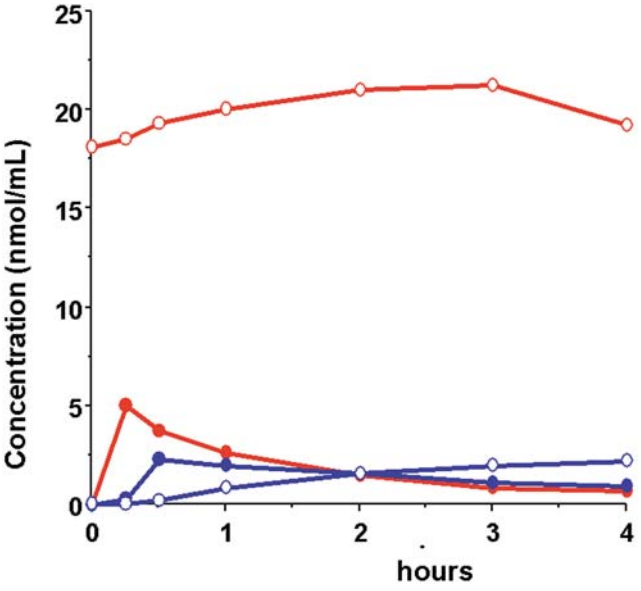

Fig. 5 Plasma concentration of dopa and 3OMD in PD patients (○ concentration of 3OMD, ● concentration of dopa, red line: long-term L-dopa therapy, blue line: L-dopa initial use)

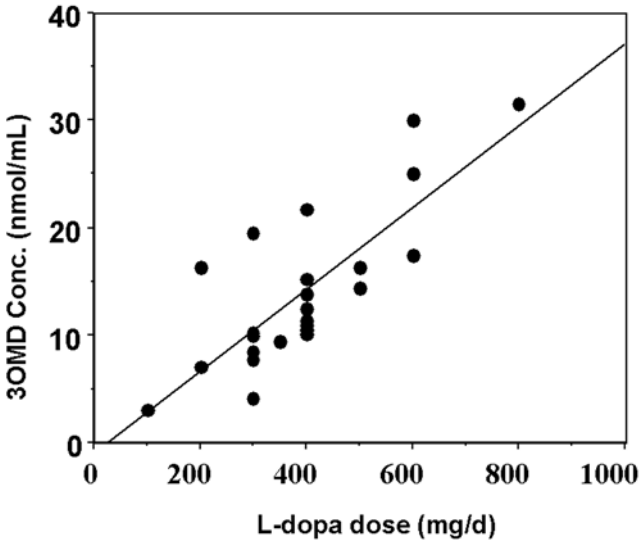

Fig. 6 Relationship between L-dopa daily dose and plasma concentration of 3OMD in PD patinets

Following L-dopa administration without a DCI, the plasma dopamine concentration is greatly increased and the 3OMD concentration is very low; however, L-dopa administration with a DCI results in synthesis of a large amount of 3OMD in plasma (Fig. 7) by activating the COMT pathway. If L-dopa is administered in combination with both a DCI and a COMT inhibitor, new metabolic pathways may be activated such as enhanced quinine formation [13].

Conclusion

Peripheral L-dopa kinetics closely reflects dopamine kinetics in the striatum so that measurements of L-dopa kinetics are useful for treating patients with PD. L-dopa is transported by a saturable active transporter system (LNAA system) in the gut and BBB. Onset age of PD, treatment duration, and food are greatly influence peripheral L-dopa kinetics. Food and onset age decrease C_{max} and prolong T_{max} and $T_{1/2}$. When L-dopa is administered with a DCI, the COMT pathway is activated and the COMT inhibitor becomes an important factor for peripheral L-dopa kinetics.

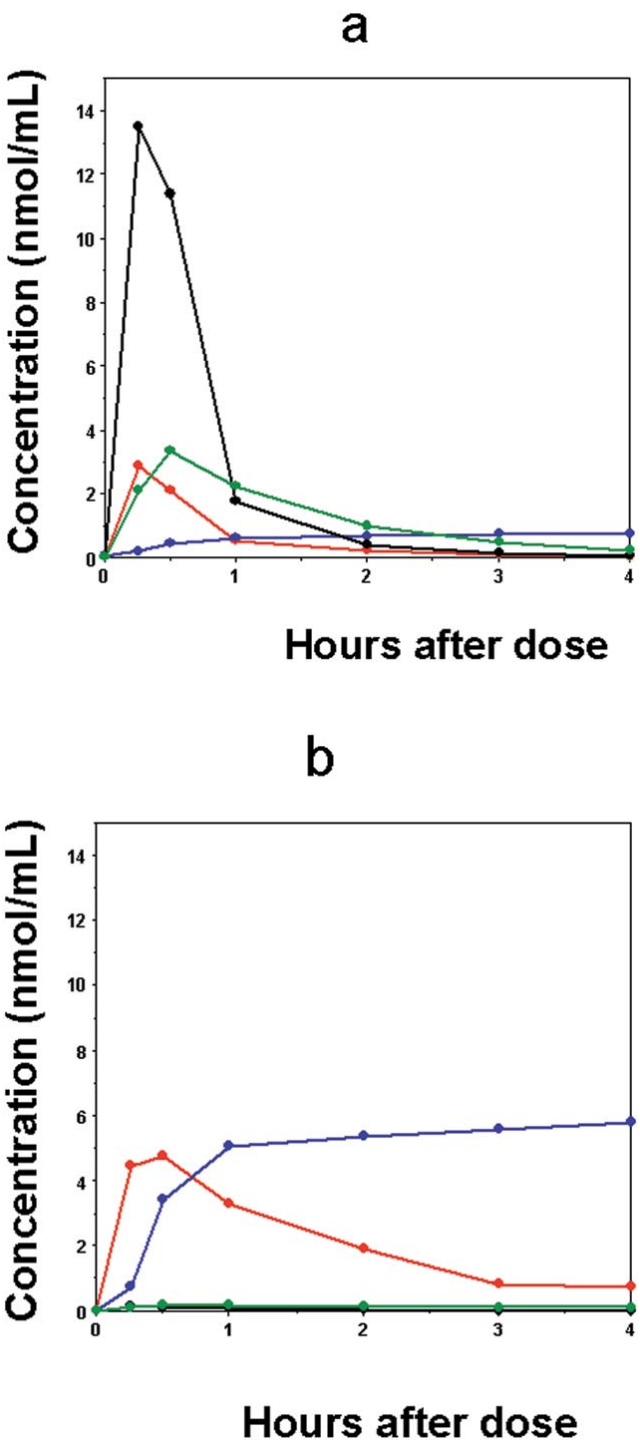

Fig. 7 Plasma concentration of DOPA and its metabolites after oral administration of L-dopa (100 mg) without DCI (**a**), and oral administration of L-dopa (100 mg) with DCI (benserazide 25 mg) (**b**) of the same PD patient (red: DOPA; black: dopamine; blue: 3OMD; green: homovanillic acid (HVA))

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