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Chronic Administration Does Not Alter the Pharmacokinetic Profile of L-Dopa in the Rat

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Abstract—Chronic administration of L-dopa (200 mg kg^{-1} day^{-1} for 12 months) plus carbidopa (25 mg kg^{-1} day^{-1}) or carbidopa (25 mg kg^{-1} day^{-1}) alone did not alter the $t_{\frac{1}{2}}$, $AUC_{0-\infty}$ k_{10}, k_{12}, k_{21}, CL_p or Vd_{ss} of L-dopa following intra-aortic (i.a.) administration (50 mg kg^{-1}) alone or after carbidopa (25 mg kg^{-1}, i.p.) pretreatment, or the $t_{\frac{1}{2}}$, $AUC_{0-\infty}$, t_{max} or the bioavailability (F) of L-dopa (50 mg kg^{-1}) administered orally, alone or after acute pretreatment with carbidopa (25 mg kg^{-1} i.p.). The peripheral metabolism of L-dopa was unaltered by chronic administration of L-dopa plus carbidopa or carbidopa alone as measured by unaltered $AUC_{0\ 360\ min}$ for 3-*O*-methyldopa, dopamine, DOPAC or homovanillic acid in the plasma of rats following acute administration of L-dopa (50 mg kg^{-1}, p.o. or i.a.) alone or following pretreatment with carbidopa, and unaltered hepatic dopa decarboxylase activity.

Long-term treatment of Parkinson's disease with L-dopa is often associated with the emergence of fluctuations in the clinical response to the drug. These may take the form of shortening of the duration of the response to the drug termed the 'wearing off' phenomenon, or rapid and unpredictable swings in response termed 'on-off' fluctuations. Such fluctuations have remained a major problem despite the introduction of peripherally-acting dopa decarboxylase inhibitors.

The pathogenesis of these alterations in clinical response to L-dopa is uncertain. It has been suggested that chronic therapy results in altered absorption of L-dopa as a result of changes in motility of the gastrointestinal tract or competition with dietary amino acids for the L-neutral amino acid transport system (Rivera-Calimlim et al 1970; Wade et al 1973; Morgan et al 1975; Nutt et al 1984). The short $t_{\frac{1}{2}}$ of L-dopa may contribute to the wearing off phenomenon in patients with severe loss of striatal dopamine neurones (Nutt 1987; Fabbrini et al 1987a, b). Indeed, primate studies have shown that striatal denervation combined with chronic L-dopa administration is essential for the manifestation of the motor complications (Clarke et al 1987; Boyce et al 1990). Studies in man have correlated the incidence of 'wearing off' with declining levels of L-dopa in the plasma, and dyskinesias with high concentrations of the drug (Muenter & Tyce 1971; Shoulson et al 1975; Nutt et al 1984; Quinn et al 1984; Nutt & Woodward 1986; Mouradian & Chase 1988). Indeed 'on-off' fluctuations can be controlled by continuous infusion of L-dopa suggesting that the pharmacokinetics of L-dopa are central to the genesis of this motor complication (Quinn et al 1984; Sage et al 1989). For this reason we have investigated the pharmacokinetics of L-dopa in the rat.

Previously we described the pharmacokinetic handling of L-dopa in the rat following an acute challenge with the drug, and demonstrated a similarity in the pharmacokinetic profile of the drug between rat and man (Rose et al 1991). We now report the results of investigations into the effect of chronic administration of L-dopa plus carbidopa on pharmacokinetics and metabolism of L-dopa in the rat.

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Materials and Methods

Chronic L-dopa treatment

Male Wistar rats, 150 ± 2 g at the start of the study (Bantin and Kingman, Hull, UK), were housed 4–6 to a cage depending on the weight of the animal, and were allowed free access to rat chow. The animals were maintained on a 12 h light-dark cycle, 0700–1900 h, at a temperature of 20 ± 1°C, with a relative humidity of 60 ± 5%. They were treated for 12 months with either L-dopa (target dose 200 mg kg^{-1} day^{-1}) plus carbidopa (target dose 25 mg kg^{-1} day^{-1}) or carbidopa alone (target dose 25 mg kg^{-1} day^{-1}). Doses were chosen from preliminary studies such that the dose of carbidopa maximally inhibited peripheral, but did not alter striatal dopa decarboxylase activity, and the dose of L-dopa produced an increase in dopamine turnover in the striatum (data not shown).

Drugs were dissolved in a minimum quantity of 2 M HCl containing 1% (w/w of L-dopa) ascorbic acid and made up to volume with glass-distilled water. The pH was adjusted to 4·5–5·0 with 5 M NaOH. The drugs were presented to the rats in blackened bottles in which they were stable for up to 4 days (data not shown). Drug solutions were changed every 3–4 days. Age-matched control rats received normal tap water. During the 12 months drug administration, the rats were weighed weekly to determine the effect of drug administration on growth rate. The dose of drug in the drinking water was corrected weekly for the volume of water imbibed and the weight of the rats. Over the 12 month period the following dose ranges were achieved: L-dopa plus carbidopa (191·4–210·4 mg kg^{-1} day^{-1} plus 23·9–26·2 mg kg^{-1} day^{-1}) and carbidopa alone (24·4–26·2 mg kg^{-1} day^{-1}). The animals were withdrawn from drug administration for a period of

four days (six half-lives of the most persistent metabolite, 3-*O*-methyldopa (see Wooten 1984)), before experimentation.

Analysis of the pharmacokinetics and metabolism of L-dopa

Two days before experimentation, rats were cannulated in the descending aorta under sodium pentobarbitone (60 mg kg^{-1}, i.p.) anaesthesia. Food, but not water was removed 16 h before testing.

On the day of testing, carbidopa (25 mg kg^{-1}, i.p.) or vehicle was given 1 h before L-dopa (50 mg kg^{-1} orally (p.o.) or via the aortic cannula (i.a.)). These doses were chosen from preliminary experiments (Rose et al 1991). A control blood sample (200 μL) was collected from the aortic cannula into Microvette heparinized blood tubes (Sarstedt Ltd, UK) 15 min before L-dopa administration. The volume of blood removed was replaced by an equal volume of heparinized saline (2000 units mL^{-1}). For intra-aortic administration of L-dopa, the drug was administered, dissolved in 0·9% NaCl (saline) containing 0·01 M HCl pH 4·5, followed by an equal volume of heparinized saline. For oral drug administration, L-dopa was given as a suspension in 1% (w/v) methyl cellulose containing 1% (w/w of L-dopa) ascorbic acid. Blood samples were collected 5, 10, 15, 30, 60, 90, 120, 150, 180, 240 and 360 min following L-dopa administration. Animals were allowed to move freely around the cage at all times during experimentation and showed no adverse effects to the methods employed. Plasma was separated from blood by centrifugation and analysed for levels of L-dopa, 3-*O*-methyldopa, dopamine, DOPAC and homovanillic acid (HVA) by HPLC with electrochemical detection as previously described (Rose et al 1991).

Pharmacokinetic analysis

For intra-aortic administration of L-dopa, the pharmacokinetics of L-dopa were calculated for plasma L-dopa concentrations according to a two-compartment model (Curry 1977). The terminal portion of the plasma decay curve (plotted as log plasma L-dopa vs time) was treated by least squares linear regression. The slope was calculated to determine the first-order elimination constant ($k_{el} = -2{\cdot}303 \times \text{slope}$) and the elimination half-life ($t_{\frac{1}{2}} = 0{\cdot}693/k_{el}$). The area under the concentration-time curve ($AUC_{0-\infty}$) was calculated by the trapezoid approximation rule and extrapolated beyond the last measured point (C_{pt}) using the formula C_{pt}/k_{el} (Gibaldi & Perrier 1975). Plasma clearance (CL_p) was calculated from the formula $CL_p = \text{dose}/AUC$. The volume of distribution at steady-state (Vd_{ss}), k_{12}, k_{21} and k_{10} were calculated according to Curry (1977).

Following oral administration of L-dopa the $t_{\frac{1}{2}}$ and $AUC_{0-\infty}$ were calculated as described above. The time to maximum plasma concentration (t_{max}) was taken from observed values.

Dopa decarboxylase assay

Animals were killed by cervical dislocation and decapitation. The abdomen was opened and a sample of liver was dissected, weighed and immediately frozen to −20°C before assay of dopa decarboxylase by the modified method of Sawaya et al (1978). The liver was homogenized in 10 vol (w/v) ice-cold buffer containing 4·4 mM KH_2PO_4, 0·56 mM $Na_2HPO_4 \cdot 2H_2O$, 0·25 mM 2-aminoethylisothiouronium bromide (AET) and 0·2% Triton X-100, using 10 strokes on setting 2·5 of a Teflon-glass variable speed homogenizer (Gallenkamp, UK). The homogenate was allowed to stand for 10 min before centrifugation at 10 000 *g* for 10 min at 4°C in a Sorvall RC-5B refrigerated centrifuge. Aliquots (50 μL) of the resultant supernatant were used to determine dopa decarboxylase activity in the tissue (equivalent to 5 mg liver per reaction vessel).

The reaction was performed in 10 mL Warburg reaction vessels. The outer chamber contained aliquots of the homogenate supernatant (50 μL), incubating buffer (containing 22·4 mM KH_2PO_4 53·4 mM $Na_2HPO_4 \cdot 2H_2O$, 3·3 mM AET and 33 mM pyridoxal phosphate; 50 μL), a solution of L-dopa in 0·1% ascorbic acid (100 μL; 44·81–358·1 nmol mL^{-1} final concentration) and a solution of [^{14}C]L-dopa (approx. 0·25 μCi mL^{-1}; 100 μL; Amersham International plc). The centre well contained a piece of Whatman Number 1 filter paper (3 × 1 cm) and methylbenzthonium chloride (hyamine; 1 M in methanol; 200 μL) to trap the [^{14}C]CO_2 liberated by the reaction. The reaction vessels were sealed with Subaseal rubber caps to prevent leakage of CO_2. The vessels were incubated, whilst being gently shaken for 15 min either at 37°C in a shaking water bath (Grant Instruments Ltd, UK) for the determination of enzymatic formation of CO_2, or in ice-water for the determination of non-enzymatic formation of CO_2. After the incubation period, the vessels were immediately placed into iced water to stop the reaction. The CO_2 formed by the reaction was liberated from the incubation mixture by injection of 500 μL 3 M trichloroacetic acid through the rubber cap into the outer chamber of the reaction vessel. The vessels were then incubated at 37°C for a further 30 min to ensure that all the CO_2 had been taken up by the hyamine-soaked filter paper. The filter paper was then placed in a scintillation vial insert with 5 mL scintillant (ES 299; Packard) and subjected to liquid scintillation counting in a Packard 2425 liquid scintillation spectrometer at an efficiency of 93–95%. The results were expressed as nmol CO_2 formed/5 mg tissue/15 min.

Statistical analysis

Results are expressed as mean ± s.e.m. The effect of chronic administration of L-dopa plus carbidopa or carbidopa alone were analysed by 2-way analysis of variance. If the resulting F-ratio was associated with a probability of less than 5%, Dunn's test was used to compare individual values.

Results

Growth rate of the rats

Chronic administration of carbidopa had no effect on the growth rate of the rats compared with age-matched control values (Fig. 1). However, the body weight of the L-dopa plus carbidopa-treated animals fell below that of the age-matched controls 2 weeks after the commencement of drug administration, and remained below for the remaining period of drug administration. At the end of the 12 month-treatment period the body weights of the rats in the L-dopa plus carbidopa group were 37% below those of the carbidopa-treated animals, and 34% below those of the age-matched controls.

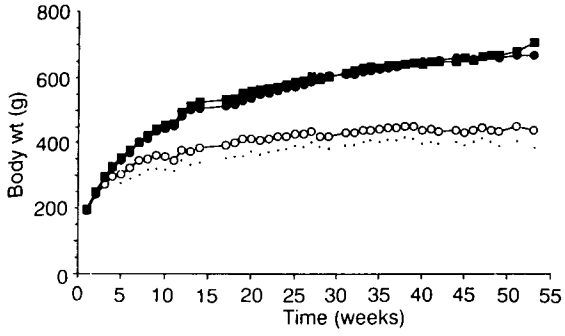

FIG. 1. The effect of administration of L-dopa (191·4–210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}), carbidopa alone (24·4–26·2 mg kg^{-1} day^{-1}) for 12 months on the body weight of rats. Values are expressed as mean ± s.e.m. for 20–24 animals from each treatment group. * $P < 0.05$ compared with control values (Dunn's test). ● Age-matched control, ■ 12 months carbidopa, ○ 12 months L-dopa plus carbidopa.

The effect of acute carbidopa administration on the pharmacokinetics of L-dopa (50 mg kg^{-1}, i.a.)

Plasma levels of L-dopa declined in a biphasic manner in all groups following acute administration of L-dopa alone or after carbidopa pretreatment (Fig. 2).

Acute carbidopa pretreatment increased the $t_{\frac{1}{2}}$ and $AUC_{0-\infty}$, and decreased the CL_p, k_{12}, k_{10} and Vd_{ss} following acute intra-aortic administration of L-dopa in animals treated chronically with L-dopa plus carbidopa, carbidopa alone and in the age-matched control animals (Table 1). There was no effect of acute carbidopa pretreatment on k_{21} following L-dopa in any of the treatment groups.

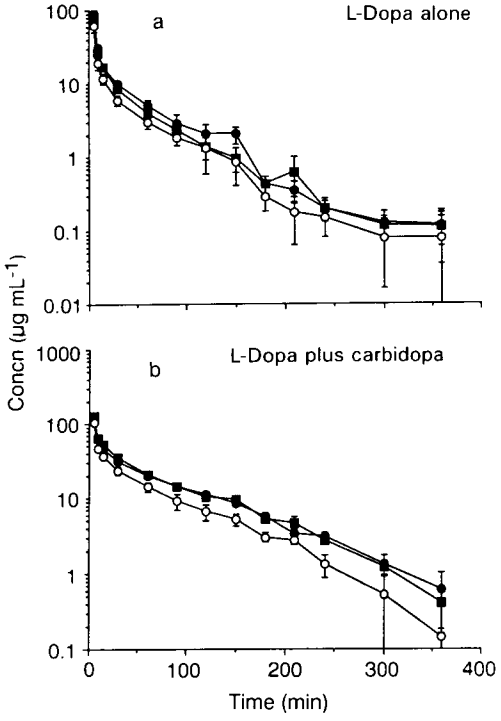

FIG. 2. The effect of administration of L-dopa (191·4–210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}) or carbidopa alone (24·4–26·2 mg kg^{-1} day^{-1}) for 12 months on plasma drug concentration following acute intra-aortic administration of L-dopa (50 mg kg^{-1}) alone (a) or after pretreatment with carbidopa (25 mg kg^{-1}, i.p., 1 h before L-dopa) (b). L-Dopa was administered acutely intra-aortically four days after withdrawal of chronic treatments. Values are expressed as mean ± s.e.m. for 3–6 animals from each treatment group. ● Age-matched control, ■ 12 months carbidopa, ○ 12 months L-dopa plus carbidopa.

Table 1. The effect of administration of L-dopa (191·4–210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}) or carbidopa (24·4–26·2 mg kg^{-1} day^{-1}) alone for 12 months on the pharmacokinetic parameters of L-dopa (50 mg kg^{-1}, p.o. or i.a.) administered alone or following pretreatment with carbidopa (25 mg kg^{-1}, i.p., 1 h before L-dopa administration). L-Dopa was administered acutely four days after withdrawal of chronic treatments.

		Age-matched control	Carbidopa	L-Dopa plus carbidopa
Intra-aortic				
$t_{\frac{1}{2}}$ (h)	L-Dopa alone	0·57 ± 0·09	0·63 ± 0·06	0·60 ± 0·04
	With carbidopa pretreatment	0·88 ± 0·05*	0·99 ± 0·13*	0·76 ± 0·09*
$AUC_{0-\infty}$ (mg h L^{-1})	L-Dopa alone	25·25 ± 1·82	30·81 ± 4·80	17·89 ± 2·80
	With carbidopa pretreatment	79·83 ± 4·70*	75·05 ± 3·10*	64·97 ± 9·46*
CL_p (L h^{-1} kg^{-1})	L-Dopa alone	2·02 ± 0·14	1·78 ± 0·25	3·03 ± 0·39
	With carbidopa pretreatment	0·63 ± 0·03*	0·67 ± 0·03*	0·80 ± 0·10*
k_{12} (h^{-1})	L-Dopa alone	7·98 ± 0·60	8·34 ± 0·72	8·58 ± 0·36
	With carbidopa pretreatment	4·62 ± 0·18*	4·44 ± 0·06*	5·22 ± 0·78*
k_{21} (h^{-1})	L-Dopa alone	0·96 ± 0·12	0·78 ± 0·07	0·84 ± 0·06
	With carbidopa pretreatment	0·96 ± 0·18	0·84 ± 0·06	0·96 ± 0·78
k_{10} (h^{-1})	L-Dopa alone	2·46 ± 0·24	2·70 ± 0·30	2·76 ± 0·18
	With carbidopa pretreatment	0·96 ± 0·06*	0·90 ± 0·06*	0·90 ± 0·06*
Vd_{ss} (L kg^{-1})	L-Dopa alone	3·37 ± 0·29	3·22 ± 0·34	4·86 ± 0·67
	With carbidopa pretreatment	1·69 ± 0·15*	1·87 ± 0·21*	1·70 ± 0·22*
Oral				
$t_{\frac{1}{2}}$ (h)	L-Dopa alone	0·71 ± 0·08	0·60 ± 0·04	0·89 ± 0·20
	With carbidopa pretreatment	1·18 ± 0·26	1·59 ± 0·11*	1·32 ± 0·29
$AUC_{0-\infty}$ (mg h L^{-1})	L-Dopa alone	7·13 ± 0·59	6·93 ± 0·92	3·47 ± 0·53
	With carbidopa pretreatment	41·19 ± 9·53*	30·78 ± 3·73*	26·40 ± 4·00*
T_{max} (min)	L-Dopa alone	45·00 ± 9·00	70·00 ± 12·00	34·00 ± 9·00
	With carbidopa pretreatment	35·00 ± 11·00*	26·00 ± 9·00*	48·00 ± 17·00
F	L-Dopa alone	0·28	0·22	0·19
	With carbidopa pretreatment	0·51	0·41	0·41

Values are expressed as the mean ± s.e.m. of 4–5 determinations from serial blood sampling in individual animals. * $P < 0.05$, acute administration L-dopa plus carbidopa compared with L-dopa alone (Dunn's test).

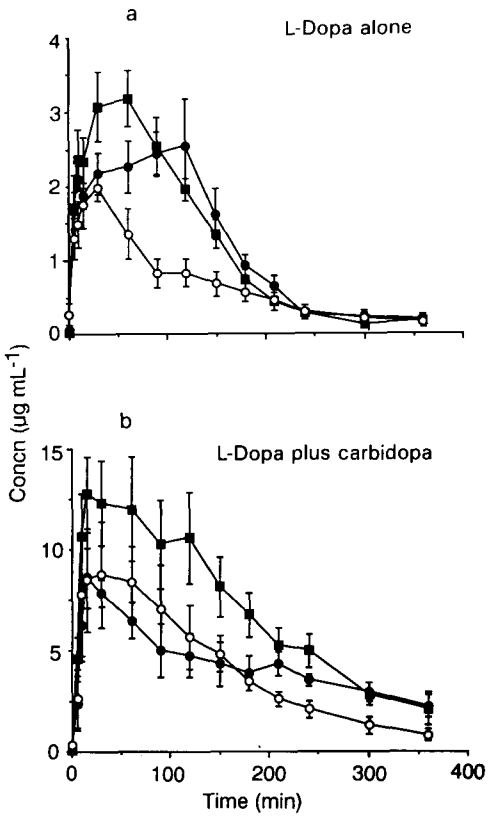

FIG. 3. The effect of administration of L-dopa (191·4–210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}) or carbidopa alone (24·4–26·2 mg kg^{-1} day^{-1}) for 12 months on plasma drug concentrations following acute oral administration of L-dopa (50 mg kg^{-1}) alone (a) or after pretreatment with carbidopa (25 mg kg^{-1}, i.p., 1 h before L-dopa) (b). L-Dopa was administered orally acutely four days after withdrawal of chronic treatments. Values are expressed as mean ± s.e.m. for 3–6 animals from each treatment group. ● Age-matched control, ■ 12 months carbidopa, ○ 12 months L-dopa plus carbidopa.

The effect of chronic administration of L-dopa plus carbidopa or carbidopa alone on the pharmacokinetics of L-dopa (50 mg kg^{-1}, i.a.)

There was no effect of chronic administration of L-dopa plus carbidopa or carbidopa alone on $t_{\frac{1}{2}}$, $AUC_{0-\infty}$, CL_p, k_{12}, k_{21}, k_{10} or Vd_{ss} following acute intra-aortic L-dopa administration with or without carbidopa pretreatment (Table 1).

The effect of acute carbidopa administration on the pharmacokinetics of L-dopa (50 mg kg^{-1}, p.o.)

Plasma levels rose rapidly following acute oral administration of L-dopa, with or without carbidopa pretreatment, and then declined in a monophasic manner (Fig. 3).

Acute carbidopa pretreatment increased the $t_{\frac{1}{2}}$ of L-dopa in rats treated chronically with carbidopa alone, and increased $AUC_{0\infty}$ in animals treated chronically with L-dopa plus carbidopa, carbidopa alone and in age-matched controls, and decreased the t_{max} in animals treated chronically with carbidopa alone and in the age-matched controls (Table 1).

The effect of chronic administration of L-dopa plus carbidopa or carbidopa alone on the pharmacokinetics of L-dopa (50 mg kg^{-1}, p.o.)

Chronic administration of L-dopa plus carbidopa or carbidopa alone did not alter the $t_{\frac{1}{2}}$, $AUC_{0-\infty}$, t_{max} or bioavailability (F) of L-dopa following acute oral administration of L-dopa with or without carbidopa pretreatment (Table 1).

$AUC_{0-360min}$ for plasma metabolites of L-dopa (Table 2)

Acute carbidopa pretreatment increased the $AUC_{0-360min}$ of 3-*O*-methyldopa after acute intra-aortic administration of L-dopa in animals treated chronically with L-dopa plus carbidopa, carbidopa alone and in age-matched controls, Acute carbidopa pretreatment tended to reduce the $AUC_{0-360min}$ for dopamine, DOPAC and HVA, compared

Table 2. The effect of administration of L-dopa (191·4 ± 210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}) and carbidopa (24·4–26·2 mg kg^{-1} day^{-1}) alone for 12 months on the area under the plasma concentration-time curve for the metabolites of L-dopa after acute challenge with L-dopa (50 mg kg^{-1}), administered orally or via the aortic cannula, alone or following pretreatment with carbidopa (25 mg kg^{-1}, i.p., 1 h before L-dopa administration). L-Dopa was administered acutely four days after withdrawal of chronic treatments.

		Route of acute administration of L-dopa			
		Oral		Intra-aortic	
Plasma metabolite	Treatment group	Without carbidopa	With carbidopa	Without carbidopa	With carbidopa
3-*O*-Methyldopa	Age-matched control	16·6 ± 2·4	112·0 ± 8·8*	30·5 ± 1·5	255·2 ± 24·8*
	Carbidopa	17·2 ± 1·8	158·9 ± 20·9*	35·9 ± 4·4	257·3 ± 38·7*
	L-Dopa + carbidopa	18·2 ± 3·4	149·2 ± 15·6*	51·8 ± 5·8	267·6 ± 71·8*
Dopamine	Age-matched control	0·31 ± 0·18	0·00 ± 0·00	1·00 ± 0·24	0·03 ± 0·01*
	Carbidopa	0·14 ± 0·04	0·01 ± 0·01*	0·75 ± 0·06	0·34 ± 0·31
	L-Dopa + carbidopa	0·27 ± 0·13	0·01 ± 0·01	1·39 ± 0·48	0·13 ± 0·08
DOPAC	Age-matched control	2·31 ± 0·68	0·67 ± 0·12	9·61 ± 2·31	0·58 ± 0·22*
	Carbidopa	2·52 ± 0·33	0·64 ± 0·27	5·87 ± 0·81	0·54 ± 0·21*
	L-Dopa + carbidopa	2·61 ± 0·32	1·08 ± 0·40	15·36 ± 3·76	3·04 ± 1·33
HVA	Age-matched control	6·08 ± 1·91	4·86 ± 1·86	26·60 ± 7·99	1·96 ± 0·76
	Carbidopa	5·54 ± 0·89	2·56 ± 0·91	10·67 ± 0·67	3·51 ± 1·79*
	L-Dopa + carbidopa	9·99 ± 4·96	4·65 ± 1·22	17·01 ± 5·52	6·56 ± 4·13

Values are expressed as the mean ± s.e.m. of 4–5 determinations from serial blood sampling in individual animals.
* $P < 0.05$, acute administration of L-dopa plus carbidopa compared with L-dopa alone (Dunn's test).

Table 3. The effect of administration of L-dopa (191·4–210·4 mg kg^{-1} day^{-1}) plus carbidopa (23·9–26·2 mg kg^{-1} day^{-1}), carbidopa alone (24·4–26·2 mg kg^{-1} day^{-1}) for 12 months on hepatic dopa decarboxylase activity. Data are expressed as the mean ± s.e.m. of six determinations.

Treatment group	K_m ($\times 10^4$ M)	V_{max} (nmol CO_2 (mg tissue)$^{-1}$)/15 min
Age-matched control	5·1 ± 0·7	30·1 ± 4·6
Carbidopa alone	6·2 ± 1·8	33·1 ± 9·1
L-Dopa plus carbidopa	10·8 ± 2·4	55·9 ± 13·0

with values obtained after intra-aortic administration of L-dopa alone in animals treated chronically with L-dopa plus carbidopa, carbidopa alone and in the age-matched controls, although individual comparisons did not reach statistical significance ($P < 0·05$).

There was no difference in $AUC_{0\text{-}360min}$ for 3-*O*-methyldopa, dopamine, L-dopa or HVA after acute intra-aortic administration of L-dopa, with or without carbidopa pretreatment between animals treated chronically with L-dopa plus carbidopa, carbidopa and the age-matched control rats.

Acute pretreatment with carbidopa resulted in an increased $AUC_{0\ 360min}$ for 3-*O*-methyldopa compared with values achieved after acute oral administration of L-dopa in rats treated chronically with L-dopa plus carbidopa, carbidopa alone and in age-matched control animals. Overall the $AUC_{0\text{-}360min}$ for dopamine and DOPAC after acute oral administration of L-dopa was reduced by acute carbidopa pretreatment in rats treated chronically with L-dopa plus carbidopa, carbidopa alone and in age-matched control animals, although no individual comparison reached statistical significance ($P < 0·05$). No overall effect of acute carbidopa pretreatment was observed on $AUC_{0\ 360min}$ for HVA after an acute oral challenge with L-dopa in rats treated chronically with L-dopa plus carbidopa, carbidopa alone and in age-matched control animals ($P > 0·05$).

The $AUC_{0\ 360min}$ for 3-*O*-methyldopa, dopamine, DOPAC and HVA after acute oral administration of L-dopa with or without dopamine pretreatment was unaltered by chronic administration of L-dopa plus carbidopa or carbidopa alone, compared with age-matched control values.

Hepatic dopa decarboxylase activity (Table 3)

There was no effect of chronic administration of L-dopa plus carbidopa or carbidopa alone on the k_m or V_{max} of hepatic dopa decarboxylase compared with values in the long-term carbidopa treatment group and the age-matched controls.

Discussion

Growth rate

The growth rate of the rats treated chronically with L-dopa plus carbidopa was reduced compared with those treated with carbidopa alone and the age-matched controls. This may be due to an inhibition of the feeding centres in the medulla by dopamine. Indeed, anorexia is common in patients with Parkinson's disease at the start of treatment with L-dopa (Bianchine 1980). However, all drugs were administered according to the body weight of the animals.

Pharmacokinetics and metabolism of L-dopa

The pharmacokinetics and peripheral metabolism of L-dopa following acute intra-aortic or oral administration of L-dopa were not altered by chronic treatment with L-dopa plus carbidopa or carbidopa alone. The only previous report of altered pharmacokinetics of L-dopa in the rat following chronic treatment was by Cheng & Fung (1975) who reported an increase in $t_{\frac{1}{2}}$ in rats treated for 2 months with L-dopa compared with control animals, all other pharmacokinetic parameters studied being unaltered.

Several studies have also described unaltered peripheral pharmacokinetics of L-dopa in man. Fabbrini et al (1987a) and Gancher et al (1987) reported that the peripheral pharmacokinetics of L-dopa did not differ between untreated, stable and fluctuating patients with Parkinson's disease. Luquin et al (1989) reported similar plasma levels of L-dopa and 3-*O*-methyldopa in stable and fluctuating patients. Nutt & Woodward (1986) also found no changes in the pharmacokinetics or pharmacodynamic response to L-dopa that may explain the incidence of fluctuations. However, Bowes et al (1991) reported a decrease in the area under the curve for L-dopa, and a tendency for increased 3-*O*-methyldopa with increasing duration of L-dopa therapy, suggesting a decrease in the bioavailability of the drug due to altered metabolism. Also, Deleu et al (1991) reported a delay in the absorption of L-dopa in some, but not all, patients exhibiting response fluctuations. However, in agreement with the former reports, no alterations were observed in the pharmacokinetics of L-dopa in rats treated for one year with the drug.

Nevertheless, there have been several reports of improvements in the control of fluctuations by the maintenance of constant plasma levels of L-dopa which would suggest a change in the pharmacokinetics of L-dopa on chronic treatment. Quinn et al (1984), for example, reported control of motor fluctuations by continuous infusion of L-dopa, and Poewe et al (1986) found that the administration of sustained release preparations of L-dopa reduced the incidence of fluctuations.

Hepatic dopa decarboxylase activity was unaltered by chronic administration of L-dopa plus carbidopa. Several authors have reported that the dopa decarboxylase activity is reduced during sustained administration of L-dopa. In these studies the animals were treated for only 5 (Dairman et al 1971), 7 (Roberge 1977) and 7–15 days (Tate et al 1971) with L-dopa alone, and the animals were not withdrawn from the drug before testing. These differences in the methodology may account for the discrepancies between the results of these sub-acute L-dopa studies and those described here.

Since it appears that the peripheral pharmacokinetics of

L-dopa are unaltered following chronic administration of L-dopa to both rats and man, it may be that the central pharmacokinetics of L-dopa are changed by chronic administration of the drug resulting in the response fluctuations. Indeed, Melamed et al (1983), Carey (1991) and Brannan et al (1991) showed a decreased cerebral metabolism of L-dopa following chronic treatment of rats with unilateral 6-hydroxydopamine lesions of substantia nigra pars compacta. The next step in the investigations into the cause of response fluctuations following chronic L-dopa treatment must involve the determination of the cerebral pharmacokinetics and metabolism following chronic L-dopa administration. If there is no change in cerebral handling of L-dopa after chronic administration, then central pharmacodynamic changes may be involved in the genesis of the fluctuations.

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