The Influence of Net Water Absorption on the Permeability of Antipyrine and Levodopa in the Human Jejunum

Dag Nilsson,[1] Urban Fagerholm,[2] and Hans Lennernäs[2,3]

Received January 13, 1994; accepted June 22, 1994

Food ingestion can influence the absorption of levodopa in the intestine and thereby contribute to fluctuations of motor functions in Parkinson patients. Obstruction of the active transport of levodopa by amino acids can be one factor. Paracellular drug absorption, a route proposed to be influenced by net transport of water across the intestinal epithelium, might occur for a small and hydrophilic drug such as levodopa. In the present study we studied how luminal L-leucine (60 mmol/L), alone or combined with hypotonicity, might stimulate net water absorption, and levodopa uptake in the human small intestine, since this possibly can contribute to the variable intestinal absorption of levodopa. The Loc-I-Gut perfusion technique was used in 10 healthy volunteers to study the effects of induced net fluid absorption on the small intestinal absorption of levodopa (2.5 mmol/L). An induced net fluid absorption was observed only when L-leucine was combined with a hypoosmolar perfusion solution. However, this did not enhance the intestinal permeability of levodopa. In conclusion, we suggest that the variability in the absorption of levodopa in Parkinson's disease cannot be explained by differences in transmucosal water flux in the human small intestine.

KEY WORDS: permeability; net water flux; solvent drag; active drug absorption; levodopa; antipyrine.

INTRODUCTION

Fluctuations between hypokinesia and hyperkinesia represent one outstanding problem in patients with advanced Parkinson's disease treated by oral administration of levodopa. Such clinical fluctuations could partially result from variations in the delivery of levodopa to the brain which depends on factors determining drug absorption (1, 2), such as gastric emptying (3) and intestinal permeability (4, 5), and levodopa uptake across the blood-brain barrier (6, 7). Based on our experience from intraduodenal infusion of levodopa to Parkinson patients, we know that a change of the infusion rate by 5–10% can alter the motor function from a hypokinetic to a hyperkinetic state or vice versa (Nilsson et al., unpublished data). Consequently is it important to identify factors that are crucial for the rate and extent of levodopa absorption from the human small intestine.

The absorption of levodopa given orally as standard tablets is rapid and its bioavailability is 85% when administered simultaneously with a decarboxylase inhibitor (8). In a previous intestinal perfusion study we demonstrated that levodopa shares the same active transport mechanism for the absorption of large neutral amino acids (LNAA) across the jejunal mucosa in humans (5). However, Frankel et al. (7) did not find any significant effect on serum concentration of levodopa in parkinsonian patients following simultaneous intraduodenal infusion of levodopa and a protein solution. We have earlier suggested that this lack of effect of a protein-rich meal is due to a higher permeability of the dietary amino acids than levodopa, which leads to a decreased competition for the transport between LNAA and levodopa further down the small intestine. We also proposed that levodopa is absorbed by the paracellular route (5). Levodopa is a small and hydrophilic molecule, and the jejunal epithelium is more leaky than the tight epithelium of rectum, where no absorption of levodopa has been demonstrated (9, 10). In animals it has been proposed that nutrients, such as L-leucine (L-leu) and D-glucose (D-glc), trigger opening of the tight junctions between the small intestinal cells, inducing a net fluid absorption across the intestinal epithelium, thereby increasing the paracellular absorption of nutrients and drugs by convective flow and/or diffusion (11–16). This effect has been shown to be most pronounced for small hydrophilic compounds (12). There are no reports of the effects of net water flux on intestinal permeability of levodopa *in vivo* in man. This possible interaction might be of clinical importance in the levodopa treatment of patients with Parkinson's disease, since it has the potential to contribute to the variability in intestinal absorption rate of levodopa.

The main objective in this study was to investigate if net water flux across the proximal jejunum epithelium in humans might contribute significantly to the variable absorption of levodopa. Furthermore, we also studied if high luminal concentration of L-leu alone was able to induce a net water absorption during isoosmotic conditions.

METHODS

Experimental Procedure and Study Design

The Loc-I-Gut® instrument (Synectics, Sweden) is a six-channel, 175 cm long, sterile and disposable perfusion tube made of polyvinyl intended for intestinal perfusions in humans (Figure 1). It is distally provided with two elongated latex balloons, placed 10 cm apart. Each balloon is separately connected to one of the smaller channels. Two wider channels in the centre of the tube are used for infusion and aspiration of perfusate, and the two remaining smaller channels are used for administration of marker substances or for drainage. The insertion and positioning of the tube is done under fluoroscopic guidance (Philips BV 21-S), and to facilitate the passage to the proximal jejunum a tungsten weight is placed in the front of the distal balloon. After positioning of the tube in the proximal jejunum the balloons are inflated with air, creating a 10 cm long closed segment allowing perfusion. A more detailed description of the tube and positioning procedures has been described elsewhere (17, 18).

Ten healthy subjects, (3 male and 7 female, aged 20–40 yrs) all gave informed consent to participate in the study which was approved by the Ethics Committee of the Medical Faculty, Uppsala University. Each subject was recumbent

[1] Department of Neurology, University Hospital, Uppsala, Sweden.
[2] Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Uppsala, Uppsala, Sweden.
[3] To whom correspondence should be addressed.

0724-8741/94/1100-1540$07.00/0

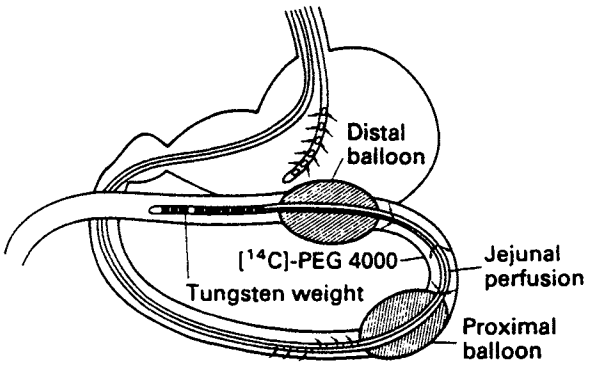

Figure 1. The Loc-I-Gut instrument allowing segmental jejunal perfusion in humans. The balloons are filled with air when the proximal balloon has passed the ligament of Treitz. A tungsten weight is placed in front of the distal balloon to facilitate its passage into the jejunum.

during the whole experiment and was perfused at one occasion in the morning after a 10 h overnight fast. After rinsing the intestinal segment with isotonic saline (37°C) for at least 10 min using a calibrated syringe pump (model 355, Sage Instrument, Orion Research Inc., Cambridge, MA) the perfusion experiment was started. The flow rate was 3 mL/min and each perfusion experiment lasted for 200 min, divided into 2 periods of 100 min. The perfusion solution was isotonic during the first period (P1) and hypotonic during the second period (P2). All of the jejunal perfusate leaving the intestinal segment was collected on ice at 10 min intervals over the whole experiment, and at the end of the perfusion the intestinal segment was rinsed with approximately 150 ml saline for 3–5 min. All syringes and perfusate samples were weighed and the samples were frozen immediately and stored at −20°C until analysis.

Drugs and Perfusate

The concentrations of levodopa and the decarboxylase inhibitor benserazide (both supplied by Hoffman La-Roche, Basel, Switzerland) in the perfusion fluid entering the intestinal segment were 2.5 and 0.625 mmol/L, respectively. The perfusion solution contained antipyrine (phenazone) (1.05 mmol/L), D-glucose (10 mmol/L), L-leucine (60 mmol/L), Na_2HPO_4 (2 mmol/L) and polyethylene glycol (PEG 4000) MW 4000 (1 g/L). The osmolarity in the perfusion solutions was (314 ± 4.2 mosm/L) (P1) and hypotonic (172 ± 5.9 mosm/L) (P2), respectively. This was created by adding NaCl (120 mmol/L) and KCl (5.4 mmol/L) (P1), and NaCl (30 mmol/L) and KCl (20 mmol/L) (P2) to the solution, respectively. Ascorbic acid was used as an antioxidant at a concentration of 5% wt/vol relative to levodopa. ^{14}C-labelled polyethylene glycol [^{14}C]PEG 4000 (Amersham Labs. Buckinghamshire, England) was added to the solution as a non-absorbable marker (2.5 μCi/L). The pH of the entering perfusion solution was approximately 7.0.

Stability and Adsorption Tests

The stability of levodopa, benserazide, antipyrine, D-glc and L-leu has earlier been assessed by incubation both under light and dark conditions at 37°C for 150 min and there was no sign of degradation of either levodopa, antipyrine, D-glc or L-leu (5). Benserazide was stable in the intestinal perfusate for 50 min but in the original perfusion solution about 10–15% was degraded within 150 min. Neither of the compounds was adsorbed to the catheter.

Analytical Methods

All chemical used were of analytical grade. Levodopa, benserazide and antipyrine were all measured by h.p.l.c. (5, 18). Perfusion and perfusate samples (0.5 g) were weighed and the total radioactivity of [^{14}C]PEG 4000 was determined by liquid scintillation counting (dpm) for 10 min (Beckman instrument, model 244) after addition of 8 ml Beckman Ready Safe®. The radioactivity was corrected for quenching using the internal standard of the instrument. The osmolarity of the perfusion and perfusate solutions was measured by the vapor pressure method (Vescor osmometer 5500).

Calculations

Steady-state in the perfusate within the intestinal segment was considered to have been achieved when the outlet solute and [^{14}C]PEG 4000 levels were stable. All calculations were made from 3–5 equilibrium concentrations. The volume of the solution within the intestinal segment (V_s) during each sampling interval was estimated using equation 1:

$$\text{Volume of the solution within the segment } (V_s) = \frac{\Sigma PEG_{in} - \Sigma PEG_{out}}{[PEG]_{out}} - \text{tube volume} \quad (1)$$

where ΣPEG_{in} and ΣPEG_{out} are the accumulated amounts of [^{14}C]PEG 4000 entering and leaving the intestinal segment and $[PEG]_{out}$ is its outlet concentration in the perfusate. The mean residence time of the solution within the segment (MRT) can be estimated by dividing the V_s by the flow rate of the perfusate leaving the intestinal segment, Q_{out}:

$$\text{Mean residence time (MRT)} = V_s/Q_{out} \quad (2)$$

The net water flux (NWF) per cm of the isolated segment was calculated by using equation 3:

$$\text{Net water flux (NWF)} = \frac{(1 - [PEG]_{out}/[PEG]_{in}) \cdot Q_{in}}{L} \quad (3)$$

where $[PEG]_{in}$ and $[PEG]_{out}$ are the inlet and outlet concentrations of [^{14}C]PEG 4000, Q_{in} is the flow rate of the perfusion solution entering the intestinal segment, and L is the length of the segment (10 cm). We assume that the fraction disappearing during passage through the segment has been absorbed. The fraction absorbed (fa) of levodopa and antipyrine was calculated from the fluid transport-corrected concentrations leaving (C_{out}) and entering (C_{in}) the intestinal segment at equilibrium (equation 4):

$$fa = (1 - (C_{out}\,[PEG]in/C_{in}\,[PEG]_{out})) \cdot 100 \quad (4)$$

We have previously described the hydrodynamics in the segment by a well-mixed model (19). Therefore, the effective intestinal permeability (Pe) of levodopa and antipyrine was calculated using equation 5:

$$Pe = \frac{Q_{in} \cdot (C_{in} - C_{out})/C_{out}}{2\pi rL} \quad (5)$$

where the area ($2\pi rL$) of the mass transfer surface within the intestinal segment is assumed to be the cylinder area with the length (L) of 10 cm and a radius (r) of 1.75 cm. To assess differences in absorption between the two periods in each perfusion experiment the Student's paired *t*-test was used. Variability is expressed as standard deviation (SD).

RESULTS

All technical and absorption parameters calculated from steady-state levels of the outlet perfusate are presented in Table 1. The equilibrium time was between 50–60 min and the test period approximately 40–50 min. The mean recovery of [^{14}C]PEG 4000 was complete during both periods, indicating successful perfusions. The pH of the perfusate leaving the intestinal segment was about 7.4, and the osmolarity was 299 ± 8.8 (P1) and 213 ± 19 (P2) mosm/L, respectively. The mean residence time of [^{14}C]PEG 4000 within the segment was approximated to be 15–20 min. During period 1 (P1) we observed a net secretion of water into the intestinal segment of 1.0 ± 1.2 mL/h/cm. A lowering of the osmolarity of the perfusion solution in period 2 (P2) significantly ($P < 0.05$) turned this secretion status to a net water absorption across the small intestinal epithelium of −1.3 ± 3.0 mL/h/cm (Figure 2a). In contrast with the increased net water absorption the mean effective permeability (Pe) of neither levodopa nor antipyrine increased (Figures 2b and 3; Table 1). Instead the Pe of levodopa decreased from 1.1 ± 0.65 (P1) to 0.85 ± 0.65 · 10^{-4} cm/s (P2) ($P < 0.01$). The corresponding estimates for antipyrine was 5.4 ± 3.1 and 4.8 ± 4.9 · 10^{-4} cm/s, respectively.

DISCUSSION

Food ingestion can influence the absorption of levodopa in the intestine and thereby contribute to the fluctuations of motoric functions in Parkinson patients. Both delayed gastric emptying in the postcibal state and obstruction of the

Table 1. The Mean (± SD) Steady State Values of Technical and Absorption Parameters from Jejunal Perfusions in 10 Healthy Volunteers. The Inlet Concentrations of Levodopa and Antipyrine were 2.5 and 1.0 mmol/L, respectively. Period 1: Control; Period 2: Experimental.

	Period 1	Period 2
[^{14}C]PEG 4000 recovery (%)	102 ± 7.1	97 ± 6.0
pH	7.3 ± 0.3	7.4 ± 0.2
Osmolarity (mosm/L)	299 ± 8.8	213 ± 19
MRT (min)	14 ± 9.5	19 ± 11
NWF (mL/h/cm)	1.0 ± 1.2	−1.3 ± 3.0*
Pe (levodopa) (· 10^{-4} cm/s)	1.1 ± 0.65	0.85 ± 0.65**
Pe (antipyrine) (· 10^{-4} cm/s)	5.4 ± 3.1	4.8 ± 4.9
fa (levodopa) (%)	19 ± 8.7	15 ± 10**
fa (antipyrine) (%)	49 ± 16	42 ± 21

MRT = mean residence time; NWF = net water flux; Pe = effective permeability; fa = fraction absorbed. The negative value of NWF denote absorption of fluid.
* $P < 0.05$; ** $P < 0.01$.

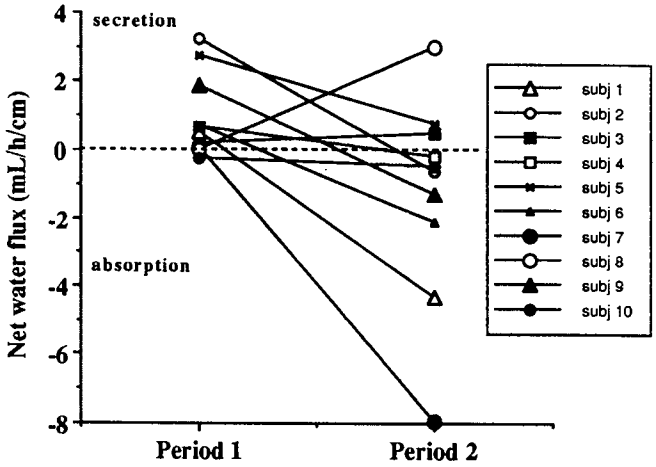

Figure 2a. The influence of hypoosmolarity on the net water flux (NWF) across the jejunal epithelium in 10 healthy volunteers. *Period 1:* Control; *Period 2:* Experimental. (Negative values indicate net water absorption).

active transport of levodopa by amino acids across the intestinal mucosa and blood brain barrier can contribute to the variability. Another intestinal absorption mechanism(s) that might be modulated by food intake is transmucosal water flux (20, 21). In this report we showed that a change of fluid flux from a net secretion to a net absorption status did not increase the permeability values of levodopa and antipyrine. Instead, the Pe of levodopa decreased from 1.1 ± 0.65 (P1) to 0.85 ± 0.65 · 10^{-4} cm/s (P2) ($P < 0.01$), respectively, during increased net water absorption. This result might be accounted for by enhanced saturation of the active transport mechanism for levodopa during the second period, because of water absorption, when the luminal concentration of levodopa, 3 mmol/L, approached the estimated K_m-value (5–10 mmol/L) for the amino acid carrier (22). This hypothesis has further support in the fact that Pe of the passive absorption marker antipyrine, was unchanged between the two periods.

In this report, we also demonstrated that the intestinal lumen concentrations of L-leu (approximately 30–60 mmol/

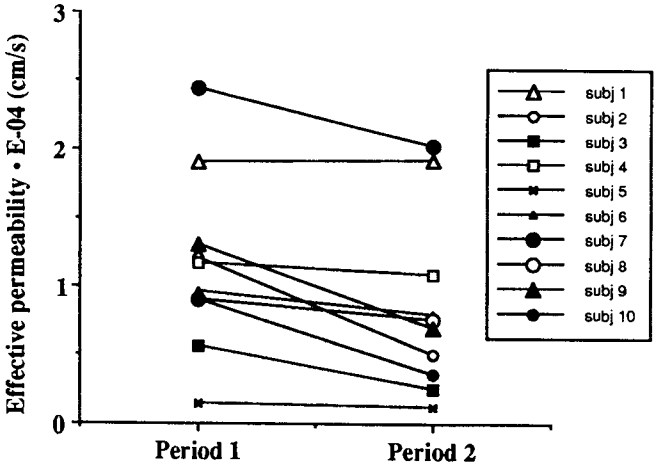

Figure 2b. The influence of induced net water absorption on the effective permeability (Pe) of levodopa (2.5 mmol/L) in the jejunum in 10 healthy volunteers. *Period 1:* Control; *Period 2:* Experimental.

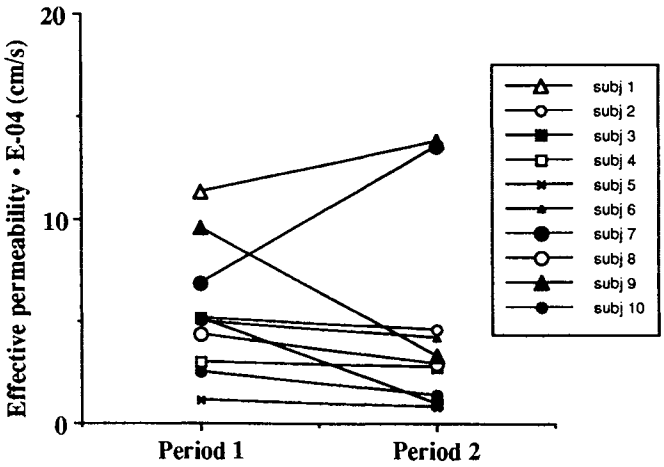

Figure 3. The influence of induced net water absorption on the effective permeability (Pe) of antipyrine (1.0 mmol/L) in the jejunum in 10 healthy volunteers. *Period 1:* Control; *Period 2:* Experimental.

L) did not induce a net water absorption across the human small intestinal epithelium. The observation was rather a net water secretion, similar to what has previously been found under isoosmotic conditions without L-leu (18, 23). This also agreed with our earlier *in vivo* results (5), but not with *in vitro* data obtained by Madara and Pappenheimer (24). They suggested that the permeability of the paracellular route might be increased several-fold in response to nutrients, such as D-glc and amino acids (24).

Water flux in mammals is a passive process driven by an osmotic gradient across the intestinal mucosa which might be a consequence of either local osmotic forces created by active transport mechanisms (20) and/or a countercurrent multiplier of Na^+ between the vascular hairpin loops in the intestinal villi (13, 25). The mechanism(s) underlying fluid flux in the intestinal tract is also influenced by the enteric nervous system and hormones and/or neurotransmitters (14). In the present study net water absorption was induced by perfusion of the jejunal segment with a hypotonic solution (172 mosm/L). The net water flux was changed from a secretion of 1.0 mL/h/cm to absorption of approximately −1.3 mL/h/cm, but the permeability of the two drugs did not increase in parallel. Furthermore, the recovery of ^{14}C-PEG 4000 was complete in both periods, which clearly indicates that the barrier function of the jejunal epithelium is maintained despite water absorption and high luminal concentration of amino acids (30–60 mmol/L). The lack of effect of drug permeability, however, does not agree with earlier animal studies showing a positive correlation between net water absorption and solute absorption (11–16, 26, 27). It has been shown in other animal studies that the permeability values of creatinine, and even a large molecule such as inulin, were increased in parallel with a convective transmucosal flow induced by a high luminal concentration of D-glc (11). This clearly indicates that the effect a convective transmucosal flow has on drug absorption *in vitro* (small intestine in animals) is different to *in vivo* results obtained in man. There are several factors that can explain this discrepancy, according to Nellans (28). He emphasised that the balance of forces determining net water and solute fluxes across the intestinal mucosa may be dramatically altered by *in vitro* conditions. If the hydrostatic pressure within the interstitium is decreased due to experimentally induced decreases in capillary blood pressure, effects on absorption may be greatly overestimated. In their study paracellular drug absorption was not stimulated by high luminal concentrations of D-glc in intact rats (28). Furthermore, intact intestinal neurotransmission is also necessary for maintenance of the normal basal absorptive state of the proximal jejunum (29).

In subjects 1 and 7, however, the Pe-values of antipyrine and levodopa were increased and unchanged (subj. 1)/decreased (subj. 7), respectively, in parallel with an extensive net water absorption (Figures 2–3). If enhanced paracellular absorption of antipyrine should be the case in subjects 1 and 7, the Pe of levodopa would have increased in parallel, because the similar molecular size of these two drugs. An alternative hypothesis for the decreased Pe of levodopa, probably the most plausible, is the higher concentration gradient of the drug obtained close to the intestinal wall as a consequence of water absorption (Figures 4a–b). This would give an increased absorption of antipyrine, but not for an actively transported drug, such as levodopa. We therefore suggest that antipyrine and levodopa are absorbed transcellularly by passive and active mechanisms, respectively (Figures 4a–b).

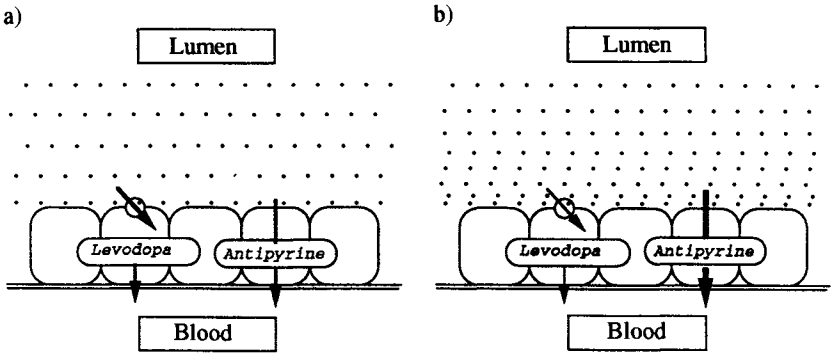

Figure 4a–b. Proposed transcellular absorption mechanisms for levodopa (active) and antipyrine (passive). The left panel shows the luminal concentrations of the drugs during isotonic condition. The right panel illustrates the higher luminal concentration gradients of the drugs close to the intestinal wall as a consequence of an extensive net water absorption.

There are several hypotheses why an increased transmucosal water absorption may not lead to higher permeability of small hydrophilic drugs in the proximal jejunum in humans (23). In a previous study we were unable to increase the permeability of antipyrine, atenolol and enalaprilat (23). One plausible explanation is that the absorption route of water in the human jejunum might be transcellular. We also proposed that the net water absorption detected during perfusion, instead could be due to a decreased outflow of fluid into the intestinal lumen, which during equilibrium flows in both directions across the intestinal mucosa. Such water transport mechanism has been discussed in a previous study, in which enhanced D_2O absorption could was not detected in plasma, despite an increased net water absorption based on intestinal perfusion data (30).

We conclude that luminal L-leu (30–60 mmol/L) during isotonic conditions did not induce a significant net water absorption across the jejunal epithelium in humans. However, when the same concentration of L-leu was combined with hypoosmolarity, a net water absorption across the human jejunal mucosa was obtained. Despite that, no significant enhancement of the permeability in general of neither levodopa nor antipyrine was obtained. However, in subjects with extensive water absorption, the permeability for passively absorbed drugs might increase, because of a higher concentration gradient close to the intestinal wall. Finally, we suggest that the large inter- and intravariability in the oral absorption (and clinical effect) of levodopa in Parkinson's disease, cannot be influenced by transmucosal water flux in the small intestine in humans.

ACKNOWLEDGMENTS

The study was supported in part by Swedish Medical Research Council, grant 4373.

REFERENCES

1. Bredberg E, Tedroff J, Aquilonius S-M, Paalzow L. Pharmacokinetics and effects of levodopa in advanced Parkinson's disease. Eur. J. Clin. Pharmacol. 39:385–89, 1990.
2. Bredberg E, Nilsson D, Johansson K, Aquilonius S-M, Johnels B, Nyström C, Paalzow L. Intraduodenal infusion of a water-based levodopa dispersion in optimizing of the therapeutic effect in severe Parkinson's disease. Eur. J. Clin. Pharmacol. 45: 117–22, 1993.
3. Kurlan A, Rothfield KP, Woodward WR, Nutt JG, Miller C, Lichter D, Shoulson I. Erratic gastric emptying of levodopa may cause "random" fluctuations of parkinsonian mobility. Neurology 38:419–21, 1988.
4. Robertson DRC, Higginson I, Macklin BS, Renwick AG, Waller DG, George CF. The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. Br. J. Clin. Pharmcol. 31:413–7, 1991.
5. Lennernäs H, Nilsson D, Aquilonius S-M, Ahrenstedt Ö, Knutsson L, Paalzow L. The effect of L-leucine on the absorption of levodopa, studied by regional jejunal perfusion in man. Br. J. Clin. Pharm. 35:243–50, 1993.
6. Leenders KL, Poewe WH, Palmer AJ, Brenton DP, Frackowiak RSJ. Inhibition of L-[^{18}F]Fluorodopa uptake into human brain by amino acids demonstrated by positron emmision tomography. Ann. Neurol. 20:258–62, 1986.
7. Frankel JP, Kempster PA, Bovingdon M, Webster R, Lees AJ, Stern GM. The effects of oral protein on the absorption of intraduodenal levodopa and motor performance. J. Neurol. Neurosurg. Psychiat. 52:1063–7, 1989.
8. Yeh KC, August TF, Bush DF, Lasseter KC, Musson DG, Schwartz S, Smith ME, Titus D. Pharmacokinetics and bioavailability of Sinemet CR: A summary of human studies. Neurology 39:25–38, 1989.
9. Schultz SG. Salt and water absorption by mammalian small intestine. In Physiology of the gastrointestinal tract, ed. Johnson LR. New York:Raven Press 983–89, 1981.
10. Eisler T, Eng N, Plotkin C, Calne DB. Absorption of levodopa after rectal administration. Neurology 31:215–7, 1981.
11. Pappenheimer JR, Reiss KZ. Contribution of solvent drag through intercellular junctions to absorption of nutrients by the small intestine of the rat. J. Membr. Biol. 100:123–36, 1987.
12. Lu H-H, Thomas J, Fleisher D. Influence of D-glucose-induced water absorption on rat jejunal uptake of two passively absorbed drugs. J. Pharm. Sci. 81:21–5, 1992.
13. Ochsenfahrt H, Winne D. The contribution of solvent drag to the intestinal absorption of the basic drugs amidopyrine and antipyrine from the jejunum of the rat. N-Schmied. Arch. Pharmacol. 281:175–96, 1974.
14. Kitazawa S, Ito H, John I, Takahashi T, Takenaka H. Generality in effects of transmucosal fluid movement and glucose on drug absorption from the rat small intestine. Chem. Pharm. Bull. 26:915–24, 1978.
15. Karino A, Hayashi M, Awazu HS, Minami H, Hanano M. Solvent drag effect in drug intestinal absorption.I. Studies on drug absorption and D_2O absorption clearances. J. Pharm. Dyn. 5: 410–7, 1982.
16. Hirasawa T, Muraoka T, Karino A, Hayashi M, Awazu S. Solvent drag in jejunal absorption of salicylic acid and antipyrine obtained by *in situ* single-pass perfusion method in rat. J. Pharm. Dyn. 7:246–53, 1984.
17. Knutsson L, Odlind B, Hällgren R. A new technique for segmental jejunal perfusion in man. Am. J. Gastroenterol. 84:1278–84, 1989.
18. Lennernäs H, Ahrenstedt Ö, Hällgren R, Knutsson L, Ryde M, Paalzow L. Regional jejunal perfusion, a new *in vivo* approach to study oral drug absorption in man. Pharm. Res. 9:1243–51, 1992.
19. Lee I-D, Fagerholm U, Lennernäs H, Amidon G.L. A study of hydrodynamic characteristics in human intestine applying residence time distribution analysis. Urtti Arto Ed.: In symposium on methods to overcome biological barriers in drug delivery. August 26–28, Kuopio University Publications A Pharm. Sci. 10:p73, 1993.
20. Yeo CJ, Bastidas A, Schmieg RE, Zinner MJ. Meal-stimulated absorption of water and electrolytes in canine jejunum. Am. J. Physiol. 259:G402–9, 1990.
21. Bastidas A, Zinner MJ, Bastidas JA, Orandle MS, Yeo CJ. Influence of meal composition on canine jejunal water and electrolyte absorption. Gastroenterol. 102:486–92, 1992.
22. Alpers DH. Digestion and absorption of carbohydrates and proteins. In Physiology of the gastrointestinal tract, ed. Johnson LR. New York:Raven Press 1469–87, 1987.
23. Lennernäs H, Ahrenstedt Ö, Ungell A-L. Intestinal drug absorption during induced net water absorption in man: A mechanistic study using antipyrine, atenolol and enalaprilat. Br. J. Clin. Pharmcol. 37:589–596, 1994.
24. Madara JL, Pappenheimer JR. Structural basis for physiological regulation of paracellular pathways in intestinal epithelia. J. Membr. Biol. 100:149–64, 1987.
25. Chadwick VS, Phillips SF, Hofmann AF. Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). II. Application to normal and abnormal permeability states in man and animals. Gastroenterol. 73:247–51, 1977.
26. Krugliak P, Hollander D, Ma TY, Tran D, Dadufalza VD, Katz KD, Le K. Mechanisms of polyethylene glycol 400 permeability of perfused and animals. Gastroenterol. 97:1164–70, 1989.
27. See N, Bass P. Nutrient-induced changes in the permeability of the rat jejunal mucosa. J. Pharm. Sci. 82:721–4, 1993.
28. Nellans HN. (B) Mechanisms of peptide and protein absorption. (1) Paracellular intestinal transport: modulation of transport. Adv. Drug Delivery 7:339–64, 1991.
29. Anthone GJ, Wang BH, Zinner MJ, Orandle MS, Yeo CJ. Meal-induced jejunal absorption requires intact neural pathways. Am. J. Surgery 163:150–6, 1992.
30. Gisolfi CV, Summers RW, Schedl HP, Bleiler TL, Oppliger RA. Human intestinal water absorption: direct vs. indirect measurements. Am. J. Physiol. 258:G216–22, 1990.