A Saturable Transport Mechanism in the Intestinal Absorption of Gabapentin Is the Underlying Cause of the Lack of Proportionality Between Increasing Dose and Drug Levels in Plasma

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Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is a neuroprotective agent with antiepileptic properties. The structure is small (molecular weight less than 200), is zwitterionic, and resembles an amino acid with the exception that it does not contain a chiral carbon and the amino group is not alpha to the carboxylate functionality. Gabapentin is not metabolized by humans, and thus, the amount of gabapentin excreted by the renal route represents the fraction of dose absorbed. Clinical trials have reported dose-dependent bioavailabilities ranging from 73.8 ± 18.3 to 35.7 ± 18.3% when the dose was increased from 100 to 1600 mg. The permeability of gabapentin in the rat intestinal perfusion system was consistent with carrier-mediated absorption, i.e., a 75 to 80% decrease in permeability when the drug concentration was increased from 0.01 to 50 m*M* (0.46 ± 0.05 to 0.12 ± 0.04). Excellent agreement was obtained between the actual clinical values and the predicted values from *in situ* results for the fraction of dose absorbed calculated using the theoretically derived correlation, $F_{abs} = 1 - \exp(-2P_{eff})$ by Amidon *et al.* (*Pharm. Res.* 5:651–654, 1988). The permeability values obtained for gabapentin correspond to 67.4 and 30.2% of the dose absorbed at the low and high concentrations, respectively. In the everted rat intestinal ring system, gabapentin shared an inhibition profile similar to that of L-phenylalanine. Characteristics of gabapentin uptake included cross-inhibition with L-Phe, sensitivity to inhibition by L-Leu, stereoselectivity as evidenced by incomplete inhibition by D-Phe, and lack of effect by Gly. Our findings support absorption of gabapentin by a saturable pathway, system L, shared by the large hydrophobic amino acids, L-Phe and L-Leu. The saturable absorption pathway makes a major contribution to the lack of proportionality in plasma levels of drug with increasing dose observed in the clinic.

KEY WORDS: gabapentin; neuroprotective agent; antiepileptic agent; nonlinear absorption kinetics; intestinal absorption; carrier-mediated transport; amino acid transport; system L.

INTRODUCTION

The availability of an orally administered drug to sites of action in the body is determined by several factors, including dissolution, absorption, metabolism, and excretion. In particular, xenobiotics that structurally resemble nutrients or endogenous substances may be substrates for carrier- or receptor-mediated events. The impact of nutrient mimetic transport or binding on drug delivery may manifest in nonlinear pharmacokinetics, i.e., a lack of direct proportionality between administered dose and drug levels in plasma.

Gabapentin (Fig. 1) is an analogue of γ-aminobutyric acid (GABA) with neuroprotective and antiepileptic properties (1). The mechanism of action for gabapentin is unknown. However, gabapentin does not interact with GABA receptors, it is not a GABA agonist or an inhibitor of GABA uptake or degradation, and unlike carbamazepine and phenytoin, the drug does not interact with sodium-dependent channels (2). Recently, gabapentin was shown to bind avidly to a novel site in rat cortical synaptic plasma membranes, which suggests a unique mechanism of action for anticonvulsant activity (3).

The human pharmacokinetics of gabapentin are straightforward. The drug does not bind to plasma proteins (4), is not metabolized (4,5), and once absorbed, is excreted entirely in the urine with an elimination half-life of 5 to 7 hr (4,5). The rate of drug absorption is relatively slow following oral administration of a drug solution (5); moreover, the extent of drug absorption decreases as the gabapentin dose is increased from 100 to 1600 mg (1,5)[3] (Fig. 2).

The structure of gabapentin closely resembles that of the bulky, hydrophobic amino acids, L-leucine and L-phenylalanine, that are substrates for the system L transporter (6). Noteworthy differences are the lack of a chiral carbon and the fact that the amino group is not alpha to the carboxylate functionality. Rat intestinal perfusion methodology *in situ* (7,8) was utilized to verify the existence of a saturable transport component as the underlying cause of the dependence of fraction absorbed on dose. The everted rat intestinal ring technique was then employed to further characterize the intestinal absorption of gabapentin.

MATERIALS AND METHODS

Materials. Gabapentin [1-(aminomethyl)cyclohexaneacetic acid; CI-945; Lot XH370889] and [^{14}C]gabapentin (Lot NO286-2701; radiochemical purity, ≥98%) were used in all studies. 2-(*N*-Morpholino)ethanesulfonic acid (MES) buffer was prepared from MES, NaCl, and KCl (Sigma Chemical Co., St. Louis, MO). All transport inhibitors, reference compounds, and PEG-4000 were also purchased from Sigma Chemical Co., with the exception of cycloleucine (1-amino-1-cyclohexane-carboxylic acid) and isonipecotic acid (Aldrich Chemical Co., Inc., Milwaukee, WI). Radiochemicals were purchased from either New England Nuclear/Dupont, Boston, MA (D-[^{3}H]mannitol, [^{3}H]acetaminophen, [^{3}H]L-Phe, [^{3}H]- and [^{14}C]PEG-4000) or Amersham, Arlington Heights, IL ([^{3}H]prednisolone). Soluene and Hionic-Fluor were purchased from Packard Instrument Co. (Meriden, CT). Neutralizing solution (PGM) was prepared from a saturated solution of sodium *p*yruvate in methanol, *g*lacial acetic acid, and *m*ethanol at the ratio of 4:3:1 by volume.

Single-Pass Intestinal Perfusion in Rats. Experiments

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[3] References refer to 300-mg data; other data are contained in Parke-Davis/Warner-Lambert Protocols 877-070 and 945-057.

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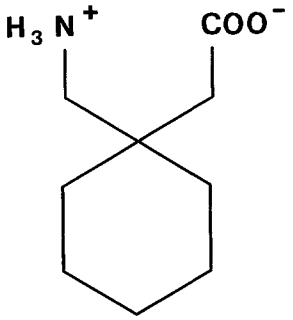

Fig. 1. Structure of gabapentin [CI-945; 1-(aminomethyl)cyclohexaneacetic acid].

were modified from the method described by Fleisher *et al.* (8). Male white Wistar rats (250 to 350 g) were fasted overnight with water *ad libitum*. Rats were anesthetized with a cocktail of ketamine, xylazine, and pentobarbital; animals were sacrificed at the end of the experiment before recovering from the anesthesia. Laparotomy was performed after onset of deep anesthesia and the upper jejunum was identified. Proximal and distal ends of an 8- to 12-cm segment of intestine were cannulated with glass tubing. Perfusion solutions of drug and PEG-4000 were prepared with radiolabeled tracer plus cold material to achieve desired concentrations in isosmotic buffer (10 m*M* MES, 135 m*M* NaCl, 5 m*M* KCl, pH 6.5). Specific activity of the tritium label was 1 to 3×10^5 dpm/mL, while that of carbon-14 label was 1 to 3×10^4 dpm/mL. Drug solution containing the nonabsorbable water marker, PEG-4000 (0.01%, w/v), was perfused into the proximal intestine at a constant concentration, C_{in}, and constant flow rate, Q (0.25, 0.5, or 0.75 mL/min), using a Harvard Apparatus Infusion Pump (Model 4200, South Natick, MA). Exiting perfusate was collected from the distal cannula at concentration, C_{out}. Drug and PEG-4000 concentrations were determined by dual-label, quench-corrected liquid scintillation spectrometry (Packard Tri-Carb 4000 Series, Downers Grove, IL). The ratio of outlet to inlet drug concentration, C_{out}/C_{in}, was normalized for Q, intestinal length, L, and calculated drug diffusivity, D, and corrected for water flux using the nonabsorbable marker, then used to calculate dimensionless, steady-state permeabilities (7):

$$P_{eff} = [\ln (C_{out}/C_{in})]/(-4Gz) \quad (1)$$

where the Graetz number, $Gz = \pi DL/2Q$

Calculation of Fraction of Dose Absorbed. Steady-state permeabilities obtained in rat intestinal perfusion experiments were related to the fraction of dose absorbed in humans (7) by

$$F_{absorbed} = 1 - \exp(-2P_{eff}) \quad (2)$$

Permeabilities were obtained for reference compounds with known values for fraction absorbed, i.e., compounds for which the fraction absorbed has been reported in the literature. These findings experimentally established the relationship between $F_{absorbed}$ and P_{eff} in our hands.

Uptake of Drug by Everted Rings of Rat Intestine. Experiments were modified from the method described by Stewart *et al.* (9). Male white Wistar rats were fasted, anesthetized, and laparotomized as described above. Animals were sacrificed after identification and removal of 15 to 20 cm of proximal jejunum. The excised intestine was floated in a tray of ice-cold, oxygenated MES buffer, everted on a slender glass rod, and cut into rings (10 to 35 mg) with a razor. Test tubes were equilibrated in a shaking water bath at 37°C. Individual rings were incubated in test tubes containing 1.0 mL radiolabeled drug solution. Specific activity of the tritium label was 1 to 5×10^5 dpm/nmol and that of the carbon-14 label, 1 to 5×10^4 dpm/nmol. Incubations were quenched by emptying the test tube contents onto a cheesecloth-covered beaker and rinsing with ice-cold saline. Tissue was gently blotted dry, placed in a tared vial, and weighed. Soluene (1.0 mL) was added to solubilize the tissue overnight, then PGM (0.1 mL) to neutralize the Soluene prior to the addition of 15.0 mL Hionic-Fluor, followed by analysis with liquid scintillation spectrometry.

In baseline experiments with gabapentin and reference compounds, uptake was determined as a function of time and water-bath shaking rate. The unbiased membrane flux J_0, was obtained from a plot of flux as a function of reciprocal shaking rate. The permeability coefficient, P_0, was calculated from the unbiased flux (J_0), concentration of the incubation medium (C), and conversion factor ($\langle cf \rangle$ = 24.0 cm^2/g) for tissue mass:surface area (10) from the relation

$$J_0 = P_0 * C * \langle cf \rangle \quad (3)$$

For inhibition studies, gabapentin or L-Phe was incubated for a fixed time over which uptake was linear as determined in the studies above. Control concentrations of L-Phe and gabapentin were 0.01 and 0.04 m*M*, respectively.

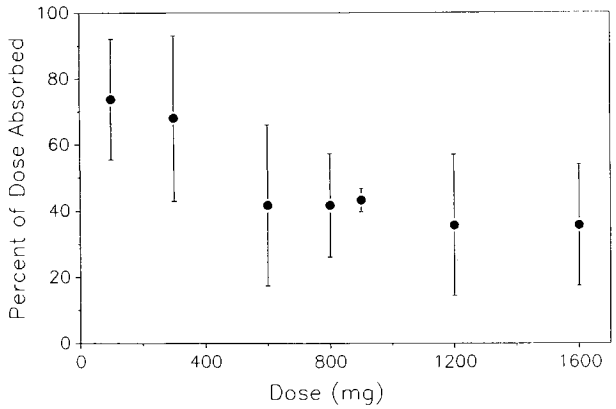

Fig. 2. Fraction of dose absorbed as a function of oral dose of gabapentin to humans. Mean values for urinary excretion are shown as a fraction of the administered dose with percentage relative standard deviation.

RESULTS AND DISCUSSION[4]

As shown in Fig. 2, the fraction of dose excreted in the urine of human volunteers decreased substantially when the oral dose of gabapentin was increased from 100 to 1600 mg. The underlying cause(s) of this disproportionality is difficult

[4] Portions of this report were presented at the 1991 National Meeting of the American Association of Pharmaceutical Scientists; see Ref. 11.

to discern from *in vivo* results due to the complex nature of competing and overlapping biological processes. Since gabapentin is freely soluble in water and is not metabolized, the saturability of intestinal absorption is suspect in explaining the observed nonlinearity. A recent report investigated the intestinal absorption of gabapentin over a wide concentration range (0.001 to 100 m*M*) using everted sacs of rat intestine (11). The authors excluded a carrier-mediated transport mechanism on the basis of an apparent linear dependence of absorption rate with concentration; however, the *in vitro* data in the range of 1 to 10 m*M* are few. This concentration range corresponds to the *in vivo* dose range 100 to 500 mg, where a sharp decrease in the fraction of dose absorbed occurs. This fact, combined with the noted leakiness of the everted sac technique for polar compounds (12), may lead to masking of the carrier-mediated component by the high nonsaturable component. In this report, the intestinal absorption component was isolated experimentally using *in situ* and *in vitro* techniques to determine whether a saturable transport mechanism was responsible for the decrease in the fraction of dose absorbed.

The relationship of permeabilities obtained from *in situ* perfusion of rat intestine with the fraction of dose absorbed in humans has been described by Amidon *et al.* (7). Compounds with reported values for the fraction of dose absorbed in humans were selected as references in our appraisal of the single-pass intestinal perfusion system in rats. These compounds included D-mannitol (5% absorbed), acetaminophen (65 to 80% absorbed), and prednisolone (90 to 100% absorbed). L-Phenylalanine, which is well absorbed (95 to 100%) and has previously been shown to be transported by a carrier-mediated process (14,15), was studied at two concentrations (0.01 and 50 m*M*). For gabapentin, values obtained from clinical trials were used for the fraction absorbed at low (100-mg) and high (1600-mg) doses. A good correlation was found between the dimensionless permeability values for each compound and the fraction absorbed in humans (Fig. 3). The results were well described by the relationship, $F_{abs} = 1 - \exp(-2P_{eff})$, as evidenced by comparison of the experimental results with the theoretical curve in Fig. 3. Effective permeabilities ranged from 0.05 ± 0.03 (D-mannitol) to 3.57 ± 0.21 (0.01 m*M* L-Phe). According to theory, permeabilities greater than 1.0 are consistent with compounds that are well absorbed; a corollary to this interpretation is that these are compounds for which membrane transport is not rate-limiting to systemic availability. L-Phe is reported to have a transport K_m in the 0.5 to 5 m*M* range (14–17). The permeability of L-Phe in the single-pass perfusion experiments decreased from 3.57 ± 0.21 to 1.41 ± 0.16, or approximately 60%, when the concentration was increased from 0.01 to 50 m*M*. This finding established that the perfusion system could be used to identify saturable transport in our hands.

The permeability of gabapentin as determined in the perfusion system was consistent with carrier-mediated transport; i.e., a 70 to 75% decrease in permeability was observed when the concentration of gabapentin was increased from 0.01 to 50 m*M* *in situ* (Fig. 4). The lowest dose administered to humans, 100 mg, dissolved in a human intestinal volume of 250 mL, corresponds to a lumenal concentration of 2.3 m*M;* the measured fraction absorbed was 74% (Table I). At the low concentration of gabapentin (0.01 m*M*) used in the perfusion study, the effective permeability (±SE) of 0.46 ± 0.05 yielded a calculated value of 67.4% of the dose absorbed. The highest dose administered in the clinic, 1600 mg, was equivalent to a 37.4 m*M* lumenal solution, and 36% of the dose was absorbed *in vivo*. At the high concentration of gabapentin (50 m*M*) perfused through rat small intestine, the P_{eff} decreased to 0.12 ± 0.04, corresponding to a calculated fraction absorbed of 30.2%. Thus, using the theoretically derived correlation for *in situ* permeability with fraction of dose absorbed *in vivo,* excellent agreement was obtained between the predicted values for fraction absorbed and those observed in humans (Table I). These findings further suggest that the K_m for gabapentin transport is in the millimolar range since the bioavailability of the lowest dose administered is somewhat higher than the fraction absorbed as estimated from the permeability obtained at 0.01 m*M* gabapentin.

The everted intestinal ring technique is an *in vitro* tool with which to obtain mechanistic information related to

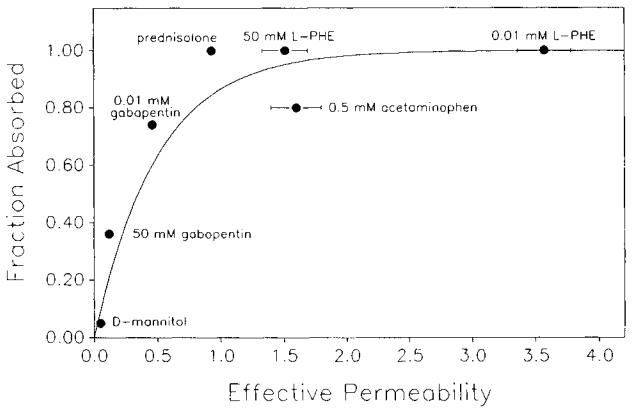

Fig. 3. Fraction of dose absorbed in humans for reference compounds versus effective permeability using single-pass perfusion of rat intestine *in situ*. The theoretical curve is calculated from $F_{absorbed} = 1 - \exp(-2P_{eff})$. Each point represents the mean permeability obtained in four to eight rats ± SE.

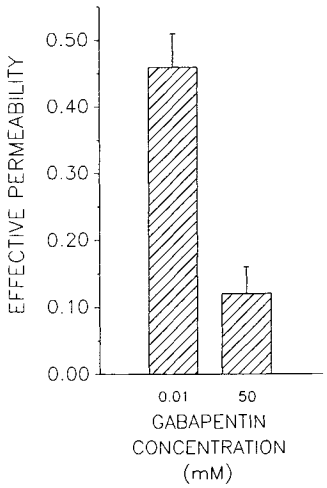

Fig. 4. Effective permeability of gabapentin at two concentrations in single-pass perfused rat intestine. Each bar is the mean of seven or eight rats plus the standard error of the mean.

Table I. Fraction Absorbed as a Function of Gabapentin Dose Administered to Humans (Observed) or Gabapentin Solution Perfused Through Rat Intestine (Predicted)

Dose (mg)	[Gabapentin] (m*M*)[a]	Fraction absorbed	
		Observed[b]	Predicted[c]
—	0.01	—	67.4
100	2.3	73.8	—
300	7.0	68.0	—
600	14.0	41.7	—
800	18.7	41.7	—
900	21.0	43.3	—
1200	28.1	35.7	—
1600	37.4	35.7	—
—	50	—	30.2

[a] Calculated using MW = 171 Da and assuming 250-mL human intestinal volume for dose dissolution.
[b] Relative standard deviation (RSD) ranged from 3.5 to 24.3% of the observed fraction absorbed.
[c] Calculated from fraction absorbed = $1 - \exp(-2P_{eff})$.

transport processes rather than an isolated screening method for *in vivo* predictions. Incubation times are relatively short, minimizing leakiness due to loss of functional integrity. Comparison of ring data between compounds of different lipophilicities and molecular weights may be misleading if the hydrodynamics of transport to the membrane are not characterized. In an empirical approach to this problem, the uptake of selected reference compounds was studied over time at three shaking rates to vary mixing of the incubation media. A representative time course for gabapentin uptake is shown in the inset to Fig. 5. Dependency of solute flux on mixing was examined by plotting the initial slope versus reciprocal shaking rate (Fig. 5). The unbiased membrane flux, J_0, was obtained by extrapolation to infinite shaking rate (8) and used to calculate the membrane permeability, P_0. Ring permeabilities for D-mannitol, gabapentin, prednisolone, and L-Phe are summarized and compared to the reported fraction absorbed in humans in Table II. D-Mannitol and L-Phe remain at the low and high extremes of the permeability–fraction absorbed correlation, as in the *in situ* perfusion studies; however, the rank order of gabapentin and prednisolone was reversed *in vitro*. It can be concluded from these limited studies that the ring system may be useful for differentiating compounds that are poorly or well absorbed, but not highly discriminating for rank order.

Saturable transport of L-Phe was established in the everted intestinal ring system by studying uptake from [^{3}H]L-Phe solutions at three concentrations, while carrier-mediated specificity was tested with potential inhibitors. Uptake decreased by approximately 40% when the L-Phe concentration was increased from 0.01 m*M* (control) to 5 m*M*, and by 73% when the concentration was 50 m*M* (Table III). The decrease in uptake at 50 m*M* L-Phe was comparable to that observed in the single-pass perfusion results (Fig. 3). Intermediate uptake at 5 m*M* was in agreement with the millimolar K_m range reported for L-Phe in the literature (14,15,17). The remaining uptake of L-Phe at 50 m*M* can be ascribed to the nonsaturable pathway (18). L-Leu was an effective inhibitor of L-Phe uptake, consistent with carrier-mediated absorption via a shared pathway. The transport of L-Phe was stereoselective, as evidenced by incomplete inhibition by D-Phe. Gly, which interacts weakly with the intes-

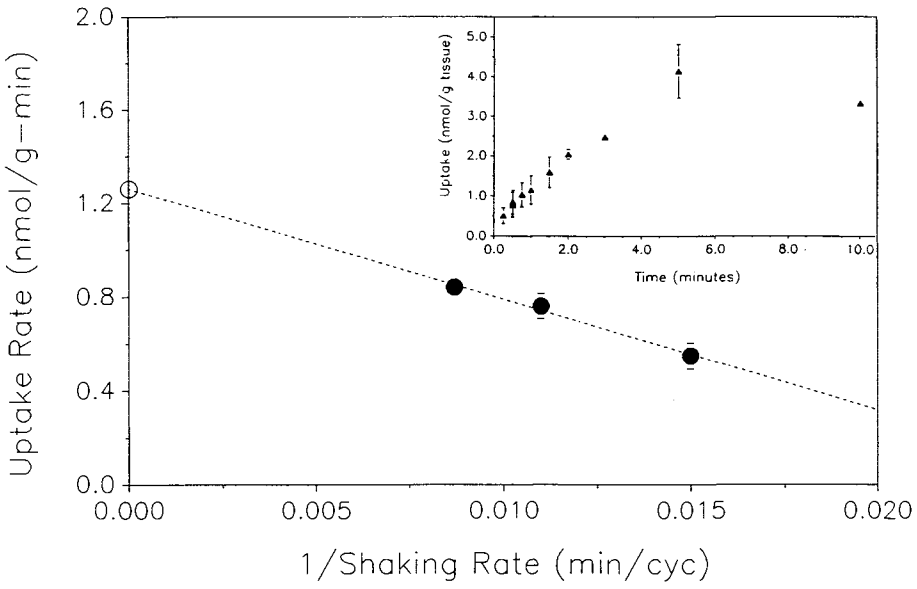

Fig. 5. Effect of water-bath shaking rate on uptake rate of gabapentin by rat everted intestinal rings. The uptake rates of gabapentin at 65, 90, and 115 cycles/min are plotted against the reciprocal of the shaking rate, then extrapolated to infinite shaking rate to obtain the uptake rate or flux unbiased by aqueous resistance. The unbiased flux was 1.26 ± 0.07 nmol/g-min. Each point represents 30 intestinal rings from one rat ± SD. Inset: Uptake of gabapentin by everted rat intestinal rings as a function of time. Incubations were conducted at 37°C and 115-cycles/min water-bath shaking rate. Each data point represents the mean of three rings ± SE.

Table II. Summary of Uptake of Reference Compounds by Rat Everted Intestinal Rings: Comparison with Fraction Absorbed (F_{abs})

Compound	Concentration (m*M*)	Flux ± SE (nmol/g-min)[a]	10^3 *P* ± SE (cm/min)[b]	F_{abs}
D-Mannitol	0.1	3.35 ± 0.14	1.40 ± 0.06	0.05
Gabapentin	0.01	1.26 ± 0.07	5.25 ± 0.27	0.74
Prednisolone	0.1	8.20 ± 0.38	3.42 ± 0.16	0.95
L-Phe	0.01	5.61 ± 1.69	23.4 ± 7.04	1.0

[a] Each flux was determined from the initial slopes of uptake-time courses at three water-bath shaking rates. Each time course consisted of a minimum of eight time points (0.5 to 10 min), with n = 3 rings per time point (one rat per time course).
[b] Calculated using Eq. (3).

tinal system L transporter at lower lumenal concentrations, inhibited L-Phe uptake approximately 50% at the 50 m*M* inhibitor concentration used in the study. Gabapentin reduced the uptake of L-Phe appreciably (66%), suggesting moderate to strong interaction with the transporter.

Inhibition studies with [^{14}C]gabapentin were consistent with the profile exhibited by L-Phe. Diminished uptake was observed when the gabapentin concentration was increased from 0.01 m*M* (control) to 5 m*M*, with a further decrease at 50 m*M*; however, the lower uptake rate measured at 50 m*M* gabapentin, while significantly different from the control uptake, was reduced by only 25% (Table III). L-Leu and L-Phe inhibited gabapentin uptake to the same degree, suggesting a shared pathway. As in previous experiments with L-Phe, D-Phe was a less effective inhibitor, implicating a stereoselective preference for the L-isomer. Significant inhibition by the structurally similar compounds, cycloleucine and isonipecotic acid, illustrated that variation in the distance between the amino and the carboxylate moieties could be tolerated. Gly did not inhibit gabapentin uptake.

Table III. Concentration Dependence and Inhibition of L-Phenylalanine and Gabapentin Uptake by Rat Everted Intestinal Rings

Concentration or inhibitor	[^{3}H]L-Phe[a]	[^{14}C]Gabapentin[a]
L-Phe		
0.01 m*M* (control)[b]	1.00 ± 0.06	nd[c]
5 m*M*	0.83 ± 0.09	nd
50 m*M*	0.22 ± 0.02	0.75 ± 0.07*
Gabapentin		
0.04 m*M* (control)[d]	nd	1.00 ± 0.07
5 m*M*	nd	0.89 ± 0.06
50 m*M*	0.34 ± 0.02	0.74 ± 0.04*
+ L-Leu	0.20 ± 0.01	0.66 ± 0.03*
+ Gly	0.53 ± 0.07	0.98 ± 0.06
+ D-Phe	0.51 ± 0.07	0.84 ± 0.08
+ Isonipecotic acid	nd	0.75 ± 0.04*
+ Cycloleucine	nd	0.75 ± 0.05*

[a] Mean value of test uptake/control uptake ± SE of 6 to 12 rings from 2 to 4 rats. Uptake was studied for 1 or 1.5 min at 37°C, 90-cycles/min water-bath shaking rate. Inhibitors were studied at 50 m*M*.
[b] Control uptake rate for L-Phe was 0.331 ± 0.026 nmol/min-g.
[c] Not determined.
[d] Control uptake rate for gabapentin was 2.04 ± 0.15 nmol/min-g.
* Statistically different from gabapentin control ($P < 0.05$).

The disparity in the amount of saturable transport between L-Phe and gabapentin in the ring experiments is most likely due to differences between tissue binding of the two compounds to mucosal as well as other surfaces exposed in the intestinal ring preparation. High nonsaturable components in this experimental system have also been observed for SQ 29,852, a dipeptidic ACE inhibitor absorbed by the peptide transporter (19). The difference in saturable transport of gabapentin between perfusion and ring experiments is most likely because the former is a steady-state and the latter an initial-rate technique.

Several lines of evidence support the conclusion that gabapentin is absorbed by the large, neutral amino acid transporter (system L), although the magnitude of the nonsaturable component complicates interpretation of the results in the everted ring system. The inhibition profiles of L-Phe and gabapentin demonstrate cross or mutual inhibition, share common patterns with structurally similar amino acids and analogues, and are stereoselective. The decrease in gabapentin uptake *in vitro* at 50 m*M* logically constitutes the entire component of gabapentin transport that is saturable, although the degree of inhibition is much less than observed with *in situ* perfusion experiments. Equivalent reduction of the saturable component by L-Phe or L-Leu supports uptake by system L as the major saturable pathway for gabapentin absorption.

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