O

OAT

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT1

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT10

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT2

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT3

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT4

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OAT7

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OATP

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

OCT1

► Organic Cation Transporters

OCT2

► Organic Cation Transporters

A.Talevi (ed.), *The ADME Encyclopedia*,
https://doi.org/10.1007/978-3-030-84860-6

OCT3

▶ Organic Cation Transporters

OCTN1

▶ Organic Cation Transporters

OCTN2

▶ Organic Cation Transporters

Oligopeptide Transporters

▶ Peptide Transporters

One-Compartment Model

▶ One-Compartment Pharmacokinetic Model

One-Compartment Pharmacokinetic Model

Alan Talevi[1,2] and Carolina L. Bellera[1,3]
[1]Laboratory of Bioactive Research and Development (LIDeB), Department of Biological Sciences, University of La Plata (UNLP), La Plata, Buenos Aires, Argentina
[2]Argentinean National Council of Scientific and Technical Research (CONICET) – CCT, La Plata, Buenos Aires, Argentina
[3]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), La Plata, Buenos Aires, Argentina

Synonyms

One-compartment model

Definition

The one-compartment pharmacokinetic model is the simplest compartmental pharmacokinetic model. As the name suggests, the model considers the whole organism as a single compartment where the drug distributes homogeneously and instantaneously, an extreme simplification that leads to a very simple mathematical description. The assumption of instantaneous and homogeneous distribution also implies that the apparent volume of distribution (Vd) will be constant. Another second and very important assumption of the model is that drug elimination within the compartment occurs following (apparent) first-order kinetics (Fig. 1). Depending on the modeled therapeutic scenario, drug absorption will be assumed to be instantaneous (intravenous bolus), or to follow zero or first-order kinetics (intravenous infusion at a constant rate or extravascular drug administration, respectively). The model has considerable didactic importance, and, despite its many shortcomings, it is able to properly fit the pharmacokinetic data of some drugs.

By solving the correspondent mass balance, it is possible to obtain equations of drug amount in the body (A) versus time t, or concentration within the compartment (equivalent, here, to plasma concentration, Cp) versus t.

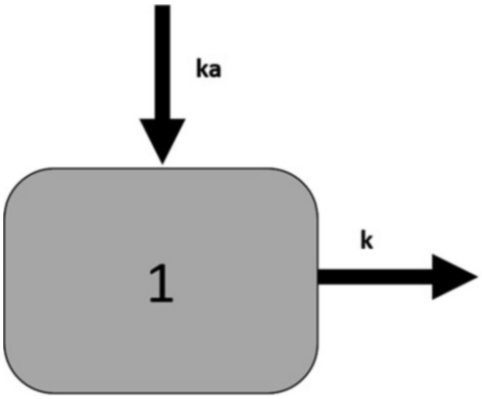
Generalities and Assumptions

All pharmacokinetic models are derived by writing the correspondent mass balance equations for the model and solving such equations mathematically. In compartmental analysis, one mass balance equation is considered for each compartment encompassed by the model. In the one-compartment model, thus, only one mass balance equation will be initially required.

Mass balance equations take the following general form:

$$\frac{dA}{dt} = [\text{rate of drug in}] - [\text{rate of drug out}] \quad (1)$$

where dA/dt denotes the instantaneous rate of change of the amount of drug in the given



One-Compartment Pharmacokinetic Model, Fig. 1 Schematic representation of the one-compartment model. Depending on the chosen route (and way) of drug administration, it will be assumed that the drug enters the compartment instantaneously or following zero or first-order kinetics

compartment and the terms on the right denote the difference between the rates at which drug molecules enter and exit the compartment. Naturally, the rates at which the drug enters the compartment are positive, as they represent drug gain, while the terms that represent drug loss for the compartment are negative.

In the one-compartment model, the body is represented by a single abstract compartment where plasma and tissue drug concentrations reach the distribution equilibrium instantaneously. Of course, drug distribution can never actually be instantaneous, as it depends on the perfusion and permeation transport to the tissues. Nevertheless, instantaneous distribution is a reasonable assumption when all the tissues that eventually receive significant levels of the drug approach the (pseudo)equilibrium with plasma in a time period that is considerably smaller than the elimination half-life [1]. The other relevant (and often less problematic) assumption of the model is that drug elimination follows apparent linear elimination kinetics (in other words, the rate of elimination is assumed to be proportional to the amount of drug remaining in the compartment). This is often a reasonable approximation, as in therapeutic settings the drug concentrations for most drugs are below the value of the Michaelis-Menten constant (Km) of saturable systems (enzymes and/or transporters) involved in the elimination process.

Intravenous Drug Administration: Bolus and Infusion

The one-compartment bolus intravenous injection is mathematically the simplest clinical scenario for pharmacokinetic modeling. For all practical purposes, the drug dose D is delivered rapidly and directly into systemic circulation by an injection over a very short time period. Intravenous injection can be thus regarded as an instantaneous absorption process. As after drug administration only elimination processes impact on the amount of drug in the body, the mass balance can be simply written as follows:

$$\frac{dA}{dt} = -kA \tag{2}$$

where k symbolizes the elimination rate constant. Note that, right after the injection (at $t = 0$), A is equivalent to the injected dose D.

Integration of Eq. (2) between $t = 0$ and any given time results in the following expression:

$$\ln(A) = \ln(D) - kt \tag{3}$$

Note that Eq. (3) corresponds to a loglinear form, where ln A is the dependent linear variable and t is the independent variable. ln D is the intercept and $-k$ is the slope. Simple algebra leads to the equivalent exponential equation (mono-exponential decay):

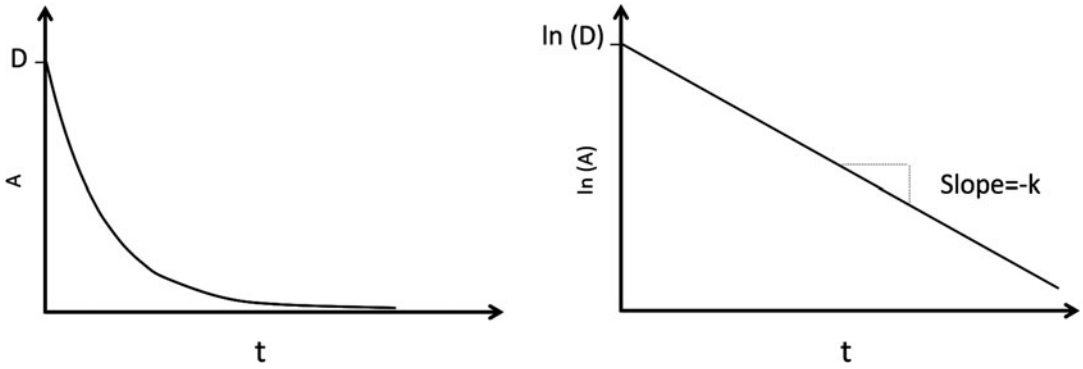
$$A = De^{-kt} \tag{4}$$

Fig. 2 presents graphical representations of Eqs. (3) and (4).

By dividing both sides of the equation by Vd, A becomes the plasma drug concentration Cp and D becomes what we will call C_0 (plasma drug concentration extrapolated at t = 0):

$$Cp = C_0\, e^{-k\,t} \tag{5}$$

Importantly, then, the shape of the graphs of Cp versus t (i.e., *the plasma concentration-time curve*) and ln (Cp) versus t will not change from those displayed in Fig. 2. k will still be the slope of the loglinear form of the equation, but the intercept will now be C_0.



One-Compartment Pharmacokinetic Model, Fig. 2 Graphical representation of the amount of drug in the body (A) versus time (t) (left) and ln(A) versus t (right) according to the one-compartment pharmacokinetic model, bolus intravenous administration

From Eq. (3), it can immediately be demonstrated that the elimination half-life of the drug, in the context of the one-compartment model, can be computed as

$$t_{1/2} = \frac{\ln(2)}{k} \tag{6}$$

Plasma samples for pharmacokinetic analysis by the one-compartment model, for an intravenous bolus injection, are typically collected at 5–12 time-points after drug administration [1]. The time interval between samples is generally small for early samples and increases for later samples. The drug concentration in each sample is determined analytically. Pharmacokinetic analysis begins log-transforming data and checking if the values of ln (Cp) versus the t fit a linear plot. Early or late data points that deviate from linear behavior can indicate, respectively, that the one-compartment model fails to adequately explain the experimental data or analytical problems (points near the analytical assay detection limit at late time-points, which should be disregarded). After checking the linear behavior, regression analysis is performed on the data, using t as the independent variable and ln (Cp) as the dependent variable. Vd can be computed from the fitted value of $C_{0,}$ which, in turn, is calculated as

$$C_0 = e^b \tag{7}$$

b being the intercept obtained from the linear equation. k corresponds to $-m$, m being the slope of the linear equation. In this way, a single linear regression analysis provides both the fundamental parameters of the model.

The area under the plasma concentration versus time curve, also called the area under the curve (AUC), is an extremely useful parameter in pharmacokinetic analysis. It can be used as a mean to determine pharmacokinetic parameters such as the total clearance (Cl) or the absolute bioavailability F. Furthermore, it is a measure of drug exposure [2] and one of the parameters typically used to compare drug products through bioequivalence studies [3], and it provides a mean to test the assumption of linear kinetics [4]. The total AUC is defined as

$$AUC = \int_0^\infty Cp\, dt \tag{8}$$

which, for an intravenous bolus, can be easily proven to correspond to

$$AUC = \frac{\mathrm{D}}{Cl} \tag{9}$$

In other words, AUC is proportional to the amount of drug reaching systemic circulation (here, D), and the proportionality factor is no other than Cl, which is constant provided that the linear elimination kinetics assumption holds true. Common approaches to estimate the partial or total AUC for an intravenous injection include the analytical approach (i.e., solving the mathematical integral), and the linear trapezoidal and linear log trapezoidal approaches [1, 5]. Further

insight into estimation of *AUC* is provided in the chapter on Noncompartmental Pharmacokinetics.

Zero-order absorption is alternatively considered when the drug enters the systemic circulation at a constant rate. An intravenous infusion at a steady flow rate represents an ideal zero-order absorption case [1]. In practice, intravenous infusion delivers the drug almost directly into systemic circulation at a constant rate over a given period ($0 < t < T$), after which the infusion is interrupted, and the rate of drug delivery instantly drops to zero ($t > T$). Independent mass balance equations are thus required for the time periods during infusion and after infusion stops. During infusion, the mass balance can be written as

$$\frac{dA}{dt} = K_0 - kA \tag{10}$$

where K_0 denotes the infusion rate. Note that, at early time-points (just after the infusion starts), the elimination term in the mass balance is small compared with the absorption term, since elimination follows first-order kinetics and the amount of drug in the body/compartment is small. Therefore, at short times after initiating the infusion, the positive term in the mass balance surpasses the negative term, and *dA/dt* is positive. Consequently, *A* and *Cp* will initially rise. Eventually, as the drug accumulates in the body, both input and output terms will become equal in magnitude, and will cancel each other out. *dA/dt* will become zero and no further change in drug levels will be observed as long as the infusion persists. In other words, a steady state will be achieved (Fig. 3).

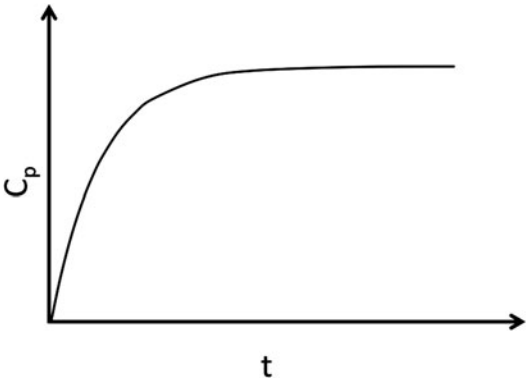
Integration by substitution of the mass balance (u substitution, $u = K_0 - k\,A$) results in the following expression:

$$A = \frac{K_0}{k}\left(1 - e^{-k\,t}\right) \tag{11}$$

Dividing both sides of Eq. (11) by *Vd* yields

$$C_p = \frac{K_0}{Cl}\left(1 - e^{-k\,t}\right) \tag{12}$$

It can be observed that when $t \to \infty$, *Cp* becomes the steady-state plasma concentration, which is equivalent to K_0/Cl. It can be easily shown that when *t* equals 5 $t_{1/2}$, the drug levels will be very similar to steady-state levels (about 97% of steady-state levels; mathematically, steady state will only be achieved at infinite time, as the concentration-time curve is asymptotic). Put in other words, the steady-state concentration Cp_{ss} depends on the infusion rate, but the time to achieve steady state is independent of the infusion rate and depends only on the drug half-life.



One-Compartment Pharmacokinetic Model, Fig. 3 Plasma concentration versus time profile for one-compartment modeling of an intravenous infusion at a constant rate

Once the infusion stops, the mass balance will become identical to Eq. (2), as only elimination prevails. When $t > T$, the concentration-time curve will decay monoexponentially, similarly to what has already been discussed for an intravenous bolus (Fig. 4).

Equations (10), (11), and (12) could be applied to describe drug delivery involving some controlled drug release systems, which deliver the drug at a sustained rate into extravascular regions of the body. Since a fraction of the drug can be metabolized or broken down pre-systemically when delivered extra-vascularly, the equation has to be corrected (or generalized) using the absolute bioavailability *F*.

Extravascular Drug Administration

It is reasonable to assume that first-order absorption occurs when the drug is administered through immediate-release drug delivery systems, using extravascular routes. The instantaneous rate at which the drug accesses systemic circulation will

then be proportional to the amount of drug remaining to be absorbed at the site of administration/absorption, Q_a. When using immediate-release drug delivery systems, absorption of most drugs is indeed linear, since simple diffusion is the most common absorption mechanism.

The correspondent mass balance can be written as

$$\frac{dA}{dt} = k_a Q_a - k\ A = k_a\ FDe^{-k_a t} - kA \quad (13)$$

as the mass balance in the absorption site can be written as

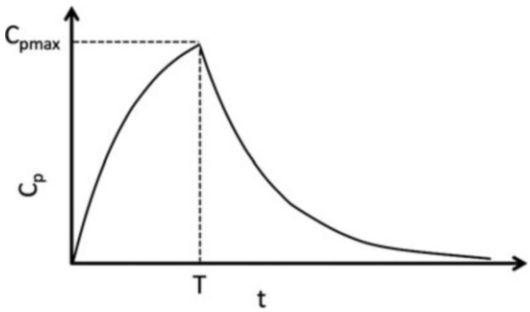
$$\frac{dQ_a}{dt} = -k_a\, Q_a \quad (14)$$

At short times after administration, the amount of drug remaining to be absorbed in the absorption site is comparatively high, whereas A is comparatively low. Furthermore, as usually $k_a >> k$ (an exception being flip-flop kinetics [6]), the positive term in the mass balance will exceed the elimination term; accordingly, A and Cp will increase. As absorption progresses, Q_a gradually decreases and A, in parallel, will increase. Both terms in the mass balance will sooner or later be identical in magnitude and will cancel out. At this point, no net change in A will be observed, and the peak concentration (Cp_{max}) will be achieved. An instant later, the magnitude of the elimination term will surpass that of the absorption term, and the drug levels will start decreasing (Fig. 5). Eventually, the absorption term may be neglected, and the mass balance can be approximated to the elimination term only (postabsorptive elimination or terminal phase).

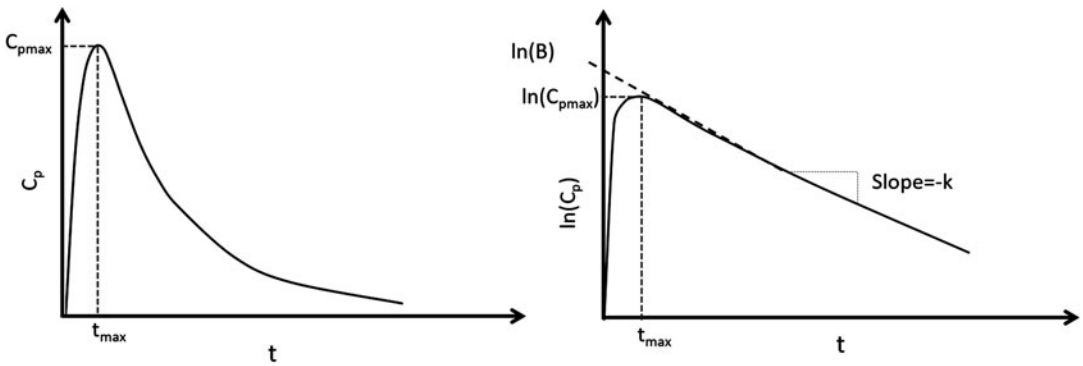
Integration of the differential Eq. (13) using Laplace transforms, assuming $k_a >> k$ and no latency, results in the following biexponential function, which is known as the Bateman function [7]:

$$Cp = \frac{F\,D}{Vd}\ \frac{k_a}{(k_a - k)}\ \left(e^{-kt} - e^{-k_a t}\right) \quad (15)$$

Note that, as $k_a >> k$, the second exponential term $-e^{-k_a t}$ becomes negligible at large values of time. It may be interpreted that, for all practical purposes, absorption has been then completed and from that moment onward only elimination remains significant.



One-Compartment Pharmacokinetic Model, Fig. 4 Evolution of the plasma concentration-time profile once the infusion is stopped at $t = T$



One-Compartment Pharmacokinetic Model, Fig. 5 Graphical representation of the plasma concentration versus time profile, and ln(Cp) versus time profile for a one-compartment (first-order absorption) pharmacokinetic model

By finding the derivative of Eq. (15) and equaling it to zero, the time to peak plasma concentration (t_{max}) can be found:

$$t_{\max} = \frac{\ln\left(\frac{k_a}{k}\right)}{(k_a - k)} \tag{16}$$

The peak plasma concentration (Cp_{max}) can be find by replacing t in Eq. 15 by $t_{\max}$.

An absorption half-life can be calculated similarly to what has already been done for the elimination half-life:

$$t_{1/2,abs} = \frac{\ln(2)}{k_a} \tag{17}$$

For extravascular administration in the framework of the one-compartment model, the rate constants are frequently determined by the *method of residuals* or *feathering* [7]; another method to estimate a valid k_a value assuming the validity of an intravenously obtained k is the method *by Wagner and Nelson* [8]. The Bateman function and the methods of residuals will fail if k_a and k show similar values [7]: if the absorption rate does not greatly exceed the elimination rate, absorption will continue while elimination is in progress, and linear approximation of the terminal data of semilogarithmic plots of concentration versus time tends to underestimate k. Interestingly, Wagner-Nelson approach provides accurate determinations of k_a even when both rate constants are similar in magnitude.

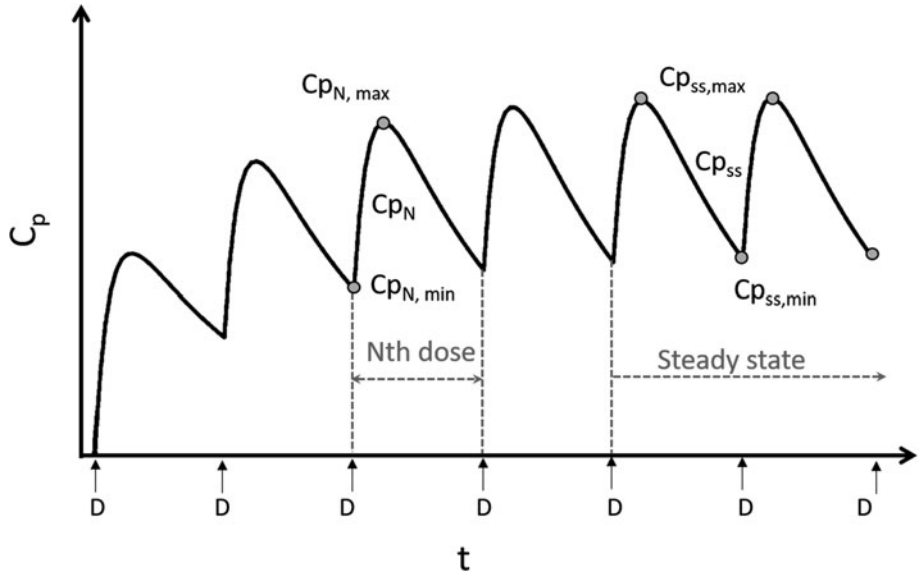
Although, as previously mentioned, the absorption rate is typically larger than elimination rate, an unusual phenomenon called flip-flop occurs when $k_a << 3k$, as k_a will be obtained from the terminal phase of the concentration-time curve, and, after feathering, k can be determined as minus the slope of the natural logarithm of the residuals plotted against time. The situation is rather uncommon in immediate-release formulations. 5-Fluorouracil is an example of drug exhibiting flip-flop [9]. The phenomenon is more common in slow-release formulations, and it's also frequently observed preclinically [6].

First-order absorption constitutes one of the cases where *AUC* values are required in order to fully assess all model parameters [1]. Though the *AUC* can be estimated analytically, in this case the linear trapezoidal method and the so-called linear-log trapezoidal rule ("linear-up log-down") are the most applied. There, trapezoidal approach is used in the rising fraction of the concentration-time curve, and the logarithmic approach in case of decreasing concentrations [5].

Multiple Dosing

Most of the equations discussed in the previous sections are applicable to describe the evolution of the drug levels in the compartment after the administration of a single dose of a drug. However, many clinical scenarios require the use of multiple dosage regimens, where typically a dose D of the drug is administered at regular time intervals that we will denote τ (most commonly, τ equals 6, 8, 12, and 24 h). Chronic conditions such as diabetes, hypertension, cardiac failure, and epilepsy are good examples of diseases that require the administration of one or more dosage units daily. Even short-duration treatments, such as oral antibiotic courses, often require multiple administrations of the drug. Adaptation of the preceding equations to a multiple dosage regimen will not only allow estimating drug levels at any moment during multiple dosing, but they will also help to decide on a convenient posology, i.e., a D, τ pair that maximizes efficacy, safety, and patient adherence.

These adapted equations are based on the principle of superposition [1], which states that the plasma levels after multiple doses of the drug will be equal to the sum of contributions from each individual dose. In other words, when giving a certain dose, the drug molecules from that dose that arrive at systemic circulation will add to the remaining molecules in from previous doses, resulting in drug accumulation. Plasma concentration will build up, and, eventually, the mean rate of drug absorption will equal the mean rate of drug elimination and a (pseudo)steady state will be reached (Fig. 6). The superposition principle will hold true as long as the drug displays linear pharmacokinetics in the therapeutically relevant concentration range.



One-Compartment Pharmacokinetic Model, Fig. 6 Evolution of plasma concentrations following consecutive extravascular drug administrations

Interestingly, the Bateman function can be easily adapted to any dose or to steady state by modifying each exponential term with the following factor:

$$\frac{1-e^{-n\,k_x\tau}}{1-e^{-k_x\tau}} \tag{18}$$

where n denotes the dose under consideration (n^{th} dose) and k_x represents the rate constant of the correspondent exponential (either *ka* or *k*). In this way, the more general equation to describe the concentration-time profile adopts the following form:

$$Cp = \frac{FD}{Vd}\,\frac{k_a}{(k_a-k)}\left(\frac{1-e^{-n\,k\,\tau}}{1-e^{-k\,\tau}}e^{-k\,t}-\frac{1-e^{-n\,k_a\tau}}{1-e^{-k_a\,\tau}}e^{-k_a t}\right) \tag{19}$$

In the preceding equation, t denotes the time passed since the administration of the n^{th} dose (i.e., the last administered dose). Observe that this general equation can be easily approximated (and simplified) depending on the context. For instance, at steady state $e^{-n\,k_a\tau}$ and $e^{-n\,k\tau}$ tend to zero. Accordingly, Equation (19) can be approximated to

$$Cp = \frac{FD}{Vd}\,\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\,\tau}}e^{-k\,t}-\frac{1}{1-e^{-k_a\,\tau}}e^{-k_a t}\right) \tag{20}$$

It can be reasoned, for instance, that the minimal concentration associated with a given dose will be observed just before administering the next dose, that is, when t equals τ, and that when t equals τ, the last dose has practically been absorbed and the absorption exponential approaches zero.

By finding the derivative of Eq. (19) and equaling zero, the time of peak plasma concentrations associated with the n^{th} dose ($t_{max,n}$) can be obtained:

$$t_{max,n} = \frac{ln\left[\frac{k_a\left(\frac{1-e^{-n\,k_a\tau}}{1-e^{-k_a\tau}}\right)}{k_{el}\left(\frac{1-e^{-n\,k\,\tau}}{1-e^{-k\,\tau}}\right)}\right]}{(k_a-k)} \tag{21}$$

Cross-References

- Drug Absorption
- Drug Distribution
- Drug Excretion
- Drug Metabolism
- Linear and Nonlinear Pharmacokinetics

- ▶ Noncompartmental Pharmacokinetics
- ▶ Real and Apparent Volumes of Distribution
- ▶ Two-Compartment Pharmacokinetic Model

References

1. Byers JP, Sarver JG. Pharmacokinetic modeling. In: Hacker M, Messer W, Bachmann K, editors. Pharmacology. Principles and practice. Burlington: Academic; 2009. p. 202–76.
2. Scheff JD, Almon RR, DuBois DC, Jusko WJ, Androulakis IP. Assessment of pharmacologic area under the curve when baselines are variable. Pharm Res. 2011;28:1081–9.
3. Tian S, Chang HH, Orange D, Gu J, Suárez-Fariñas M. A bioequivalence test by the direct comparison of concentration-versus-time curves using local polynomial smoothers. Comput Math Methods Med. 2016;2016:4680642.
4. Chau NP. Area-dose relationships in nonlinear models. J Pharmacokinet Biopharm. 1976;4:537–51.
5. Allgoewer A, Schmid M, Radermacher P, Asfar P, Mayer B. Area under the curve-derived measures characterizing longitudinal patient responses for given thresholds. Epidemiol Biostat Public Health. 2018;15:e12948-1–e12948-11.
6. Yánez JA, Remsberg CM, Sayre CL, Forrest ML, Davies NM. Flip-flop pharmacokinetics – delivering a reversal of disposition: challenges and opportunities during drug development. Ther Deliv. 2011;2:643–72.
7. Gattett I. The Bateman function revisited: a critical reevaluation of the quantitative expressions to characterize concentrations in the one compartment body model as a function of time with first-order invasion and first-order elimination. J Pharmacokinet Biopharm. 1994;22:103–28.
8. Wagner JG, Nelson E. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. J Pharm Sci. 1964;53:1392–403.
9. Jacobs BAW, Deenen MK, Joerger M, Rosing H, de Vries N, Meulendijks D, et al. Pharmacokinetics of capecitabine and four metabolites in a heterogeneous population of cancer patients: a comprehensive analysis. CPT Pharmacometrics Syst Pharmacol. 2019;8:940–50.

Oral Administration

- ▶ Oral Drug Delivery

Oral Delivery

- ▶ Oral Drug Delivery

Oral Drug Delivery

Alan Talevi
Laboratory of Bioactive Research and Development (LIDeB), Department of Biological Sciences, University of La Plata (UNLP), La Plata, Buenos Aires, Argentina
Argentinean National Council of Scientific and Technical Research (CONICET) – CCT, La Plata, Buenos Aires, Argentina

Synonyms

Oral administration; Oral delivery; Oral route; *Per os*; *Peroral*

Definition

Whereas broadly speaking, oral drug delivery might include all medications taken by mouth *(per os*, p.o.), this chapter specifically deals with those systemic medications taken by mouth and intended for intestinal absorption of the active pharmaceutical ingredient(s). Buccal and sublingual drug delivery will not be considered here, as they are separately covered by other entries (▶ "Buccal Route of Drug Delivery" and ▶ "Sublingual Route of Drug Delivery").

Advantages and Disadvantages of the Oral Route

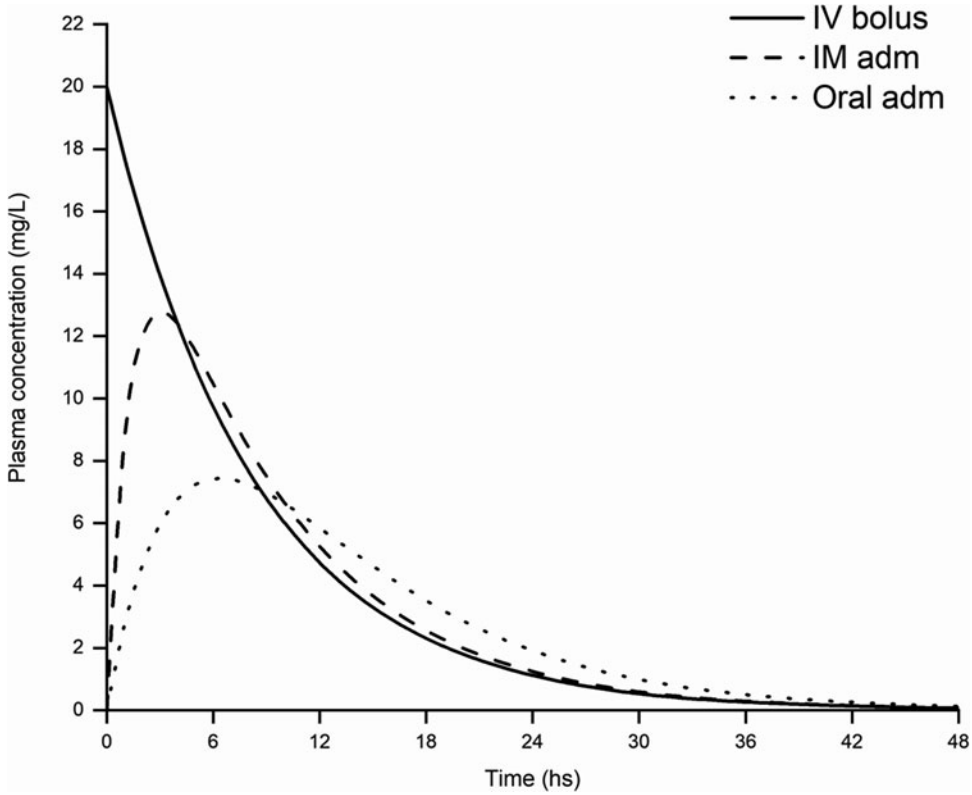
Owing to several reasons, oral delivery is the most preferred and convenient route of drug administration. To begin with, it is a physiological, noninvasive, and painless way of entry for solid and liquid materials to the body. This, combined with the patient autonomy regarding oral administration of drugs (as no assistance from health care providers or special devices is usually needed when using this route), explains patients' preference for this route [1–3], therefore characterized by high patient compliance. From a formulation and manufacturing perspective, it can be regarded

as versatile (as it admits a broad spectrum of dosage forms) and cost-efficient, due to least sterility constrains. Solid dosage forms are much more stable than liquid or semisolid formulations, which are the only options when using other routes (e.g., intramuscular, intravenous). Finally, the oral route tends to be safer than other routes, mainly due to the relatively slower bioavailability that results in a rather flatter drug plasma concentration-time curve (Fig. 1) compared with other routes of administration. This reduces the probabilities of acute drug reactions.

There are also some limitations or drawbacks associated to the oral route. First, it is not an adequate choice in emergencies, as the slow absorption that is advantageous from a safety perspective also results in relatively slow onset of action. It is not a viable route for unconscious or uncooperative patients, or for patients who are vomiting. It is possibly the administration route with greater variability in absorption, as it depends on a diversity of factors which are discussed in detail in the following section of this entry. Some drugs can be destroyed in the acidic gastric environment or by digestive enzymes (including gastric and pancreatic enzymes) or might undergo absorption problems, which are especially relevant factors for biopharmaceutical/biologic medical products [4, 5] (see the entry ►"Absorption of Biotechnology-Derived Biologics Drug Products"). Last, unpalatable or highly irritant drugs can also pose a challenge for oral delivery.

Factors Impacting on the Rate and Extent of Oral Absorption

The oral route is, by far, the drug administration route that is influenced by the widest diversity of



Oral Drug Delivery, Fig. 1 Comparison of typical plasma concentration-time curves for oral, intramuscular (IM), and intravenous (IV) administration. The slower kinetics of absorption through the oral route results in a flattened concentration-time curve, which reduces the probability of acute adverse reactions (much more common for IV administration). *The image has been gently provided by Prof. María E. Ruiz, section editor of this book*

factors. From the aggressive environment found in the stomach and/or the small intestine to the potential effects of the gut microbiota on absorption, some of the most relevant factors to take into consideration are discussed in the following subsections.

Gastric Environment

The first significant biological challenge against orally administered drugs is the aggressive acidic conditions found within the stomach, which usually are in the pH range 1–2.5.

The acidic gastric environment exerts its influence on orally administered drugs in two manners. *First, some drugs are degraded in acidic conditions*. For example, benzylpenicillin (penicillin G) is unstable at low pH, and it is thus rapidly inactivated in the stomach, which generally precludes its oral delivery [6]. The proton pump inhibitor omeprazole is also acid labile, requiring its oral administration as enteric-coated formulations [7]. Moreover, the lack of stability of omeprazole in the stomach led to the development of a Multiple Unit Pellet System, a tablet formulation which contains a large number of small and individually enteric-coated micropellets; MUPS tablets disintegrate rapidly in the stomach, and due to their small size, the pellets readily empty to the site of absorption in the small intestine [8], with a much more predictable absorption than conventional enteric-coated formulations. Second, as most drugs are either weak acids or bases, their degree of ionization (and therefore, their apparent solubility and permeability) will be influenced by the pH of the environment (see entry ▶ "pH Partition Theory"). At the low pH values of the stomach, basic drugs will be positively charged, and thus they will be more soluble but less permeable; the inverse will be true for acid drugs. On the one hand, poorly soluble weak bases might undergo precipitation upon entry into the small intestine due to the raise in the pH value of the environment (in the first portions of the small intestine, pH is usually above 5). This would naturally affect the amount of soluble drug available for absorption through the intestinal mucosa. On the other hand, gastric acid-suppressing agents can interfere with the absorption of drugs for which gastric pH is a determinant of their solubility and bioavailability. A good example are some antiretrovirals such as atazanavir or rilpivirine, which are preferably solubilized at acidic conditions; their coadministration with antiacid drugs results in reduced bioavailability owing to the increase in the gastric pH [9].

Gastric proteases can also limit the oral bioavailability of their substrates, as in the well-known case of insulin. Oral delivery of insulin (much more convenient than the usual subcutaneous administration) is one of the major long-term goals for the management of type 1 diabetes. However, the oral bioavailability of insulin is markedly low (less than 1%) due to proteolysis by digestive enzymes (including pepsins), and also owing to limited permeability related to its high molecular weight and hydrophilicity [10, 11].

Gastric Emptying

Gastric emptying is the process by which the content of the stomach passes through the pyloric sphincter and accesses the small intestine. The rate of gastric emptying is influenced by several factors including physiological (e.g., fasted or postprandial) and physiopathological states (e.g., depression [12] and anxiety [13]), the volume and composition of the stomach content, patterns of previous nutrient intake [14], biological sex [15], or even posture [16]. In fact, gastric retentive dosage forms and formulations that favor gastric emptying have been developed to regulate gastric emptying and thus the kinetics of drug absorption [17, 18].

Gastric emptying is closely related to drug absorption since, despite that the absorption of acid and neutral drugs may start in the stomach, where nonionized (and more permeable) sepecies predominate, the small intestine still is the preferred absorption site for most of the therapeutic agents. This is because it presents different levels of absorptive specializations, including folds in mucosa and submucosa called *circular folds*, finger-like projections of the mucosa called *villi*, and microscopic cellular membrane protrusions on the luminal surface of the enterocytes called *microvilli*, which are the major absorptive specialization. Combined, these three specializations provide an increase in the surface area (available for absorption) of about 600-fold. The expression

of influx transporters in the small intestine also favors absorption of their substrates.

Further discussion on this matter can be found in the entries ▶ "Gastric Emptying" and ▶ "Migrating Motor Complex".

Absorption Window

Some drugs display region-specific absorption [19], which is known as *absorption window*. This phenomenon can be associated to a constellation of factors, such as differential solubility, permeability and/or stability in different regions of the gastrointestinal tract due to changes in the environmental pH, and/or interaction with endogenous elements as digestive enzymes or bile salts. If intestinal transit moves the drug molecules beyond that region, drug absorption (and, thus, bioavailability) will be compromised, as the dose will not be completely absorbed [20].

The absorption window of a drug could also be influenced by the differential regional expression of metabolizing enzymes as well as influx and efflux drug transporters (see further details in next subsections) across the small intestine [21, 22]. For instance, the well-known ATP-binding cassette (ABC) efflux transporter P-glycoprotein (Pgp) is expressed in much higher levels in the ilium than in the duodenum. Accordingly, Pgp substrates will be preferably absorbed in the proximal regions of the small bowel.

Supersaturating self-emulsifying drug delivery systems (SEDDS) can be used to improve bioavailability of poorly soluble lipophilic drugs, including Pgp substrates [23]. SEEDS are isotropic mixtures of oils, surfactants, solvents, and cosolvents, orally administered in gelatin capsules [24]. This type of formulations improves the dissolution and apparent solubility of highly lipophilic drugs, so that they can better exploit the absorptive specializations in the small bowel. In the case of Pgp substrates, rapidly achieving concentrations above their intrinsic solubility at the proximal small intestine (where Pgp is present in comparatively low levels) can be beneficial for absorption. There, the efflux transporter would be more easily saturated upon exposure to relatively high concentrations of the solubilized active pharmaceutical ingredient. What is more, some of the usual constituents of self-emulsifying systems may transiently impair Pgp activity [25].

Levodopa, the mainstay symptomatic treatment of Parkinson's disease, constitutes another example of a drug with a narrow absorption window, being actively absorbed in the upper intestine by amino-acid transporters [26]. Controlled-release gastroretentive delivery systems have been proposed to achieve a slow release of this drug into the upper gastrointestinal tract at a constant rate, maximizing levodopa absorption at its absorption window [27].

Intestinal and Hepatic First-Pass Effect

The oral route is the route of administration for which the first-pass effect is more pronounced. During absorption, and before reaching systemic circulation, the drug molecules will encounter two major biotransformation organs: the intestine and the liver. The liver is universally recognized as the main drug metabolizing organ, owing to the coordinated activity of a wide diversity of metabolizing enzymes and transporters expressed in high levels in the hepatocytes [28, 29]. However, the intestinal wall has also been established as an important site of presystemic elimination, where some of the most relevant metabolizing enzymes are found in high levels.

CYP3A is the most abundant CYP subfamily expressed in the small intestine, accounting for over 80% of the total intestinal CYP content, with CYP2C representing the second most abundant (around 15% of the total content) [30]. Note that the CYP3A subfamily includes CYP3A4, arguably the most relevant Phase I drug-metabolizing enzyme owing to its broad substrate specificity. The levels of intestinal CYP3A4 (expressed as mass unit per mg of microsomal protein) have been found to be comparable to those in the liver [31], with the highest ones being found in the duodenum and jejunum. The CYP isoforms are however only significantly expressed in the enterocytes, and not in other intestinal cell populations.

The small bowel also expresses a range of uridine diphosphate-glucuronyltransferases (UGTs) [32]. Their expression varies along the intestine, but to a lesser extent than that of CYPs.

CYPs' expression and activity are subjected to large inter- and intraindividual variation, due to both genetic polymorphism and environmental agents that activate transcription factors that induce metabolizing enzymes [33, 34]. For instance, the interindividual differences in CYP2C9 and CYP2C19 across individuals can be as high as 9-fold and 6.5-fold, respectively [30].

Intestinal and Hepatic Transporters

Whereas the impact of drug-metabolizing enzymes has been established decades ago, the relevance of drug transporters as key determinants of drug pharmacokinetics has become evident much more recently [35], with initial focus on liver and kidney transport systems, and presently expanded to intestinal transporters. Broadly speaking, transporters can be classified as: *Uptake transporters,* which import their substrates into a cell and usually belong to the superfamily of solute carriers (SLCs), that mediate facilitated diffusion and secondary active transport. The presence of these transporters in the gut wall greatly contributes to the uptake of (polar and/or large) compounds of nutritional value, such as vitamins, amino acids, peptides, nucleosides, or sugars.

Efflux transporters from the ABC superfamily, which export their substrates out of the cell (see entries ▶ "ABC Transporters: An Overview" and ▶ "Solute Carrier (SLC) Transporters: An Overview" for further details), contributing to the gut role as a barrier for xenobiotics.

Drugs which are substrates for SLCs (e.g., levodopa, methyldopa, valaciclovir, and methotrexate) are often molecularly similar to, or share molecular features with, the physiologic substrates of these transporters. In general terms, SLCs in the intestine wall will contribute to their uptake and bioavailability. Pharmacokinetically relevant ABC transporters, contrariwise, are polyspecific, meaning that they show affinity for a wide diversity of substrates. They can be regarded as a detoxification system: By functioning in coordination with metabolizing enzymes, they are determinants of the disposition of numerous xenobiotics, generally diminishing their bioavailability (see entry on ▶ "Phase 0 and Phase III Transport").

As previously stated, intestinal transporters are differentially expressed in different regions of the intestine [21, 36]. For instance, Pgp levels increase from proximal to distal regions of the small intestine, whereas the highest concentrations of multidrug resistance-associated protein 2 (MRP2) are detected in the proximal jejunum, with minimal expression levels in the distal ileum.

As in the case of metabolizing enzymes, regulatory elements controlling protein levels (e.g., inducers) and genetic polymorphisms that lead to increased or diminished function of transporters are important avenues by which the transporters' impact on the absorption and disposition of their substrates may be modified [36].

Intestinal Motility and Splanchnic Blood Flow

Except for the intermediate phase of the interdigestive migrating complex (see entry ▶ "Migrating Motor Complex"), gastrointestinal motility is mostly a function of digestive period. Postprandially, the pattern of gastric and intestinal activity is associated with the trituration, digestion, and absorption of food [20]. The gastrointestinal transit time is thereof modified by meal composition. Factors that shorten transit time, such as diarrhea or laxatives, will generally worsen drug absorption [37, 38], especially for drugs with poor permeation.

Splanchnic blood flow rate is also a significant factor as blood is the primary vehicle that carries the drug from the site of absorption to the systemic circulation [20], which in general results in a *sink* condition (as the drug is constantly removed from its absorption site). Moreover, blood drainage from most of the gastrointestinal tract (except for the more distal part of the rectum) occurs through the portal vein and leads directly to the liver. How fast this occurs can influence the extent of the first-

pass hepatic extraction. Diminished splanchnic circulation could hence reduce the rate of intestinal uptake of lipophilic drugs and increase the first-pass effect.

Intestinal Microbiota

Gut microbiota is recognized as another relevant determinant of a drug pharmacokinetics. It plays a key role in enterohepatic circulation, as enzymes secreted by the microbiota, like the β-glucuronidase, can reverse Phase II metabolism (by de-conjugating the drug) and favor intestinal reabsorption, thus increasing drug bioavailability [39]. Also importantly, some drugs are transformed by the intestinal microbiota to metabolites that cannot be formed in the liver, altering the drug pharmacodynamics. For instance, the narrow therapeutic drug digoxin can be inactivated by the microbiota, markedly altering the state of digitalization [39, 40].

The effects of the microbiota on drug pharmacokinetics and pharmacodynamics might be altered by coadministration of antibiotics that alter the composition of the intestinal flora.

See entries ▶ "Gut Microbiota: Impact on Pharmacokinetics" and ▶ "Enterohepatic Recycling" for more details.

Disease States

Gastrointestinal and nongastrointestinal disease states can alter drug absorption owing to several reasons. For instance, gastrointestinal disease states (e.g., Chron's disease, ulcerative colitis, and diarrhea) can radically modify the gastrointestinal transit time, the luminal pH, and/or the gastrointestinal permeability, as well as the abundance of metabolizing enzymes and transporters and the microflora composition [37].

Any nongastrointestinal disease that affects any of the factors discussed in the previous subsections can potentially affect oral drug absorption. For example, drug absorption following oral administration may be decreased in shock states due to a reduced perfusion of the splanchnic organs [41]. The reduced cardiac output with peripheral hypoperfusion observed in patients with heart failure could reduce drug absorption too [42].

Food-Drug Interactions

The oral route is, naturally, the route of drug administration in which food-drug interactions are most frequently found. Such interactions could relate to the interactions of food constituents with metabolizing enzymes and/or transporters (e.g., competitive or noncompetitive inhibition), or to the direct physical or chemical reactions between nutritional elements and the drug itself (e.g., by forming insoluble or nonabsorbable complexes).

A food-drug interaction can also occur due to food-triggered initiation of several physiological processes, including fluctuations in the gastrointestinal pH, enhanced gastrointestinal motility, delayed gastric emptying, prolonged intestinal residence time, bile salts release, and increased splanchnic and hepatic blood flow [43]. For instance, the solubility and bioavailability of lipophilic drugs increases when coadministered with a high-fat food, which provides a lipophilic environment to solubilize otherwise poorly soluble drugs, and stimulates bile secretion (which in turn induces the formation of micelles that solubilize drugs) and the intestinal lymphatic transport pathway [44–46].

Depending on the underlying mechanism of the interaction, the result may be an increase or a decrease of drug absorption. Therefore, some drugs are recommended to be taken with meals, whereas others are preferably administered in the fasting state.

For a more detailed description on food-drug interactions, the reader is referred to the entry ▶ "Oral Drug Delivery and Food-Drug Interactions".

Cross-References

- ▶ ABC Transporters: An Overview
- ▶ Absorption of Biotechnology-Derived Biologics Drug Products

- Buccal Route of Drug Delivery
- Gastric Emptying
- Migrating Motor Complex
- Oral Drug Delivery and Food-Drug Interactions
- pH Partition Theory
- Phase 0 and Phase III Transport
- Solute Carrier (SLC) Transporters: An Overview
- Sublingual Route of Drug Delivery

References

1. Stewart KD, Johnston JA, Matza LS, Curtis SE, Havel HA, Sweetana SA, et al. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence. 2016;10:1385–99.
2. Alten R, Krüger K, Rellecke J, Schiffner-Rohe J, Behmer O, Schiffhorst G, et al. Examining patient preferences in the treatment of rheumatoid arthritis using a discrete-choice approach. Patient Prefer Adherence. 2016;10:2217–28.
3. Quante M, Thate-Waschke I, Schofer M. Was Sind die Gründe der Patientenpräferenz? Vergleich von oraler und subkutaner Darreichungsform [What are the reasons for patient preference? A comparison between oral and subcutaneous administration]. Z Orthop Unfall. 2012;150:397–403.
4. Liu C, Kou Y, Zhang X, Cheng H, Chen X, Mao S. Strategies and industrial perspectives to improve oral absorption of biological macromolecules. Expert Opin Drug Deliv. 2018;15:223–33.
5. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019;11:129.
6. Ball AP, Gray JA, Murdoch JM. The natural penicillins – Benzylpenicillin (penicillin g) and phenoxymethylpenicillin (penicillin v). In: Antibacterial drugs today. Dordrecht: Springer; 1978. p. 6–18.
7. Lampkin TA, Ouellet D, Hak LJ, Dukes GE. Omeprazole: a novel antisecretory agent for the treatment of acid-peptic disorders. DICP. 1990;24:393–402.
8. Geus WP, Mathôt RA, Mulder PG, Lamers CB. Pharmacodynamics and kinetics of omeprazole MUPS 20 mg and pantoprazole 40 mg during repeated oral administration in helicobacter pylori-negative subjects. Aliment Pharmacol Ther. 2000;14:1057–64.
9. Wang X, Boffito M, Zhang J, Chung E, Zhu L, Wu Y, et al. Effects of the H2-receptor antagonist famotidine on the pharmacokinetics of atazanavir-ritonavir with or without tenofovir in HIV-infected patients. AIDS Patient Care STDs. 2011;25:509–15.
10. Ibie CO, Knott RM, Thompson CJ. Complexation of novel thiomers and insulin to protect against in vitro enzymatic degradation – towards oral insulin delivery. Drug Dev Ind Pharm. 2019;45:67–75.
11. Fonte P, Araújo F, Reis S, Sarmento B. Oral insulin delivery: how far are we? J Diabetes Sci Technol. 2013;7:520–31.
12. Haj Kheder S, Heller J, Bär JK, Wutzler A, Menge BA, Juckel G. Autonomic dysfunction of gastric motility in major depression. J Affect Disord. 2018;226:196–202.
13. Geeraerts B, Vandenberghe J, Van Oudenhove L, Gregory LJ, Aziz Q, Dupont P, Demyttenaere K, Janssens J, Tack J. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology. 2005;129:1437–44.
14. Shi G, Leray V, Scarpignato C, Bentouimou N, Bruley des Varannes S, Cherbut C, Galmiche JP. Specific adaptation of gastric emptying to diets with differing protein content in the rat: is endogenous cholecystokinin implicated? Gut. 1997 Nov;41:612–8.
15. Mori H, Suzuki H, Matsuzaki J, Taniguchi K, Shimizu T, Yamane T, et al. Gender difference of gastric emptying in healthy volunteers and patients with functional dyspepsia. Digestion. 2017;95:72–8.
16. Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. Effect of body posture on radionuclide measurements of gastric emptying. Dig Dis Sci. 1988;33:1592–5.
17. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 2011;18:97–110.
18. Newton JM. Gastric emptying of multi-particulate dosage forms. Int J Pharm. 2010;395:2–8.
19. Davis SS. Formulation strategies for absorption windows. Drug Discov Today. 2005;10:249–57.
20. Golub AL, Frost RW, Betlach CJ, Gonzalez MA. Physiologic considerations in drug absorption from the gastrointestinal tract. J Allergy Clin Immunol. 1986;78:689–94.
21. Englund G, Rorsman F, Rönnblom A, Karlbom U, Lazorova L, Gråsjö J, Kindmark A, Artursson P. Regional levels of drug transporters along the human intestinal tract: co-expression of ABC and SLC transporters and comparison with Caco-2 cells. Eur J Pharm Sci. 2006;29:269–77.
22. Fritz A, Busch D, Lapczuk J, Ostrowski M, Drozdzik M, Oswald S. Expression of clinically relevant drug-metabolizing enzymes along the human intestine and their correlation to drug transporters and nuclear receptors: an intra-subject analysis. Basic Clin Pharmacol Toxicol. 2019;124:245–55.
23. Aboul Fotouh K, Allam AA, El-Badry M, El-Sayed AM. Self-emulsifying drug-delivery systems modulate P-glycoprotein activity: role of excipients and formulation aspects. Nanomedicine (Lond). 2018;13:1813–34.
24. Camargo SM, Vuille-dit-Bille RN, Mariotta L, Ramadan T, Huggel K, Singer D, et al. The molecular mechanism of intestinal levodopa absorption and its possible implications for the treatment of Parkinson's disease. J Pharmacol Exp Ther. 2014;351:114–23.
25. Chen C, Cowles VE, Sweeney M, Stolyarov ID, Illarioshkin SN. Pharmacokinetics and pharmacodynamics of gastroretentive delivery of levodopa/

carbidopa in patients with Parkinson disease. Clin Neuropharmacol. 2012;35:67–72.
26. Goo YT, Song SH, Yeom DW, Chae BR, Yoon HY, Kim CH, Park SY, Kang TH, Lee S, Choi YW. Enhanced oral bioavailability of valsartan in rats using a supersaturable self-microemulsifying drug delivery system with P-glycoprotein inhibitors. Pharm Dev Technol. 2020;25:178–86.
27. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58:173–82.
28. Jennen DG, Gaj S, Giesbertz PJ, van Delft JH, Evelo CT, Kleinjans JC. Biotransformation pathway maps in WikiPathways enable direct visualization of drug metabolism related expression changes. Drug Discov Today. 2010;15:851–8.
29. Faber KN, Müller M, Jansen PL. Drug transport proteins in the liver. Adv Drug Deliv Rev. 2003;55:107–24.
30. Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC. The human intestinal cytochrome P450 "pie". Drug Metab Dispos. 2006;34:880–6.
31. de Waziers I, Cugnenc PH, Yang CS, Leroux JP, Beaune PH. Cytochrome P 450 isoenzymes, epoxide hydrolase and glutathione transferases in rat and human hepatic and extrahepatic tissues. J Pharmacol Exp Ther. 1990;253:387–94.
32. Ritter JK. Intestinal UGTs as potential modifiers of pharmacokinetics and biological responses to drugs and xenobiotics. Expert Opin Drug Metab Toxicol. 2007;3:93–107.
33. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One. 2013;8:e82562.
34. Xie F, Ding X, Zhang QY. An update on the role of intestinal cytochrome P450 enzymes in drug disposition. Acta Pharm Sin B. 2016;6:374–83.
35. International Transporter Consortium, Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, et al. Membrane transporters in drug development. Nat Rev Drug Discov. 2010;9:215–36.
36. Estudante M, Morais JG, Soveral G, Benet LZ. Intestinal drug transporters: an overview. Adv Drug Deliv Rev. 2013;65:1340–56.
37. Effinger A, O'Driscoll CM, McAllister M, Fotaki N. Impact of gastrointestinal disease states on oral drug absorption – implications for formulation design – a PEARRL review. J Pharm Pharmacol. 2019;71:674–98.
38. Altree TJ, Galletly C. Laxative use and altered drug absorption. Aust N Z J Psychiatry. 2013;47(7):686.
39. Zhang J, Zhang J, Wang R. Gut microbiota modulates drug pharmacokinetics. Drug Metab Rev. 2018;50:357–68.
40. Tuteja S, Ferguson JF. Gut microbiome and response to cardiovascular drugs. Circ Genomic Precis Med. 2019;12:421–9.
41. Mangoni AA, Jarmuzewska EA. The influence of heart failure on the pharmacokinetics of cardiovascular and non-cardiovascular drugs: a critical appraisal of the evidence. Br J Clin Pharmacol. 2019;85:20–36.
42. Lainscak M, Vitale C, Seferovic P, Spoletini I, Cvan Trobec K, et al. Pharmacokinetics and pharmacodynamics of cardiovascular drugs in chronic heart failure. Int J Cardiol. 2016;224:191–8.
43. Cheng L, Wong H. Food effects on oral drug absorption: application of physiologically-based pharmacokinetic modeling as a predictive tool. Pharmaceutics. 2020;12:672.
44. Deng J, Zhu X, Chen Z, Fan CH, Kwan HS, Wong CH, et al. A review of food-drug interactions on oral drug absorption. Drugs. 2017;77:1833–55.
45. Gershkovich P, Hoffman A. Effect of a high-fat meal on absorption and disposition of lipophilic compounds: the importance of degree of association with triglyceride-rich lipoproteins. Eur J Pharm Sci. 2007;32:24–32.
46. Yáñez JA, Wang SW, Knemeyer IW, Wirth MA, Alton KB. Intestinal lymphatic transport for drug delivery. Adv Drug Deliv Rev. 2011;63:923–42.

Oral Drug Delivery and Food-Drug Interactions

P. Zarmpi and N. Fotaki
Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

Synonyms

Fed state; Food administration; Food ingestion; Food-drug interactions; Meal intake

Definition

Food interactions refer to the changes in the composition of the fluids and parameters of the gastrointestinal tract that may (or may not) affect the rate and extent of oral drug absorption through the lumen.

Impact of Food on the Composition of Gastrointestinal Fluids

Mouth cavity and esophagus: Meal intake stimulates the secretion of saliva by the salivary glands.

Secretion is triggered centrally or by chewing. Saliva is mainly composed of water, electrolytes, enzymes, and antimicrobial agents [1] and maintains a pH of approximately 7.0. Processing of meal begins in the oral cavity by mastication, which increases the surface area of the food and facilitates swallowing [2]. Masticated food is transferred to the stomach through the esophagus; meal or drug absorption in the mouth or esophagus is limited due to the tough and thick surface layer stratified-squamous epithelium [2].

Stomach: The stomach serves in mixing and digesting food components. Food administration will instantly increase the gastric pH (from 1.4–2.1 to 4.3–5.4 in the fasted and fed state, respectively, [4]) according to the type of meal [3]. Gastric pH values will return to their fasting levels due to meal dilution by gastric secretions and meal removal by gastric emptying [3]. This is a gradual and variable process depending on the type of the ingested food [3]. Approximately, a 3.5 h time window is suggested after which fasting pH level will be restored [5]. Changes in the bile salt level in the fed stomach are considered minor [6]; however, the concentrations of lipids increase post-meal administration (0.56 mg/mL and 150 mg/mL in the fasted and fed state, respectively) [4]. The buffer capacity (7 mmol L^{-1} ΔpH^{-1} and 14–28 mmol L^{-1} ΔpH^{-1} in the fasted and fed state, respectively) and osmolality (98 mOsm kg^{-1} and 559 mOsm kg^{-1} in the fasted and fed state, respectively) of the gastric fluids will increase in food presence [4]. Values for both the aforementioned parameters depend on the characteristics (input values) of the meal [5]. A 30% reduction in the surface tension of the gastric fluids has been observed in fed (30.0–31.0 mN m^{-1}) as compared to fasted (41.9–45.7 mN m^{-1}) conditions [5]. An increase in the viscosity of the gastric fluids can be anticipated according to the type of meal [7]. The volume of the gastric contents is expected to increase with food, according to the amount of the ingested solid or liquid [4].

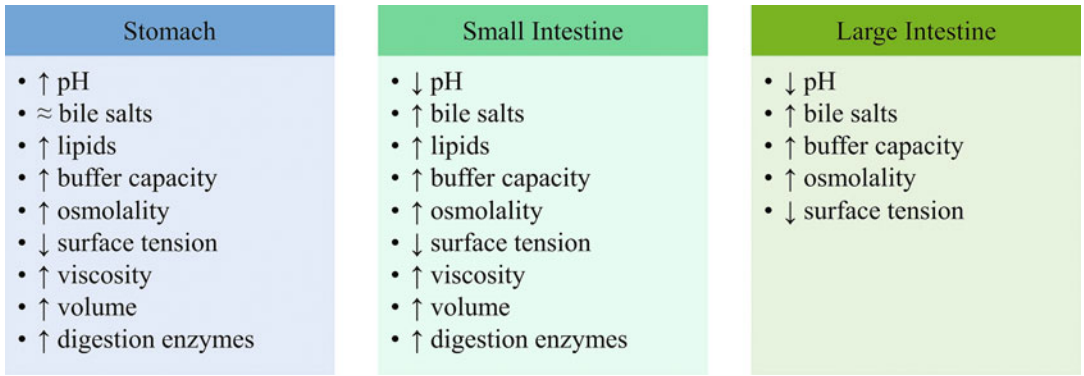
The stomach plays a key role in digesting the administered food. Meal ingestion stimulates the secretion of gastric lipase, a lipolytic enzyme secreted by the chief cells in the fundus [8] and able to hydrolyze a significant fraction of triglycerides (10%–30%) to fatty acids and glycerol [9, 10]. An increase in the gastric lipase levels is observed from the time of meal administration and until the 100% of the food has been emptied from the stomach. Reported levels of gastric lipase are 15–20μg/mL and 108μg/mL at 50% and 100% gastric emptying, respectively. Pepsin is another key enzyme in the gastric digestion process. It is an endopeptidase (secreted by the chief cells in the stomach) responsible for the digestion of the proteinic components of the food. Pepsin levels increase after meal ingestion in the stomach (mean values of 0.87 mg/mL and 1.68 mg/mL in the fasted and fed state, respectively) [4]. Variations in the pepsin levels in vivo, attributed to differences in experimental protocols, have been reported [5]. An overview of the changes that food intake induces in the stomach is shown in Fig. 1.

Small Intestine: The small intestine is the main gastrointestinal part in which dietary components or drugs will be absorbed into the systemic circulation. Post-meal administration, the pH of the fluids in the different small intestinal segments will decrease due to the emptying of the gastric fluids: (i) duodenum: 5.8–6.5 (fasted state) and 3.1–6.7 (fed state), (ii) jejunum: 4.4–6.5 (fasted state) and 5.2–6.0 (fed state), and (iii) ileum: 6.8–8.0 (fasted state) and 6.8–7.8 (fed state) [4]. Changes in the pH of the intestinal fluids depend on the buffer capacity of the administered meal [5]. The introduction of meal components in the small intestine stimulates the secretion of cholecystokinin, which in turn triggers gallbladder contraction, and the release of bile into the small intestine [1]. As a result, bile salt levels increase post-meal administration [(i) duodenum: 1–5.3 mM (fasted state) and 1.6–6.2 mM (fed state), (ii) jejunum: 0.8–5.5 mM (fasted state) and 0.5–40 (fed state) and (iii) ileum: 2–10 mM (fasted state) and 0.5–30 (fed state)] [4]. Significant increase is also expected in the levels of lipids and phospholipids due to meal ingestion [4]. As in the fed stomach, the buffer capacity [(i) duodenum: 4–13 mmol L^{-1} ΔpH^{-1} (fasted state) and 18–30 mmol L^{-1} ΔpH^{-1} (fed state), (ii) jejunum: 2.4–2.8 mmol L^{-1} ΔpH^{-1} (fasted state) and 13.2–14.6 mmol L^{-1} ΔpH^{-1} (fed state), (iii) ileum: data non available] and

osmolality [(i) duodenum: 124–266 mOsm kg^{-1} (fasted state) and 250–367 mOsm kg^{-1} (fed state), (ii) jejunum and ileum: data non available] in the small intestine will increase after meal intake [4]. The increase in bile salt levels triggers a reduction in the surface tension in the small intestine [(i) duodenum: 33.3–46.0 mN m^{-1} (fasted state) and 32.2–36.7 mN m^{-1} (fed state), (ii). jejunum: 28 mN m^{-1} (fasted state) and 27 mN m^{-1} (fed state) and (iii) ileum: data non available] [4]. As per the stomach, changes (increase) in the viscosity of upper gastrointestinal fluids may occur post administration of food (e.g., fibers) [7]. The volume of the intestinal fluids is expected to increase (30–420 mL and 18–660 mL in the fasted and fed state, respectively) depending on the rate at which fluids are emptied from the stomach [4].

Digestion of dietary products occurs in the small intestine. The pancreatic juice contains several key enzymes for digestion [1]. Pancreatic enzymes are able to cleave proteins, polypeptides, triglycerides, and phospholipids, and to assist in the absorption of dietary components. Pancreatic lipase is the enzyme responsible for the degradation of lipids (40–70%) in the small intestine [11]. It assists in the conversion of triglycerides into fatty acids and monoglycerides [1]. Postprandially, a 5–10-fold increase in the levels of pancreatic lipase has been reported [11]. Phospholipase A2 mediates the conversion of phospholipids into fatty acids and lysophospholipids, with an approximately five-fold increase in its levels reported in the fed state [11]. Differences in the levels of other nonspecific esterases in the small intestine were minor between the fasted and fed state [11]. The compositional parameters that change upon food administration in the small intestine are presented in Fig. 1.

Large Intestine: The large intestine is responsible for the absorption of water and electrolytes, formation of feces and bacterial fermentation of certain indigestible materials. Data on colonic (ascending colon) contents indicate a reduction in the pH of the fluids in the fed state (median values of 7.8 and 6.0 in the fasted and fed state, respectively) [12]. Total bile acid concentrations are significantly higher in the fed state, when compared to the fasted state, as a result of the gallbladder stimulation by food (mean values of 115.2μM and 587.4μM in the fasted and fed state, respectively) [12]. As a result of food administration and lipid digestion, the average levels of carbohydrates [8.1 mg/mL (fasted state) and 14 mg/mL (fed state)], long chain fatty acids [120μM (fasted state) and 225μM (fed state)], phosphatidylcholine [362μM (fasted state) and 539μM (fed state)] and cholesterol [594μM (fasted state) and 1502μM (fed state)] are increased in the fed colon [13]. An increase in the buffer capacity [21.4 mmol L^{-1} ΔpH^{-1} (fasted state) and 37.7 mmol L^{-1} ΔpH^{-1} (fed state)] and osmolality [81 mOsm kg^{-1} (fasted state) and



Oral Drug Delivery and Food-Drug Interactions, Fig. 1 Overview of the induced changes in the composition of the gastrointestinal fluids upon meal administration. ↑, ↓ and ≈ indicate increase, decrease and no change in the values of each parameter, respectively

227 mOsm kg^{-1} (fed state)] of colonic fluids post-meal administration has also been reported [12, 13]. As in the stomach and small intestine, the surface tension of the fluids in the large intestine is lower in food presence (39.2 mN m^{-1}) as compared to food absence (42.7 mN m^{-1}) [12, 13] (Fig. 1).

Impact of Food on Gastrointestinal Physiological Processes

Hydrodynamics: The primary role of the gastrointestinal system is the digestion and absorption of dietary components. Food softening and mixing with the gastrointestinal fluids is, therefore, critical. In the fasted state, the migrating motor complex (MMC; cycles of motor activity migrating from the stomach to the distal ileum [1]) promotes the movement of luminal contents toward the large intestine. MMC consists of four phases during the fasted state: (i) Phase 1: quiescence, (ii) Phase 2: irregular contractions of medium amplitude, (iii) Phase 3: regular contractions of high amplitude, (iv) Phase 4: irregular contractions of descending amplitude [14]. Upon food ingestion, these cycles are interrupted by one phase of regular and frequent contractions of high amplitude. These peristaltic movements in the stomach and small intestine facilitate mixing and bring particles into contact with the intestinal mucosal cells.

Gastric emptying: Passage of fluids from the stomach into the small intestine is regulated by gastric emptying. It is controlled by peristaltic waves, and the contraction of the antrum followed by the contraction of the pylorus and duodenum [1]. The rate at which liquids and solids are emptied into the small intestine depends on the amount, size/nature of ingested meal, and the MMC phase during which meal was ingested [4]. An increase in the gastric residence times and delay in gastric emptying is expected post-meal administration with mean times for complete gastric emptying of 25 and 40 min in the fasted and fed state, respectively [4]. For solid meals, the time to reach 50% of gastric emptying may range between 70 and 130 min [15].

Intestinal Transit Times: An increase in the intestinal transit times is observed post-meal administration to allow for food digestion and absorption. Reported mean transit times in the entire small intestine were 192 min and 276 min in the fasted and fed state, respectively [4]. Reported mean transit times from the duodenum to jejunum and ileum in the fed state were 32 min and 59 min, respectively [4].

Impact of Food on Oral Drug Delivery

The aforementioned changes in the gastrointestinal fluids and processes may be rendered critical for oral drug delivery. The effects of food on drug bioavailability can be more complex and depend on the characteristics of the drug, dosage form, and administered meal [16]. In general, the impact of food intake on oral drug absorption is categorized as: (i) zero food effect (no changes in oral drug absorption), (ii) positive food effects (increase in oral drug absorption) and (iii) negative food effects (reduction in oral drug absorption).

Zero Food Effect: In certain cases, the rate and extent of oral drug absorption can be unaffected by meal presence. Usually, this relates to drugs that:

- Are not influenced by the food-induced gastrointestinal changes [17]
- Are completely and rapidly absorbed in the fasted state [17]
- Are readily absorbed throughout the different regions of the gastrointestinal tract [17]

The changes in the pH of the gastrointestinal fluids may not influence the performance of certain drugs/formulations for which dissolution is pH independent [18]. The food-induced delay in gastric emptying may delay oral drug bioavailability, as the amount of drug entering in the small intestine can be reduced. For drugs with dose vs pharmacodynamic response relationship insensitive to small changes in dose, the effects of meal intake on oral drug absorption can be insignificant [19]. The presence of food may increase

the small intestinal transit times. As a result, the increased contact time with the intestinal mucosa may increase oral drug bioavailability. For drugs administered in certain formulations (e.g., sustained release) that are well absorbed along the entire length of the intestine under fasted conditions, the prolonged residence time in the small intestine in the fed state may not be critical [16]. A list of drugs for which meal intake has been found insignificant for absorption is presented in Table 1.

Positive food effect: An increase in oral drug absorption is reflected by an increase in the area under the curve (AUC) of the plasma concentration vs time profile and the C_{max} of the absorbed drug. Meal intake may significantly improve oral drug bioavailability in certain cases and usually poorly soluble drugs benefit from food intake. The main reported mechanisms for increased oral drug bioavailability include:

- Enhanced drug solubilization in the lipidic (fat) meal phase
- Enhanced drug solubilization by the increased levels of bile salts
- Improved dissolution by bile salts and food lipids
- Accelerated dissolution for drugs with higher solubility at gastric pH values due to delayed gastric emptying
- Increased contact time with intestinal mucosa due to prolonged transit times
- Absence of drug supersaturation and/or precipitation in the small intestine for weak bases due to reduced pH

As the majority of drugs are poorly soluble lipophilic compounds, food (specially lipidic components) can help solubilize the drug and/or increase its solubility, thus increasing the driving force for absorption through the gastrointestinal tract [20]. Moreover, dietary lipids can directly facilitate the dissolution of lipophilic compounds [21]. The increased levels of solubilizing components (e.g., bile salts) in food presence can also be a confounding factor for lipophilic drugs [20, 21]. The delayed gastric emptying allows for the accelerated dissolution of certain poorly soluble lipophilic drugs and has been suggested as a mechanism for the increased absorption of certain drugs [22]. "Dose-dumping" (phenomenon describing the earlier than expected release of the active pharmaceutical ingredient) effects, as a result of meal intake, are particularly critical in the case of modified release formulations. The presence of fats, high bile salt levels, and pH changes after meal intake have been identified as factors affecting the integrity of matrices or coatings, hence resulting in increased drug release rates [23]. Such effects are of great risk and can compromise patient safety. For the interesting case of weak bases in vivo, food effects can be critical. The differences in the solubility of weak basic compounds in the stomach and small intestine (due to the different pH of the fluids in the two compartments) may induce a state of drug supersaturation and subsequent drug precipitation upon transfer of the drug in the small intestine, in the fasted state. However, the reduced pH values in the intestinal fluids under fed conditions are unlikely to contribute to the generation of a

Oral Drug Delivery and Food-Drug Interactions, Table 1 List of drugs for which meal intake has been found to exert zero, positive and negative food effect (information obtained from [30])

Zero food effect	Positive food effect	Negative food effect
Alprazolam	Amiodarone	Alendronate
Amlodipine	Astemizole	Atenolol
Bambuterol	Cefuroxime	Didanosine
Bisoprolol	Clarithromycin	Metformin
Brofaramine	Danazol	Methotrexate
Bromocriptine	Diltiazem	Naproxen
Carbamazepine	Felodipine	Phenutoin
Cimetidine	Itraconazole	Pravastatin
Cyclosporine	Nifedipine	Rufloxacin
Diazepam	Progesterone	Verapamil
Ibuprofen	Theophylline	Zidovudine

supersaturation state once the drug enters into the small intestine. Such effect has been suggested as a potential mechanism for the improved bioavailability of weak bases post-meal administration [24]. A list of drugs for which meal intake has been found to improve absorption is presented in Table 1.

Negative food effect: A negative food effect may either relate to delayed and/or decreased (reduced AUC and C_{max}) oral drug absorption [17]. Delayed oral drug absorption refers to a slower rate but unaffected extent of oral drug absorption. A delay in oral drug absorption is usually caused by highly soluble and rapidly absorbed drugs as a result of the delay in gastric emptying by food presence [25]. Decreased oral drug absorption relates to lower AUC and C_{max} values. The main mechanisms by which food can reduce oral drug bioavailability include:

- Incomplete drug dissolution due to elevated gastric pH values (case of weak bases)
- Drug instability in gastric fluids
- Binding of drugs or gastrointestinal components with food
- Reduced drug diffusion rate

For weak bases, complete dissolution in the stomach is feasible due to the low gastric pH. The increase in the gastric pH values post-meal administration can lead to incomplete drug dissolution and hence low drug bioavailability [26]. The delay in gastric emptying can be critical for certain acid-labile drugs, as their prolonged residence in the stomach may increase their degradation and reduce the bioavailability of the parent molecule [17]. Interactions of certain food components with bile salts can reduce the amount of solubilizing components, and hence decrease drug absorption [27]. Certain drugs can also form insoluble complexes with iron or calcium-containing food and exhibit lower oral bioavailability. The increased viscosity of the gastrointestinal fluids can as well be detrimental for oral drug absorption. Suggested mechanisms behind the impact of food viscosity on the reduced oral drug absorption include: (i) inhibition of gastric emptying and/or modification of intestinal transit times; (ii) slower diffusion of drugs towards the intestinal membrane; (iii) reduced disintegration of the dosage form; and (iv) reduced drug dissolution [28]. A list of drugs for which food has been found to reduce absorption is presented in Table 1.

Simulated Fed Fluids

To date, simulation of the contents of the gastrointestinal fluids post-meal administration in vitro is critical to evaluate and predict the impact of food effects on oral drug absorption in vivo.

Stomach: The physicochemical characteristics of the fed stomach are complex and change over time. Two approaches have been developed for simulation of the fed gastric fluids: (i) development of snapshot media which reflect the pH values, buffer capacity, and osmolality of the stomach 75 min (early), 75–165 min (middle) and after 165 min (late) post-meal intake; and (ii) gradual digestion of milk by adding physiologically relevant amounts of hydrochloric acid containing pepsin [29]. The digestion process can be further simulated by addition of gastric lipase in the medium [29].

Small Intestine: Various media have been developed to simulate the contents of the fed small intestine. These include the two versions of the standardized Fed State Simulated Intestinal Fluids (FeSSIF) and snapshot media taking into account the gradual digestion process [29].

Large Intestine: Simulation of the fed colonic contents is currently based on the use of the Fed State Simulated Colonic Fluid (FeSSCoF), which has been found to adequately predict solubility data when compared to human colonic fluids [13].

Cross-References

- ▶ Bioavailability
- ▶ Biorelevant Dissolution Media
- ▶ Gastric Emptying
- ▶ Migrating Motor Complex
- ▶ Oral Drug Delivery

References

1. Barrett KE, Ganong WF. Ganong's review of medical physiology. 15th ed. New York: McGraw-Hill Medical; 2012.
2. Vertzoni M, Augustijns P, Grimm M, Koziolek M, Lemmens G, Parrott N, et al. Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption: an UNGAP review. Eur J Pharm Sci. 2019;134:153–75.
3. Sams L, Paume J, Giallo J, Carrière F. Relevant pH and lipase for in vitro models of gastric digestion. Food Funct. 2016;7(1):30–45.
4. Mudie DM, Amidon GL, Amidon GE. Physiological parameters for oral delivery and in vitro testing. Mol Pharm. 2010;7(5):1388–405.
5. Kalantzi L, Goumas K, Kalioras V, Abrahamsson B, Dressman JB, Reppas C. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. Pharm Res. 2006;23(1):165–76.
6. Rhodes J, Barnardo DE, Phillips SF, Rovelstad RA, Hofmann AF. Increased reflux of bile into the stomach in patients with gastric ulcer. Gastroenterology. 1969;57(3):241–52.
7. Reppas C, Eleftheriou G, Macheras P, Symillides M, Dressman JB. Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption in dogs. Eur J Pharm Sci. 1998;6(2):131–9.
8. Carrière F, Renou C, Lopez V, de Caro J, Ferrato F, Lengsfeld H, et al. The specific activities of human digestive lipases measured from the in vivo and in vitro lipolysis of test meals. Gastroenterology. 2000;119(4):949–60.
9. Pafumi Y, Lairon D, de la Porte PL, Juhel C, Storch J, Hamosh M, et al. Mechanisms of inhibition of triacylglycerol hydrolysis by human gastric lipase. J Biol Chem. 2002;277(31):28070–9.
10. Wojdemann M, Olsen O, Norregaard P, Sternby B, Rehfeld JF. Gastric lipase secretion after sham feeding and cholinergic blockade. Digest Dis Sci. 1997;42(5):1070–5.
11. Riethorst D, Mols R, Duchateau G, Tack J, Brouwers J, Augustijns P. Characterization of human duodenal fluids in fasted and fed state conditions. J Pharm Sci. 2016;105(2):673–81.
12. Diakidou A, Vertzoni M, Goumas K, Söderlind E, Abrahamsson B, Dressman J, et al. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. Pharm Res. 2009;26(9):2141–51.
13. Vertzoni M, Diakidou A, Chatzilias M, Söderlind E, Abrahamsson B, Dressman JB, et al. Biorelevant media to simulate fluids in the ascending colon of humans and their usefulness in predicting intracolonic drug solubility. Pharm Res. 2010;27(10):2187–96.
14. Shargel L, Wu-Pong S, Yu ABC. Applied biopharmaceutics and pharmacokinetics. 6th ed. New York: Appleton and Lange Reviews/McGraw0Hill, Medical Pub. Division; 2005.
15. Dressman JB. Comparison of canine and human gastrointestinal physiology. Pharm Res. 1986;3(3):123–31.
16. Pargal A, Kelkar MG, Nayak PJ. The effect of food on the bioavailability of ibuprofen and flurbiprofen from sustained release formulations. Biopharm Drug Dispos. 1996;17(6):511–9.
17. Abuhelwa AY, Williams DB, Upton RN, Foster DJR. Food, gastrointestinal pH, and models of oral drug absorption. Eur J Pharm Biopharm. 2017;112:234–48.
18. Eller MG, Della-Coletta AA. Absence of effect of food on alprazolam absorption from sustained release tablets. Biopharm Drug Dispos. 1990;11(1):31–7.
19. Whitfield LR, Stern RH, Sedman AJ, Abel R, Gibson DM. Effect of food on the pharmacodynamics and pharmacokinetics of atorvastatin, an inhibitor of HMG-CoA reductase. Eur J Drug Metab Pharm. 2000;25(2):97–101.
20. Emami Riedmaier A, Lindley DJ, Hall JA, Castleberry S, Slade RT, Stuart P, et al. Mechanistic physiologically based pharmacokinetic modeling of the dissolution and food effect of a biopharmaceutics classification system IV compound – the venetoclax story. J Pharm Sci. 2018;107(1):495–502.
21. Aoyagi N, Ogata H, Kaniwa N, Ejima A. Effect of food on the bioavailability of griseofulvin from microsize and PEG ultramicrosize (GRIS-PEG) plain tablets. J Pharm Dyn. 1982;5(2):120–4.
22. Hamaguchi T, Shinkuma D, Irie T, Yamanaka Y, Morita Y, Iwamoto B, et al. Effect of a high-fat meal on the bioavailability of phenytoin in a commercial powder with a large particle size. Int J Clin Pharmacol Therapy Toxicol. 1993;31(7):326–30.
23. Klein S. Predicting food effects on drug release from extended-release oral dosage forms containing a narrow therapeutic index drug. Diss Tech. 2009;16(3):28–40.
24. Shono Y, Jantratid E, Dressman JB. Precipitation in the small intestine may play a more important role in the in vivo performance of poorly soluble weak bases in the fasted state: case example nelfinavir. Eur J Pharm Biopharm. 2011;79(2):349–56.
25. Davit BM, Conner DP. Food effects on drug bioavailability: implications for new and generic drug development. In: Krishna R, Yu L, editors. Biopharmaceutics applications in drug development. Boston: Springer; 2008. p. 317–35.
26. Männistö PT, Mäntylä R, Nykänen S, Lamminsivu U, Ottoila P. Impairing effect of food on ketoconazole absorption. Antimicrob Agents Chemother. 1982;21(5):730–3.
27. Huupponen R, Seppälä P, Iisalo E. Effect of guar gum, a fibre preparation, on digoxin and penicillin absorption in man. Eur J Clin Pharmacol. 1984;26(2):279–81.
28. Radwan A, Amidon GL, Langguth P. Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity. Biopharm Drug Dispos. 2012;33(7):403–16.

29. Fotaki N, Vertzoni M. Biorelevant dissolution methods and their applications in in vitro-in vivo correlations for oral formulations. Open Drug Deliv J. 2010;4(1):2–13.
30. Welling PG. Effects of food on drug absorption. Ann Rev Nutrit. 1996;16:383–415.

Oral Route

► Oral Drug Delivery

Organ Clearance

► Total Clearance and Organ Clearance

Organic Anion Transporters and Organic Anion Transporting Polypeptides

Alan Talevi[1,2] and Carolina L. Bellera[1,3]
[1]Laboratory of Bioactive Research and Development (LIDeB), Department of Biological Sciences, University of La Plata (UNLP), La Plata, Buenos Aires, Argentina
[2]Argentinean National Council of Scientific and Technical Research (CONICET) – CCT, La Plata, Buenos Aires, Argentina
[3]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), La Plata, Buenos Aires, Argentina

Synonyms

OAT; OAT1; OAT10; OAT2; OAT3; OAT4; OAT7; OATP; Organic Anion Transporting Polypeptides; SLC21; SLC22A; SLCO; URAT1

Definition

Organic anion transporters (OATs) are members of the solute carrier (SLC) group of transporters and belong to the Major Facilitator superfamily (MFS). According to the Human Genome Organization (HUGO), they are assigned to the SLC22A family, that also includes the Organic Cation Transporters (OCTs) and the Organic Carnitine (zwitterion) Transporters (also known as Novel Organic Cation Transporters, OCTNs), with which OATs share many general structural features. OATs are multispecific carriers that transport rather small organic anions, including endogenous compounds, such as p-aminohippurate, prostaglandins, guanine nucleotide-related compounds, cGMP, and steroid conjugates, among others, and also exogenous compounds including many antivirals, nonsteroidal anti-inflammatory drugs, statins, diuretic agents, antimetabolites, and antibiotics, among others [1]. They have a pivotal role in the basolateral (Phase 0) uptake of their substrates into epithelial cells of drug-eliminating organs and also in drug reabsorption. In humans, most OATs are highly expressed in the human liver and kidneys, and at lower levels in the brain, placenta, testis, and prostate [2]. OATs from the SLC22A family include OAT1-10 (SLC22A6, SLC22A7, SLC22A8, SLC22A11, SLC22A10, SLC22A20, SLC22A9, SLC22A25, SLC22A27, SLC22A13, in that order) and the urate transporter URAT1 (SLC22A12). Whereas prototypical members of the SLC22A family can mediate the bidirectional movement of substrates, most of the OATs generally facilitate the uptake of organic anions into epithelial cells (functioning as influx transporters) by secondary/tertiary active transport (specifically, by exchange with dicarboxylates, such as α-ketoglutarate) or monocarboxylates [2, 3].

Organic Anion Transporting Polypeptides (OATPs) are also SLCs that belong to the MFS. According to the HUGO, they are currently assigned to the SLCO family (formerly SLC21). They also participate in the cellular uptake of their substrates and, as OATs, possess wide substrate specificity. However, they preferably transport larger (>350 g/mol) amphiphilic or hydrophobic anionic substrates [1, 4, 5], including bile acids, conjugated steroids, peptides, and thyroid hormones, as well as many drugs such as sartans, statins, antibiotics, and anticancer agents. In

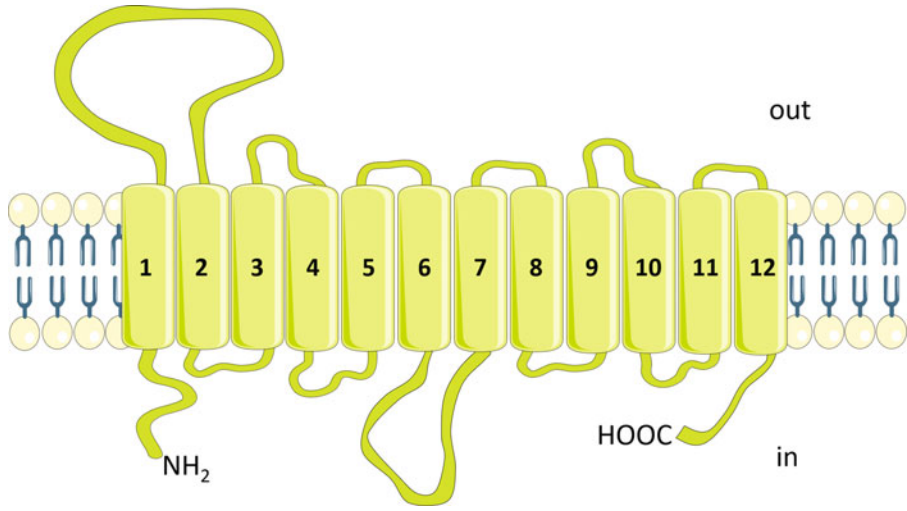
humans, OATPs include 11 members: OATP1A2 (SLCO1A2), OATP1B1 (SLCO1B1), OATP1B3 (SLCO1B3), OATP1C1 (SLCO1C1), OATP2A1 (SLCO2A1, also known as the prostaglandin transporter PGT), OATP2B1 (SLCO2B1), OATP3A1 (SLCO3A1), OATP4A1 (SLCO4A1), OATP4C1 (SLCO4C1), OATP5A1 (SLCO5A1), and OATP6A1 (SLCO6A1) [1, 5]. The transport mechanism via OATP transporters is believed to occur by electroneutral exchange, where uptake is coupled to the efflux of other anions such as glutathione or bicarbonate [1, 6].

Structure, Mechanism of Transport, and Regulation of OATs and OATPs

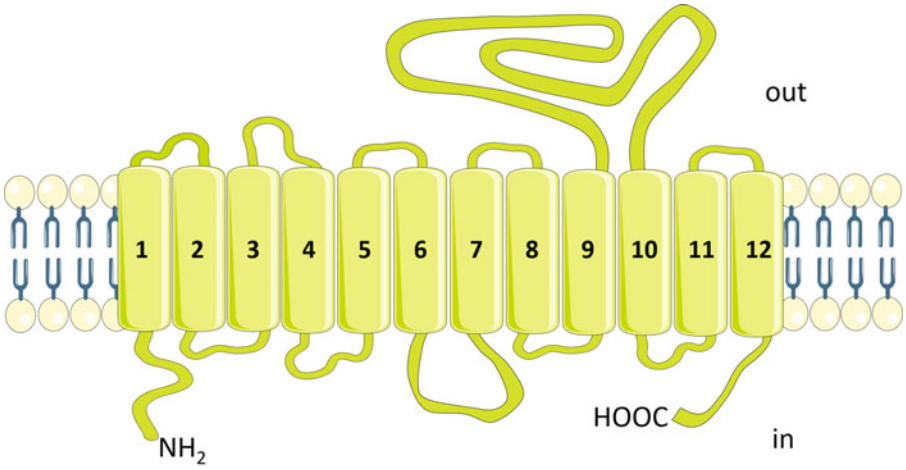
OATs, alike the rest of the transporters of the SLC22A family, share a similar predicted membrane topology [1] (Fig. 1) that involves twelve alpha-helical transmembrane domains (TMDs); a large extracellular loop between TMDs 1 and 2, which presents conserved glycosylation sites; a large intracellular loop between TMDs 6 and 7, which contains conserved phosphorylation sites; and intracellular C- and N-termini. The consensus sequences for phosphorylation and glycosylation play a relevant role in rapid, posttranscriptional regulation of the transporter activity [7–9].

Regarding OATPs, available data is consistent with 12 TMDs with six extracellular loops and five intracellular loops and both termini on the cytoplasmic side [1, 5] (Fig. 2). A large extracellular loop locates between TMDs 9 and 10, and amino acids subject to N-glycosylation are found in the extracellular loop linking TMDs 3 and 4, and 9 and 10 [8]. It has been proven that rat Oatp1a1 and (human) OATP1B1 are N-glycosylated in the second and fifth extracellular loops and that the non-glycosylated proteins are retained intracellularly, with consequent reduced transport function [10, 11]. It is thus probable that other mammalian OATPs exhibit the same behavior.

OATs and OATPs general mode(s) of transport corresponds to the alternating access model, usually described as a "rocker-switch" mechanism [12–14]. According to this model, these transporters expose a central binding cavity to either the extracellular or intracellular spaces and concurrently seal the opposing face of the transporter, preventing a continuous channel or pathway across the membrane. When a substrate binds on one side of the membrane, the protein undergoes a conformational shift that enables the release of the substrate on the other site. A substrate that is preferably uptaken by the cell would display higher affinity for the outward-open conformation and reduced affinity for the inward-open



Organic Anion Transporters and Organic Anion Transporting Polypeptides, Fig. 1 Proposed topology of OATs



Organic Anion Transporters and Organic Anion Transporting Polypeptides, Fig. 2 Proposed topology of OATPs

conformation. As observed in other polyspecific transporters, available evidence (fundamentally from site-directed mutagenesis and homology modeling studies) suggests that the binding pocket contains multiple binding sites that allow accommodating structurally distinct substrates and modulators [15–17]. Several conserved positively charged amino acids (which have been regarded as "positive binding pocket"), including basic amino acids arginine and lysine, are deemed crucial for anionic substrate recognition and translocation [15, 18–20] in both OATs and OATPs.

Noteworthy, unlike OCTs, transporters for anionic substrates have to translocate ionized species against the membrane potential, which normally is inside-negative. To overcome this energetically unfavorable process, it is proposed that both OATs and OATPs mediate secondary/tertiary active transport by exchanging their anionic substrates by other negatively charged species [5, 21].

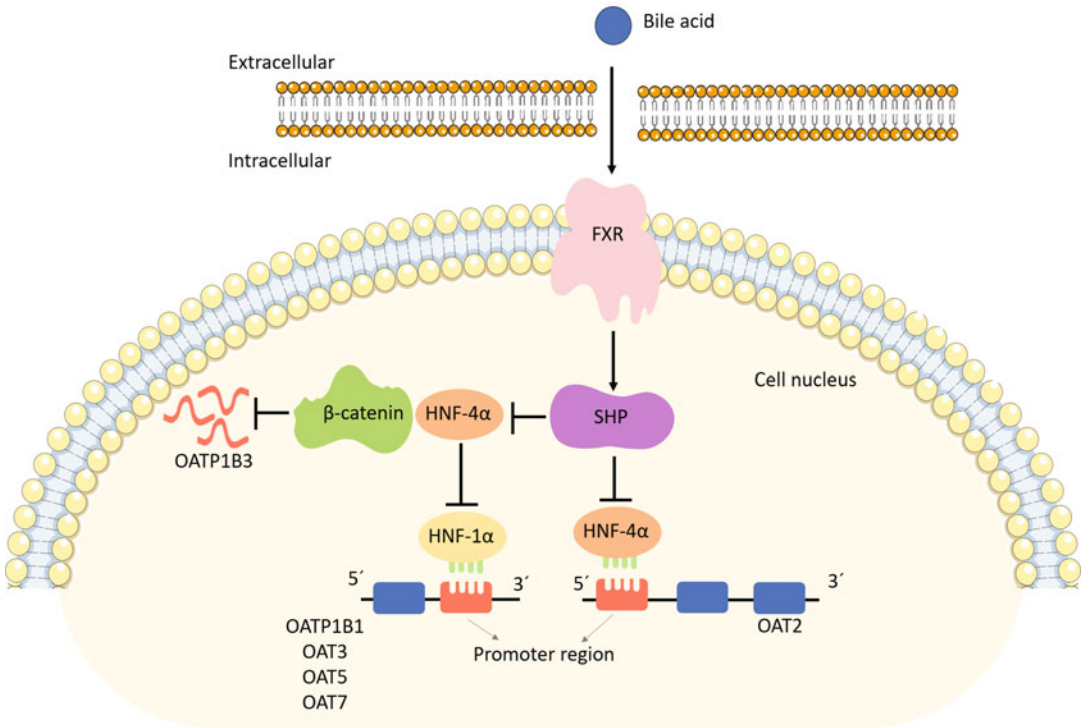
In the case of OATs, the overall transport process can be deemed as tertiary active transport, based on its placement subsequent to secondary active transport [21]. The steps determining the organic anion transport can be summarized as follows: Firstly, the Na^+/K^+-ATPase pump uses ATP to fuel an inwardly driven Na^+ gradient across the cell membrane; secondly, a symporter (e.g., the Na^+/dicarboxylate cotransporter) utilizes the energy stored as Na^+ gradient to move another ion (usually, a readily available endogenous divalent anion such as α-ketoglutarate) against its electrochemical gradient, therefore building up an outwardly directed gradient for this exchange substrate; thirdly, an OAT exchanges this counter-anion by an extracellular substrate, which is also usually an anion. In the case of OATPs, the counter ion to which the substrate uptake is coupled may be bicarbonate, glutathione, conjugated glutathione, or glutamate [22].

OATs and OATPs expression are regulated at different levels, both transcriptionally and post-transcriptionally. At the transcriptional level, both transcription factors and epigenetics play a role in the regulation of OATs and OATPs [1, 3, 8]. Transcription factors regulate gene expression by binding to genomic elements and recruiting transcriptional machinery, chromatin-modifying complexes, etc. They respond to diverse signals, acting as "sensors" of molecules elaborated in remote tissues (e.g., hormones) or of exogenous molecules (e.g., nutrients, drugs, toxins) [3] (some additional insight into transcriptional factors can be found in the entry ▶ "Enzyme Induction and Drug Metabolism"). For example, hypothalamic-pituitary-gonadal axis, mediated by estrogens, androgens, and growth hormone, has been implicated in the regulation of some SLC22A/SLCO transporters in animals, and it is possible that pituitary hormones may also contribute to regulate

transporter function in humans. Liver-specific transcription factors are key regulators of human OAT and OATP genes. Hepatocyte nuclear factor-1α (HNF1α) upregulates OAT1, OAT3, OAT5, OAT7, OATP1B1, and OATP1B3; the nuclear receptor HNF4α also transactivates OAT1, OAT2, OATP1B1, OATP1B3, and OATP2B1 promoters [1, 8]. Bile acids such as chenodeoxycholic acid, deoxycholic acid, and lithocholic acid are endogenous ligands that activate the farnesoid X receptor (FXR), which plays a pivotal role in bile acid feedback regulation systems [1, 23]. FXR, in turn, induces different target genes, among them the transcriptional repressor small heterodimer partner, SHP, another nuclear receptor that counteracts HNF-4α [24] (Fig. 3). FXR may also directly bind to a negative response element in the HNF-4α promoter [1].

Epigenetic mechanisms are also relevant in the regulation of certain OATs and OATPs genes. For instance, extensive methylation of nucleotides around the transcription start site of OAT1 and OAT3 in the human liver may explain the kidney-specific expression of such transporters [25].

Short-term regulation of OATs and OATPs may be mediated by phosphorylation, which can modulate the subcellular trafficking and turnover of transporters [8] (as previously said, the intracellular loop and -COOH terminus include conserved phosphorylation sites). *N*-glycoxidation and oligomerization are essential to target the nascent transporter copies to the plasma membrane [26, 27]. In contrast, ubiquitination regulates internalization and subsequent proteasomal and lysosomal degradation [8].



Organic Anion Transporters and Organic Anion Transporting Polypeptides, Fig. 3 Hepatocyte nuclear factors (HNF) are among the transcription factors that regulate organic anion transporters (OATs) and Organic Anion Transporting Polypeptides (OATPs). Different bile acids can activate the farnesoid X receptor (FXR), which in turn activates the target gene small heterodimer partner (SHP). SHP negatively regulates HNF-4α. HNF-1α is also regulated by HNF-4α; thus, downregulation of HNF-4α can also indirectly downregulate target genes that codify for OATP1B1, OAT3, OAT5, and OAT7. Finally, HNF4-α downregulation by SHP inhibits the interaction between HNF4α and β-catenin, therefore downregulating the expression of OATP1B3

Role of OATs in Drug Disposition

The major OATs and OATPs expressed in the liver and the kidneys are critical for the first step in renal and/or biliary excretion of their substrates, including endogenous compounds as urate and several acidic drugs. That is, they mediate the basolateral uptake of their substrates, acting as Phase 0 transporters that facilitate the translocation of their substrates from the blood to the intracellular space of the eliminating cell, across the cellular membrane. This is a crucial step in drug disposition as ionized species would not be able to permeate through the cell membrane by simple diffusion and against the negative potential gradient (see the entries ▶ "Phase 0 and Phase III Transport" for further discussion). Accordingly, OATs and OATPs are a potential source of drug-drug interactions and genetic variability in the pharmacological response. Noteworthy, OATs and OATPs usually work in tandem with members of the ATP-binding Cassette superfamily which also transport acidic compounds and complete the elimination cycle, prominently MRPs (e.g., MRP2, MRP4) and BCRP.

The reader may also refer to the entries ▶ "Phase 0 and Phase III Transport", ▶ "Biliary Drug Excretion", and ▶ "Renal Drug Excretion" for illustrative schemes.

OAT1 and OAT3 are the key OATs that mediate the Phase 0 transport of small anionic compounds in the proximal tubule cells, whereas OAT2 is the key OAT at the sinusoidal membrane of the hepatocytes (where OAT5 and 7 are also expressed) [2, 28]. Drugs transported by OAT1 include tetracycline, several antiviral drugs (adefovir, acyclovir, zidovudine, ganciclovir, and others), the histamine receptor subtype 2 (H2) antagonists cimetidine and ranitidine, the diuretics furosemide and bumetanide, and the nonsteroidal anti-inflammatory drugs ketoprofen and ibuprofen, among others. OAT2 substrates include tetracycline, zidovudine, ranitidine, diclofenac, methotrexate, paclitaxel, 5-fluorouracil, and allopurinol, among others. Drugs that are transported by OAT3 include tetracyclines; the antivirals cidofovir, valacyclovir, zidovudine, adefovir, and others; the H2 receptor antagonists ranitidine, cimetidine, fexofenadine, and famotidine; and the diuretics furosemide, bumetanide, and torasemide; pravastatin and rosuvastatin; and methotrexate, among others. Other members of this group, like OAT4, OAT10, and URAT1, mediate the tubular reabsorption of their substrates (e.g., urate, nicotinate).

Regarding OATPs, OATP1B1, OATP1B3, and OATP2B1 are mainly expressed at the sinusoidal membrane of the hepatocytes, where they mediate the Phase 0 uptake of their substrates. OATP2B1 is also expressed in the apical membrane of the enterocytes and the endothelial cells of the blood-brain barriers (along with OATPA2), where they can facilitate the intestinal absorption and/or brain distribution of their substrates [2, 6]. OATP1B1 substrates include benzylpenicillin, bile acids, bilirubin, estradiol-17β-glucuronide, methotrexate, pravastatin, and olmesartan, among others. OATP1B3 substrates include benzylpenicillin, bilirubin, bile acids, estradiol-17β-glucuronide, methotrexate, paclitaxel, rosuvastatin, and saquinavir, among others. Benzylpenicillin, bilirubin, fexofenadine, montelukast, and several statins and steroids are among OATP2B1 substrates.

OATs have rather low genetic variability (particularly OAT1 and OAT2) in comparison, for instance, with OCTs [28]; polymorphisms found in the coding region of both OAT1 and OAT2 do not substantially contribute to interindividual variability in drug elimination. At least ten missense mutations have been found in the gene that codifies for OAT3 [29]. Contrariwise, a large number of genetic variants have been described for OATPs [6]. For example, the c.521T>C single nucleotide polymorphism has been linked to a substantially diminished transport activity of OATP1B1. Such polymorphism could have particular relevance for cholesterol-lowering therapies of the statins group as their mode of action involves the inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A reductase in the hepatocytes; consequently, reduced OATP1B1-mediated transport into the liver may simultaneously reduce the efficacy and enhance the risk of adverse effects (e.g., myopathy) of statins.

Some drugs, such as probenecid and some non-steroidal anti-inflammatory drugs, can exert inhibitory effects on OATs (e.g., OAT1). Their coadministration has been proposed to induce beneficial drug-drug interactions, for instance, by reducing the renal uptake of nephrotoxic drugs. The coadministration of probenecid and cidofovir, for instance, has been suggested to protect patients against cidofovir-induced nephrotoxicity linked to excessive renal accumulation [30].

Cross-References

- ABC Transporters: An Overview
- Biliary Drug Excretion
- Enzyme Induction and Drug Metabolism
- Organic Cation Transporters
- Phase 0 and Phase III Transport
- Renal Drug Excretion
- Solute Carrier (SLC) Transporters: An Overview

References

1. Li TT, An JX, Xu JY, Tuo BG. Overview of organic anion transporters and organic anion transporter polypeptides and their roles in the liver. World J Clin Cases. 2019;7:3915–33.
2. Koepsell H. The SLC22 family with transporters of organic cations, anions and zwitterions. Mol Asp Med. 2013;34:413–35.
3. Nigam SK, Bush KT, Martovetsky G, Ahn SY, Liu HC, Richard E, et al. The organic anion transporter (OAT) family: a systems biology perspective. Physiol Rev. 2015;95:83–123.
4. Roth M, Obaidat A, Hagenbuch B. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012;165:1260–87.
5. Stieger B, Hagenbuch B. Organic anion-transporting polypeptides. Curr Top Membr. 2014;73:205–32.
6. Niemi M. Role of OATP transporters in the disposition of drugs. Pharmacogenomics. 2007;8:787–802.
7. Tanaka K, Xu W, Zhou F, You G. Role of glycosylation in the organic anion transporter OAT1. J Biol Chem. 2004;279:14961–6.
8. Murray M, Zhou F. Trafficking and other regulatory mechanisms for organic anion transporting polypeptides and organic anion transporters that modulate cellular drug and xenobiotic influx and that are dysregulated in disease. Br J Pharmacol. 2017;174:1908–24.
9. Mayati A, Moreau A, Le Vée M, Stieger B, Denizot C, Parmentier Y, et al. Protein kinases C-mediated regulations of drug transporter activity, localization and expression. Int J Mol Sci. 2017;18:764.
10. Wang P, Hata S, Xiao Y, Murray JW, Wolkoff AW. Topological assessment of oatp1a1: a 12-transmembrane domain integral membrane protein with three N-linked carbohydrate chains. Am J Physiol Gastrointest Liver Physiol. 2008;294:G1052–9.
11. Yao J, Hong W, Huang J, Zhan K, Huang H, Hong M. *N*-glycosylation dictates proper processing of organic anion transporting polypeptide 1B1. PLoS One. 2012;7:e52563.
12. Svoboda M, Riha J, Wlcek K, Jaeger W, Thalhammer T. Organic anion transporting polypeptides (OATPs): regulation of expression and function. Curr Drug Metab. 2011;12:139–53.
13. Meier-Abt F, Mokrab Y, Mizuguchi K. Organic anion transporting polypeptides of the OATP/SLCO superfamily: identification of new members in non-mammalian species, comparative modeling and a potential transport mode. J Membr Biol. 2005;208:213–27.
14. Quistgaard EM, Löw C, Guettou F, Nordlund P. Understanding transport by the major facilitator superfamily (MFS): structures pave the way. Nat Rev Mol Cell Biol. 2016;17:123–32.
15. Weaver YM, Hagenbuch B. Several conserved positively charged amino acids in OATP1B1 are involved in binding or translocation of different substrates. J Membr Biol. 2010;236:279–90.
16. Hoshino Y, Fuita D, Nakanishi T, Tamai I. Molecular localization and characterization of multiple binding sites of organic anion transporting polypeptide 2B1 (OATP2B1) as the mechanism for substrate and modulator dependent drug–drug interaction. Med Chem Commun. 2016;7:1775–82.
17. Volk C. OCTs, OATs, and OCTNs: structure and function of the polyspecific organic ion transporters of the SLC22 family. WIREs Membr Transp Signal. 2014;3:1–13.
18. Feng B, Dresser MJ, Shu Y, Johns SJ, Giacomini KM. Arginine 454 and lysine 370 are essential for the anion specificity of the organic anion transporter, rOAT3. Biochemistry. 2001;40:5511–20.
19. Glaeser H, Mandery K, Sticht H, Fromm MF, König J. Relevance of conserved lysine and arginine residues in transmembrane helices for the transport activity of organic anion transporting polypeptide 1B3. Br J Pharmacol. 2010;159:698–708.
20. Mandery K, Sticht H, Bujok K, Schmidt I, Fahrmayr C, Balk B, et al. Functional and structural relevance of conserved positively charged lysine residues in organic anion transporting polypeptide 1B3. Mol Pharmacol. 2011;80:400–6.
21. VanWert AL, Gionfriddo MR, Sweet DH. Organic anion transporters: discovery, pharmacology, regulation and roles in pathophysiology. Biopharm Drug Dispos. 2010;31:1–71.

22. Ali Y, Shams T, Wang K, Cheng Z, Li Y, Shu W, Bao X, et al. The involvement of human organic anion transporting polypeptides (OATPs) in drug-herb/food interactions. Chin Med. 2020;15:71.
23. Ohtsuka H, Abe T, Onogawa T, Kondo N, Sato T, Oshio H, et al. Farnesoid X receptor, hepatocyte nuclear factors 1alpha and 3beta are essential for transcriptional activation of the liver-specific organic anion transporter-2 gene. J Gastroenterol. 2006;41:369–77.
24. Lee YK, Dell H, Dowhan DH, Hadzopoulou-Cladaras M, Moore DD. The orphan nuclear receptor SHP inhibits hepatocyte nuclear factor 4 and retinoid X receptor transactivation: two mechanisms for repression. Mol Cell Biol. 2000;20:187–95.
25. Jin L, Kikuchi R, Saji T, Kusuhara H, Sugiyama Y. Regulation of tissue-specific expression of renal organic anion transporters by hepatocyte nuclear factor 1 α/β and DNA methylation. J Pharmacol Exp Ther. 2012;340:648–55.
26. Zhou F, Xu W, Hong M, Pan Z, Sinko PJ, Ma J, et al. The role of N-linked glycosylation in protein folding, membrane targeting, and substrate binding of human organic anion transporter hOAT4. Mol Pharmacol. 2005;67:868–76.
27. Hänggi E, Grundschober AF, Leuthold S, Meier PJ, St-Pierre MV. Functional analysis of the extracellular cysteine residues in the human organic anion transporting polypeptide, OATP2B1. Mol Pharmacol. 2006;70:806–17.
28. Lozano E, Briz O, Macias RIR, Serrano MA, Marin JJG, Herraez E. Genetic heterogeneity of SLC22 family of transporters in drug disposition. J Pers Med. 2018;8:14.
29. Erdman AR, Mangravite LM, Urban TJ, Lagpacan LL, Castro RA, de la Cruz M, et al. The human organic anion transporter 3 (OAT3; SLC22A8): genetic variation and functional genomics. Am J Physiol Renal Physiol. 2006;290:F905–12.
30. Morrissey KM, Stocker SL, Wittwer MB, Xu L, Giacomini KM. Renal transporters in drug development. Annu Rev Pharmacol Toxicol. 2013;53:503–29.

Organic Anion Transporting Polypeptides

► Organic Anion Transporters and Organic Anion Transporting Polypeptides

Organic Carnitine Transporters

► Organic Cation Transporters

Organic Cation Transporters

Alan Talevi[1,2] and Carolina L. Bellera[1,3]
[1]Laboratory of Bioactive Research and Development (LIDeB), Department of Biological Sciences, University of La Plata (UNLP), La Plata, Buenos Aires, Argentina
[2]Argentinean National Council of Scientific and Technical Research (CONICET) – CCT, La Plata, Buenos Aires, Argentina
[3]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), La Plata, Buenos Aires, Argentina

Synonyms

SLC22A; Novel organic cation transporters; OCT1; OCT2; OCT3; OCTN1; OCTN2; Organic cation/carnitine transporters; Organic carnitine transporters; Organic zwitterion transporters

Definition

Organic cation transporters (OCTs) are members of the solute carrier (SLC) group of transporters and belong to the major facilitator superfamily. According to the Human Genome Organisation (HUGO), they are assigned to the SLC22A family, which includes electrogenic and electroneutral OCTs, and also the organic anion transporters (OATs), a large group of carriers involved in the uptake of organic anions. OCTs are multispecific, bidirectional carriers that transport organic cations, including (among others) endogenous compounds such as serotonin, norepinephrine, dopamine, and histamine. They are also critically involved in the absorption, disposition, and excretion of many exogenous compounds including (among others) metformin, platinum-based antineoplastic drugs, nucleoside analogs, antiarrhythmics such as procainamide and quinidine, sumatriptan, pentamidine, acyclovir, and fluoxetine [1]. In humans, OCTs from the SLC22A family include OCT1 (SLC22A1), OCT2 (SLC22A2), OCT3 (SLC22A3), and also the

novel organic cation transporters OCTN1 (SLC22A4) and OCTN2 (SLC22A5).

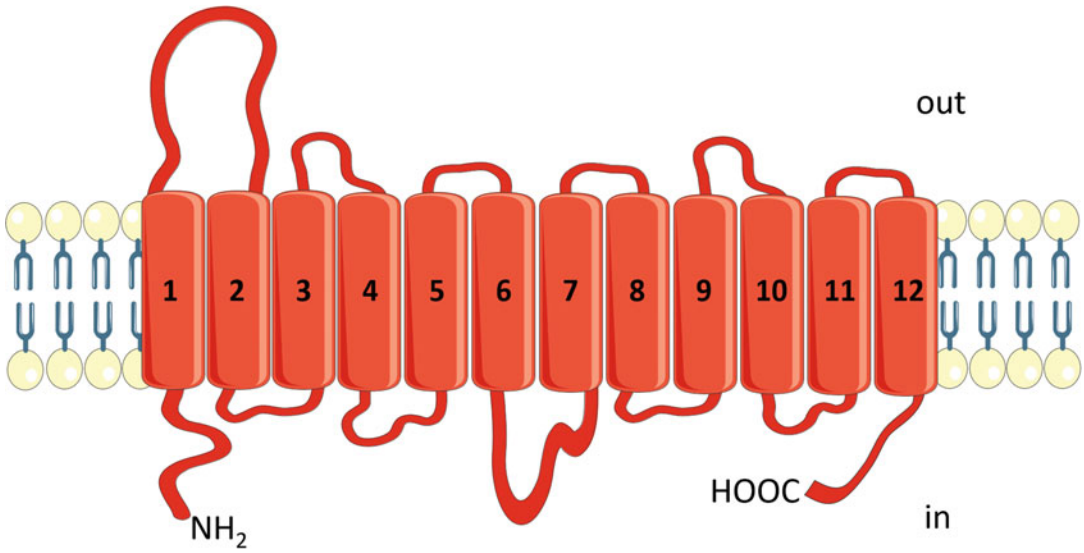
Whereas this entry will focus on the abovementioned transporters, cation transporters from other families that work in tandem with OCTs during the efflux transport in drug elimination organs (i.e., Phase III transport) will also be mentioned and briefly discussed.

Structure and Mechanism of Transport

All OCTs, alike the rest of the transporters of the SLC22A family, share a similar predicted membrane topology [1, 2] (Fig. 1), which comprises 12 alpha-helical transmembrane domains (TMDs), a large extracellular loop between TMDs 1 and 2, which presents at least one consensus sequence for N-glycosylation, and a large intracellular loop between TMDs 6 and 7, plus intracellular C- and N-termini. Both the intracellular loop and the C-termini include consensus sequences for phosphorylation (which play a role in rapid regulation of the transporter activity [2–4]).

OCTs mode of transport corresponds to the alternate access model, which postulates that transporters work by undergoing conformational changes, which alternately create access to a large hydrophobic binding region (in which, according to homology models, 7 of the 12 transmembrane domains participate [5, 6]) from either the intracellular side or the extracellular side [7]. When a substrate binds on one side of the membrane, the protein undergoes a conformational shift that enables to release the substrate on the other side. A substrate that is preferably uptaken by the cell would display higher affinity for the outward-open cleft and reduced affinity for the inward-open cleft. Numerous mutagenesis studies have identified a conserved aspartate residue in the TMD 11 which is critically important for determining affinity and transport in OCT1, OCT2, and OCT3. This TMD 11 aspartate may function as the singular binding site for the cationic region of transported substrates and may be essential for substrate coordination and stabilization of the cation's positive charge [8].

As observed in other polyspecific transporters, available evidence supports the hypothesis that a large binding pocket defined by the TMDs contains multiple, close, partially overlapping binding sites for different substrates and inhibitors [1, 9]. OCTs contain low-affinity binding sites that are directly involved in substrate translocation, but also high-affinity binding sites



Organic Cation Transporters, Fig. 1 Predicted topology of OCTs

that may be related to allosteric modulation of transport [9].

When cationic substrates are only present on one side of the TMDs, OCT1, OCT2, and OCT3 operate as electrogenic uniporters (i.e., the transport process leads to the translocation of net charge across the membrane, and a single substrate unit is translocated per transport cycle). When acting as uniporters, OCTs mediate facilitated diffusion (either uptake or efflux). The driving force for this process is provided by the substrate concentration gradient and/or the membrane potential, which normally is inside-negative. Therefore, cation uptake is normally preferred, whereas cation efflux can occur in depolarized cells or in the presence of a large outwardly directed gradient that energetically compensates membrane potential.

When the cytoplasmic concentration of a substrate is high enough, the transporters can operate as electroneutral cation exchangers. The uptake of a given cation can be stimulated when a different cationic substrate is present on the other side of the membrane; in this case, the reorientation of the inward-open to the outward-open conformation is faster compared with the reorientation of an unloaded transporter (this is termed *trans-stimulation*) [9, 10].

All in all, OCT1, OCT2, and OCT3 preferably facilitate electrogenic cellular uptake of organic cations, but they can operate as electroneutral exchangers if the intracellular and extracellular concentrations of different substrates are similar, or facilitate substrate efflux in the absence of extracellular cations, as in the OCT2-mediated efflux of acetylcholine in bronchial epithelial [11].

In the case of OCTNs, it has been shown that OCTN1 can transport cations by proton-cation antiport [1], and l-carnitine can be co-transported with sodium by OCTN2 [12].

Role of OCTs in Drug Absorption and Disposition

The major OCTs expressed in the liver and kidney mediate the basolateral uptake of their substrates, including many drugs; that is, they act as Phase 0 transporters that facilitate the translocation of their substrates from the blood to the intracellular space of the eliminating cell, across the cellular membrane. This is a crucial step in drug disposition, as cationic species would not be able to permeate through the cell membrane by simple diffusion (see the entry ▶ "Phase 0 and Phase III Transport" for further discussion). Noteworthy, OCTs usually work in tandem with multidrug and toxin extrusion (MATEs) proteins and/or multidrug resistance transporter 1 (MDR1 or P-glycoprotein), which also recognize organic cations and mediate apical secretion, thus completing the elimination cycle. In the intestine, OCTs and OCTNs mainly mediate the absorption of their substrates; OCTNs expressed at the tubular brush border can participate in reabsorption (note, however, that these transporters are low-affinity, high-capacity carriers and the possible interaction of some of their substrates with other more selective, high-affinity carriers expressed in the same cells should be considered).

The relevance of OCTs in the disposition of organic cations has been proven in studies with OCT1 or OCT2 knockout mice and OCT1/2 double-knockout mice. The hepatic uptake and biliary excretion of organic cations were greatly reduced in OCT1 knockout animals, in consistence with the role of this transporter in the liver (see next subsection) [13]. Tubular secretion of tetraethylammonium was fully abolished in OCT1/OCT2 double-knockout rodents, with the subsequent increase in plasma levels [14], suggesting that the deficiency in these transporters could be associated with increased drug sensitivity and toxicity.

From a genetic perspective, the members of the OCT subfamily are highly polymorphic; changes in the activity of these variants alter intestinal absorption, uptake by key drug-eliminating organs (reducing hepatic or renal clearance), and target tissue uptake, thus affecting the efficacy and safety of the treatment [15]. Pharmacogenomic studies have also shown that variants in genes related to the SLC22 family may have a considerable effect on the response to different antineoplastic medications [16].

The following sections will discuss the main organs where OCTs are expressed in comparatively high levels. The reader may also refer to entries ▶ "Phase 0 and Phase III Transport", *Biliary Drug Excretion*, and *Renal Drug Excretion* for illustrative schemes.

Transporters that Facilitate the Transport of Organic Cations in the Liver

In the hepatocytes, the uptake of organic cations from the sinusoidal blood into the cell is mainly facilitated by OCT1. OCT3 also contributes to basolateral translocation but, in general, to a lesser extent than OCT1. This Phase 0 activity (i.e., uptake) is complemented by Phase III transport (i.e., efflux) of cations at the canalicular membrane, which is performed by the proton-cation exchanger hMATE1 (from the SLC47 family). MDR1 is also located in the canalicular membrane and is relevant for the efflux of hydrophobic cationic substrates (see the entry on *Biliary drug excretion* for further insight).

OCT1 expression is regulated at different levels, both transcriptionally and posttranscriptionally [1]. Among the transcription factors that activate the transcription of OCT1, there are the upstream binding stimulating factors 1 and 2 and the hepatocyte nuclear factors 1 and 4α. Inversely, the OCT1 gene is suppressed by bile acids [17]. Posttranscriptional regulation includes intracellular trafficking (which is regulated by N-glycosylation) and, as previously stated, phosphorylation of the intracellular domains by multiple kinases.

Metformin is the first-line treatment for type 2 diabetes. It is a hydrophilic biguanide positively charged at physiological pH. It exerts its glucose-lowering effects by inhibiting the mitochondrial respiratory chain in the liver, leading to the activation of AMPK, enhancing sensitivity to insulin, and lowering cAMP, thus decreasing the expression of gluconeogenic enzymes, among other effects [1, 18]. Metformin uptake into the hepatocytes (its site of action!) is mediated by OCT1 and OCT3 in the sinusoidal membrane. It has been shown that the hepatic uptake of orally delivered metformin was decreased in reduced-function OCT1 variants [19]. It has also been reported that the glucose-lowering effect of metformin is blunted in (healthy) individuals with reduced OCT1 function [20].

The antimalarial proguanil is another example of the impact that polymorphic variants of OCTs can have on a drug efficacy. It is a prodrug positively charged in blood which is uptaken into the hepatocytes via OCT1 and, to a smaller extent, by OCT3. There, the active metabolite cycloguanil is produced by the CYP450 (specifically CYP2C19); cycloguanil attacks preerythrocytic *Plasmodium* forms in the liver and within erythrocytes. It was recently reported that the concentration of cycloguanil and the cycloguanil/proguanil ratio in the blood are correlated with the functionality of OCT1 alleles, suggesting that loss of function genetic variants of OCT1 may be at least a partial explanation of proguanil treatment failure in patients [21].

Transporters that Facilitate the Transport of Organic Cations in the Kidney

Expression of high levels of OCT2 at the basolateral membrane of tubular epithelial cells is crucial for the cellular uptake, and subsequent secretion, of multiple organic cations (Phase 0 transport). Uptake of organic cations across the abluminal membrane is complemented by OCT3. On the luminal membrane, in contrast, OCTN1 and OCTN2, MATE-1 and MATE2-K, and MDR1 may conclude the Phase III tubular secretion of cations (remember that OCTN1 and OCTN2 may function bidirectionally depending on the intracellular cation concentration; besides, OCTN1 can work as a proton-cation exchanger, similar to MATEs). Alike, OCT2 and OCT3 could eventually also release cations from the cell into the interstitial space, if cation levels inside the tubular cell reach sufficiently high values. Predictably, OCT1, OCTN1, and OCTN2 can also mediate cation reabsorption.

OCT2 may be regulated transcriptionally (e.g., basal transcription of OCT2 is activated by the upstream binding stimulating factor 1 and suppressed epigenetically by hypermethylation) and posttranscriptionally (by endosomal recruitment and phosphorylation) [1].

Cimetidine is a good example of drug interactions caused by inhibition of OCTs in the kidney (thus, resulting in reduce renal clearance of the "victim" drug). Cimetidine has been identified as substrate of OCT1, OCT2, MATE1, and MATE2-K and as inhibitor of OCTN1, OCTN2, and OCT3 [1, 22]. In other words, almost all the polyspecific renal transporters involved in tubular secretion can be inhibited competitively or not competitively by cimetidine. Therefore, co-administration of cimetidine reduces the renal excretion of several drugs, among them procainamide and gabapentin, possibly worsening the incidence of side effects like disturbances of the cardiorhythm and dizziness, respectively [1].

Platinum compounds represent another example of how drug interactions or genetic variants involving OCT2 may influence treatment outcome. In particular, cisplatin presents severe, dose-limiting side effects that include nephrotoxicity and ototoxicity. Nephrotoxicity has been linked to basolateral transport mechanisms [23]. OCT2 and MATE1, among others, are involved in the tubular uptake and secretion of cisplatin [24]. OCT1/OCT2 knockout mice are (partially) protected against cisplatin-induced nephrotoxicity and also ototoxicity [25]. Consistently, a few clinical studies suggest that co-administration of cimetidine and mutations in OCT2 protect patients from nephrotoxicity [26–28], by reducing the accumulation of the drug in the tubular cells.

Transporters that Facilitate the Transport of Organic Cations in the Small Intestine

In the small intestine enterocytes, OCT1, OCT3, OCTN1, and OCTN2 are expressed in the brush-border membrane, where they are primarily involved in the absorption of organic cations from the diet. The OCTs in the luminal membrane may occasionally mediate the efflux of cations by cation exchange. The role of these transporters is complemented by other more selective transporters from the SLC superfamily expressed in the small intestine, such as the dopamine transporter and the thiamine transporter.

Gastrointestinal adverse effects to metformin, which are supposedly caused by high concentrations of the drug in the gut lumen, have been associated with a loss of function of OCT1 variants that would impair metformin absorption [29].

Transporters that Facilitate the Transport of Organic Cations in Other Organs

Some OCTs, in particular, OCT1 and OCT3, are expressed quite ubiquitously throughout the body (though not always in high levels). The role of OCTs in the brain is of particular relevance, as the relatively high levels of these transporters in brain capillaries are possibly involved in the adjustment of neurotransmitter concentration in the brain [1]. In the lungs, OCT2 and OCTN1 located at the luminal membrane of bronchial epithelial cells can mediate cellular release of acetylcholine [30], thus being involved in the subsequent cholinergic reaction. OCT1, OCT2, and, in particular, OCT3 and MATE-1 are expressed in the placenta [31], where they possibly exert protective roles on the fetus at different stages of gestation.

Cross-References

- ▶ ABC transporters: an overview
- ▶ ABC transporters: P-glycoprotein
- ▶ Biliary drug excretion
- ▶ Phase 0 and Phase III transport
- ▶ Renal drug excretion
- ▶ Solute Carrier (SLC) Transporters: An Overview

References

1. Koepsell H. Organic cation transporters in health and disease. Pharmacol Rev. 2020;72:253–319.
2. Ciarimboli G. Organic cation transporters. Xenobiotica. 2008;38:936–71.
3. Ciarimboli G, Struwe K, Arndt P, Gorboulev V, Koepsell H, Schlatter E, et al. Regulation of the human organic cation transporter hOCT1. J Cell Physiol. 2004;201:420–8.
4. Ciarimboli G, Koepsell H, Iordanova M, Gorboulev V, Dürner B, Lang D, et al. Individual PKC-phosphorylation sites in organic cation

transporter 1 determine substrate selectivity and transport regulation. J Am Soc Nephrol. 2005;16: 1562–70.
5. Popp C, Gorboulev V, Müller TD, Gorbunov D, Shatskaya N, Koepsell H. Amino acids critical for substrate affinity of rat organic cation transporter 1 line the substrate binding region in a model derived from the tertiary structure of lactose permease. Mol Pharmacol. 2005;67:1600–11.
6. Zhang X, Shirahatti NV, Mahadevan D, Wright SH. A conserved glutamate residue in transmembrane helix 10 influences substrate specificity of rabbit OCT2 (SLC22A2). J Biol Chem. 2005;280:34813–22.
7. Quistgaard EM, Löw C, Guettou F, Nordlund P. Understanding transport by the major facilitator superfamily (MFS): structures pave the way. Nat Rev Mol Cell Biol. 2016;17:123–32.
8. Li DC, Nichols CG, Sala-Rabanal M. Role of a hydrophobic pocket in polyamine interactions with the polyspecific organic cation transporter OCT3. J Biol Chem. 2015;290:27633–43.
9. Koepsell H. Multiple binding sites in organic cation transporters require sophisticated procedures to identify interactions of novel drugs. Biol Chem. 2019;400: 195–207.
10. Keller T, Elfeber M, Gorboulev V, Reiländer H, Koepsell H. Purification and functional reconstitution of the rat organic cation transporter OCT1. Biochemistry. 2005;44:12253–63.
11. Lips KS, Volk C, Schmitt BM, Pfeil U, Arndt P, Miska D, et al. Polyspecific cation transporters mediate luminal release of acetylcholine from bronchial epithelium. Am J Respir Cell Mol Biol. 2005;33:79–88.
12. Tamai I, China K, Sai Y, Kobayashi D, Nezu J, Kawahara E, et al. Na(+)-coupled transport of L-carnitine via high-affinity carnitine transporter OCTN2 and its subcellular localization in kidney. Biochim Biophys Acta. 2001;1512:273–84.
13. Jonker JW, Wagenaar E, Mol CA, Buitelaar M, Koepsell H, Smit JW, Schinkel AH. 2001. Reduced hepatic uptake and intestinal excretion of organic cations in mice with a targeted disruption of the organic cation transporter 1 [Slc22a1] gene. Mol Cell Biol. 2001;21:5471–7.
14. Jonker JW, Wagenaar E, Van Eijl S, Schinkel AH. Deficiency in the organic cation transporters 1 and 2 (Oct1/Oct2 [Slc22a1/Slc22a2]) in mice abolishes renal secretion of organic cations. Mol Cell Biol. 2003;23:7902–8.
15. Lozano E, Briz O, Macias RIR, Serrano MA, Marin JJG, Herraez E. Genetic heterogeneity of SLC22 family of transporters in drug disposition. J Perinat Med. 2018;8:14.
16. El-Gebali S, Bentz S, Hediger MA, Anderle P. Solute carriers (SLCs) in cancer. Mol Asp Med. 2013;34: 719–34.
17. Saborowski M, Kullak-Ublick GA, Eloranta JJ. The human organic cation transporter-1 gene is transactivated by hepatocyte nuclear factor-4alpha. J Pharmacol Exp Ther. 2006;317:778–85.
18. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60: 1577–85.
19. Sundelin E, Gormsen LC, Jensen JB, Vendelbo MH, Jakobsen S, Munk OL, et al. Genetic polymorphisms in organic cation transporter 1 attenuates hepatic metformin exposure in humans. Clin Pharmacol Ther. 102:841–8.
20. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest. 2007;117:1422–31.
21. Matthaei J, Seitz T, Jensen O, Tann A, Prukop T, Tadjerpisheh S, et al. OCT1 deficiency affects hepatocellular concentrations and pharmacokinetics of cycloguanil, the active metabolite of the antimalarial drug proguanil. Clin Pharmacol Ther. 2019;105: 190–200.
22. Müller F, Weitz D, Mertsch K, König J, Fromm MF. Importance of OCT2 and MATE1 for the cimetidine-metformin interaction: insights from investigations of polarized transport in single- and double-transfected MDCK cells with a focus on perpetrator disposition. Mol Pharm. 2018;15:3425–33.
23. Ludwig T, Riethmüller C, Gekle M, Schwerdt G, Oberleithner H. Nephrotoxicity of platinum complexes is related to basolateral organic cation transport. Kidney Int. 2004;66:196–202.
24. Ciarimboli G. Membrane transporters as mediators of cisplatin side-effects. Anticancer Res. 2014;34: 547–50.
25. Ciarimboli G, Deuster D, Knief A, Sperling M, Holtkamp M, Edemir B, et al. Organic cation transporter 2 mediates cisplatin-induced Oto- and nephrotoxicity and is a target for protective interventions. Am J Pathol. 2010;176:1169–80.
26. Sleijfer DT, Offerman JJ, Mulder NH, Verweij M, van der Hem GK, SchraffordtKoops HS, et al. The protective potential of the combination of verapamil and cimetidine on cisplatin-induced nephrotoxicity in man. Cancer. 1987;60:2823–282.
27. Filipski KK, Mathijssen RH, Mikkelsen TS, Schinkel AH, Sparreboom A. Contribution of organic cation transporter 2 (OCT2) to cisplatin-induced nephrotoxicity. Clin Pharmacol Ther. 2009;86:396–402.
28. Zhang J, Zhou W. Ameliorative effects of SLC22A2 gene polymorphism 808 G/T and cimetidine on cisplatin-induced nephrotoxicity in Chinese cancer patients. Food Chem Toxicol. 2012;50:2289–93.
29. Tarasova L, Kalnina I, Geldnere K, Bumbure A, Ritenberga R, Nikitina-Zake L, et al. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion

1 transporter protein genes with the gastrointestinal side effects and lower BMI in metformin-treated type 2 diabetes patients. Pharmacogenet Genomics. 2012;22:659–66.
30. Lips KS, Volk C, Schmitt BM, Pfeil U, Arndt P, Miska D, et al. Polyspecific cation transporters mediate luminal release of acetylcholine from bronchial epithelium. Am J Respir Cell Mol Biol. 2005;33:79–88.
31. Ahmadimoghaddam D, Zemankova L, Nachtigal P, Dolezelova E, Neumanova Z, Cerveny L, et al. Organic cation transporter 3 (OCT3/SLC22A3) and multidrug and toxin extrusion 1(MATE1/SLC47A1) transporter in the placenta and fetal tissues: expression profile and fetus protective role at different stages of gestation. Biol Reprod. 2013;88:55.

Organic Cation/Carnitine Transporters

► Organic Cation Transporters

Organic Zwitterion Transporters

► Organic Cation Transporters