Oral Bioavailability and Regulatory Aspects

Subjects: Pharmacology & Pharmacy

Contributor: Eva Rath

Oral bioavailability refers to the extent a substance or drug becomes completely available to systemic circulation or to its intended biological destination(s) via the oral route. High oral bioavailability reduces the amount of a drug necessary to achieve a desired pharmacological effect, therefore reducing the risk of side-effects and toxicity. Low oral bioavailability results in low efficacy and is a major reason for drug candidates failing to reach the market. Hence, oral bioavailability is one of the most important properties in drug design and development.

intestinal organoids | regulatory aspects | nutrient absorption | drug uptake | non-animal models | 3R | intestinal transport processes | intestinal epithelial cells

1. Overview

The intestinal epithelium critically contributes to oral bioavailability of drugs by constituting an important site for drug absorption and metabolism. In particular, intestinal epithelial cells (IEC) actively serve as gatekeepers of drug and nutrient availability. IEC transport processes and metabolism are interrelated to the whole-body metabolic state and represent potential points of origin as well as therapeutic targets for a variety of diseases. Human intestinal organoids represent a superior model of the intestinal epithelium, overcoming limitations of currently used in vitro models. Caco-2 cells or rodent explant models face drawbacks such as their cancer and non-human origin, respectively, but are commonly used to study intestinal nutrient absorption, enterocyte metabolism and oral drug bioavailability, despite poorly correlative data. In contrast, intestinal organoids allow investigating distinct aspects of bioavailability including spatial resolution of transport, inter-individual differences and high-throughput screenings. As several countries have already developed strategic roadmaps to phase out animal experiments for regulatory purposes, intestinal organoid culture and organ-on-a-chip technology in combination with in silico approaches are roads to go in the preclinical and regulatory setup and will aid implementing the 3Rs (reduction, refinement and replacement) principle in basic science.

2. Oral Bioavailability

Oral bioavailability refers to the extent a substance or drug becomes completely available to systemic circulation or to its intended biological destination(s) via the oral route [1]. High oral bioavailability reduces the amount of a drug necessary to achieve a desired pharmacological effect, therefore reducing the risk of side-effects and toxicity. Low oral bioavailability results in low efficacy and is a major reason for drug candidates failing to reach the market. Hence, oral bioavailability is one of the most important properties in drug design and development.

Critical determinants of oral bioavailability include the gastrointestinal (GI) tract physiology, hepatic first-pass metabolism, plasma protein binding and excretion via the kidneys. In the GI tract, the intestinal epithelium crucially contributes to oral bioavailability by constituting an important site for drug absorption, distribution, metabolism, and excretion (ADME). Exposed to high concentrations of food-borne, microbiota-derived, or other exogenous xenobiotics, including toxins and carcinogens, intestinal epithelial cells (IEC) are trained to defend themselves and the body from harmful substances. Hence, expression of enzymes and transporters involved in drug metabolism and xenobiotic defense including cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferase isoforms (UGTs) and ATP binding cassette (ABC) transporters, e.g., the multidrug efflux pump P-glycoprotein (P-gp), give rise to the concept of the intestinal epithelium as a pharmacogenetic barrier [2]. Additionally, the inert function of enterocytes, the subtype of IECs specialized in uptake processes, to absorb nutrients, contributes to oral bioavailability of drugs. For example, certain inhibitors of angiotensin-converting enzyme, protease inhibitors, antivirals, and peptidomimetics like β-lactam antibiotics are absorbed by the peptide transporter 1 (PEPT1) [3]. The main route of orally administered drugs into the systemic circulation is by direct passage from the IEC layer into the mesenteric blood capillaries, yet certain drugs gain access to the systemic circulation via intestinal lymphatic absorption. Following this pathway, absorbed drugs associate with fats and lipoproteins within IECs as they are processed into chylomicrons. [4]. Vice versa, enterocyte fatty acid oxidation (FAO), which has been implicated in the in the control of eating, can be pharmacologically modified [5][6]. Consequently, intestinal transport processes, IEC metabolism and their interconnection to whole-body metabolic state are relevant to a variety of diseases and represent potential therapeutic targets. Next to intestinal pathologies like malabsorption syndromes or inflammatory diseases, these pathologies comprise metabolic disorders such as obesity and type 2 diabetes, and additionally, diseases treated with drugs and prodrugs that are actively absorbed and/or metabolized by enterocytes. Thus, beyond constituting a physical barrier separating the host from its environment including the intestinal microbiota, IECs actively serve as gatekeepers of nutrient availability and metabolic health for the whole organism.

Despite this importance, many aspects of nutrient absorption, enterocyte metabolism, and drug bioavailability are still unknown, e.g., the underlying causes of fructose malabsorption remain elusive [7]. Hence, there is a need for advanced model systems that enable studying intestinal transport processes and IEC metabolism, especially in the context of drug development. Commonly used in vitro models of the intestinal epithelium, such as Caco-2 cells or rodent explant models (Ussing chamber, everted gut sac models) are of limited value due to their cancer and non-human origin, respectively. In particular, species differences result in poorly correlative data, and findings obtained in these models cannot be translated reliably to humans. Contrarily, human intestinal organoids allow investigating different aspects of oral bioavailability, form inter-individual differences to broad uptake screenings, thus representing a superior model of the intestinal epithelium. Intestinal organoid lines created from biopsies of healthy and diseased individuals [8] can be readily expanded and maintain their region-specific expression patterns upon differentiation. Functional characteristics including absorption studies and metabolomics have already been conducted on three-dimensional organoids derived from human small and large intestinal biopsies [9]. Cultured in 2D on trans-well membranes, organoid-derived cell lawns provide a valuable tool to study drug permeability in spatial resolution as well as inter-individual differences. Of note, intestinal organoids not only enable measurement

of intestinal transport and intracellular (drug-) metabolism in a dynamic way, downstream events like molecular signalling pathways resulting in hormone secretion can be investigated in parallel [10].

Several countries have already developed strategic roadmaps to phase out animal experiments for regulatory purposes. This increases the need for a timely substitute that reflects physiology in the best possible manner. Intestinal organoid culture and organ-on-a-chip technology are promising ways forward in the preclinical and regulatory setup and will aid implementing the 3Rs (reduction, refinement and replacement) principle in basic science.

3. Future Directions

MPS and organoid models can be combined with in silico approaches, complex computer-based models that precisely predict ADME processes and pharmacokinetics in pharmaceutical and toxicological research [11]. It has been proven that in silico approaches even provide a better predictability in toxicology testing compared to animal experiments [12][13]. Computational methods can also be used as alternatives to animal testing in safety and efficacy testing such as Quantitative Structure–Activity Relationship (QSAR) modelling and physiologically based kinetic and dynamic modelling. QSAR models predict biological and toxicological effects of drugs and other chemicals based on their physicochemical and structural properties. Chemical properties can also be predicted by “read-across”, grouping of chemicals on the basis of structural and biological similarity. Read-across is typically carried out in addition to QSAR, to increase the overall confidence in the predicted properties. Complementary, PBK models predict the distribution of a drug or chemical in a living organism. PKB models are used to interpret in vitro toxicity data simulating internal concentrations following exposure to the chemical via the diet, skin or inhalation. Coupling PBK with other mathematical models describing biological responses in a specific organ is called physiologically based kinetic and dynamic (PBKD) modelling. The virtual cell-based assay (VCBA) is a mathematical model developed by the JRC [14]. It simulates the distribution and biological effects of chemicals in a range of in vitro systems. Integrated approaches combining computational modelling, human studies and human-based in vitro models, such as advanced cell cultures or MPS will improve human safety assessment and accelerate medical development.

4. Conclusions

There is no doubt that human-based model systems are needed to produce human-relevant data for medical, pharmacological or toxicological purposes. High failure rates within the drug development pipeline constitute a problem increasingly recognised and targeted by the scientific community including academia, industry and regulatory bodies [15][16][17][18][19]. Failure rates calculated based on statistical analyses of drug approvals in a certain time frame account to as much as 95% [20][21][22], with oncology, neurology and cardiovascular diseases displaying the worst results [22]. To a large extent, this failure which occurs mainly in safety and efficacy testing, can be attributed to a lack of transferability of preclinical data including animal experiments to the human trials. Computational approaches together with advanced in vitro models complemented by human clinical and

epidemiological studies offer a research portfolio that is capable of reliably investigating human-relevant issues related to health and disease. We are on a good way having human-based techniques available that provide excellent tools to study drug bioavailability and other pharmaceutical issues in a human-relevant manner.

References

1. Currie, G.M. Pharmacology, part 2: Introduction to pharmacokinetics. J. Nucl. Med. Technol. 2018, 46, 221–230.
2. Dietrich, C.G.; Geier, A.; Oude Elferink, R.P. Abc of oral bioavailability: Transporters as gatekeepers in the gut. Gut 2003, 52, 1788–1795.
3. Wenzel, U.; Kuntz, S.; Diestel, S.; Daniel, H. Pept1-mediated cefixime uptake into human intestinal epithelial cells is increased by Ca2+ channel blockers. Antimicrob. Agents Chemother. 2002, 46, 1375–1380.
4. Brocks, D.R.; Davies, N.M. Lymphatic drug absorption via the enterocytes: Pharmacokinetic simulation, modeling, and considerations for optimal drug development. J. Pharm. Pharm. Sci. 2018, 21, 254s–270s.
5. Langhans, W.; Leitner, C.; Arnold, M. Dietary fat sensing via fatty acid oxidation in enterocytes: Possible role in the control of eating. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2011, 300, R554–R565.
6. Ramachandran, D.; Clara, R.; Fedele, S.; Michel, L.; Burkard, J.; Kaufman, S.; Diaz, A.A.; Weissfeld, N.; De Bock, K.; Prip-Buus, C.; et al. Enhancing enterocyte fatty acid oxidation in mice affects glycemic control depending on dietary fat. Sci. Rep. 2018, 8, 10818.
7. Ebert, K.; Witt, H. Fructose malabsorption. Mol. Cell Pediatr. 2016, 3, 10.
8. VanDussen, K.L.; Marinshaw, J.M.; Shaikh, N.; Miyoshi, H.; Moon, C.; Tarr, P.I.; Ciorba, M.A.; Stappenbeck, T.S. Development of an enhanced human gastrointestinal epithelial culture system to facilitate patient-based assays. Gut 2015, 64, 911–920.
9. Zietek, T.; Giesbertz, P.; Ewers, M.; Reichart, F.; Weinmüller, M.; Urbauer, E.; Haller, D.; Demir, I.E.; Ceyhan, G.O.; Kessler, H.; et al. Organoids to study intestinal nutrient transport, drug uptake and metabolism—Update to the human model and expansion of applications. Front. Bioeng. Biotechnol. 2020, 8, 1065.
10. Zietek, T.; Rath, E.; Haller, D.; Daniel, H. Intestinal organoids for assessing nutrient transport, sensing and incretin secretion. Sci. Rep. 2015, 5, 16831.
11. Raasch, M.; Fritsche, E.; Kurtz, A.; Bauer, M.; Mosig, A.S. Microphysiological systems meet hipsc technology—New tools for disease modeling of liver infections in basic research and drug

development. Adv. Drug Deliv. Rev. 2019, 140, 51–67.

12. Hartung, T. Predicting toxicity of chemicals: Software beats animal testing. EFSA J. 2019, 17, e170710.
13. Noorden, R.V. Software beats animal tests at predicting toxicity of chemicals. Nature 2018, 559, 163.
14. Comenges, J.M.Z.; Joossens, E.; Benito, J.V.S.; Worth, A.; Paini, A. Theoretical and mathematical foundation of the virtual cell based assay—A review. Toxicol. In Vitro 2017, 45, 209–221.
15. Herrmann, K.; Pistollato, F.; Stephens, M.L. Beyond the 3rs: Expanding the use of human-relevant replacement methods in biomedical research. ALTEX Altern. Anim. Exp. 2019, 36, 343–352.
16. Pound, P.; Ram, R. Are researchers moving away from animal models as a result of poor clinical translation in the field of stroke? An analysis of opinion papers. BMJ Open Sci. 2020, 4, e100041.
17. Smirnova, L.; Kleinstreuer, N.; Corvi, R.; Levchenko, A.; Fitzpatrick, S.C.; Hartung, T. 3s—Systematic, systemic, and systems biology and toxicology. ALTEX Altern. Anim. Exp. 2018, 35, 139–162.
18. Urani, C.; Bruschi, M.; Casati, S.; Gribaldo, L. Use of alternative methods: From fundamental to industrial research. ALTEX Altern. Anim. Exp. 2019, 36, 320–321.
19. Veening-Griffioen, D.H.; Ferreira, G.S.; van Meer, P.J.K.; Boon, W.P.C.; Gispen-de Wied, C.C.; Moors, E.H.M.; Schellekens, H. Are some animal models more equal than others? A case study on the translational value of animal models of efficacy for alzheimer’s disease. Eur. J. Pharmacol. 2019, 859, 172524.
20. Mullard, A. Parsing clinical success rates. Nat. Rev. Drug Discov. 2016, 15, 447–448.
21. Wong, C.H.; Siah, K.W.; Lo, A.W. Estimation of clinical trial success rates and related parameters. Biostatistics 2019, 20, 273–286.
22. Thomas, D.; Burns, J.; Audette, J.; Carroll, A.; Dow-Hygelund, C.; Hay, M. Clinical Development Success Rates 2006–2015; Biotechnology Innovation Organization (BIO): Washington, DC, USA, 2016; pp. 1–16.