A lipid 'trap' inside cells reduces drug effectiveness

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Cellular lipids are more efficient than proteins in trapping most drugs and hence reducing the free intracellular drug concentration. This is shown by researchers at Uppsala University in an article published in Molecular Pharmaceutic.

After administration, drug molecules have to travel a long way before they reach their site of action, which in many cases is located inside the cells of the diseased organ or tissue. Once the site of the target is reached, only the fraction of the drug that is not bound to cellular structures is free to interact with its specific target and exert the desired effect.

It is well established that during their journey through our bodies, drug molecules bind to proteins in the blood stream and it has therefore been assumed that protein binding is the most important "trap" for drugs also inside cells.

"Our results show that cellular lipids are more efficient than proteins in trapping most drugs and hence reducing the free intracellular drug concentration. However, drug binding to intracellular proteins remains important e.g. for shuttling drugs between different sites inside the cells." says Andrea Treyer, a Ph.D. student in the Drug Delivery group headed by professor Per Artursson at Uppsala University.

The group also found that for most drugs, it is the most abundant constituent of cellular membranes —the phospholipids—that plays the

major role in intracellular drug binding.

The research group made use of their new small-scale method, which enables the measurement of the so-called intracellular drug bioavailability, to address this question. Cells have many different lipid constituents and in order to discriminate between the different types of lipids, normal cells were transformed into cells with increased lipid contents, for example adipocytes. Comparisons between drug binding in these lipid-enhanced cells to the binding of the same drugs in untreated cells show that phospholipids are the major binding site of drugs. A strong correlation between drug binding to cell constituents and to purified phospholipids gave further evidence for the cellular lipid "sink." Another class of lipids—neutral lipids—which are the major constituent of the fat droplets in adipocytes, did not increase cellular drug binding further.

"This was surprising, since adipocytes are known to accumulate "fat soluble compounds." Our findings can be explained by our focus on "normal drug molecules," which have moderate lipid solubility in comparison to the most lipid soluble ones," says Treyer.

The intracellular bioavailability of drug varies between different cells and tissues in our bodies. The researchers have now related this difference to the phospholipid content of the cells. In addition to drug transport and metabolism, it's now possible to add lipid content as a major factor that influences the desired drug effect inside cells.

"Our new findings will contribute to enabling better predictions of intracellular drug efficacy in drug discovery and pharmacokinetic modelling," says Treyer.

More information: Andrea Treyer et al. Intracellular Drug Bioavailability: Effect of Neutral Lipids and Phospholipids, *Molecular*

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