This Week's Citation Classic®

Lüllmann H, Lüllmann-Rauch R & Wassermann O. Drug-induced phospholipidoses. *CRC Crit. Rev. Toxicol.* 4:185-218, 1975.
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The review article describes the cellular and biochemical features of lysosomal storage of polar lipids as induced by various therapeutically different drugs. It is proposed that the cationic, amphiphilic character common to all these drug molecules leads to formation of undigestible drug-lipid complexes and is essential for the induction of lipidosis. [The *SCI*® indicates that this paper has been cited in over 185 publications.]

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Around 1970 an increased number of clinical cases of pulmonary hypertension was observed in central Europe. It was suggested that the chronic use of anorectic drugs might be causally related to the occurrence of pulmonary hypertension.

Since no animal experiments were known—at least not to us—we considered it worthwhile to treat rats chronically with anorectic drugs, such as menocil and chlorphentermine, and to measure their pulmonary blood pressure. The outcome of these experiments was surprising: menocil clearly raised pulmonary pressure.[1] Chlorphentermine induced additional alterations: upon gross examination, the lungs appeared grayish, did not readily collapse, and the specific weight was increased from 0.45 (controls) to about 0.75 g/ml. Light microscopical examination revealed the presence of numerous large "foam cells" within the alveolar spaces. My wife, Renate Lüllmann-Rauch, who is a reader in microscopical anatomy, joined us and demonstrated by electron microscopy the storage of lamellated material—possibly phospholipids—within the lysosomes of alveolar macrophages and of all other pulmonary cell types.

The next and decisive steps were: (a) to demonstrate that the lipidosis-like cellular alterations occurred not only in the lung but also in many other organs of the rat and of other animal species, (b) to demonstrate by biochemical methods that phospholipids accumulated in the organs of chlorphentermine-treated rats,[2] and (c) to perform pharmacokinetic studies by chronically administering ^{3}H-labeled chlorphentermine and phentermine to rats. We obtained a very exciting result: the lung and many other organs showed a disproportionate accumulation of chlorphentermine but not of phentermine, i.e., the tissue-plasma ratio for chlorphentermine increased with time. This is quite unusual and had never been published before, at least to our knowledge.

It was not easy to get the results accepted for publication; only a shortened version was published.[3] The profound pharmacokinetic differences between chlorphentermine and the non-chlorinated analog phentermine (which did not induce lipidosis-like alterations) suggested to us that the pronounced amphiphilic character of chlorphentermine was essential for the disproportionate accumulation and for its cytological side effects. We speculated that the accumulating phospholipids might provide new "binding sites" occurring in the course of chronic chlorphentermine treatment.

In fact, it could be shown that chlorphentermine strongly interacts with polar lipids *in vitro*[4] and that there was a close temporal and spatial correlation between the accumulation of chlorphentermine and of phospholipids *in vivo*. A further step was to test other drugs that could be assumed to be cationic, amphiphilic compounds. It turned out that lipidosis could indeed be induced by several other compounds that had nothing but the amphiphilicity in common. Finally, the concept emerged that cationic, amphiphilic drugs become trapped within lysosomes and are complexed by electrostatic and hydrophobic forces to phospholipids, thereby rendering them indigestible by phospholipases and finally leading to a storage of the lipid-drug complexes.

Since 1975 we have investigated a large series of amphiphilic drugs with respect to their interactions with polar lipids *in vitro* and their lipidosis-inducing potencies *in vivo*. It turned out that predictions made on the basis of molecular structures could be quite consistently verified by the use of cultured cells, though not as consistently when intact animals were involved; this seems to be due to interfering factors such as drug metabolism. It has become evident that drug-induced lipidosis has significance also for humans treated by cationic, amphiphilic drugs, such as chloroquine, perhexiline, and amiodarone. We know of several drug firms that specifically check the possible lipidosis-inducing potencies of new drugs in order to avoid this side effect. We believe that this practical aspect is the reason why our article has been highly cited. More recent reviews have been published.[5,6]

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2. **Schmien R, Seiler K U & Wassermann O.** Lipid composition and chlorphentermine content of rat lung tissue and alveolar macrophages after chronic treatment. *Naunyn-Schmied. Arch. Pharmacol.* 283:331-4, 1974.
3. **Lüllmann H, Rossen E & Seiler K U.** The pharmacokinetics of phentermine and chlorphentermine in chronically treated rats. *J. Pharm. Pharmacol.* 25:229-34, 1973. (Cited 55 times.)
4. **Seydel J K & Wassermann O.** NMR-studies on the molecular basis of drug-induced phospholipidosis. *Naunyn-Schmied. Arch. Pharmacol.* 279:207-10, 1973. (Cited 55 times.)
5. **Reasor M J.** Drug-induced lipidosis and the alveolar macrophage. *Toxicology* 20:1-33, 1981.
6. **Hruban Z.** Pulmonary and generalized lysosomal storage induced by amphiphilic drugs. *Environ. Health Perspect.* 55:53-76, 1984.

1-15