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Case Report

Membranes as Therapeutic Targets-Liposomes as Therapeutic Options

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ABSTRACT

Damaged or chemically altered membranes are highly likely to play a central role at the molecular level in many chronic and acute diseases as well as in aging. Damage is often related to inflammatory processes that release large amounts of Radical Oxygen Species (ROS). For several years, membrane replacement has been investigated as a therapeutic option for various diseases. Furthermore, liposomes represent potentially valuable tools for this purpose to force the integration of membrane material into the body's own tissue. Unfortunately, however, this method has not yet arrived in practice. Therefore, we have made our own efforts to establish membrane replacement in our practice, including the therapeutic use of liposomal products of high quality. Here we report on two successfully treated cases.

Keywords: Membrane damage, Liposomes, Phospholipids

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INTRODUCTION

Membrane damage can be detected in many chronic and acute diseases as well as in the natural process of aging. These damages are known from patients with fatigue, cardiovascular and neurodegenerative diseases, as well as tumors and infections (Nicolson GL, Ash ME, 2017; Torres M, *et al*., 2021). From cell physiology, the consequences of membrane damage can be estimated. There are changes in membrane potentials, transport processes, signaling cascades, etc. Furthermore mitochondria, with their compact inner membrane material, can be expected to become worse in energy production. All these changes impair cell function and vitality and can lead to tissue and organ damage in the long run.

To compensate membrane damage, it is useful to administer intact membrane material to patients. This can be done by diet or infusion. Liposomes are a special form of administration of membrane material by diet. These small vesicles, synthetically produced from natural materials, are enclosed by a membrane layer, a simple phospholipid bilayer (van Meer G, 1986). The liposomes carry an aqueous phase inside. Thus, they can be used firstly as a therapeutic agent of membrane replacement therapy or second as a vehicle to transport additional hydrophilic or lipophilic substances directly into the cells *(Figure 1)*. In particular, the administration of substances whose absorption is regulated (e.g., vitamin C (Kraft JC, *et al*., 2014; Davis JL, *et al*., 2016)) or impeded (curcumin (Shaikh J, *et al*., 2009)) can lead to higher uptake for the patient through liposomal preparation.

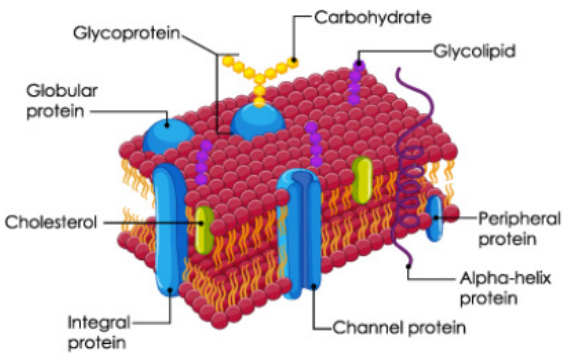

Figure 1: Structure of liposomal membrane

Liposomes can be manufactured in such a way that they are only slightly affected during digestion and instead fuse with other membranes as soon as they come into contact with them *(Figure 2)*. Meanwhile, liposomes can also be targeted to specific tissues of the body. For these reasons, liposomes are already serving as a transport option for poorly tolerated drugs as a dosage form to protect patients (especially tumor therapies). Dietary supplements in liposomal form, on the other hand, have only been on the market for a few years. We use products based on plant lecithins that contain a high concentration of active ingredients (phosphatidylcholine content 97%) and remain stable in solution for a long time in an aqueous environment. In order to be able to assess the quality of a product, we have developed a simple test that shows which liposome preparation remains in solution for a longer period of time and is thus more stable and presumably more easily distributed in the digestive tract. This test is based on mixing the respective product with water in a transparent container in a place free from vibrations. If the solution remains stable for more than ten minutes, good aqueous solubility and intestinal distribution of the product can be assumed.

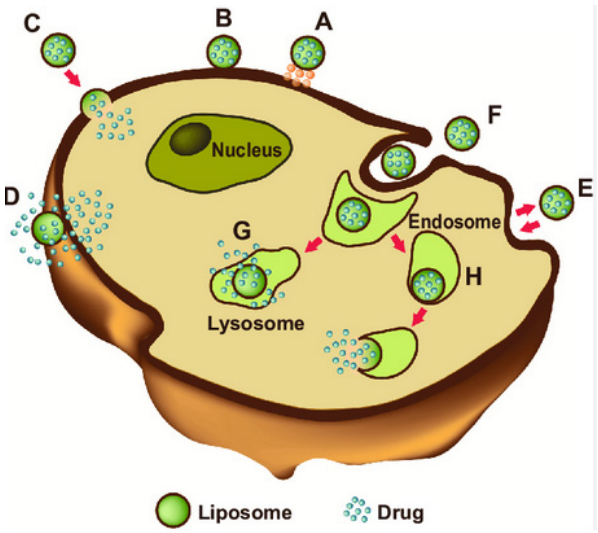

Figure 2: Drug interaction with liposome
Note: (○): Liposome; (⁘): Drug

Poor products quickly show phase separation and often clumping of the liposomes, thus forfeiting their potential superior absorption and efficacy. We have been using liposomal products as well as infusions with membrane material (mainly phosphatidylcholine) in our medical clinic for many patients for several years. Mostly, however, these administrations are part of a comprehensive orthomolecular and mitochondrial therapy. Thus, in addition to membrane materials and liposomal products, other therapeutic agents were used to a considerable extent. Therefore, it is difficult to demonstrate the effect of membrane therapy alone. Nevertheless, we would like to attempt here to depict the effect of membrane-targeted therapy on the basis of two cases that received more limited treatments.

CASE PRESENTATION

Case 1: Brain fog, fatigue and more

The patient came to us in April 2017. She was 36 years old and a physician in specialist training as a pathologist. She reported about 'brain fog', muscle pain, fatigue to the point of being unable to work, increased susceptibility to infections, especially of the bronchial tubes, and for years already very frequent urinary bladder infections, significantly worsened in the last three to five years.

Our diagnostics revealed chronic infections with Chlamydia and Candida. As gene polymorphisms, we found activity-reducing heterozygosity for the glutathione S-transferases *GSTM1* and *GSTT1* and the catechol O-methyltransferase COMT. Thus, the patient's detoxification capacity is significantly impaired in both phase I and II biotransformation. Furthermore, *via* COMT heterozygosity, endogenous stress hormone as well as estrogen degradation is very likely to be impaired and thus may produce additional disorders. In addition, we found a genetic polymorphism of superoxide dismutase SOD 2, which worsens the patient's endogenous antioxidant activity. The detected polymorphism combination exposes the patient to increased exposure to toxins and oxidative stress. The additional analysis for DNA adducts confirmed this interpretation-DNA adducts with formaldehyde, lindane, aflatoxin B and organophosphates were detected. Unfortunately, some of these were localized on cytochrome *P450* gene segments of the patient, which may further deteriorate the patient's detoxification capacity. Later, the patient was also found to be heavily contaminated with metals.

Case 2: Parkinson's disease

A 74-year-old patient came to us in October 2021. He had been diagnosed with Parkinson's disease two years earlier and suffered from the classic symptoms of dopamine depletion: he showed the typical gait disturbances with difficulty in starting, tripping steps and tendency to fall, exhibited cognitive problems as well as motor and mental drive weaknesses and speech disorders. The classical neurological medication administered so far had not led to any improvement of the course in the two years. In addition to Parkinson's disease, the patient had an artherosclerotic disease with a heart attack and subsequent stent implantation. Due to limited financial resources, further diagnostics had to be omitted in this patient.

Phospholipids were applied as therapeutic options by infusion and orally in liposomal administration. Within two months, the patient received ten infusions of 2 g phosphatidylcholine each. In addition, he took 5 ml of Mitolipo P-Cholin® and MITOlipo curmin® three times a day with each meal.

RESULTS AND DISCUSSION

Case 1

The therapeutic option used was phospholipids by infusion and orally in liposomal administration (Mazliak P, 1977). The patient received a total of eight infusions with 2 g phosphatidylcholine each. In addition, she was prescribed two liposomal products for oral therapy (Mitolipo P-Cholin® and MITOlipo Curmin®). Both products contain 97% phosphatidylcholine as raw material, the curcumin product additionally 500 mg curcumin per administration (5 ml). The patient took 5 ml of Mitolipo P-Cholin® 4 times daily and 5 ml of MITOlipo curmin® twice daily. After the first infusions, the patient received additional infusions for chelation (edetate calcium disodium 1900 mg and Dimercaptosuccinic acid each). The subsequently excreted urine was analyzed for metals. It showed a very high excretion of aluminum and lead. Only a little later the patient quickly felt better. She was physically, mentally and emotionally fitter and able to work again. After a total of three months of therapy, the patient became pregnant. Therefore, only oral treatment with the liposomal phospholipids could be continued.

In the summer of 2019-after the child was weaned, the therapy was continued. At the beginning, the patient reported that her child was very exhausting for her and that she had significantly less energy available again. She could just about manage her daily routine. After another eight infusions and supportive oral therapy, repeated chelation infusions were given When urine was sampled after chelation, high excretion of aluminum was again documented. Phospholipid infusions continued until she had received a total of 24 infusions of 2 g each of phophatidylcholine. The aspiring pathologist was doing very well thereafter and was able to resume her life with job, family, and child.

In the spring of 2022, when asked, the patient stated that she was doing well, that she was again suffering from fatigue and increased stress, but that she was still able to work well. In this case, a genetically determined increased susceptibility to toxins and oxidative stress was revealed, which, however, had not clinically manifested for a long time. However, presumably due to increased exposure to formaldehyde in the course of her specialized training as a pathologist, the patient's body system became overwhelmed. The elimination of considerable amounts of metal could be accelerated appreciably by the use of phospholipids. This is because the provision of the most important membrane material, phosphatidylcholine-in large quantities by infusion about once to four times a week and daily orally with liposomal products-very likely stimulates the exchange of damaged membrane sections (Zierenberg O, *et al*., 1981). As a result, the metals stored in membranes also start to move and can thus be released in greater quantities and, together with chelation, lead to a rapid and demonstrable therapeutic success. However, the chemical stress basically persists in the patient. In this case, it is therefore recommended to reduce the toxins accumulating in the body at regular intervals and to take a daily support against oxidative stress.

Case 2

Already during the course of therapy, improvements became apparent. The gait disturbances decreased and the patient developed a more fluid gait pattern without start inhibition. Mentally, he reported a more alert mind. Also, in direct contact with him, a more fluent and multifaceted speech could be observed. By the end of the therapy period, the patient was able to actively participate in family life again. He was even able to take care of a grandchild and meet with friends. After another two months without infusions, but with oral intake of liposomal products as before. The patient's situation is fortunately consistently stable.

Unfortunately, the lack of diagnostics in this case did not allow to clarify causes or background of disease pathology. Nevertheless, the course of Parkinson's disease could be stopped and the previous symptoms could even be significantly improved. Since no further therapy could be derived from the lack of diagnostics (detoxification problems/infection problems, etc.), there is unfortunately a risk that the improvements may not remain stable in the long term if the stress presumably continues.

CONCLUSION

A therapy aiming at improvements of membrane structures is potentially able to eliminate these molecular aberrations and thus to achieve an improvement of the respective disorders. At the same time, however, the

causes of membrane damage, such as inflammatory processes, oxidative stress, etc., must of course be discovered and, if possible, eliminated too. In order to store liposomal product longer period of time, we have developed a simple test that shows which liposome preparation remains in solution for a longer time, thereby increasing its stability and presumably more easily distributed in the digestive tract.

REFERENCES

1. Nicolson GL, Ash ME. Membrane lipid replacement for chronic illnesses, aging and cancer using oral glycerolphospholipid formulations with fructooligosaccharides to restore phospholipid function in cellular membranes, organelles, cells and tissues. Biochim Biophys Acta Biomembr. 2017; 1859(9): 1704-1724.
2. Torres M, Parets S, Fernández-Díaz J, Beteta-Göbel R, Rodríguez-Lorca R, Román R, *et al*. Lipids in pathophysiology and development of the membrane lipid therapy: New bioactive lipids. Membranes. 2021; 11(12): 919.
3. van Meer G. The lipid bilayer of the ER. Trends Biochem Sci. 1986; 11(5): 194-195.
4. Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. J Pharm Sci. 2014; 103(1): 29-52.
5. Davis JL, Paris HL, Beals JW, Binns SE, Giordano GR, Scalzo RL, *et al*. Liposomal-encapsulated ascorbic acid: Influence on vitamin C bioavailability and capacity to protect against ischemia-reperfusion injury. Nutr Metab Insights. 2016; 9: NMI-S39764.
6. Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MR. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci. 2009; 37(3-4): 223-230.
7. Mazliak P. Glyco-and phospholipids of biomembranes in higher plants. Springer. 1977.
8. Zierenberg O, Assmann G, Schmitz G, Rosseneu M. Effect of polyenephosphatidylcholine on cholesterol uptake by human high density lipoprotein. Atherosclerosis. 1981; 39(4): 527-542.