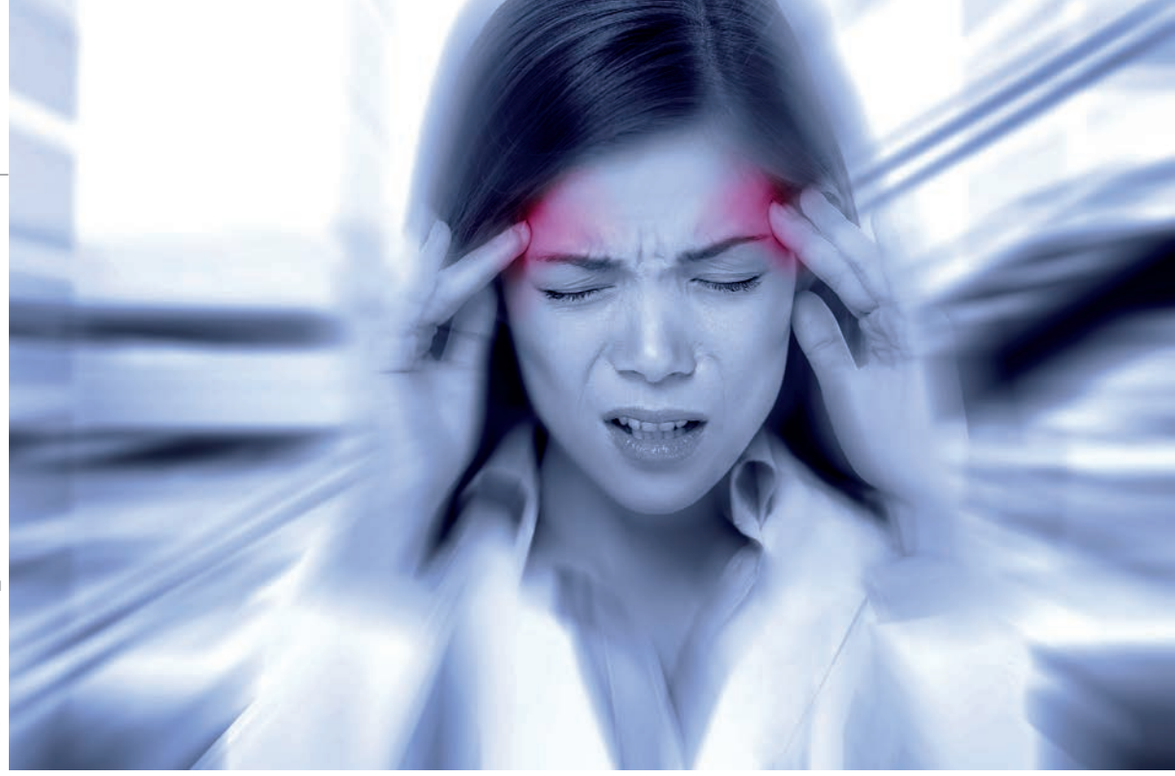

Photo©: AdobeStock_Maridav

Coenzyme Q10 for migraine prophylaxis: Natural phospholipids increase the bioavailability

Philipp Gebhardt

Migraine is one of the most common forms of headache. The cause is an increased release of inflammatory and vasodilator neurotransmitters, such as calcitonin gene-related peptide (CGRP). As a new therapeutic option, an antibody directed against the CGRP receptor has been developed, whose efficacy has been confirmed in clinical trials. A reduction in CGRP levels and an improvement in migraine symptoms could also be demonstrated by supplementation with the body's own coenzyme Q10. However, coenzyme Q10, which is taken up in the form of powder capsules, is absorbed only to a small extent. By formulation with phospholipids, that occur naturally in the bile, the bioavailability can be significantly increased.

Migraine is characterized by attacks of severe, often unilateral pulsating throbbing headache, that increase in intensity during physical exertion and typically recur periodically. In addition, symptoms such as nausea, vomiting, photosensitivity (photophobia) and sensitivity to noise (phonophobia) may occur. Migraine attacks are often preceded by a migraine aura, in which visual cognitive disorders announce the subsequent headache (1). The prevalence of the disease is highest between ages 20 and 50. Women are up to three times more likely to be affected than men (Fig. 1) (2).

According to a currently preferred hypothesis, migraine is caused by an expansion of cerebral blood vessels (vasodilation). Through activation of pain and stretch receptors of the trigeminal nerve, this leads to the triggering

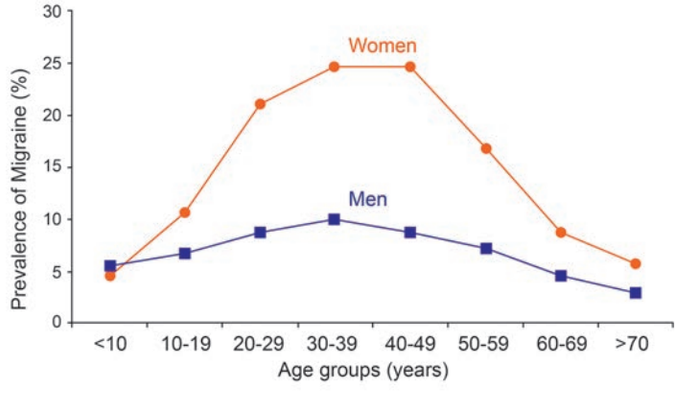

Fig. 1: Migraine prevalence in Europe in different age groups (after (2)).

of painful stimuli. The widening of blood vessels is caused by vasodilating neurotransmitters, such as calcitonin gene-related peptide (CGRP). The 37 amino acid neuropeptide CGRP is one of the strongest blood vessel-expanding substances. It is encoded by the same gene as calcite-lowering calcitonin and is mainly expressed in the central and peripheral nervous system (3).

In addition to vasodilation, CGRP causes the degranulation of mast cells, that goes along with the release of inflammatory mediators such as tumor necrosis factor-α (TNF-α). As TNF-α itself further stimulates CGRP secretion, the process leads to a self-reinforcing crisis state with the typical migraine symptoms. Increased irritation of sensory nerves leads to increased pain and hypersensitivity to environmental stimuli (Fig. 2) (4, 5).

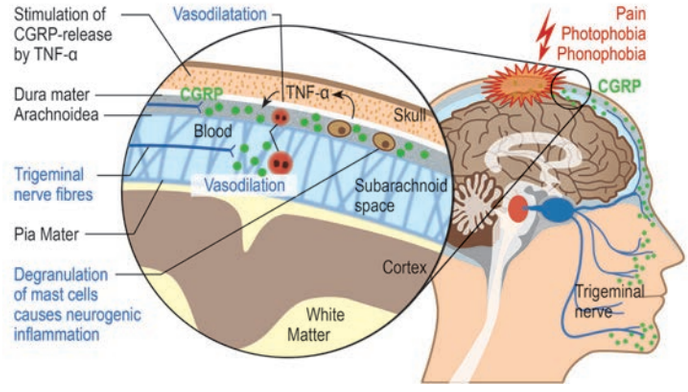

Fig. 2: The neuropeptide CGRP, which is released from trigeminal nerve fibres during a migraine attack, leads to irritation of the sensory nerves via vasodilation. By degranulation of mast cells, the inflammatory mediator TNF-α is increasingly released. Since TNF-α further stimulates the release of CGRP, there is an increase in vasodilation and a further increase in symptoms (4, 5).

Erenumab: an anti-migraine antibody

Due to the key role of CGRP in the development of migraine, monoclonal antibodies have been developed that prevent the headache attacks by blocking the receptors of the neuropeptide. A first representative of this new class of drugs is Erenumab, an antibody directed against the CGRP receptor. The antibody was approved in Germany in July 2018. In a clinical trial involving 955 participants who complained about 8.3 monthly migraine attacks prior to enrolment, Erenumab reduced seizure frequency by an average of 3.7 per month (6). In another study with 577 participants, with also 8.3 migraine attacks per month, a monthly subcutaneous injection of the antibody reduced the seizure frequency by an average of 2.9 days (7).

Coenzyme Q10 for migraine prophylaxis

Migraine is associated with a deficit of the body's own coenzyme Q10 (8). Coenzyme Q10 plays an essential role in cellular energy metabolism. It serves as an electron and proton carrier in the respiratory chain located in the mitochondria. In addition, it is a potent antioxidant that can regenerate other antioxidants such as vitamins C and E (9). Coenzyme Q10 has also anti-inflammatory properties. A markedly lowering effect on the levels of the inflammatory mediator TNF-α by coenzyme Q10 supplementation could be demonstrated in corresponding studies (10, 11). Because of these properties, coenzyme Q10 is investigated in clinical settings for migraine prophylaxis.

In an open-label study, 31 participants who suffered an average of 7.34 migraine days per month at baseline received 150 mg of Coenzyme Q10 daily for three months. After this period, a reduction of the monthly migraine days to an average of 2.95 could be recorded. Side effects did not occur during Coenzyme Q10 supplementation (12).

In a double-blind, randomized study, 42 participants with an average of 4.4 monthly migraine attacks received either 300 mg coenzyme Q10 or a placebo. After three months, the number of migraine attacks in the verum group was reduced to 3.2, while this number was only 4.3 in the placebo group. Coenzyme Q10 was well tolerated (13).

In another randomized double-blind study, in addition to the migraine symptoms, the effect of the coenzyme on the levels of CGRP and the inflammatory mediator TNF-α were also examined. Forty-five female participants received either 400 mg coenzyme Q10 daily or a placebo. Over the three-month study period, the number of monthly migraine attacks in the coenzyme Q10 group was reduced from an average of 8.47 to 3.10. A significant reduction in CGRP and TNF-α levels could be demonstrated. No side effects associated with coenzyme Q10 supplementation were reported (Figure 3) (10).

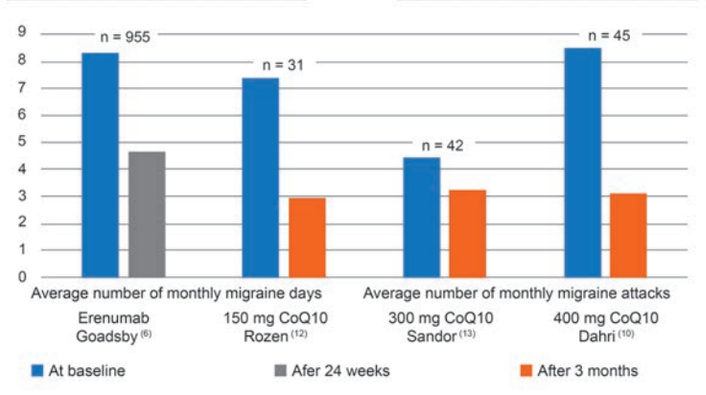

Fig. 3: Efficacy of Erenumab (left) versus coenzyme Q10 in migraine prophylaxis.

Improvement of bioavailability of coenzyme Q10 by natural phospholipids

Coenzyme Q10 is contained in animal and plant cells, so it is also provided with food. Relevant sources are fish, meat, oils, nuts and cereals. However, the daily intake, that is in the range of 5 mg, is considered insufficient to significantly affect blood or tissue levels (14). In the form of powder capsules, supplemented coenzyme Q10 is absorbed only to a small extent because the active substance is insoluble in water and has also a low solubility in fats (9).

An alternative with markedly increased bioavailability are emulsions with natural phospholipids (lecithin) in which the coenzyme is "prepacked" in ultra-small droplets. As a component of bile, phospholipids physiologically contribute to the digestion of fats. Because phospholipids consist of a hydrophilic ("water-loving") and a lipophilic ("fat-loving") part, they can combine with fats and disperse them in an aqueous environment. In the form of the resulting small droplets, fat-soluble nutrients can be absorbed much better into the epithelial cells of the small intestine (enterocytes). In the enterocytes, fats and fat-soluble nutrients are packaged in transport vesicles called chylomicrons, that consist of about 10 % phospholipids (15). The hydrophilic head groups of the phospholipids form a shell that surrounds the fat droplets and allows their transport in the aqueous environment of the lymph and the blood (Fig. 4). With the help of phospholipids, fats are also packed in so-called lipoproteins in the liver, to be released into the blood for transportation. The size of the lipoproteins is about 50 nm (VLDL), that is in the range of the size of coenzyme Q10 emulsion droplets (16).

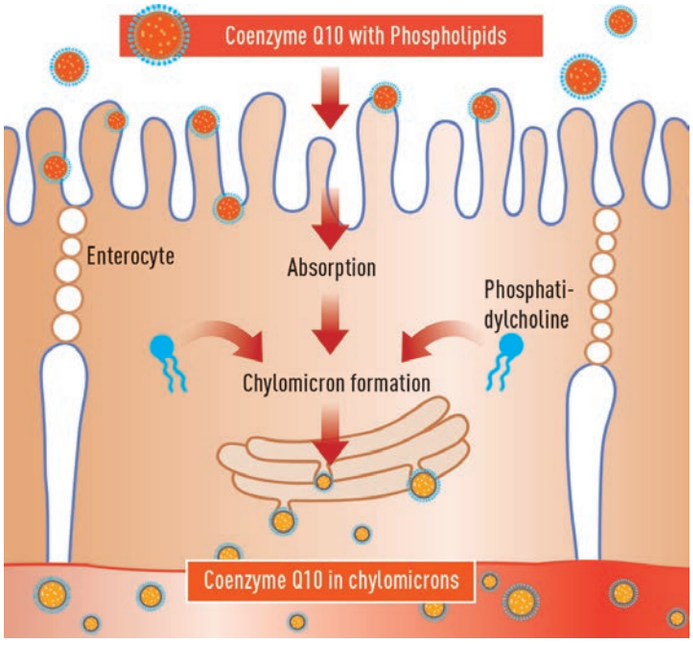

Fig. 4: Phospholipids, that are also naturally present in the bile, can be used to package fat-soluble nutrients such as coenzyme Q10 into small emulsion droplets. In this way, the uptake into the enterocytes of the small intestine is significantly facilitated. The enterocytes require phospholipids to pack dietary fats and lipophilic nutrients into chylomicrons, that are then released into the lymph. Formulation with phospholipids considerably increases the systemic availability of coenzyme Q10.

The improvement of the bioavailability of coenzyme Q10 by an emulsion with phospholipids could also be demonstrated in a comparative crossover study with 23 participants. Compared to the intake of 100 mg of unformulated coenzyme Q10, a five-fold increase in bioavailability (as area under the curve) could be confirmed (Fig. 5) (17).

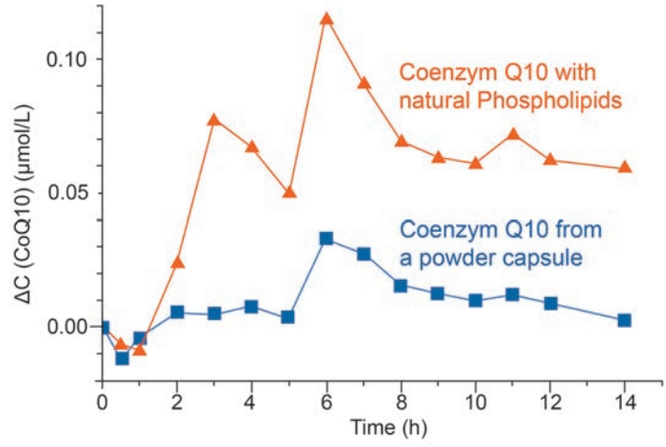

Fig. 5: Mean change in coenzyme Q10 plasma concentrations after taking 100 mg coenzyme Q10 in unformulated form or as an emulsion with natural phospholipids.

Conclusion

In addition to pharmacological treatment options, substances that occur naturally in the body are investigated for the prophylactic treatment of migraine. Coenzyme Q10 is particularly suitable for migraine prophylaxis because of the fact that side effects are not to be expected. In clinical studies, a clear efficacy could be demonstrated. However, coenzyme Q10 is absorbed only to a small extent after oral intake in the form of powder capsules. Formulation with natural phospholipids can significantly increase the bioavailability. The resulting emulsions are in the form of small droplets whose size is in the range of lipoproteins, that are produced in the liver for the transport of fats in the blood.

References

1. Diener, H. C., Gaul, C., & Kropp, P. (2018). Therapie der Migräneattacke und Prophylaxe der Migräne. Nervenheilkunde, 37(10), 689-715.
2. Stovner, L. J., Zwart, J. A., Hagen, K., Terwindt, G. M., & Pascual, J. (2006). Epidemiology of headache in Europe. European journal of neurology, 13(4), 333-345.
3. Brain, S. D., & Grant, A. D. (2004). Vascular actions of calcitonin gene-related peptide and adrenomedullin. Physiological reviews, 84(3), 903-934.
4. Durham, P. L. (2006). Calcitonin gene-related peptide (CGRP) and migraine. Headache: The Journal of Head and Face Pain, 46, S3-S8.
5. Bowen, E. J., Schmidt, T. W., Firm, C. S., Russo, A. F., & Durham, P. L. (2006). Tumor necrosis factor–α stimulation of calcitonin gene-related peptide expression and secretion from rat trigeminal ganglion neurons. Journal of neurochemistry, 96(1), 65-77.
6. Goadsby, P. J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J. H., Zhang, F., & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. New England Journal of Medicine, 377(22), 2123-2132.
7. Dodick, D. W., Ashina, M., Brandes, J. L., Kudrow, D., Lanteri-Minet, M., Osipova, V., & Lenz, R. A. (2018). ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia, 38(6), 1026-1037.
8. Hershey, A. D., Powers, S. W., Vockell, A. L. B., LeCates, S. L., Ellinor, P. L., Segers, A., ... & Kabbouche, M. A. (2007). Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache: the journal of head and face pain, 47(1), 73-80.
9. Bhagavan, H. N., & Chopra, R. K. (2006). Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. Free radical research, 40(5), 445-453.
10. Dahri, M., Tarighat-Esfanjani, A., Asghari-Jafarabadi, M., & Hashemilar, M. (2018). Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. Nutritional neuroscience, 1-9.
11. Zhai, J., Bo, Y., Lu, Y., Liu, C., & Zhang, L. (2017). Effects of coenzyme Q10 on markers of inflammation: a systematic review and meta-analysis. PloS one, 12(1), e0170172.
12. Rozen, T. D., Oshinsky, M. L., Gebeline, C. A., Bradley, K. C., Young, W. B., Shechter, A. L., & Silberstein, S. D. (2002). Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia, 22(2), 137-141.
13. Sândor, P. S., Di Clemente, L., Coppola, G., Saenger, U., Fumal, A., Magis, D., ... & Schoenen, J. (2005). Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology, 64(4), 713-715.
14. Weber, C., Bysted, A., & Hølmer, G. (1997). Coenzyme Q10 in the diet-daily intake and relative bioavailability. Molecular aspects of medicine, 18, 251-254.
15. Hussain, M. M. (2000). A proposed model for the assembly of chylomicrons. Atherosclerosis, 148(1), 1-15.
16. Cheung, M. C., Wolfbauer, G., Deguchi, H., Fernández, J. A., Griffin, J. H., & Albers, J. J. (2009). Human plasma phospholipid transfer protein specific activity is correlated with HDL size: implications for lipoprotein physiology. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1791(3), 206-211.
17. Wajda, R., Zirkel, J., & Schaffer, T. (2007). Increase of bioavailability of coenzyme Q10 and vitamin E. Journal of medicinal food, 10(4), 731-734.

For more information, please contact

Philipp Gebhardt
MitoTherapie
65779 Kelkheim Germany
p.gebhardt@mitotherapie.de
www.mitotherapie.de