BASIC PRINCIPLES – REGULATION OF THE LIVER METABOLISM

THYROID GLAND HORMONES T_3 AND T_4

The thyroid gland hormones triiodothyronine (T_3) and tetraiodothyronine (T_4) are derivates of the amino acid tyrosine. Iodine is used for the synthesis of T_3 and T_4, which is absorbed with food as iodide, from which blood gets into the follicle cells, actively concentrates and is transferred through the thyroidal peroxidase in organic iodine (organification). The follicle cells surround a space that is filled with colloid, which consists of tyrosine-rich thyroglobulin, which contains tyrosine in its matrix. Tyrosine is iodized upon contact with the membrane of the follicle cells at one (monoiodotyrosine) or two (diiodotyrosine) points. It is then that respectively two molecules are combined with one another. Thus, the two thyroid hormones T_3 and T_4 arise. Due to their lipophiles in the blood, both are transported 75 % with the thyroid hormone binding protein (TBP) and 25 % with albumin and the thyroxine-binding prealbumin transthyretin.

Approximately 0.3 % of the total serum-T_3 and 0.03 % of the total seru-T_4 are present as free hormones in balance with bound hormones. Only free T_3 and T_4 can be effective in the periphery.

STANDARD VALUES

The height of the plasma concentrations for both thyroid hormones is dependent on the method. The free plasma concentration of T_3 amounts to approx. 5–10 pmol/l, the total 1.5–3.5 nmol/l. For T_4, the free plasma concentration is about 20–40 pmol/l. the total at 60-140 nmol/l. In the target tissue, the largest share of T_4 is converted into the activating T_3, which has a shorter half-life.

BREAKDOWN

The half-life and the duration of efficacy of the thyroid hormone is several hours for T_3, or several days for T_4. All iodothyronines are metabolized in the liver by glucuronidation and sulfation of the phenolic 4'-OH-group. As a result, they are water-soluble and partly eliminated renally, partly excreted with the bile. In the intestine, it is partially hydrolyzed and reabsorbed as intact hormones or in the form of fragments.

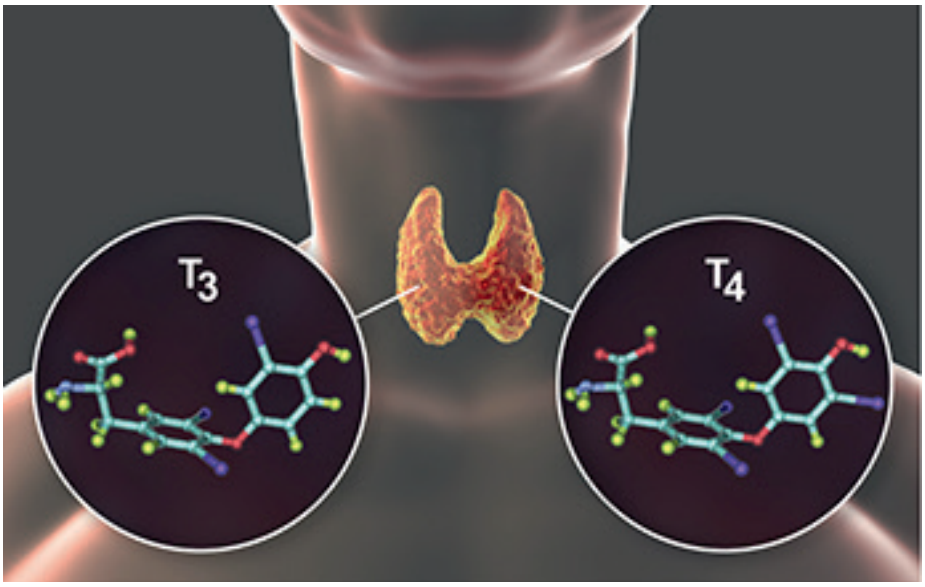

FIGURE: Molecules of the thyroid gland hormones T_3 and T_4 Source: Kateryna_Kon@Adobe_Stock

REGULATION OF RELEASE

The secretion of thyroid hormone is controlled by the hypothalamus and the hypophysis. The tripeptide thyroliberin (TRH, thyrotropin releasing hormone), which originates in the hypothalamus, activates the release of thyrotropin (TSH, thyroid stimulating hormone) from the hypophysis. The release of thyroliberin is primarily activated by cold.

In the thyroid gland TSH binds to the TSH receptors of the follicle epithelial cells. This stimulates the thyroid gland to absorb more iodine and stimulates the formation of the thyroid hormones T_3 and T_4, which are secreted into the bloodstream.

EFFECT

The effect of T_3 and T_4 is complex and affects not only the liver, but also the majority of the body. The thyroid gland hormone influences both the metabolic rate as well as the growth process and the differentiation. As a result, T_3 and T_4 play a significant role in the oxygen uptake and the thermogenesis in the tissue. In the liver, the capacity for oxygen uptake and for gluconeogenesis as well as glycolysis increases. They also facilitate the lipolysis and proteolysis in the fatty tissue and in the muscle.

Furthermore, the thyroid gland hormone supports bone growth and brain development. It increases the contractility of the heart muscle and the cardiac output and regulate the metabolism of connective tissue.

The series will be continued in the next issue of Hepa News®.

NAFLD – COGNITIVE DYSFUNCTION THROUGH METABOLIC AND HEPATIC DISORDERS

The Non-alcoholic fatty liver disease (NAFLD) is gaining increasingly more significance as a hepatic component of the metabolic syndrome. NAFLD is associated with a series of intra- and extra-hepatic complications, among which is also cognitive dysfunction. In a current study, the evidence of underlying mechanisms was investigated in corresponding publications.[1]

NAFLD is one of the largest health problems worldwide. It is assumed that around a quarter of the world's population is affected. Fatty liver disease itself, as well as the extra-hepatic complications linked to it and the metabolic syndrome increase the patient's risk of morbidity and mortality. The cognitive dysfunction with NAFLD is gaining Increasing awareness as a risk factor, which is indicated by memory problems, awareness and concentration disorders, forgetfulness, and confusion. It is assumed that approx. 70 % of NAFLD patients are affected by it, and that their everyday life and quality of life are affected by it.

TIGHT CORRELATION BETWEEN THE SEVERITY OF NAFLD AND COGNITIVE DISORDERS

A current study analysis provides indication of a correlation between the severity of the fatty liver disease and cognitive restrictions. Systemic and neuroinflammation, vascular dysfunction, and sleep apnea are being discussed as possible mechanisms, which are observed with both a metabolic syndrome and also NAFLD.

More recent investigations indicate that NAFLD itself could be an independent risk factor for the development of a cognitive dysfunction. Alongside the indicated risk factors, there is also a dysbiosis of the intestinal microbiota and an impaired function of the urea cycle, which is the primary path to ammonia poisoning, among NAFLD patients. As a result, a systemic ammonia accumulation favored, and system inflammations are further triggered.

AMMONIA AS THE KEY TO NEUROINFLAMMATION

The neurotoxin ammonia can break down the blood-brain barrier and is applicable as a significant pathogenetic factor of hepatic encephalopathy (HE). Studies have shown that the cognitive dysfunctions caused by ammonia are worse in an inflammatory environment, and that ammonia is the key, which opens the blood-brain barrier to the systemic inflammation. A reduction in ammonia levels or an anti-inflammatory treatment can lead to an improvement of cognitive disorders and neuroinflammation.

Arteriosclerosis and cerebrovascular dysfunction are also connected with the cognitive disorders in NAFLD. Accumulation of fat in the liver appears to cause a microvascular hemodynamic dysfunction with endothelial dysfunction, which reduced cerebral blood-flow and thus leads to cerebrovascular dysfunction. It is possible that neurodegenerative developments are induced in the brain as a result of this, like dementia and Alzheimer's.

DIAGNOSTIC PROCEDURE MUST BE EXTENDED

The current studies indicate that NAFLD patients develop a cognitive dysfunction, which is a multi-factorial, metabolic encephalopathy with characteristics of both, hepatic and diabetic encephalopathy. Furthermore, with these patients there are also unspecific mental and physical symptoms, which can indirectly impair the cognitive functions. The cognitive phenotype of NAFLD is not yet specified in sufficient measure. Therefore, the psychometric and neuropsychological test methods used in previous studies cannot adequately address the extensive metabolic encephalopathy implied by the current evidence. To record the whole spectrum of cognitive dysfunction for NAFLD diagnostically, the validated test for diagnosis of hepatic encephalopathy must be complemented by at least one test for the learning and/or working memory.

INTENSIFICATION OF RESEARCH OF PATHOLOGY REQUIRED

In addition to improvements in diagnostic procedures, further research on the pathological basis of cognitive disorders in NAFLD is urgently required.

Treatment is currently essentially supported by a change in lifestyle and the bariatric operations, which lead to a reduction in weight, and thereby potentially improving the described neurological disorders.

The cognitive and functional restrictions as a result of NAFLD will have increasing social effects, and be lined with a cost increase for healthcare systems. People's quality of life gets worse, work productivity decreases, while the need for care increases. All of this illustrates an urgent need for medicative treatments for the treatment of patients with NAFLD.

LITERATURE

1 Kjaergaard K et al., J. Clin. Med. 2021;10:673. https://doi.org/10.3390/jcm10040673.