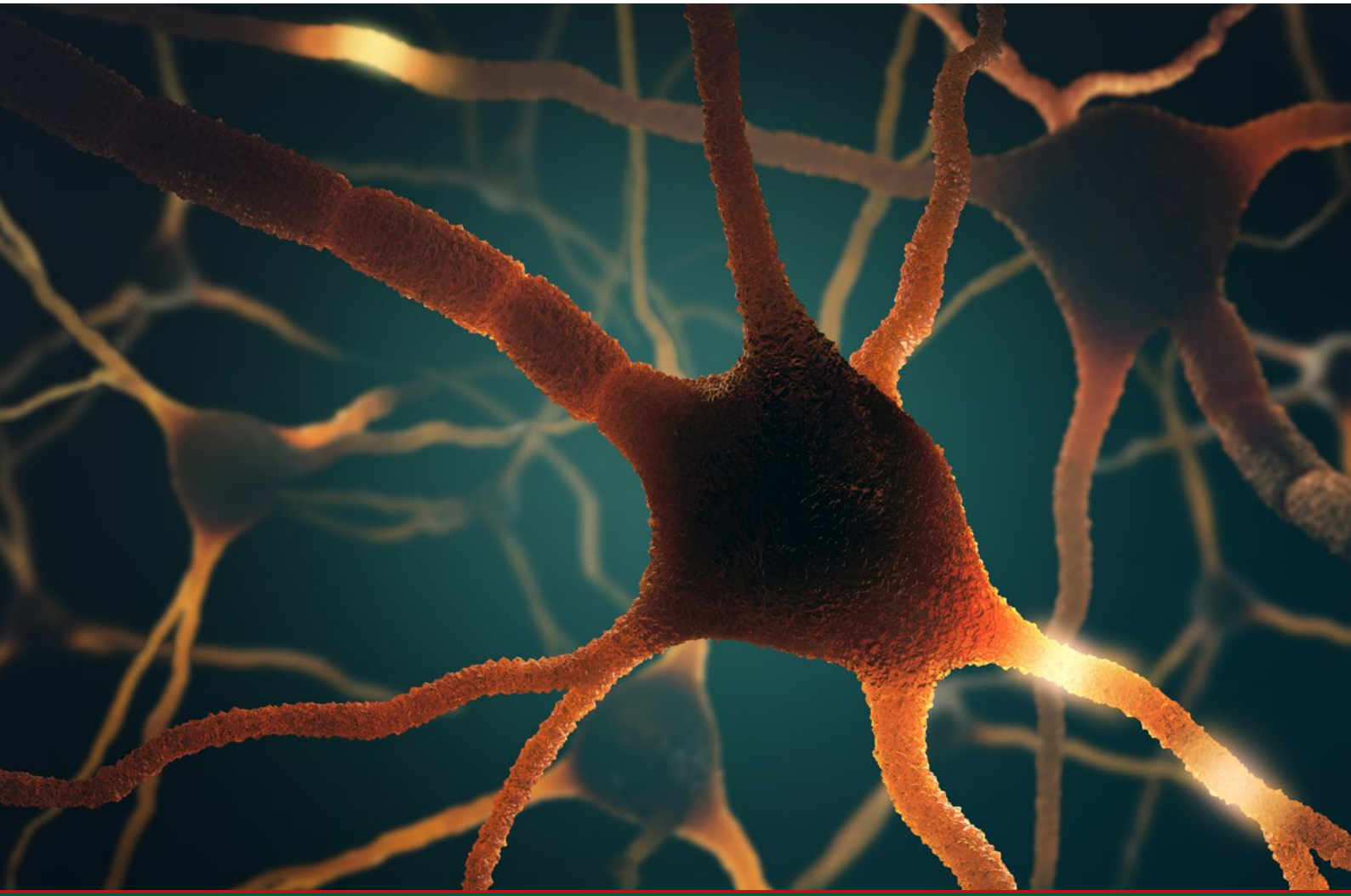
bio|vis' DIAGNOSTIK

Tryptophan metabolism



Potential for new treatment approaches
and better chances of healing

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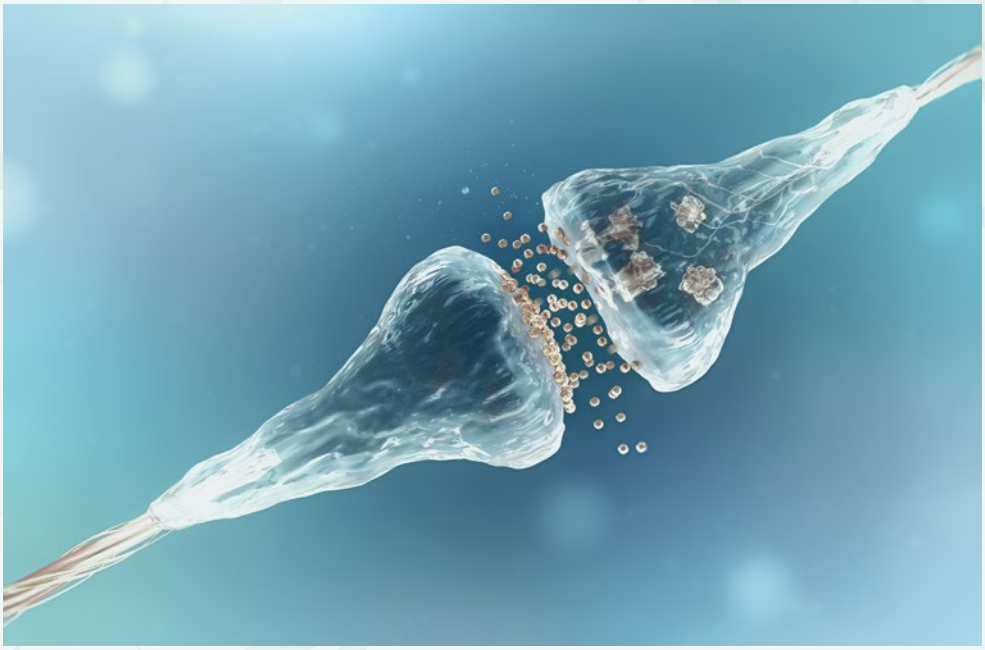


Subclinical inflammations are recognized as contributing factors to many chronic illnesses. Wellestablished examples of this are:

- **Arthritis**
- **Alzheimer's**
- **Arteriosclerosis**
- **Osteoporosis**
- **Diabetes mellitus**
- **Crohn's disease**
- **Ulcerative Colitis**

Subclinical inflammations are recognized as contributing factors to many chronic illnesses. ***Arthritis, Alzheimer's, Arteriosclerosis, Osteoporosis, Diabetes mellitus, Crohn's disease, Ulcerative Colitis etc.*** *are well-established examples of this. The cytokines released by the inflammatory processes not only affect the immune cells, but also the various metabolic pathways. This applies in particular to the tryptophan metabolism, as research over the past few years clearly shows. These advances in research can spur treatment for many patients by breaking the previously known "course of the illness" and to clearly increase the chances of healing.*

The amino acid tryptophan (TRP) has long been known as a precursor of serotonin. However, in terms of quantity, the importance of this metabolic pathway is secondary. The majority TRP goes into the formation of **kynurenine**:

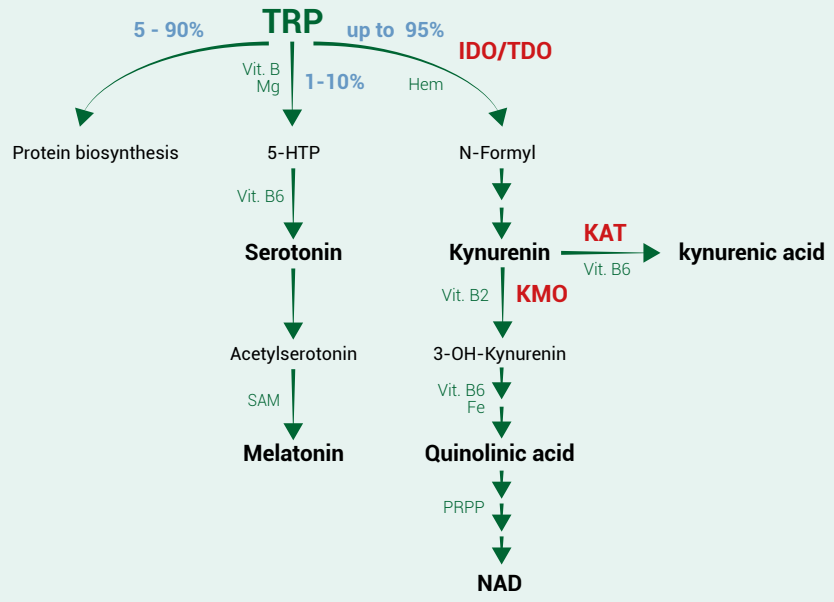
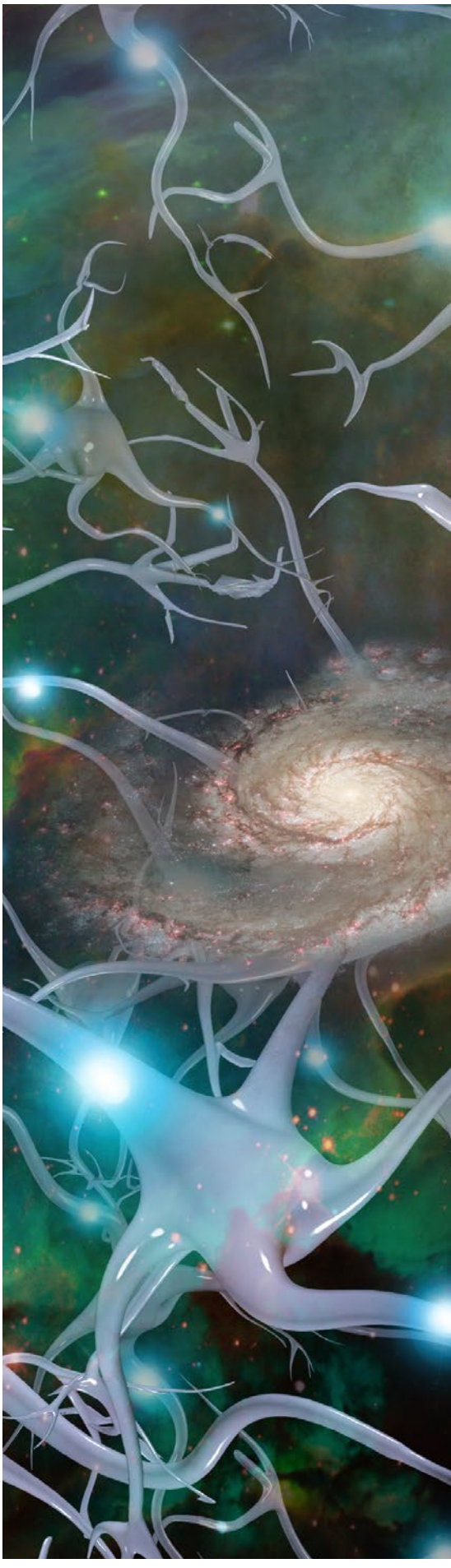
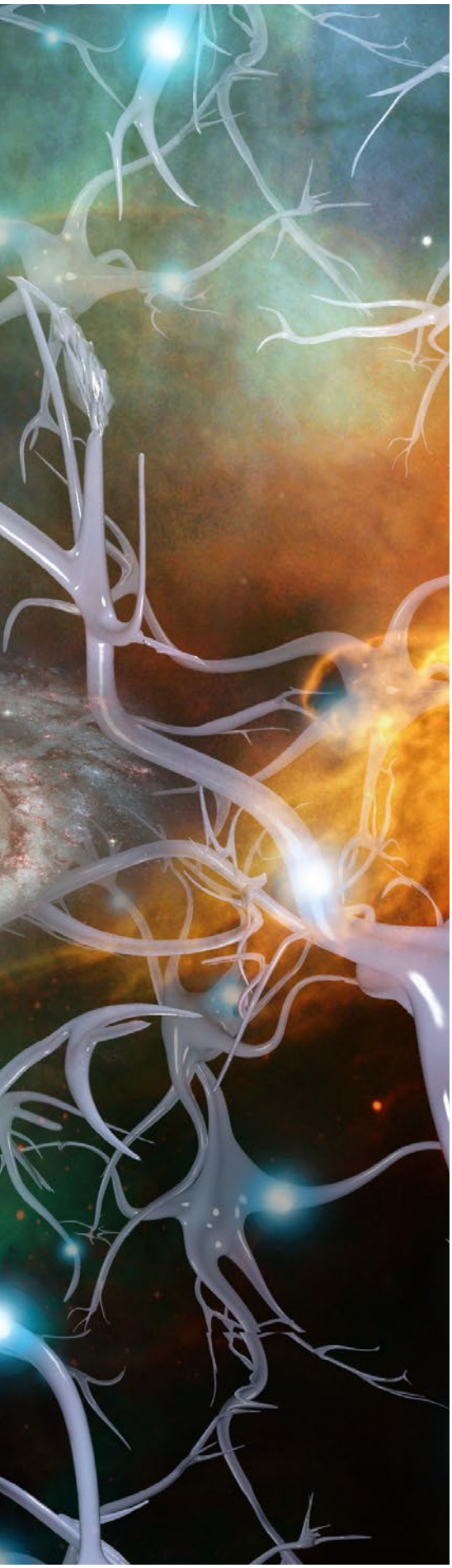


Fig. 1: Metabolic pathway

TRP = Tryptophan
TDO = Tryptophan-2,3-Dioxygenase (mostly in liver, heart, lungs, brain)
IDO = Indolamine-2,3-Dioxygenase (other tissues)
5-HTP = 5-Hydroxy-Tryptophan
KMO = Kynurenine-Monooxygenase
KAT = Kynurenine-Oxoglutarate-Transaminase
NAD = Nicotinamide-Dinucleotide (oxidized form, coenzyme)
SAM = S-Adenosylmethionine
PRPP = α-5'-Phosphoribosyl-1'-pyrophosphate





The enzymes **IDO/TDO** as well as **KMO** are activated by inflammatory cyotkines (IFN-α, -ß, -γ, TNF-α, IL-6 and PAF). Inflammations this way promote the formation of kynurenine and quinolinic acid. The formation of serotonin and melatonin, however, removes TRP; and for this reason, the synthesis can decrease by up to 50% and limit the supply of both of these substances.

The importance of TRP and its metabolites

TRP in the digestive tract is important for the regeneration of the intestinal mucous membrane and protects against an increase of potentially pathogenic germs (via IL-22). Moreover, it is available for the formation of **serotonin** (see below) in the enterochromaffin cells. If the intestinal lumen has inadequate amounts of TRP, these functions cannot be fulfilled for the digestive tract. A lack of **TRP** in the stool can often be established in patients with inflammatory **intestinal illnesses** [i, ii], **irritable bowel syndrome** , or other **pain symptomatics** [iii] in the intestines.

Diagnosis	Material
TRP in feces	Feces

Deficiency of **TRP** in the stool can occur when the oral supply of amino acids is too low. If there is sufficient consumption, inflammatory mucous membrane reactions or microbiome changes (too few H2O2 creators) can explain the deficiency. In these cases, the degradation pathway of the intestinal **TRP** is enhanced by the activation of the enzymes **IDO** and **KMO**. **TRP** get lost to the body and above all in the intestinal mucous membrane. Therefore, treatment in this case should not only consist of **TRP** and the cofactors of its conversion to **serotonin / melatonin** (vitamin B6, Mg, SAM), but should also aim to regenerate the intestinal mucous membrane, including administration of probiotics, prebiotics, as well as anti-inflammatory phosphatidylcholine.

Beware! No **TRP** should be administered if medications are taken that affect the serotonergic system, e.g. MAO inhibitors (e.g. moclobemide!), SSRI (e.g. Citalopram, Fluoxetin), SNRI (e.g. Venlafaxine), Triptane (e.g. Naratriptan, Sumatriptan) or dextrometorphane.

Serotonin is known as an inhibitory **neurotransmitter** and as a precursor of **melatonin**. In the CNS, it has a mood-lifting, relaxing, anxiety-resolving, anti-depressant effect, and supports learning and memory. Peripherally, serotonin is playing a role in blood clotting (thrombocytes) and wound healing, but is also very important for the intestines, in that it affects peristalsis, resorption, immune activity, and enteric pain perception (irritable bowel syndrome, etc.). 95% of the serotonin is formed in the intestine.

Melatonin is the sleep hormone that regulates the day-night rhythm. It is formed in the CNS in the pineal gland. In addition, it is formed in the retina of the eyes and in the intestines. Melatonin has antioxidative properties along with its importance as a hormone.

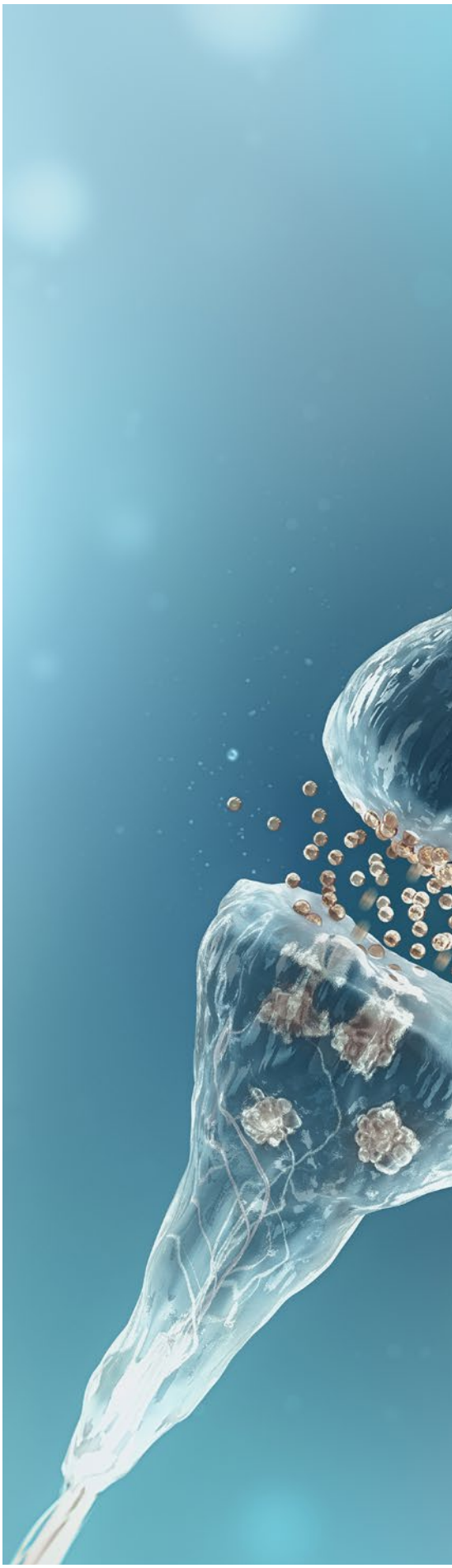
A lack of serotonin / melatonin thus produces various symptoms.

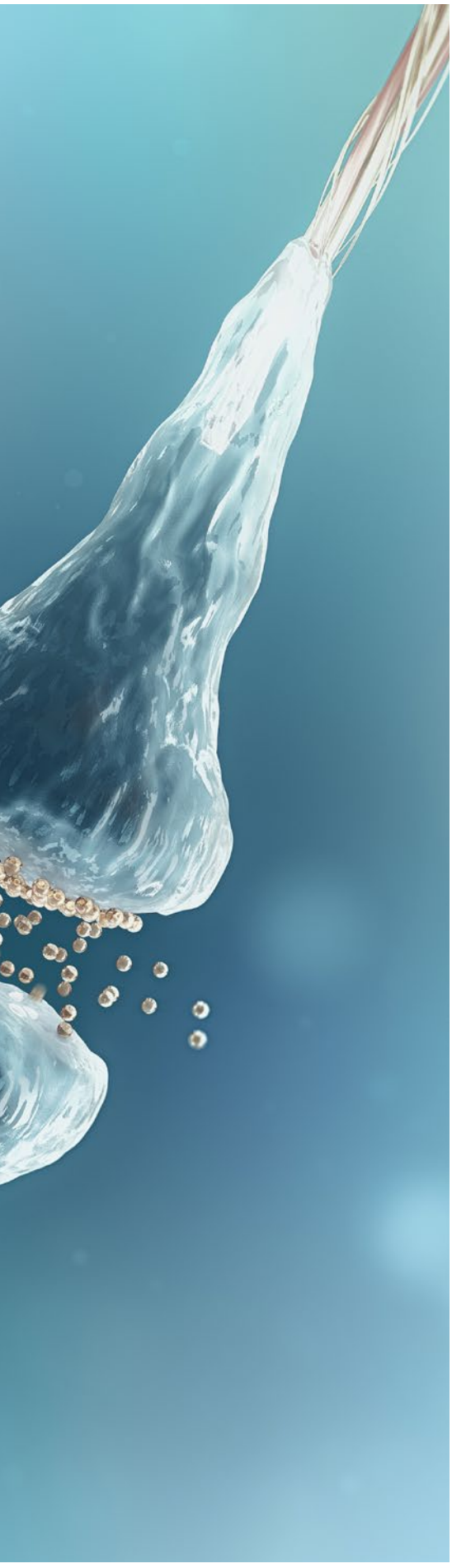
Diagnosis	Material
Serotonin in the blood	Blood spot (high test stability), 1 field
Melatonin in the saliva	Test set 923

The administering of **TRP** can be a treatment for a lack of **serotonin / melatonin**. However, this measure can only be successful if no **IDO** and **KMO** activating inflammations are present in the body. In such cases, a sustainable antiphlogistic treatment (see below) should also be part of the treatment for the lack of **serotonin / melatonin.** The problem can be circumvented at the beginning of the treatment through administering 5-HTP which is present at the intermediate stage of the synthesis until the inflammation situation has improved and the TRP metabolism has normalized.

Beware! 5-HTP can lead to a loss of NAD and thus to a lack of energy.

Kynurenine is formed from **TRP** via the enzyme **IDO**. The ratio of these two substances in the serum or the blood spot tells us about **IDO activity**. If there is relatively more kynurenine, the IDO **is highly active**. This is often found in patients with obesity, metabolic syndrome, chronic stress (burnout, CFS), depression, chronic pains, cardiovascular illnesses [iv], tumor illnesses, bacterial





infections [v], chronic virus infections (e.g. EBV, HHV), autism, multiple sclerosis, and autoimmune illnesses [vi, vii, viii, ix]. Moreover, there are also indications that inadequate **mitochondrial activity** or ATP formation is accompanied by a high kynurenine/TRP ratio (see NAD) [x]. On the other hand, the situation is different with rheumatoid arthritis and some autoimmune illnesses, viral infections, and other intracellular pathogens. Here, **low IDO activities** as well as **sinking kynurenine levels** [xi] can be established**.**

If an irregular IDO activity is dealt with therapeutically, it is possible to positively influence the course of the above illnesses. The results include improved survival rate in case of tumor illnesses [ii, xiii, xiv, xv], a faster healing of infections, or preventive effect in the case of cardiovascular or stress-related illnesses, as well as depression, etc.

Diagnosis	Material
IDO activity: TRP, kynurenine in the blood	Blood spot (high test stability), 2 fields or serum (2 ml)

An **excess of kynurenine** will stunt the innate (TH1/TH17) and strengthen the adaptive immune system (TH2). Thus, it lowers patients' ability to fight against viruses and tumor cells, reduces immunity; because it leads to inactivation of cytotoxic T-cells. Regulatory T-cells are activated. The tolerance of the patient increases [xvi].

The consequence of impaired **IDO activity** and **kynurenine deficiency** is, on the contrary, lack of immunosuppression, which creates a Th1 > Th2 imbalance [xvii].

The positive effect of converting **TRP** to kynurenine becomes clear in the next step: Kynurenine is metabolized by the enzyme **KAT** into **kynurenine acid**, an NMDA receptor antagonist and antioxidant that has anti-inflammatory and pain-reducing effect. An increase of the reactant kynurenine is this way important for the body in the formation of an inhibitor of inflammation in the inflammatory metabolism.

Kynurenine can pass through the **blood-brain barrier** and thus into the brain. The enzyme KAT is not present in the macrophages and the microglia cells, so there, **kynurenine** is exclusively metabolized into quinolinic acid, an NMDA receptor agonist.

Quinolinic acid is a neurotoxin, with inflammatory and oxidizing effect [xviii]. It can affect the integrity of the blood-brain barrier. Many neuropsychiatric and neurodegenerative disease patterns are associated with an increased level of quinolinic acid: Anxiety disorders, depression, Alzheimer's, Parkinson's, and multiple sclerosis [xix, xx]. In the astrocytes of the brain, kynurenine can be converted into **kynurenic acid**, which, in addition to the already mentioned positive properties, also has a neuroprotective effect. The quinolinic acid from the other types of cells can be degraded in the astrocytes, however, the capacity of the corresponding enzymes is limited [xxi]. A high conversion rate of **TRP** into **kynurenine** thus also brings an increased risk for neuroinflammatory or neurotoxic damages.

Rivals: Quinolinic and kynurenine acid [xxii]

Quinolinic acid ...	Kynurenine acid ...
...increases formation of radical oxidative substances (ROS)	**...scavenges** ROS radical oxidative substances
...inhibits anti-oxidative enzymes	**...protects** anti-oxidative enzymes
...reduces mitochondrial activity	**...increases** mitochondrial activity in case of stress
...oxidizes proteins and lipids of the mitochondrial membrane	**...protects** proteins and lipids of the mitochondrial membrane
...disrupts breathing processes	**...animates** breathing processes
➔ **Quinolinic acid** is **a strong mitochondrial killer**	➔ **Kynurenic acid** is **an important protector of mitochondria**

The prognosis of patients with neuropsychiatric or degenerative illnesses can thus be evaluated by looking at the ratio of the opposing acids, quinolinic and kynurenic acid (= activity of the KMO). A targeted effect on TRP metabolism makes a cause-oriented, effective treatment possible.

Diagnosis	Material
KMO activity:Quinolinic, kynurenic acid in the urine	Test set 928

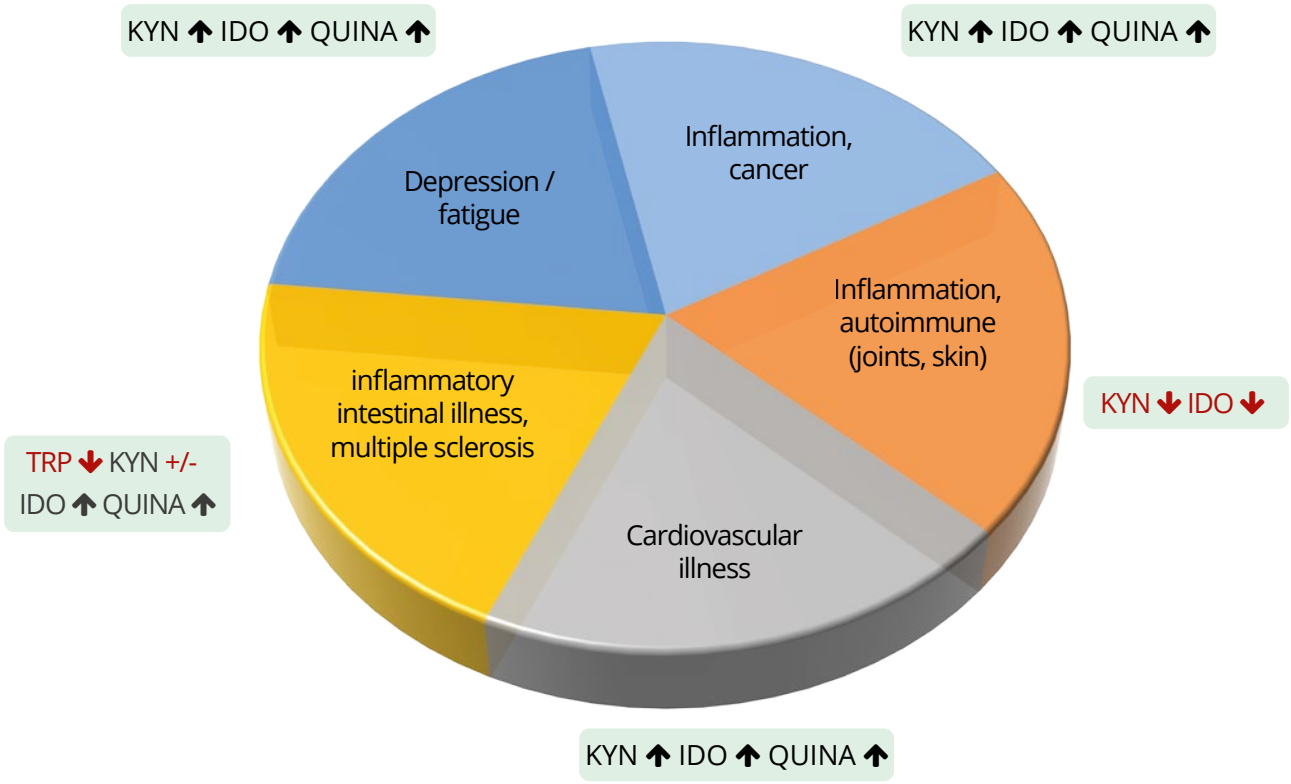


Fig. 2: Illnesses with chronic inflammation

NAD is a co-factor necessary in many redox metabolic pathways, that can receive hydrogen ions. When loaded (NADH2), it works as a reduction equivalent. **NAD** is particularly important as a hydrogen carrier between the citric acid cycle and the respiration chain. The synthesis of **NAD** from **TRP** is especially important when sufficient supply of Vitamin B3 is not ensured via diet. If **quinolinic acid formation** increases, **NAD** synthesis slows down. This can result in a lower supply of reduction equivalents for the respiration chain and declining cellular energy supply. In certain patient groups, frequent patterns of findings point to the correct diagnosis.

The fate of TRP in the body is therefore determined by the activities of the enzymes IDO/TDO, KMO and KAT, all of them important in the TRP metabolism, and this in turn determines the prognosis for each patient.

The treatment measures below are listed with the above findings in mind, to improve the course of illnesses:

Lack of TRP in the stool

- Administering TRP plus co-factors (B6, Mg, SAM) **Beware! (see above)**
- Measures for intestinal mucous membrane regeneration
- Antiphlogistic measures

Lack of serotonin/melatonin

- Determination, if necessary administering co-factors of serotonin synthesis (Vit. B6, Mg, SAM)
- Determination, if necessary administering Vit. D (increases synthesis of 5-HTP)
- If necessary, administering 5-HTP **Beware! (see above)**
- Antiphlogistic measures

Increased IDO activity
(increased kynurenine-TRP ratio)

- Administering IDO inhibitor:

  Curcumin

  Berberin

  Resveratrol

  Quercetin
- Antiphlogistic measures

Slower IDO activity
(lower kynurenine-TRP ratio)

- Epigallocatechin-3-Gallat (green tea extract) after IDO activation:
- Omega-3 fatty acids (→ FA analysis)
- Boswellia

Increased KMO activity
(increased quinolenic / kynurenic acid ratio)

- Administering omega-3 fatty acids (above all DHA)
- Administering Boswellia
- Moderate sport (supports KAT and thus formation of kynurenic acid)
- Antiphlogistic measures

Antiphlogistic measures

- Phytotherapeutics (e.g. rampion, eucalyptol, thymol, nettle, willow bark, garlic, curcumin)
- High doses of Vitamin E
- Reduction of arachidonic acid
- (→ Anti-inflammatory fatty acids)
- Administering omega-3 fatty acids (→ FA analysis)
- Moderate sport (supports **KAT** and thus formation of kynurenic acid)
- Vitamin C infusions
- Vitamin B12 injections
- Administering phosphatidylcholine

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