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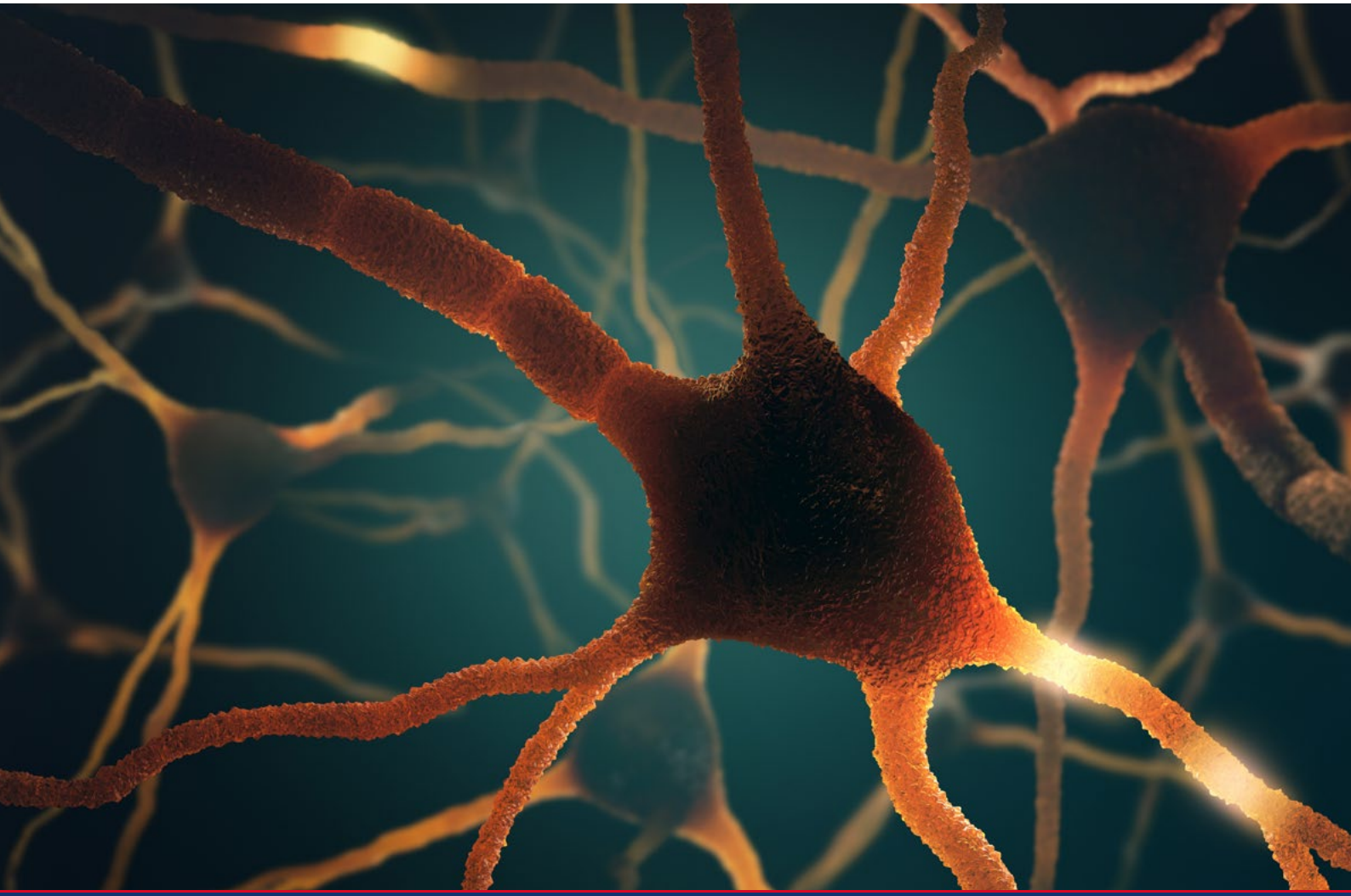
Tryptophan Metabolism



Increasing Recovery Chances Through Novel Therapeutic Approaches

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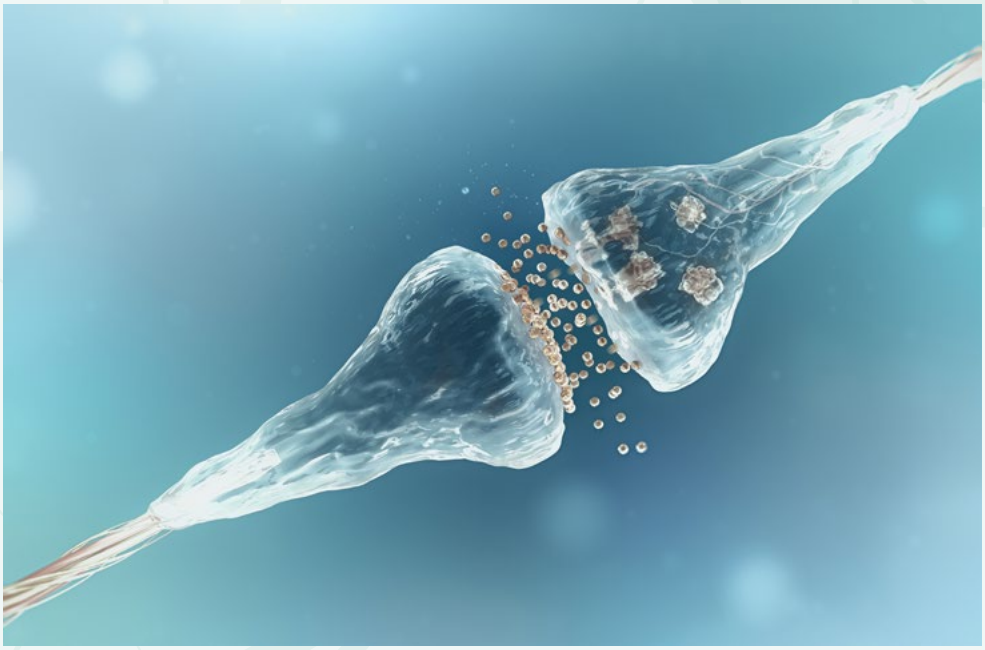

Subclinical inflammation is known to be a contributing factor in many chronic diseases. Some well-documented examples are:

- **Rheumatoid arthritis**
- **Alzheimer's disease**
- **Atherosclerosis**
- **Osteoporosis**
- **Diabetes mellitus**
- **Crohn's disease**
- **Ulcerative colitis and many more**

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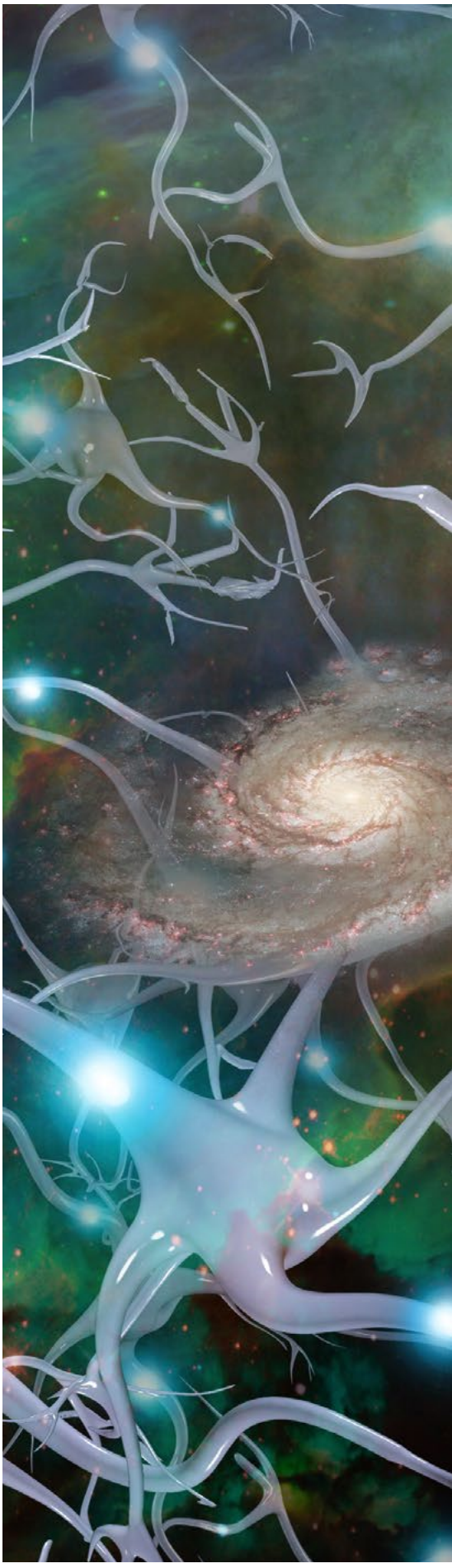
Subclinical inflammation is recognized as a contributing factor to many chronic diseases. Conditions such as ***arthritis, Alzheimer's disease, atherosclerosis, osteoporosis, diabetes mellitus, Crohn's disease, and ulcerative colitis are well-documented examples****. The cytokines released during the inflammatory process not only affect immune cells but also influence various metabolic pathways, particularly the tryptophan metabolism, as evidenced by recent publications. These new insights can provide innovative approaches to treatment, helping to interrupt the progression of these diseases and significantly improve recovery chances for many patients.*



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

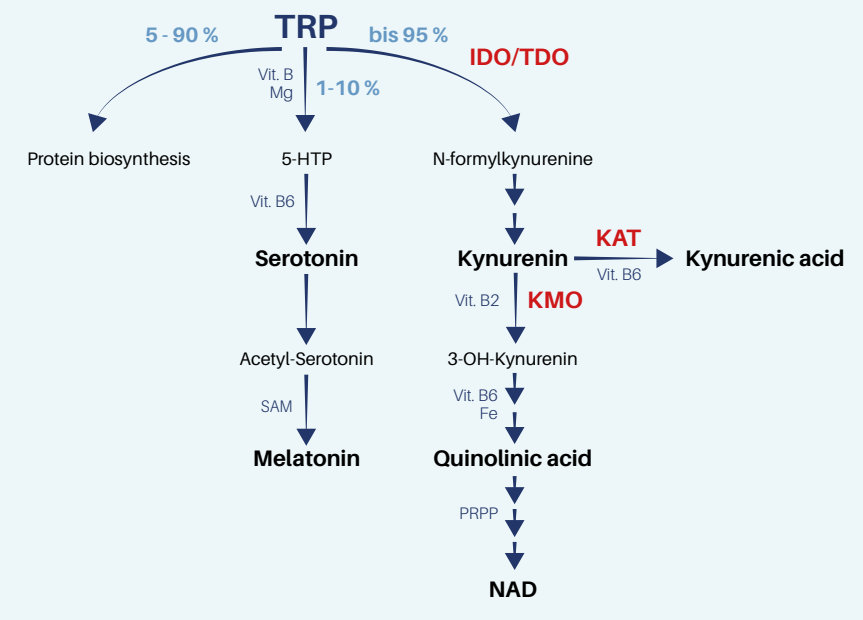
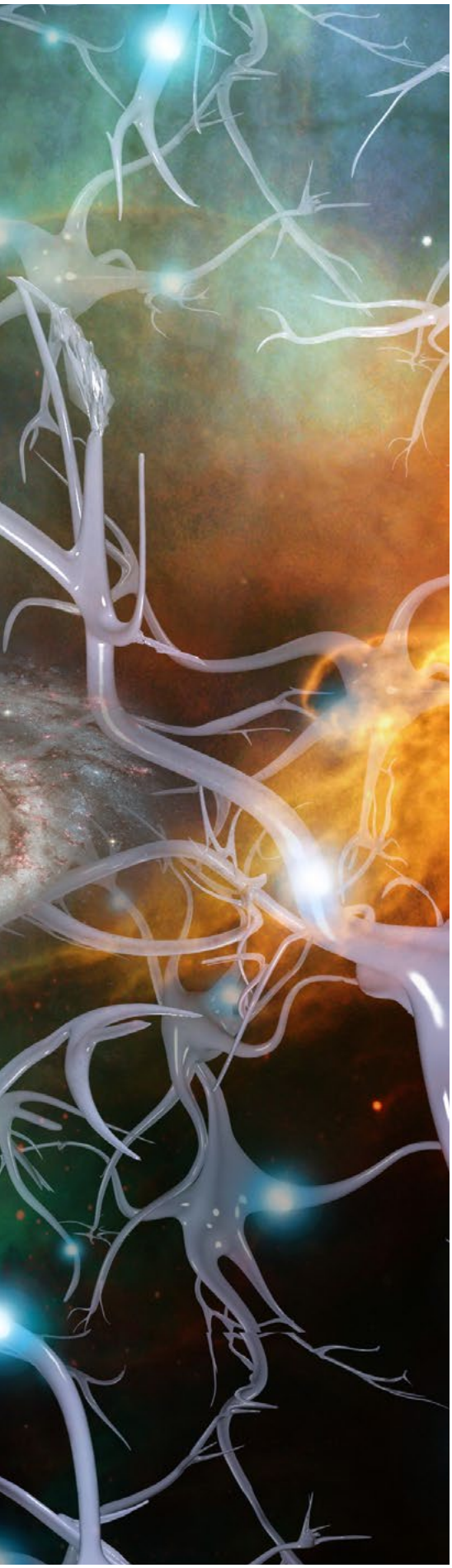


Fig. 1: *Metabolic pathway of tryptophan*

TRP = Tryptophan
TDO = Tryptophan-2,3-dioxygenase (mainly found in the liver, heart, lungs, and brain)
IDO = Indoleamine-2,3-dioxygenase (found in other tissues)
5-HTP = 5-hydroxy-tryptophan
KMO = Kynurenine monooxygenase
KAT = Kynurenine oxoglutarate transaminase
NAD = Nicotinamide dinucleotide (reduction equivalent, cofactor)
SAM = S-Adenosylmethionine
PRPP = α-5'-phosphoribosyl-1'-pyrophosphate



The enzymes **IDO/TDO** and **KMO** are activated by inflammatory cytokines such as IFN-α, IFN-ß, IFN-γ, TNF-α, IL-6 and PAF. This activation promotes the production of kynurenine and quinolinic acid. Consequently, inflammation redirects TRP away from the synthesis of serotonin and melatonin, potentially reducing their production by up to 50 % and limiting the availability of these critical substances.

The Importance of TRP and its Metabolites

TRP plays a crucial role in the digestive tract by aiding in the regeneration of the intestinal mucosa and protecting against the proliferation of potentially pathogenic germs via IL-22. It is also involved in the formation of **serotonin** in the enterochromaffin cells (see below). When **TRP** levels in the intestinal lumen are too low, these essential functions cannot be carried out effectively. Patients with **inflammatory bowel disease** [1,2], **irritable bowel syndrome**, or other bowel-related **pain symptoms** [3] often exhibit low faecal **TRP** levels.

Diagnostics	Material
Faecal TRP levels	Faecal sample (stool tube)

A lack of faecal **TRP** can be due to insufficient oral intake of the amino acid. If intake is adequate, inflammatory mucosal reactions or changes in the microbiome (such as too few H_2O_2-forming bacteria) may be responsible for the deficiency. In such cases, the degradation pathway of intestinal **TRP** is upregulated by the activation of the enzymes **IDO** and **KMO**, leading to a loss of **TRP** from the body, particularly from the intestinal mucosa. The cofactors involved in the conversion of **TRP** to **serotonin** and **melatonin** (vitamin B6, magnesium, and SAM) are also affected. To address this, it is important to regenerate the intestinal mucosa, which can be achieved through the administration of probiotics, prebiotics, phosphatidylcholine, an anti-inflammatory substance.

Caution! Do not administer TRP if you are taking medications that affect the serotonergic system, such as MAO inhibitors (e.g., moclobemide), SSRIs (e.g., citalopram, fluoxetine), SNRIs (e.g., venlafaxine), triptans (e.g., naratriptan, sumatriptan), or dextromethorphan.

Serotonin is known as an inhibitory **neurotransmitter** and a precursor to **melatonin**. In the central nervous system (CNS), it enhances mood, relaxes, relieves anxiety, and has antidepressant effects, while also promoting learning and memory. Peripherally, serotonin plays a role in blood clotting (thrombocytes) and wound healing. It is crucial for intestinal health, influencing peristalsis, nutrient absorption, immune system activity, and enteric pain sensation, which is particularly relevant for conditions like irritable bowel syndrome. Notably, 95 % of serotonin is produced in the intestines.

Melatonin, known as the sleep hormone, regulates the sleep-wake cycle and is produced in the pineal gland in the CNS. It is also synthesized in the retina of the eye and the intestine. Besides its role as a hormone, melatonin possesses antioxidant properties.

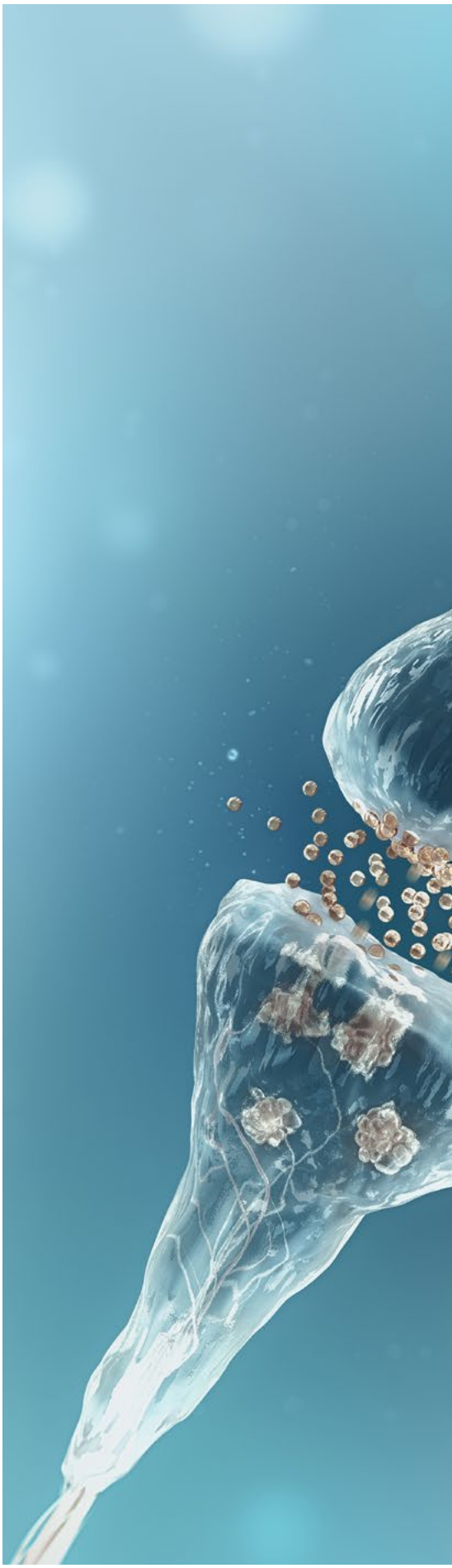
Hence, a lack of serotonin or melatonin can cause a variety of symptoms.

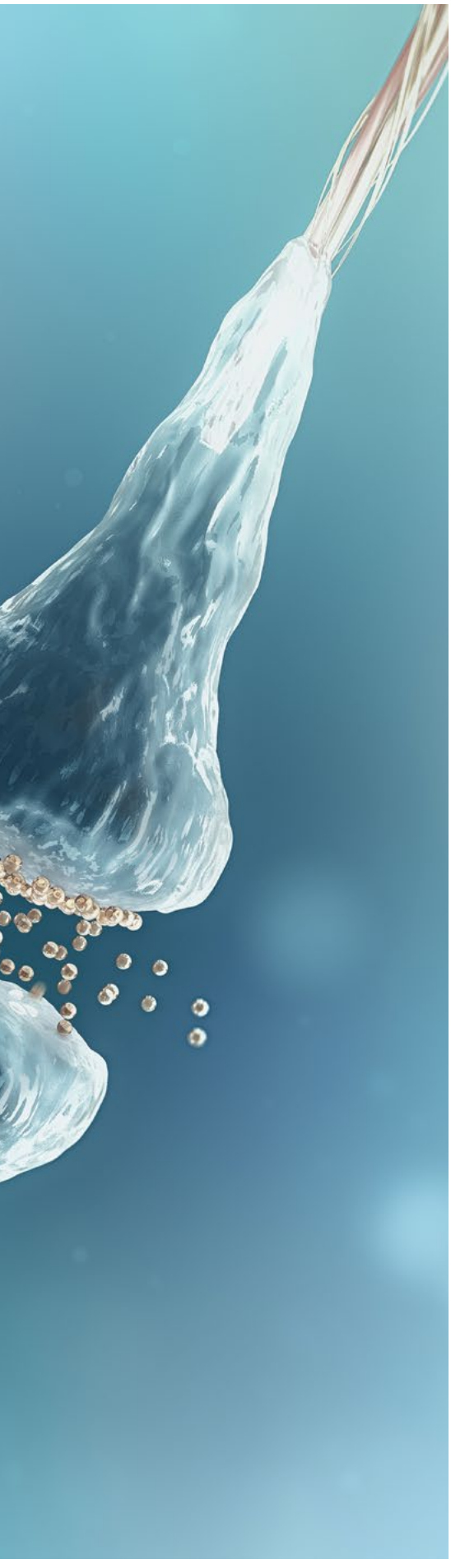
Diagnostics	Material
Serotonin blood levels	BloodSpot (high sample stability), 1 field
Melatonin saliva levels	Test kit 923

One therapy for **serotonin** and melatonin **deficiency** is the administration of TRP. However, this approach will only be effective if there is no **IDO** and **KMO** activating inflammation in the body. In such cases, a sustainable anti-inflammatory treatment should also be part of the strategy for addressing serotonin and melatonin deficiency. To bypass the problem at the start of therapy, the direct precursor of serotonin, 5 HTP, can be administered until the inflammation has subsided and TRP metabolism has normalized.

Caution! 5-HTP can lead to a loss of NAD, resulting in reduced energy levels and fatigue.

Kynurenine is produced from **TRP** by the enzyme **IDO**. **IDO** activity can therefore be assessed by the ratio of these two substances (determined in serum or via a **BloodSpot analysis**). Such findings are often observed in patients with obesity, metabolic syndrome, chronic stress (burnout, CFS), depression, chronic pain, cardiovascular diseases [4], tumor diseases, bacterial infections [5], chronic viral infections (e.g., EBV, HHV), autism, multiple sclerosis,





and autoimmune diseases. [6,7,8,9]. There is also evidence that deficient **mitochondrial activity** or ATP formation is associated with a high kynurenine/TRP ratio (see NAD) [10]. The situation differs in rheumatoid arthritis and in some autoimmune diseases, viral infections, and other intracellular pathogens, where low **IDO activities** and **decreasing kynurenine levels** can be observed [11].

Treating increased IDO activity can positively impact the course of the diseases mentioned. This can lead to improved survival rates in tumour diseases [12,13,14,15], faster healing of infections, or a preventive effect in cardiovascular or stress-related diseases, as well as depression, and other illnesses.

Diagnostics	Material
IDO activity: blood levels of kynurenine and TRP	BloodSpot (high sample stability) 2 fields or serum (2 ml)

Excess kynurenine inhibits the innate immune system (TH1/TH17 cells) and strengthens the adaptive immune system (TH2 cells). This reduces the effectiveness of the patient's defenses against viruses and tumor cells, diminishing immunity by inactivating cytotoxic T cells while activating regulatory T cells, thereby increasing the patient's tolerance [16].

The consequence of inhibited **IDO activity** and **a lack of kynurenine**, on the other hand, is a lack of immunosuppression which creats a TH1/TH2 imbalance, favoring TH1 immune cell acitivity [17].

The positive significance of the conversion of **TRP** to kynurenine becomes evident in the subsequent step: kynurenine is metabolized by the enzyme **KAT** into **kynurenic acid**, which acts as an NMDA receptor antagonist. This compound possesses antioxidant, anti-inflammatory, and pain-relieving properties. Therefore, an increase in kynurenine, the precursor, is beneficial for the body, particularly in patients that exhibit an increased activity in inflammatory metabolic pathways.

Kynurenine can cross the **blood-brain barrier**, allowing it to enter the brain. However, unlike other tissues, macrophages and microglial cells within the brain lack the enzyme KAT. Consequently, kynurenine undergoes exclusive metabolism in these cells to quinolinic acid, which acts as an NMDA receptor agonist.

Quinolinic acid is known for its neurotoxic, pro-inflammatory, and oxidative effects [18], which can compromise the integrity of the blood-brain barrier. Elevated levels of quinolinic acid are associated with several neuropsychiatric and neurodegenerative disorders such as anxiety disorders, depression, Alzheimer's disease, Kynurenine can cross the **blood-brain barrier**, allowing it to enter the brain. However, unlike other tissues, macrophages and microglial cells within the brain lack the enzyme KAT. Consequently, **kynurenine** undergoes exclusive metabolism in these cells to quinolinic acid, which acts as an NMDA receptor agonistParkinson's disease, and multiple sclerosis [19,20]. In the brain's astrocytes, kynurenine can alternatively be converted to kynurenic acid, which not only exhibits the positive properties mentioned earlier but also possesses neuroprotective effects. Although astrocytes can degrade quinolinic acid originating from other cell types, their enzymatic capacity for this process is limited [21]. Therefore, an increase in the conversion of TRP to kynurenine carries an increased risk of neuroinflammatory or neurotoxic damage.

Quinolinic and kynurenic acid [22]

Quinolinic acid...	Kynurenic acid...
...**promotes** the formation of reactive oxygen species (ROS)	...**intercepts** reactive oxygen species (ROS)
...**inhibits** antioxidant enzymes	...**protects** antioxidant enzymes
....**reduces** mitochondrial activity	...**increases** mitochondrial activity during stress
...**oxidises** proteins and lipids of the mitochondrial membrane	...**protects** proteins and lipids of the mitochondrial membrane
...**disrupts** complexes of the respiratory chain	...**revitalises** the complexes of the respiratory chain
➔ Quinolinic acid is **a powerful mitochondrial killer**	➔ Kynurenic acid is **an important mitochondrial protector**

Die Prognose von Patienten mit neuropsychiatrischen oder -degenerativen Erkrankungen kann also über das Verhältnis der beiden entgegengesetzt wirkenden Säuren Quinolinsäure und Kynureninsäure (= Aktivität der KMO) beurteilt werden. Ein gezieltes Einwirken auf den TRP-Stoffwechsel ermöglicht eine ursachenorientierte, effektive Therapie.

Diagnostics	Material
KMO activity: Urinary quinolinic acid and kynurenic acid levlels	Test kit 928

NAD is a cofactor essential in numerous redox metabolic pathways, capable of accepting hydrogen ions. When reduced (NADH2), it functions as a reducing agent. **NAD** plays a crucial role as a hydrogen carrier between the citric acid cycle and the respiratory chain. The synthesis of **NAD** from **TRP** becomes especially critical in cases of insufficient dietary vitamin B3. Elevated **quinolinic acid production** can hinder **NAD synthesis**, potentially leading to inadequate delivery of reducing equivalents to the respiratory chain and consequent reduction in cellular energy production. Common patterns observed in specific patient groups often indicate the correct diagnosis.

The activities of the enzymes IDO/TDO, KMO, and KAT, which are pivotal in TRP metabolism, thus dictate the metabolites to which TRP is converted and influence the current prognosis of the respective patient

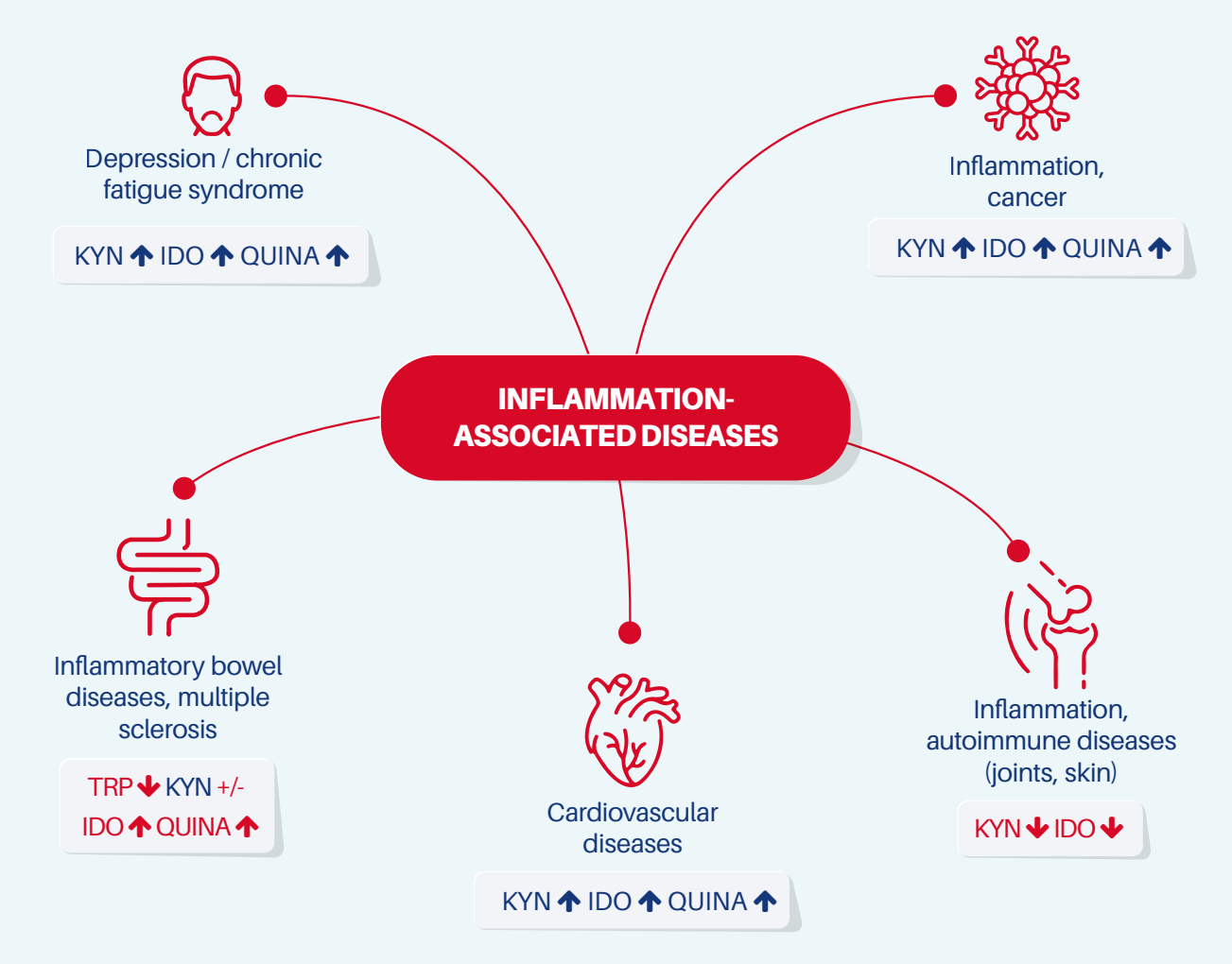


Fig. 2: *Diseases with a chronic inflammatory component*

The Following Therapeutic Measures Are Suitable for Achieving Noticeable Improvements for the Patient:

In cases of faecal TRP deficiency

- Administration of TRP and cofactors (B6, Mg, SAM)
  Caution: Intake of psychotropic drugs!
- Measures for intestinal mucosa regeneration
- Anti-inflammatory measures (see below)

In cases of serotonin/melatonin deficiency

- Determination and, if necessary, administration of cofactors of serotonin synthesis (vitamin 6, Magnesium, SAM)
- Determination and, if necessary, administration of vitamin D (increases synthesis of 5-HTP)
- Administration of 5-HTP, if necessary
  Caution: Intake of psychotropic drugs!
- Antiphlogistic measures (see below)

In cases of increased IDO activity (increased kynurenine-TRP ratio)

- Administration of IDO inhibitors:
  - Curcumin
  - Barbary
  - Resveratrol
  - Quercetin
- Antiphlogistic measures (see below)

In cases of reduced IDO activity (reduced kynurenine-TRP ratio)

•Epigallocatechin-3-gallate (green tea extract)
After IDO activation:

- Omega-3 fatty acids
  (→ fatty acid analysis)
- Frankincense extract

In cases of increased KMO activity (increased quinolinic / kynurenic acid ratio)

- Administration of omega-3 fatty acids (especially DHA)
- Administration of frankincense extract
- Moderate exercise (promotes KAT and thus the formation of kynurenic acid)
- Anti-inflammatory measures (see below)

Anti-inflammatory measures

- Phytotherapeutics (e.g. devil's claw, cineole, thymol, nettle, willow bark, garlic, curcurmin)
- high doses of vitamin E
- Reduction of arachidonic acid
  (→ pro-inflammatory fatty acid)
- Administration of omega-3 fatty acids (→ fatty acid analysis)
- Moderate exercise (promotes **KAT** and thus the formation of kynurenic acid)
- Vitamin C infusions
- Vitamin B12 injections
- Administration of phosphatidylcholine

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Do you have questions about tryptophan and its metabolites, relevant diagnostic markers or subsequent therapeutic options?

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