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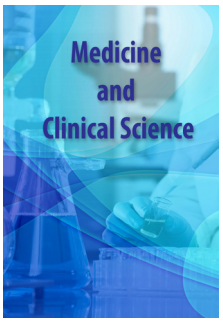

DPP4 Valorphin Activate NR4As Pathway and OPA1 That Protect from CoQ10 Deficiency, OPA1 Dysfunctions and WMH

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Hemorphin (valorphin) , Chronic cerebral hypoperfusion, Oxidative stress, Inflammation , White Matter Hyperintensity , glucocorticoid-beta, B-arrestins, B-adrenergic, oxytocin, Nrf2, Ang2-AT2, VEGF-A, Microglia, Astrocytes, Primary coenzyme CoQ10,01110 mTORC1, S6K, tyrosine, Thr, Leu, Île,, Val, Glu/Gln, Gly, Ser, tryptophan, Arginine, Plasma glial fibrillary acidic protein (GFAP), IL6, IL17, T-cells, mitochondrial OPA1 disorders, Severe Traumatic Brain, Mineralocorticoid, WMH Tissue with high cations binding, tissue with proper anions binding, cellular tissue of CoQ10 deficiency contains high cations binding, GTPase, ATPase, dopamine, serotonin, melatonin

Abstract

Deficiencies in Threonine (Thr), Tryptophan hydroxylase (Tph), Glutamate (Glu), Glutamine (Gln), and Leucine can result from increased polarizability in mTORC1 and its subunits. These deficiencies may lead to disorders in OPA1 repair, which can be a primary cause of Coenzyme Q10 (CoQ10) deficiency disease. CoQ10 is crucial for maintaining the inner mitochondrial membrane and is necessary for the synthesis of the glucocorticoid receptor (GCR).

Mitochondrial damage or dysfunction can lead to the accumulation of pro-inflammatory molecules, which may cause mutations in subunits and proteins. Reduced levels of Tryptophan, Glycine (Gly), and Arginine (Arg) can result in decreased Proline synthesis, subsequently reducing tRNA levels. This, in turn, can impair mitochondrial OPA1 repair and function due to decreased GTPase activity. The reduced function of GTPase can lead to decreased IL-17 synthesis and the accumulation of pro-inflammatory molecules, resulting in a reduction in serotonin production, as well as decreased production of GC-beta, oxytocin, and Nrf2. These changes can lead to a decrease in the proliferation of megakaryocytes and, consequently, reduced hematopoiesis, which is associated with white matter hyperintensity.

Opioid receptors play a role in producing powerful analgesia, contributing to the function of immune cells, and modulating acquired immune responses, including the function of lymphocytes.

Tryptophan, Leucine, and Tyrosine kinases are crucial for activating mitochondrial OPA1 repairs, which are essential for CoQ10 synthesis. Tryptophan (TGG) is necessary for activating Proline, which is essential for both OPA1 function and tRNA production. Additionally, it plays a role in IL17 synthesis and the activation of the NR4As pathway, which includes the activation of GCs-beta, oxytocin, and Nrf2 production, respectively.

Cytotoxic edema can result from uncontrolled or uncompensated cation influx, primarily sodium (Na+). This edema occurs due to high levels of potassium (K) and sodium (Na) binding toxicity, leading to coagulation and reduced ATPase and GTPase activity. It starts with a decrease in CoQ10 synthesis and an increase in Plasma Glial Fibrillary Acidic Protein (GFAP), resulting in decreased mineralocorticoid.

Increased sodium and potassium binding, associated with decreased anions binding in biological molecules, can be due to reduced GTPase and OPA1 function. This reduction in anions function is the result of a primary Coenzyme Q10 (CoQ10) deficiency, leading to elevated GFAP levels in cognitively normal older adults at risk of Alzheimer's disease.

Primary Coenzyme Q10 (CoQ10) deficiency is typically associated with multisystem involvement, including neurologic manifestations such as fatal neonatal encephalopathy with hypoxia, late-onset multiple-system atrophy-like symptoms, dystonia, spasticity, seizures, and intellectual disability.

Autoimmune diseases and skin inflammatory disorders can start due to increased cation binding toxicity, which reduces ATPase and GTPase function, characterized by a deficiency in proper GTPase production, leading to a reduction in mitochondrial OPA1 function and a deficiency in GCs-beta synthesis via the NR4As pathway.

GFAP is an important neuroinflammation biomarker, and an increase in its levels may indicate OPA1 dysfunction, a decrease in CoQ10, neuroinflammation, and a reduction in the NR4As pathway. The increase in GFAP during acute ischemic stroke can be initiated by increased cation binding to anions, leading to enhanced energy stability and decreased tRNA production, which is proline-dependent. This decrease in tRNAs and GTPase activity can result in a decrease in IL17 production, increased inflammation, decreased blood flow to the brain, and reduced oxygen supply to the brain, ultimately contributing to neuronal damage.

A decrease in hemorphin (valorphin) reflects reduced lymphocyte function and a loss of choline-containing phospholipids (CCPLs). Valorphin contains Tyrosine, which is essential for kinases production, required for choline kinases synthesis, and crucial for activating tRNAs, serotonin, oxytocin, and Nrf2 via the NR4As pathway, all of which are essential for lymphocyte function and anti-inflammatory growth.

Nrf2 dysfunction, connected to NR4As and oxytocin dysfunction, plays a significant role in the pathogenesis of vascular cognitive impairment and dementia (VCID).

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Introduction

An increase in GFAP levels may be attributed to elevated cation concentrations in certain cellular tissues, leading to increased interactions between cations and anions. This, in turn, results in a reduction of free anions, which can lead to decreased mitochondrial OPA1 function due to a decrease in GTPase activity. This reduction in GTPase activity can be linked to a decrease in tryptophan hydroxylase (Tph) activity, followed by a decline in proline levels. The synthesis of proline is regulated by tryptophan, as indicated by the relationship: CCA <¬¬> Tph TGG.

Additionally, a deficiency in threonine (Thr) amino acids can lead to a shortage of Tph amino acids, which, in turn, affects the production of proline and cysteine (Cys), essential for oxytocin. This deficiency can result in lower serotonin levels and reduced synthesis of tRNAs. Tryptophan is an important amino acid for generating energy, which is crucial for the synthesis of GTPase necessary for OPA1 repair, ultimately affecting heart and brain functions. This deficiency can lead to reduced Nrf2 production via the NR4As pathway.

Serotonin, a neurotransmitter regulated by Tph, plays a vital role in various physiological functions, including memory consolidation, sleep, pain modulation, and mood regulation. Depleted serotonin levels, often caused by a lack of Tph, can lead to cognitive impairments, such as deficits in verbal reasoning, episodic memory, and working memory. On the other hand, supplementation with tryptophan (TGG) can have positive effects on attention and memory, as it activates GTPase and stimulates the Glu/Gln circuit, which is necessary for leucine synthesis, thereby enhancing brain functions.

Tryptophan (TGG) is essential for GTPase synthesis, which is crucial for OPA1 repair and the activation of synthase and phospholipase functions necessary for growth pathways. A decrease in TGG and Val GTP levels leads to a reduction in GTPase, followed by diminished OPA1 repair, decreased tRNA production, and an accumulation of inflammation, including cholesterol.

Methods and Results

Opioid receptors and their ligands provide potent analgesia, which is effective in pre-operative and chronic pain management. Opioids not only play a role in immune cell functions but also modulate both innate and acquired immune responses [1]. Autoimmune diseases and skin inflammatory disorders are characterized by deficiencies in GTPase production, leading to a subsequent deficiency in the NR4As pathway. These conditions involve reduced tryptophan levels, resulting in decreased serotonin and melatonin production, followed by impaired OPA1 function and compromised T-cell maintenance. It has been reported that melatonin can upregulate the expression of CD28, p21, MT1A, and MT1B mRNA [2].

Melatonin is regulated by serotonin synthesis and significantly influences T-cell activation, differentiation, particularly for Th17 and Treg cells, and memory T cells [3]. It's essential to note that proline-rich proteins, such as Proline Rich 7 (Prr7), are critical for proper T-cell development [4]. Thus, melatonin and proline both play essential roles in regulating normal T-cell functions. I will clarify later that tryptophan is important for improving OPA1 repairs and tRNA production, all of which are necessary for activating normal T-cell functions via the NR4As pathway.

Activating proline by tryptophan can promote T-cell development (Tryp TGG <¬¬> CCA Pro <¬> Gly GGT). Glycine stimulates serotonin production [5], underscoring its importance in regulating both serotonin and T-cell functions. Glycine also plays a critical role in activating tRNA production, followed by the activation of IL-17 production, which in turn activates GCs-beta synthesis via the NR4As pathway.

Melatonin plays a crucial role in T cell-mediated immune responses against cancer, infections, and the development of many autoimmune diseases [6]. Therefore, glycine, tryptophan, proline, and serotonin all have significant functions in regulating T cell-mediated immune responses against cancer, infections, and immune development in autoimmune diseases.

We can consider glycine as a mirror of tryptophan triplets (Tryp TGG <¬> GGT Gly), which can help ensure and stabilize the function of tryptophan hydroxylase (Tph). Threonine is also essential for tryptophan TGG synthesis, which, in turn, is necessary for serotonin production: ACC "Thr" <¬¬> TGG "Trp".

The deficiency in threonine (Thr), as well as in the essential tryptophan (Tph) (TGG), which may be due to an increase in polarizability, can reflect a deficiency in serotonin and a decrease in melatonin. This deficiency can also impact T-cell activation and differentiation, leading to a decrease in GTPase activity, followed by a decrease in the NR4As pathway (resulting in an accumulation of pro-inflammatory molecules). This could be a major factor contributing to disorders and a deficiency in OPA1 repair, leading to damage in the inner mitochondrial membrane, which causes a decrease in CoQ10 production and a decrease in tRNAs (regulated by both tryptophan and proline).

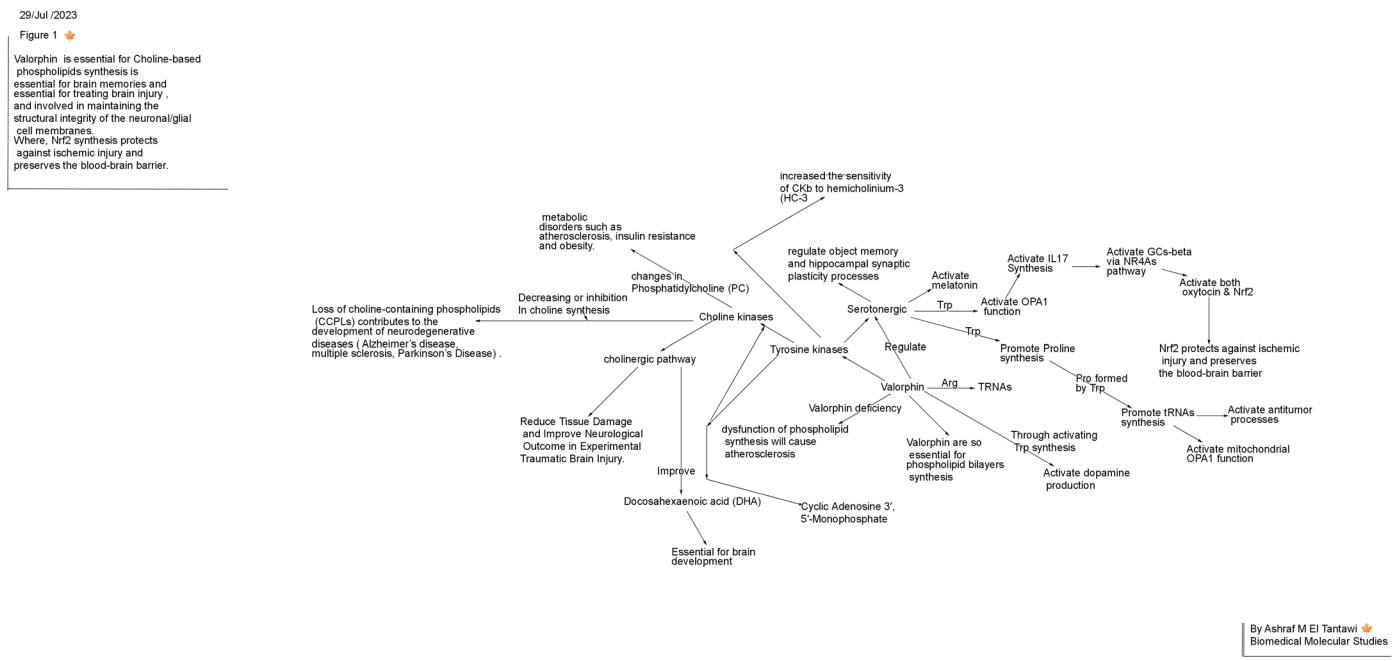
As a result of the accumulation of pro-inflammatory molecules and changes in the generation of energy through phosphorylation, mutated genes, subunits, and molecules may form, potentially causing mitochondrial disorders.

The role of tryptophan (TGG) regulated by threonine (ACC) and proline in treating autoimmune diseases is significant. Firstly, the main composition of valorphin, also known as VV-hemorphin-5, consists of nine essential amino acids: Leu, Val, Val, Tyr, Pro, Pro, Thr, Gln, and Arg.

Threonine amino acids are the primary source for tryptophan (Tph) synthesis, which plays an important role in activating mitochondrial OPA1 function, serotonin, and melatonin synthesis through translation processes: Thr ACC -> Tph (TGG) -> melatonin -> activation of OPA1 -> activation of the NR4As productive pathway. At the same time, both threonine and tryptophan play important roles in activating GTPase, which is necessary for mitochondrial OPA1 repair and stimulates the production of interleukin-2 and IL-17, responsible for activating glucocorticoid-beta synthesis via the NR4As pathway.

Activating OPA1 repair (regulated by Tyr, Pro, Leu, and Trp) reflects proper synthase functional activities, which in turn activate interleukin-17 (IL17) synthesis, a strong activator for glucocorticoid-beta production. This is followed by the activation of B-arrestins, beta-adrenergic receptors, oxytocin, and Nrf2 synthesis.

Threonine is necessary for tryptophan TGG synthesis, which is essential for serotonin synthesis and proline production: ACC "Thr" <- -> TGG "Trp". "Trp" TGG <- activates -> CCA "Proline".



It has been reported that tryptophan metabolism, activated by indoleamine 2,3-dioxygenase 1 (IDO1) but not arginine metabolism, is often associated with protective effects in autoimmune disorders [7]. Thus, tryptophan and serotonin have protective effects in autoimmune diseases. In contrast, arginine activates proline synthesis (Arg is necessary for activating tRNA production but cannot directly promote serotonin and the NR4As pathway):

"Arg" CGG <- -> CCG "Proline" (Arg activates proline similarly to tryptophan but through different triple codons that cannot directly activate the NR4As pathway and astrocyte functions but can directly activate tRNA production).

It's worth noting that L-arginine also acts as an inflammatory modulator in various pathologies. Arginase, a key enzyme, is involved in ammonia detoxification and regulates T cell functions [8].

In my previous work, I noted that arginine only activates pro functions necessary for tRNA production, which is important for treating malaria and preventing the accumulation of valine and leucine in cardiovascular disease (CVD) patients. In contrast, tryptophan activates proline, similar to arginine, but additionally positively activates serotonin and melatonin synthesis. This activation is essential for lymphocytes mediated by IL17 production, which, in turn, promotes glucocorticoid-beta synthesis through synthase activation (primarily regulated by tryptophan and proline) via the NR4A2 pathway. This ultimately leads to the promotion of oxytocin and Nrf2 production through the same pathways, which then activate Ang2-AT2 and VEGF-A synthesis for heme oxygenase and anti-inflammatory effects.

Branched-chain amino acids, including leucine, are crucial for brain function. Leucine is essential for activating enkephalin tissue through the synthesis of Leu pentapeptides, and it plays a key role in Nrf2 synthesis, which is important for brain function.

It has been reported that branched-chain amino acids (including tyrosine, proline, leucine, valine, and isoleucine) enhance the cognitive recovery of patients with severe traumatic brain injury [9].

Leucine is also necessary for Nrf2 synthesis and cardio-protection. Leucine induces cardio-protection by promoting mitochondrial function through mTOR and OPA-1 signaling [10]. Furthermore, leucine supplementation has been shown to improve glucose homeostasis [11].

Nrf2 and its target genes are crucial components for maintaining cellular redox homeostasis by reducing oxidative stress-related pathological processes [12].

Leucine is the primary regulator amino acid for Nrf2 functions and is activated by glutamine and glutamate functions, which play a role in promoting hepatic glucose homeostasis. When Nrf2 is activated, it promotes the production of Ang2-AT2 and VEGF-A, which regulate heart constriction, activate heme oxygenase (regulated by Nrf2), and stimulate anti-inflammatory responses.

Nrf2 biosynthesis is activated through the NR4As productive pathway, primarily regulated by serotonin biosynthesis, which, in turn, is regulated by tryptophan functions. This cascade leads to the activation of mitochondrial OPA1 function and IL17 production, which is necessary for glucocorticoid-beta synthesis, mineralocorticoid and B-arrestin synthesis, followed by oxytocin and Nrf2 production, respectively.

Primary coenzyme Q10 (CoQ10) deficiency can result from a decrease in leucine and GTPase levels, which may be due to a decrease in the functions of free anions. Many tumorigenic tissue cancers are associated with increased cation activity, higher polarizability, decreased anion function, and reduced GTPase activity. Additionally, increased cation activity and polarization are often associated with heightened viral activity.

Severe strokes are linked to high thermal stability and increased polarization, which can inhibit the activation of anion functions in cellular processes. This inhibition can hinder the reduction of inflammatory molecule accumulation and lead to toxicity from K and Na binding.

Biophysical studies suggest that primary CoQ10 deficiency can result from increased polarization in mTORC1, S6K1, and serotonin molecules, potentially causing mutations or disorders in their molecular subunits. This can lead to the inhibition of GTPase production by affecting free anion functions and ultimately result in a deficiency in tryptophan, glutamate, leucine, and GTPase functions, inhibiting CoQ10 production.

A decrease or absence of anionic functions reflects an increase in cationic functions related to anions that can hold purines and pyrimidine functions, potentially leading to a decrease in GTPase production. This situation may result from mitochondrial OPA1 dysfunction.

The negative anion gap and elevated osmolar gap are associated with lithium overdose [13].

The ability of a cation to distort an anion is known as its polarization power, and the tendency of the anion to become polarized by the cation is known as its polarizability [14].

Polarization increases with an increase in cationic size and a decrease in anionic size, causing significant distortion. Thus, thermal stability and lattice energy increase with larger cationic size. In essence, as polarization increases, thermal stability increases with larger cationic size and smaller anionic size, leading to a decrease in anionic functions such as oxidative functions by OPA1, ATPase, and GTPase [15].

Larger anion size (high anionic functions) will result in a decrease in cation-anion interaction and an increase in anionic functions, associated with proper cellular functions. Conversely, larger cation size (such as binding with Na, K, Ca) will show more cation-anion interaction, leading to a decrease in free anionic functions (including OPA1 function, serotonin, and Nrf2 functions) associated with high energy stability, as seen in tumor content with high energy stability.

Thermal stability is defined as the ability of a fluid (including blood plasma) to resist breaking down under heat stress (heat energy) or upon energy utilization.

In plasma, as cation binding increases, the functional activities of free anions decrease, leading to increased thermal stability. This, in turn, results in a decrease in respiratory oxidative functions in plasma with resistance to thermal degradation.

Divalent cations are involved in the pathogenesis of HIV-1 and affect the host's ability to control HIV-1 replication [16].

As divalent cations increase in binding with amino acids like leucine, tryptophan, tyrosine, etc., the functions of tryptophan, leucine, and tyrosine kinases are reduced. This reduction may lead to an increase in pathogenic symptoms and OPA1 dysfunctions.

Severe mitochondrial disorders, damage, and dysfunction can occur when polarization increases due to increased cation binding with leucine, tyrosine, tryptophan, and proline. This can inhibit or decrease the functions of leucine, tyrosine, and GTPase, and may also result in a decrease in tRNA production. Such conditions can be the result of mutations in mitochondrial membranes and may inhibit OPA1 repair, which is dependent on GTPase. To ensure optimal thermal stability with proper anionic percentages in active subunits, it's important to reduce sodium and potassium binding (which can lead to increased cation functions and polarization) through mineralocorticoid functions. Note that mineralocorticoids, regulated by glucocorticoids-beta, are necessary to protect the heart from sodium and potassium binding toxicity, which can lead to the removal of sodium and potassium-binding molecules by the kidneys.

Mineralocorticoids, regulated by GCs-beta via the NR4As pathway, play a role in reducing polarization in the myocardial and epicardium layers, protecting the heart and brain functions from binding toxicity and the accumulation of subunits, as well as preventing the growth of molecular disorders.

An increase in sodium binding sites (representing cation binding activities) in mTOR S6K can affect the decrease in GTPase and OPA1 repairs, potentially causing damage to astrocytes. It has been reported that sodium binding is accompanied by an induced-fit mechanism that leads to new conformations and reduces local dynamics [17].

The reduction in local dynamics implies a decrease in cellular functions, including myocardial functions, due to an increase in sodium binding and a decrease in anionic functions, resulting in OPA1 dysfunctions, as well as dysfunction in proline, leucine, tyrosine, and reductions in tRNA production (regulated by tryptophan and arginine).

Cytotoxic edema results from unchecked or uncompensated influx of cations, primarily sodium (Na+), through cation channels [18].

Binding sodium (Na+) to serotonin can reduce its transportation and decrease local dynamic activities. Potassium (K) plays a similar role to sodium (Na+), and an increase in their binding sites in genes can result in a decrease in surrounding cellular activities, increased plasma toxicity (higher polarities), and damage to neuronal cell functions. This damage can be due to an increase in plasma glial fibrillary acidic protein (GFAP), which can still be promoted and regulated by mTORC1/S6K.

A decrease in oxytocin can reflect an increase in sodium and potassium cations binding to purines and pyrimidines in leucine, tryptophan, tyrosine, and cysteine triplets. An increase in sodium and potassium binding can accelerate and promote antagonist characters. Note that antagonists have higher energy stability, while an increase in free anions promotes agonist functions. It has been reported that antagonists promote sodium binding, while agonists attenuate sodium binding [19].

An increase in sodium binding (related to anionic binding functions) will reduce surrounding passive transport and migration, reflecting a reduction in proline and tRNA levels. The increase in both sodium and potassium, where their binding is considered as positive cation binding, will reduce the function of free anions binding, leading to an increase in acidic binding activities. This, in turn, reduces most brain functions (including tRNA synthesis), heart function, and cellular activities, while potentially leading to an increase or accumulation of plasma glial fibrillary acidic protein (regulated by mTORC1/S6K), which increases the risk of Alzheimer's disease.

Glial Fibrillary Acidic Protein (GFAP) can be used as a neuroinflammation biomarker. An increase in GFAP levels can reflect increasing neuroinflammation due to a reduction in the NR4As productive pathway, which is a result of decreased anionic functions and an increase in GFAP. This increase can be observed in cases of acute ischemic stroke and may gradually lead to increased neuronal damage.

The increase in plasma glial fibrillary acidic protein (GFAP) is

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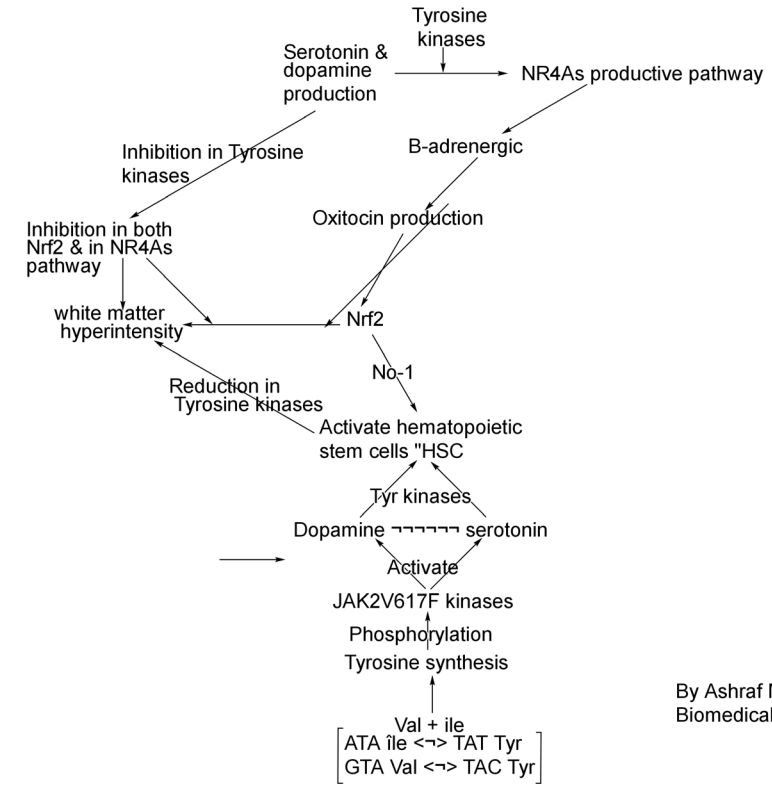
Figure 2

Activating hematopoietic cells will Treaat and improve cerebral white matter abnormalities. Where, dopamine promote melatonin production which will activate NR4As productive pathway which activate hematopoietic cells Functional activities



attributed to an increase in cations binding to anions necessary for activating GFAP production. This results in increased polarization, leading to increased toxicity and the accumulation of mutated inactive subunits with high thermal stability. Consequently, mitochondrial OPA1 function decreases, contributing to damage in astrocyte cells.

Cysteine and tyrosine are improved by threonine and isoleucine, respectively, for activating oxytocin, which improves cardiac function.

Arrhythmia and stroke can occur due to an increase in sodium and potassium binding (positive cations binding) and a severe decrease in arginine, leucine, and tryptophan functions. Arginine and tryptophan are necessary to activate proline, which is essential for tRNA production and OPA1 mitochondrial function. Tryptophan itself is crucial for both serotonin and proline production, promoting tRNA synthesis and mitochondrial function, reducing pro-inflammatory cytokines, and activating IL17 production, followed by the activation of glucocorticoid-beta via the NR4As pathway. This includes the activation of oxytocin and Nrf2 synthesis, subsequently promoting heart and immune functions.

Serotonin and dopamine are interconnected in their functions and biosynthesis, and inhibition in serotonin biosynthesis can be associated with inhibition in dopamine biosynthesis. There is evidence of the activation and recycling of the serotonin 2A receptor by dopamine [20].

Tryptophan (Trp or Tph) is essential for both serotonin and dopamine production, while leucine activation promotes Nrf2 functions, mediated by the activation of oxytocin biosynthesis. This can influence the percentage of Glial Fibrillary Acidic Protein (GFAP).

Valorphin is composed of nine important amino acids, including threonine, cysteine, proline, and tyrosine. These amino acids stabilize each other for the synthesis of GTPase, the production of tRNAs, threonine phosphorylation processes, and the biosynthesis of both tryptophan and oxytocin:

- Gly GGT <- -> Pro CCA
- Thr ACC <- -> Trp TGG
- Thr ACC <- -> Gly GGT
- Thr ACC <- -> Cys TGA
- Thr ACC <- -> Cys TGT
- Thr ACC <- -> Cys TGC

Threonine ACG is important for cysteine TGC synthesis. Valine and isoleucine are necessary for tyrosine synthesis:

- Val ATG <- -> Tyr TAC
- ÎLe ATA <- -> Tyr TAT

Valine and isoleucine are important for tyrosine kinases production. As mentioned previously, threonine, proline, and cysteine play a role in stabilizing tryptophan biosynthesis. This is necessary for OPA1 repairs, as well as for both serotonin and melatonin biosynthesis, which in turn leads to the activation of IL17 production. This activation is followed by the initiation of GCs-beta synthesis via the NR4As pathway. Subsequently, B-arrestins are reactivated, which are essential for maintaining

myocardial functions, along with B-adrenergic activation. This process is followed by the biosynthesis of oxytocin and Nrf2. Both oxytocin and Nrf2 play crucial roles in antioxidative stress, myocardial constriction, and the activation of astrocyte and lymphocyte functions, mediated by Ang2-AT2 and VEGF-A production. This cascade is further linked to heme oxygenase and anti-inflammatory growth, as well as normal T-cell functions.

Cysteine, which is included in oxytocin, is essential for contributing to the activation of tryptophan synthesis, especially through the activation of threonine phosphorylation. This process reactivates tryptophan synthesis (ACC "Thr" <¬¬> TGG "Trp), which is crucial for serotonin and melatonin production. Additionally, it helps to reactivate OPA1 functions through the activation of GTPase production. GTPase activation is essential for IL17 production, which, in turn, is necessary for the activation of GC-beta via the NR4A2 pathway, regulated by synthase. This sequence ultimately leads to the reactivation of B-arrestins, B-adrenergic, oxytocin, and Nrf2.

Tyrosine (TAT and TAC) is activated by the glutamate/glutamine cycle and methionine functions. Methionine is crucial for brain function as it activates methionine pentapeptides in enkephalin tissue, contributing to the stability of antioxidative function in the brain and the regulation of lymphocyte activities.

Nrf2 activators upregulate oxytocin mRNA expression and may upregulate oxytocin receptor expression by interacting with MAFF (basic leucine zipper transcription factor) [21]. Oxytocin mRNA is activated by MAFF and activated by MAFF to reactivate oxytocin receptor expression, subsequently reactivating Nrf2 expression for antioxidative functions.

B-adrenergic activation, important for promoting oxytocin and Nrf2 expression in the NR4As productive pathway, is essential for promoting oxytocin expression, which plays a key role in protecting brain function and preventing an increase in Glial Fibrillary Acidic Protein (GFAP).

Activating oxytocin biosynthesis will activate heart and brain functions mediated by Nrf2 production via the NR4As pathway. It has been reported that oxytocin production appears to prevent stroke by activating Leucine functions through the glutamate/glutamine cycles and threonine phosphorylation [22]. Nrf2 will be activated via the NR4As pathway, leading to antioxidative stress, heme oxygenase activation, Ang2-AT2 synthesis, VEGF-A synthesis, and anti-inflammatory growth.

Tyrosine can be activated by isoleucine and valine, both of which are involved in the composition of valorphin. This process is important for protecting tyrosine's functional stability:

ATA île <- -> TAT Tyr

GTA Val <- -> TAC Tyr

Arginine in valorphin is necessary for activating proline synthesis, which is essential for tRNA production, preventing the accumulation of protein rich in leucine, isoleucine, and valine, which poses a risk in cardiovascular disease.

Oxytocin treatment, regulated by B-arrestins and followed by B-adrenergic activation, improves cardiac function and reduces apoptosis and inflammation. It plays important roles in reactivating threonine phosphorylation and tryptophan synthesis, promoting serotonin and melatonin functions. This is mediated by the activation of OPA1 repair functions, followed by the reactivation of IL17 production. This cascade promotes GC-beta production via the NR4As pathway, followed by the activation of B-adrenergic and the stabilization of oxytocin and Nrf2 functions. Additionally, it leads to Ang2-AT2 and VEGF-A production, which are necessary for anti-inflammatory processes.

Treatment with oxytocin reduces the expression of pro-inflammatory cytokines, and activating oxytocin production is essential to prevent Glial Fibrillary Acidic Protein (GFAP), attenuate early brain injury, and improve brain functions and neurobehavioral function, especially in cases of reduction in positive binding cations toxicity such as sodium and potassium binding toxicity [23].

Cysteine is also important for activating brain functions and helps improve chronic respiratory conditions and fertility. It has been reported that l-cysteine treatment significantly ameliorated brain edema, improved neurobehavioral function, and attenuated neuronal cell death in the prefrontal cortex; these effects were associated with a decrease in the Bax/Bcl-2 ratio [24]. Cysteine is necessary for improving neurobehavioral function and attenuating neuronal cell death through activating Nrf2 synthesis via the NR4As pathway, followed by Ang2-AT2 and VEGF-A production necessary for activating anti-inflammatory growth.

Increasing both potassium and sodium binding will restrict the functions of cysteine and tyrosine, leading to brain edema. This restriction is followed by a reduction in B-adrenergic and Nrf2 productive functions, which can result in an increase in GFAP, regulated by the mTORC1/S6K pathway functions, and a subsequent reduction in heart and brain function.

Increasing B-adrenergic activities (beyond the cation binding percentage) will restrict cation binding by activating both oxytocin and Nrf2, which, in turn, activate brain and cardiovascular functions. It has been reported that beta-adrenergic receptor function accompanies sympathetic activation during sodium restriction and converting enzyme inhibition [25]. The sodium restriction and β2-adrenergic receptor polymorphism modulate cardiovascular function in humans [26].

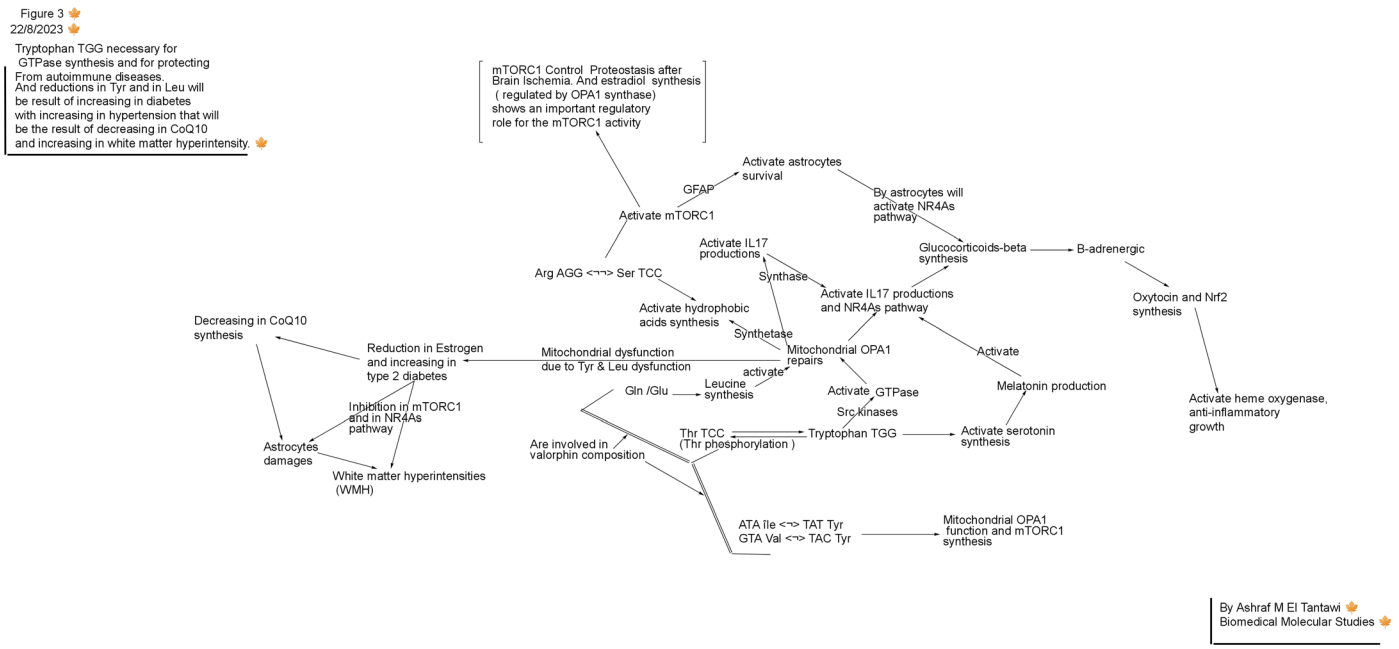
Due to the importance of oxytocin functions, it has been reported that oxytocin rapidly changes astrocytic GFAP "plasticity" by differentially modulating the expressions of pERK 1/2 and protein kinase A [27].

Serine/threonine phosphorylation is necessary for tryptophan, cysteine, and tyrosine kinase synthesis for oxytocin synthesis, which helps prevent mitochondrial dysfunction and the increase in GFAP.

"Ser/Thr phosphorylation pathways play a key role in the synthesis of Tryptophan (Tph) and Cysteine (Cys). Tph is essential for serotonin synthesis, followed by melatonin synthesis, while Tyrosine (Tyr) and Cys are necessary for oxytocin synthesis, promoting Nrf2 synthesis, which is crucial for heme oxygenase and for activating anti-inflammatory processes and growth mediated by Ang2-AT2 and VEGF-A production.

The pathways involved include:

- AGT - Ser <¬¬> TCA Thr
- ACT - Thr <¬¬¬> TGA Cys
- ACC - Thr <¬¬> TGG Trp



Tryptophan (Tph) activation leads to both melatonin production and IL17 production, followed by GCs-beta, B-arrestins, and B-Adrenergic production. This is followed by oxytocin synthesis for Nrf2 production and Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth processes. This pathway helps prevent mitochondrial dysfunction and inhibits an increase in GFAP.

Ser/Thr phosphorylation has a strong role in activating mitochondrial OPA1 function through the production of Tph, Cys, and Tyr, promoting the production of serotonin, oxytocin, and Nrf2, mediated by OPA1 and IL17 production. This activates GCs-beta through the NR4A2 pathway, as studies have reported the importance of serine in supporting mitochondrial function and cell proliferation through ceramide metabolism [28].

Additionally, mitochondrial ClpP serine protease is essential for cellular survival and development, regulating the mitochondrial permeability transition pore [29,30].

These studies highlight the critical roles of both serine and threonine amino acids in improving Tph, Cys, and Tyr biosynthesis for enhancing mitochondrial OPA1 functions. Deficiencies in Ser/Thr phosphorylation can result in reduced Tph, Tyr, and Leu amino acids, which may be attributed to a deficiency in CoQ10 synthesis, reflecting a deficiency in lipid metabolism with cholesterol accumulation and an increase in GFAP.

Tyrosine and Leucine are crucial for mitochondrial OPA1 repairs, and DRP1 phosphorylation or dephosphorylation plays a role in mitochondria fission. Inhibition of DRP1 and scavenging mtROS can attenuate endothelial permeability [31].

Tyrosine plays an important role in Leucine synthesis, while Valine is essential for Tyrosine synthesis. Tyrosine is necessary for stabilizing Leucine's productive functions.

In summary, Tph, Tyr, and Leucine play important roles in activating mitochondrial function and CoQ10 biosynthesis.

Firstly, all of Tph "TGG," Tyr, and Leucine are necessary for activating mitochondrial function and adopting antioxidative functions. Sufficient availability of these three amino acids will prevent the accumulation of inflammatory molecules by activating synthase function and IL17 synthesis, which in turn activates GCs-beta synthesis.

The synthesis of Tph "TGG" is promoted by threonine "ACC," which, in the presence of ATPase, utilizes GTPase to activate mitochondrial OPA1 fusion, preventing the accumulation of inflammation. Additionally, the Kyn pathway of Trp metabolism is activated due to inflammation and stress, further skewing immune balance. [32]

Tryptophan serves as a precursor for the biosynthesis of co-enzymes and neuromodulators, including NAD/NADP(H), kynurenic acid, melatonin, and serotonin [33]. Stimulating the TRP-NAD+ pathway with NAD+ precursors improves hepatic mitochondrial and overall metabolic function through SIRT1 modulation. [34]

Therefore, it's clear that tryptophan is necessary for activating mitochondrial functions by activating GTPase, which is required for mitochondrial OPA1 repairs and is activated by Ser/Thr phosphorylation.

Mitochondrial fusion is regulated by GTPase-dependent proteins, including MFN1, MFN2, and OPA1. [35] Additionally, leucine plays a role in activating mitochondrial fusion. It has been reported that leucine imparts cardioprotective effects by enhancing mTOR activity and mitochondrial fusion in myocardial ischemia/reperfusion injury. [36]

It's essential to note that both tyrosine and leucine are necessary for building the promoters in active genes and subunits:

- Tyr _ TAT, TAC
- Leu _ TTA, TTC This activation is essential for mitochondrial repair and functions, which, in turn, activate CoQ10 synthesis.

Expression of phosphorylation-deficient, catalytic hypomorph PDHK1 mutants in cancer cells leads to decreased cell proliferation under hypoxia and increased oxidative phosphorylation with enhanced mitochondrial utilization of pyruvate, reducing tumor growth [37].

Studies have confirmed the necessity of Tyr with leucine for

activating mitochondrial repairs (fusion) and functions. It has been demonstrated that stable c-Src activation decreases the distance between the ER and outer mitochondrial membrane (OMM) [38]. Additionally, GTPase synthesis, promoted and regulated by Tyr kinases' functions, is necessary for the fusion of the outer mitochondrial membrane [39].

It's approved that a major component of the tethering structures between the two organelles is mitofusin 2 (Mfn2), a GTPase associated with the fusion of the outer mitochondrial membrane. Tryptophan, tyrosine, and leucine have important functions in activating mitochondrial function and CoQ10 synthesis. The importance of tyrosine in activating mitochondrial repair and functions boils down to the activation of CoQ10 synthesis, which is regulated by coenzyme B6, necessary for converting tyrosine to p-hydroxybenzoic acid. The deficiency of coenzyme B6, which is necessary for converting tyrosine to p-hydroxybenzoic acid, can cause dysfunctions before the formation of vitamin Q10 in DNA [40]. Additionally, human cells synthesize CoQ10 from tyrosine through eight steps that require adequate levels of vitamins [41].

It has been reported that the phosphorylation, protection against apoptosis, and the antioxidant capacity of OXT may contribute to the observed increase in cell proliferation. Oxytocin (OXT) and its receptor (OXTR) appear to be fundamental for the cell growth and viability of glial cells [42].

Note that tyrosine (TAT) does not correspond to ATA isoleucine ("Île"), while Tyr (TAC) does not correspond to ATG Methionine in the translation process. Tyr synthesis is crucial for manufacturing active promoters that control gene activities and direct them to promote their own functions for the immune system. The presence and availability of Tyr with Leu (Tyr - TAT, TAC; Leu - TTA, TTC) will form important active promoters for their active subunits. These promoters play a role in activating mitochondrial OPA1 fusion and repairs and are involved in activating their signal migration through tRNA synthesis, regulated by Trp, Pro, and Arg functions.

As tyrosine kinases promote CoQ10 production, a decrease in phosphorylation (by reducing Tyr kinases) will reflect a decrease in CoQ10 production and, in turn, a decrease in the adoption of sodium and potassium channels. This can lead to an increase in Na+ and K+ binding toxicity. It has been reported that severe CoQ10 deficiency is associated with a marked decrease in cellular ATP content [43]. The severe decrease in CoQ10 is mainly due to a failure in reactivating OPA1 repairs and functions, where Trp (TGG) is necessary for reactivating GTPase synthesis, which is necessary for activating OPA1 repairs followed by reactivating the IL17 and NR4As pathway.

Tyrosine kinases and leucine are necessary for the phosphorylation of OPA1 repairs and IL17 production, which, in turn, activates the NR4As pathway and lymphocytes.

Opioid receptors and their ligands produce powerful analgesia that is effective in the peri-operative period and chronic pain management, accompanied by various side effects [44]. Opioids can also interfere with the immune system, participating not only in the function of immune cells but also in modulating both innate and acquired immune responses [44].

It's important to note that opioids are accompanied by various side effects due to their interference with cellular processes for organizing and rearranging essential amino acids, which are critical for immunity. This is why it has been mentioned that opioids certainly have the ability to reorganize the immune response and reconfigure important receptors that play a crucial role in cellular processes.

Firstly, morphine and the endogenous opioid peptides, including β-endorphin and dynorphin peptides, modulate the function of lymphocytes, which includes modulating both innate and acquired immune responses [45].

It's worth noting that the activation of tyrosine kinase, where tyrosine is included in valorphin, is necessary for creating autophosphorylation. This process is mechanistically coupled to the recruitment of adaptor proteins, which are necessary to initiate and activate the immune response.

It's approved that the activation of tyrosine kinase activity results in autophosphorylation, which is mechanistically coupled to the recruitment of adaptor proteins and the conjugation of ubiquitin to receptor tyrosine kinases [46].

Additionally, it's approved that Na/K-ATPase-mediated signal transduction (autophosphorylation) is regulated and promoted by Src family kinases, which are membrane-associated non-receptor tyrosine kinases. They play an essential role in the signal transduction pathways provoked by many extracellular stimuli [47].

Furthermore, tyrosine kinases (note that tyrosine with leucine is necessary for reactivating OPA1 proper functions) have a necessary role in activating mitochondrial function, which is necessary for adopting proper immune responses, through protein phosphorylation and dephosphorylation [48].

Src-tyrosine kinases are considered the major agents in mitochondrial tyrosine phosphorylation [49]. It's clear that the modulation of thymocytes and mature lymphocytes is promoted by tyrosine kinases, leading to the activation of dopamine and serotonin, followed by IL17 production, which is necessary for glucocorticoid-beta synthesis via the NR4As pathway, started by activating OPA1 function.

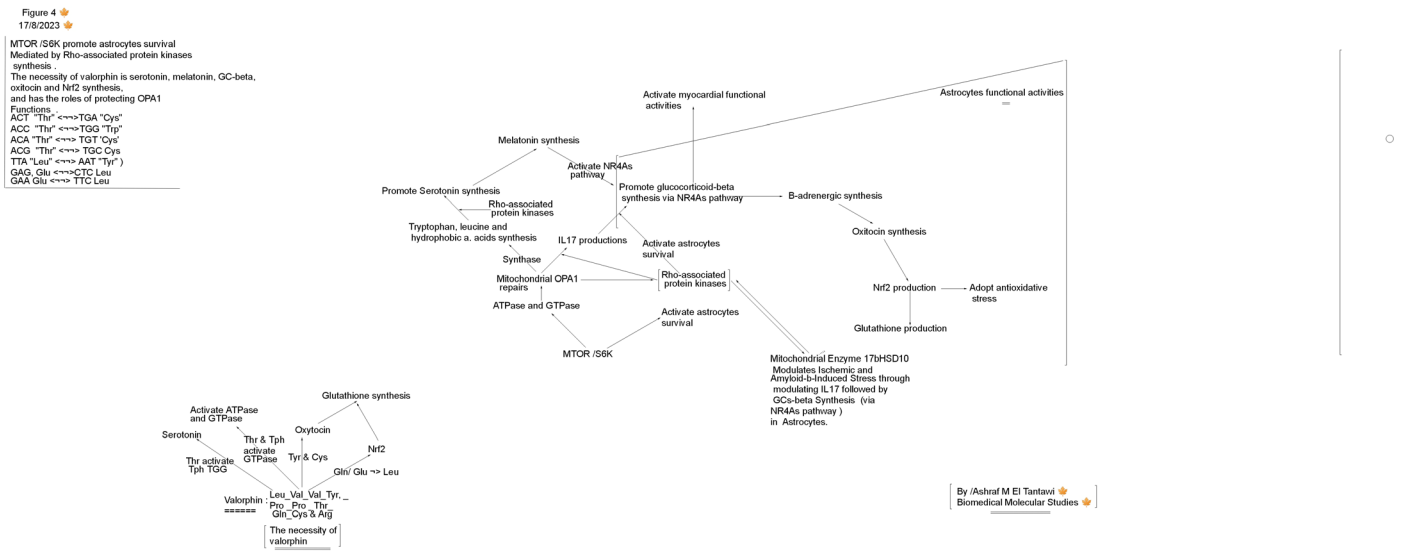
It has been reported that the modulation of Itk, Txk, and Lck (tyrosine kinases) in thymocytes and mature lymphocytes is another mechanism by which glucocorticoids modulate T-cell activation and differentiation [50]

Non-receptor tyrosine kinases integrate fast glucocorticoid signaling, promoting fast IL17 synthesis for glucocorticoid-beta synthesis via the NR4As pathway in hippocampal neurons [51].

The promotion of wound repair is driven by coenzyme Q10, which is activated by PI3K/Akt and regulated by mitochondrial OPA1 proper functions [52]. CoQ10 also inhibits platelet integrin αIIbβ3 outside-in signaling, with the inhibitory effects mainly mediated by upregulating the cAMP/PKA pathway [53].

Thus, Src kinases (with the availability of leucine functions) are necessary for activating mitochondrial OPA1 functions, which, in turn, are necessary for activating CoQ10. This activation is followed by activating both serotonin and IL17, which are necessary for activating glucocorticoid-beta via the NR4As pathway, followed by activating oxytocin and Nrf2 production, which is necessary for astrocyte survival [51].

White matter hyperintensities (WMHs) are associated with a decrease in tyrosine kinases and leucine, reflecting a decrease in OPA1 functions, cerebral blood flow, and Nrf2 synthesis.



WMHs are a feature of small vessel disease, associated with reduced cerebral blood flow [54].

Inhibition of the JAK2V617F kinase with a small molecule inhibitor leads to the inhibition of the proliferation of hematopoietic cells [55].

It's important to note that a reduction in Tyr kinases synthesis reverses a decrease in both valine and isoleucine. Additionally, the reduction in Gln reverses the reduction in Leu and, consequently, Nrf2 functions. HO-1 is important for the proper function of hematopoietic stem cells (HSC), such as self-renewal. HO-1 expression in hematopoietic stem and progenitor cells (HSPC) is low in steady-state levels but increases in hematopoietic stress, such as hematopoiesis [56].

The Nrf2 transcription factor promotes the expression of HO-1, especially if it originates from Trp and Proline function, to remove excess heme and protect against oxidative stress, thereby adopting antioxidative functions [57].

The activation of D2-type dopamine receptors on hematopoietic stem cells (HSCs) and LSK cells can promote hematopoietic reconstitution [58].

Therefore, the activation of D2-type dopamine receptors, which is connected to and dependent on tryptophan functions and GTPase, is necessary to promote hematopoietic reconstitution. This is mediated by oxytocin and Nrf2 production, followed by Ang2-AT2 and VEGF-A productions, which promote heme oxygenase and anti-inflammatory growth [58].

Reducing tryptophan, tyrosine, and leucine results in a decrease in serotonin, both OPA1 functions, and Nrf2, which is followed by a reduction in platelet production [58]. Serotonin (5-hydroxytryptamine; 5-HT) is a growth factor for hematopoietic cells, promoting the proliferation of megakaryocytes (MKs), which produce platelets [59].

Users of atypical antidepressants, selective serotonin reuptake inhibitors, and depressed individuals displayed markers of cerebral small vessel disease [60]. It's imperative to avoid using atypical antidepressants and selective serotonin reuptake inhibitors, as they are not the right approach to activate white matter hyperintensity survival and prevent strokes.

A reduction in serotonin results in a decrease in megakaryocyte proliferation, followed by a reduction in hematopoiesis and its association with white matter hyperintensity. It has been reported that clonal hematopoiesis with DNMT3A mutation is associated with lower white matter hyperintensity volume [61]. Hematopoietic stem cell transplant, if performed early in metachromatic leukodystrophy, can not only stabilize but even improve cerebral white matter abnormalities [62]

It's necessary to declare that activating both serotonin and dopamine, through the activation of Tyr kinases and tryptophan (Trp), promotes melatonin production, which in turn activates hematopoietic cells. This activation is mediated by the expression of oxytocin and Nrf2, which are essential for promoting heme oxygenase and the production of Ang2-AT2 and VEGF-A. These factors are necessary for activating hematopoietic cell functions and anti-inflammatory growth via the NR4As pathway [63].

Dopamine receptors on hematopoietic stem cells (HSCs) and LSK cells can reflect the production of IL17, which, in turn, activates glucocorticoid-beta via the NR4As pathway. This activation is followed by the activation of B-adrenergic and oxytocin receptors, which are necessary for Nrf2 production, promoting heme oxygenase and Ang2-AT2 and VEGF-A production, all of which are essential for hematopoietic reconstitution [63].

Inhibiting the activation of the NR4As pathway by inhibiting both serotonin and dopamine will inhibit hematopoietic cell functions and result in the inhibition or decrease of Nrf2 production. This dysfunction in the modulation of antioxidative stress and anti-inflammatory processes leads to the survival of white matter hyperintensity.

Reducing serotonin results in a decrease in megakaryocyte proliferation, followed by a reduction in hematopoiesis, which is associated with white matter microstructure and affects processing speed in cerebral small vessel disease [63].

Activating mitochondrial OPA1 function through the activation of tryptophan and proline, which are contained in the valorphin composition, plays a crucial role in activating lymphocyte functions and protecting against cerebral small vessel disease. It also protects the heart and blood vessels from immunometabolic injuries by activating serotonin and promoting megakaryocyte proliferation, mediated by IL17 production,

which activates glucocorticoid-beta production via the NR4As pathway. This is followed by oxytocin and Nrf2 production, which are necessary for heme oxygenase and the activation of Ang2-AT2 and VEGF-A, essential for anti-inflammatory growth and lymphocyte functions. Threonine, tyrosine, and leucine are also important for OPA1 repairs and functions, necessary for serotonin synthesis, and they boost dopamine production. This is followed by the activation of the NR4As pathway, which regulates B-adrenergic production, followed by oxytocin synthesis, which is regulated by cysteine and tyrosine. These amino acids are also important for improving Nrf2 synthesis. A deficiency in cysteine leads to a decrease in oxytocin and Nrf2, which can result in Alzheimer's disease, followed by a decrease in Ang2-AT2 and VEGF-A, which is associated with white matter hyperintensity, reduction in cerebral blood flow, and WMH. Deficiency of Nrf2, reflecting serotonin deficiency, exacerbates white matter damage and microglia/macrophage levels in a mouse model of vascular cognitive impairment [64].

Additionally, activating Nrf2 induces antioxidative responses and enhances red blood cells (RBC) through the activation of the NR4As pathway, mediated by activating B-adrenergic and oxytocin receptors. This process helps protect Nrf2 functional stability, promoting heme oxygenase and anti-inflammatory growth, which includes RBC phagocytosis by various tissues such as bone marrow, spleen, and astrocytes [65].

Nrf2 dysfunction plays a significant role in vascular cognitive impairment and dementia (VCID) pathogenesis [66].

Activating oxytocin followed by Nrf2 via the NR4As pathway (and initially promoted by tryptophan functions, which promote both serotonin and proline) will up-regulate the phagocytosis-mediating scavenger receptor CD36. This upregulation can protect against White Matter Hyperintensity in Cerebral Small Vessel Disease and mitigate the process of Vascular Cognitive Impairment and Dementia (VCID).

Serotonin (regulated by Src functions and influenced by both leucine and tryptophan) acts as an inhibitor of the increased expression of glial fibrillary acidic protein (GFAP).

The increase in the binding of positively charged cations with threonine and tryptophan will inhibit their functions. This inhibition is the main reason for a decrease in serotonin and dopamine production, leading to a deficiency in OPA1 repair (due to the reduced availability of GTPase from tryptophan functions) and a subsequent deficiency in CoQ10 synthesis. This deficiency results in an accumulation of IL2 and cholesterol and leads to a decrease in IL17, GCs-beta synthesis, and the reduction of the NR4As pathway.

Tryptophan is necessary for GTPase synthesis, which is crucial for activating OPA1 repair processes. Consequently, it is necessary for activating synthase and phospholipase functions. Notably, a deficiency in threonine reflects a deficiency in cysteine amino acids, which, in turn, leads to a deficiency in both oxytocin and Nrf2 functions.

It has been reported that tryptophan is the most complex and one of the rarest amino acids in the proteome [67].

Coexpression of Src results in PP2-sensitive increases in SERT function and expression [68].

SIRT1 improves hepatic mitochondria and is associated with mTORC1/S6K expression and GFAP expression. Sirt3 is important for Nrf2 production, which is necessary for antioxidative functions and activates proper astrocyte functions, correlating with GFAP expression.

The decrease in mitochondrial OPA1 functions, followed by a reduction in both serotonin and dopamine levels, and subsequently, a reduction in the NR4As pathway, can lead to an increase in glial fibrillary acidic protein (GFAP) expression.

It has been reported that serotonin may act as an inhibitor of GFAP expression, affecting either its transcription or the stability of GFAP mRNA [69].

So, it's clear that a decrease in threonine, cysteine, leucine, tyrosine, and tryptophan will inhibit or decrease serotonin synthesis, followed by a decrease in the activation of the NR4As pathway, resulting in a decrease in IL17, GCs-beta, B-arrestins, B-adrenergic activation, and Nrf2, along with an increase in accumulated cholesterol and pro-inflammatory molecules.

A deficiency in threonine will be followed by a deficiency in cysteine and tryptophan (TGG), ultimately leading to fatal neonatal encephalopathy with hypotonia and reflecting deficiencies in both melatonin (which is promoted by serotonin synthesis) and oxytocin biosynthesis. Both serotonin and oxytocin are considered essential for improving both brain and heart functions through activating Nrf2 functions, thereby activating heme oxygenase, Ang2-AT2, and VEGF-A production, which are necessary for anti-inflammatory growth.

Both dopamine and serotonin are interconnected, such that the activation of serotonin leads to a reduction in dopamine levels, and vice versa.

Serotonin agonists reduce dopamine synthesis in the striatum only when the impulse flow of Nigro-Striatal neurons is intact [70].

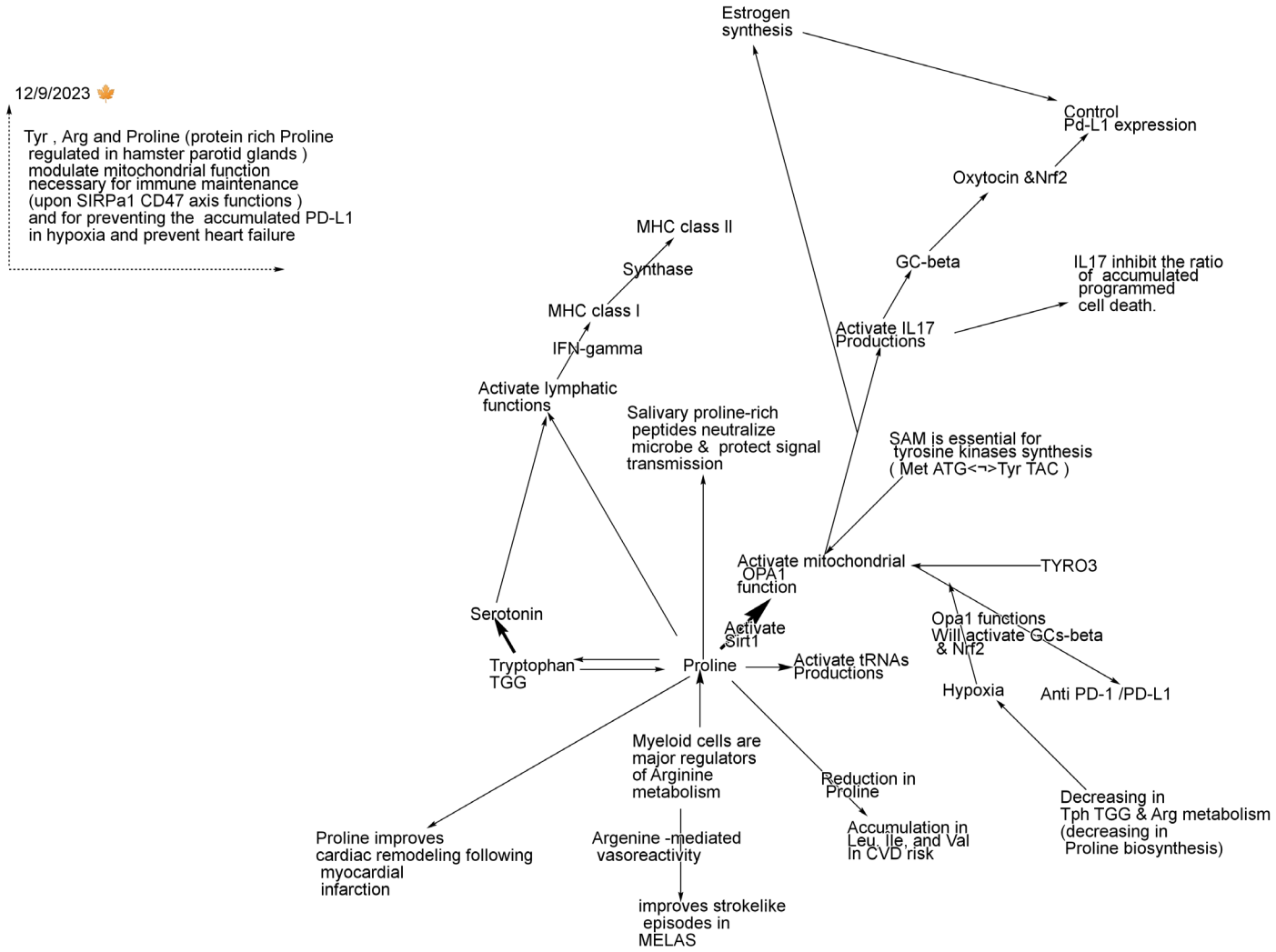
Serotonin inhibits impulsive behavior, while dopamine enhances impulsive behavior. Serotonin neuron activation does not induce the inhibition of motor behaviors [71].

The effectiveness of dopamine in activating brain memories suggests that patients with Parkinson's disease dementia (PDD) experience extensive cholinergic and dopamine (DA) loss. The combined loss of DA and ACh may be sufficient for the pathogenesis of specific cognitive deficits in PDD [72].

Extensive cholinergic and dopamine loss can result from deficits in both genes and their productive pathways, primarily due to the loss of tyrosine kinases, which are necessary for choline kinases and dopamine synthesis. This combined loss of DA and ACh reflects severe deficits in tyrosine kinases, a major component of valorphin, and could be sufficient for the pathogenesis of PDD [72].

Melatonin, regulated mainly by threonine, plays a significant role in neuroprotection by activating the NR4As pathway. Disturbances in melatonin levels in conditions such as stroke, Alzheimer's disease, and Parkinson's disease indicate its involvement in the pathophysiology of these diseases, making it a promising potential therapeutic neuroprotective agent [73].

Melatonin also possesses important antimicrobial properties and can mediate the activation and proliferation of intestinal mucosal immune cells through the activation of the full NR4As productive pathway [74]. Additionally, melatonin exerts anti-gastrointestinal cancer actions by inhibiting proliferation, invasion, metastasis, angiogenesis, and promoting apoptosis



and cancer immunity [75].

The antimicrobial properties of melatonin are described through its role in activating the NR4As pathway, mediated by activating IL17 synthesis, which promotes glucocorticoid-beta as the first active step in the NR4As pathway. This is followed by B-arrestins synthesis, B-Adrenergic productions, oxytocin, Nrf2 production, Ang2-AT2, and VEGF-A productions, which subsequently lead to heme oxygenase and anti-inflammatory growth.

The synthesis of serotonin and oxytocin, respectively, is affected by decreases in serotonin and dopamine levels, leading to decreased attention and brain memory. This is followed by a decrease in oxytocin synthesis, which is promoted by B-adrenergic signaling. The reduction in antimicrobial properties is due to the decreased production of melatonin, which is necessary for activating the NR4As pathway, resulting in reduced oxytocin levels and decreased anti-inflammatory growth, potentially leading to gastrointestinal cancer.

Melatonin's antineoplastic effect is achieved through its role in activating the NR4As pathway, inhibiting various cancer hallmarks, including proliferation, metastasis, and apoptosis, against tumor cells [76].

Melatonin's role in activating the NR4A2 productive pathway can help in preventing neonatal encephalopathy with hypotonia and reactivating brain functional activities. This makes melatonin a promising agent to improve the outcomes of infants with neonatal encephalopathy [77].

Melatonin is essential for neuroprotection as it activates GTPase, which is necessary for inner membrane repair and CoQ10 synthesis. It also activates the NR4As productive pathway, leading to anti-inflammatory growth.

The safety and benefits of using melatonin for neuroprotection in asphyxiated newborns have been reported [78]. It also appears to be safe and beneficial in protecting neonatal brains from perinatal hypoxic-ischemic encephalopathy (HIE) [79].

Melatonin promotes the production of Rho-family GTPases, which are key regulators of the actin cytoskeleton and play essential roles in orchestrating the development and remodeling of spines and synapses [80].

Melatonin, which is regulated by tryptophan (TGG) and serotonin synthesis, is primarily regulated by threonine, which is involved in valorphin. It plays a crucial role in activating the NR4As productive pathway. The synthesis of melatonin reflects the role of tryptophan in promoting GTPase synthesis, inner membrane repair, and CoQ10 synthesis, preventing neonatal encephalopathy and hypotonia. This is mediated by IL17 synthesis and GCs-beta synthesis, followed by B-arrestins synthesis, B-Adrenergic and Nrf2 synthesis, reactivating anti-

inflammatory growth, and brain functional activities.

Valine is crucial for stabilizing tyrosine kinases synthesis and functions, with the role of glu/Gln cycles in stabilizing valine synthesis .

GTC Valine <<¬>> CAG Glutamine

GTA Val <<¬>> TAC Tyrosine

ATA Isoleucine <<¬>> TAT Tyrosine

Both valine and isoleucine are involved in the composition of valorphin, which is necessary for activating Tph synthesis and tyrosine kinases production, essential for serotonin and dopamine production. The presence of leucine is also necessary for Nrf2 production.

Defective OPA1 membranes can result from the accumulation of inflammatory subunits. Mitochondrial dysfunctions can occur due to severe deficiencies in tryptophan (TGG), glycine (Gly), and, in some cases, arginine (Arg), and the necessity of hydrophobic amino acids like leucine (Leu), tyrosine (Tyr), glutamine (Glu), and valine (Val), among others. Tryptophan (Trp), leucine (Leu), tyrosine (Tyr), and glycine (Gly) play important roles in mitochondrial repair and functions, leading to the activation of astrocyte functions. Threonine phosphorylation is necessary for serotonin, oxytocin, and Nrf2 synthesis.

The Glu-Gln cycle is crucial for activating valine synthesis and functions, which, in turn, are necessary for activating tyrosine synthesis. Threonine phosphorylation promotes the synthesis of both tryptophan (TGG) and cysteine (Cys), where both tyrosine and cysteine activate oxytocin synthesis, while tryptophan activates serotonin and melatonin synthesis [75]. Glutamatergic signaling stimulates melatonin synthesis at night [81].

Glu functions stimulate Trp functions to activate melatonin biosynthesis and also play a role in activating IL-17 production through its involvement in activating OPA1 functions. Inhibition of Thr phosphorylation and the inhibition of Cys and Trp synthesis will decrease the synthesis of serotonin, melatonin, and oxytocin.

Threonine plays a crucial role in activating Cys and Trp synthesis, while Glutamate can activate Leu synthesis. Additionally, glutamine can modulate melatonin synthesis through a mechanism that begins with the activation of leucine synthesis:

GAA (Glutamate) -> CTT (Leucine)

TTA (Leucine) activates AAT (Tyrosine)

ACA (Threonine) activates TGT (Cysteine)

ACT Thr activates TGA Cysteine

ACA Thr activates TGT Cysteine

ACG Thr activates TGC Cysteine

ACC Thr activates TGG Tryptophan, which is important for serotonin and melatonin synthesis. This activation leads to the NR4As productive pathway.

The synthesis of Tyr and Cys will activate oxytocin synthesis, which is regulated by B-adrenergic receptors.

Glutamate stimulates leucine synthesis, enhancing Tyr synthesis, which, in turn, activates Tyr kinase, necessary for serotonin and dopamine production. This pathway is followed by the activation of melatonin synthesis, which, in turn, activates the NR4As productive pathway. The primary formation of Cys and Tyr will activate oxytocin synthesis, while Leu, formed by glutamate, will activate Nrf2 productive functions.

It has been reported that glutamate modulates pineal melatonin synthesis.

It's important to note that Leu and Gln stabilize and regulate each other throughout translation processes:

- GAA (Glutamine) <--> CTT (Leucine)
- GAG (Glutamine) <--> CTC (Leucine)

Additionally, Thr (ACT) activates TGA, resulting in Cys production, and TCA (Ser) activates AGT, leading to oxytocin synthesis.

L-leucine stimulates glutamate dehydrogenase activity and glutamate synthesis by regulating mTORC1 [83].

Tryptophan (Trp), regulated by TGG, is necessary for activating melatonin synthesis. Leucine (Leu) is necessary for Nrf2 synthesis. Melatonin plays a crucial role in activating immune cells by stimulating the NR4As productive pathway for IL17 synthesis, which is necessary for GCs-beta synthesis. This is followed by B-arrestins, promoting B-adrenergic signaling, oxytocin synthesis, Nrf2 synthesis, and the activation of Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth.

Tryptophan's necessity is related to the regulation of mitochondria OPA1 repairs through GTPase synthesis. Decreases in tryptophan can lead to a reduction in GTPase activity, brain function, CoQ10 levels, and may cause autoimmune diseases.

Mitochondrial fission is primarily regulated by tryptophan (Tph), which stimulates GTPase synthesis, necessary for OPA1 repairs [84].

Tryptophan (Tph) and GTPases play strong roles in regulating mitochondrial dynamics in Parkinson's disease [85].

The ARL2 GTPase is required for mitochondrial morphology, motility, and the maintenance of ATP levels [86].

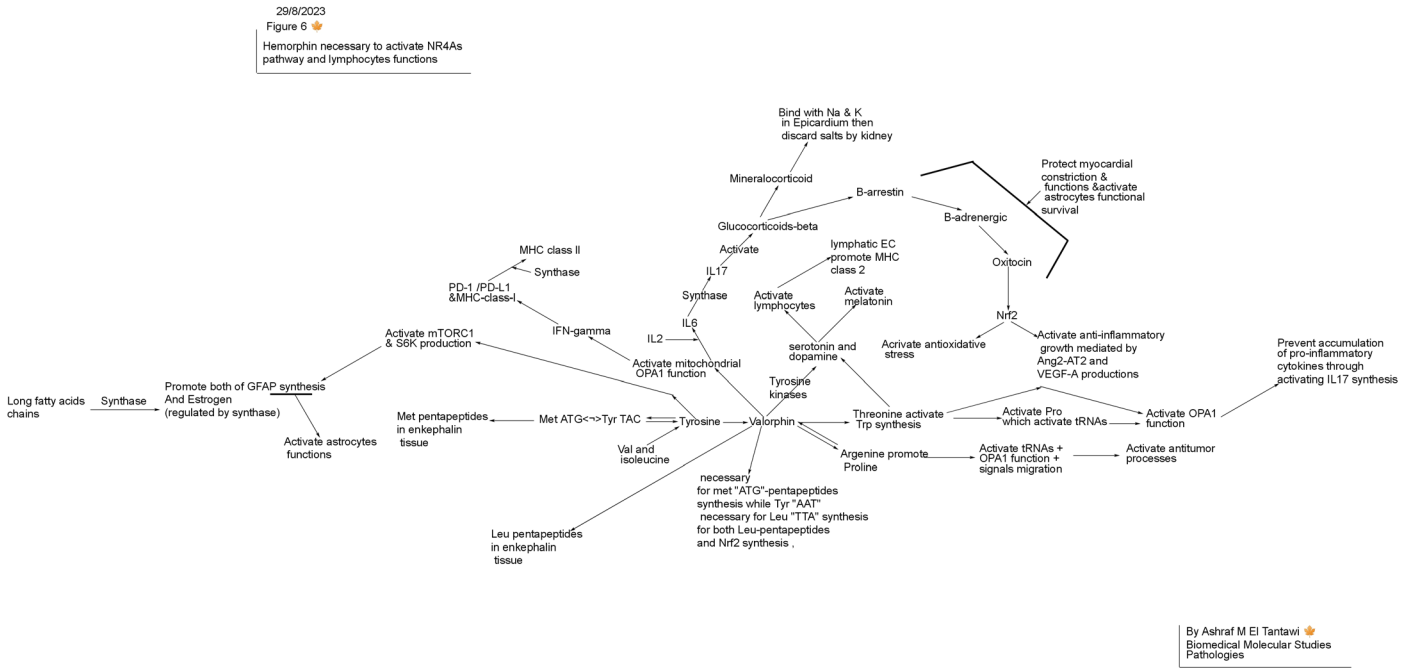
A decrease in GTPase production can lead to a reduction in ATPase activities, which can result in increased inflammation and potential toxicity from sodium and potassium binding.

GTPase synthesis is essential for protein synthesis. The breakdown of tryptophan promotes the phosphorylation pathway of serine (Ser) and threonine (Thr), which in turn promotes both cysteine (Cys) and tyrosine (Tyr) synthesis. These activate oxytocin synthesis and complete the NR4As productive pathway, leading to Nrf2 synthesis and the production of Ang2-AT2 and VEGF-A for anti-inflammatory growth.

It has been reported that NOA1 is an essential GTPase required for mitochondrial protein synthesis. NOA1-deficient mice exhibit midgestation lethality associated with severe developmental defects in the embryo and trophoblast [87]. GTPase synthesis plays a crucial role in activating proliferation by first activating glucocorticoid_beta, followed by B-arrestins, which are essential for activating Ang2-AT2 (for heart constriction) and then activating VEGF-A synthesis to support anti-inflammatory growth mediated by B-adrenergic and Nrf2 synthesis via the NR4As pathway. Deficiency in GTPase synthesis or production can lead to defects in anti-inflammatory pathways and impact embryo and trophoblast development.

Additionally, Rho-GTPases are regulators of T lymphocytes [88].

GTPase synthesis by Tph is required for OPA1 inner membrane repairs and inner membrane fusion. Defects in OPA1 function are closely related to GTPase Deficiency and subsequently



linked to tryptophan Deficiency, which is considered one of the most complex and energy-consuming amino acids, and one of the rarest in the proteome.

It's important to note that Thr TCC is necessary for preventing Tph TGG synthesis. Valorphin contains Thr TCC and Leu in its composition. Valorphin has significant advantages for Tph synthesis and function, as well as mitochondrial OPA1 repair and function. In brief, Tph and Leu are essential for activating the NR4As pathway in astrocyte cells, initiating mitochondrial OPA1 repairs and functions. This is followed by serotonin and dopamine synthesis, which is then followed by activating melatonin and IL-17 production, ultimately leading to the activation of GCs-beta and B-Adrenergic productive functions. This sequence leads to oxytocin and Nrf2 production, which adopts heme oxygenase and antioxidative stress, followed by Ang2-AT2 and VEGF-A synthesis, both necessary for anti-inflammatory growth and TH17 production, respectively .

It is also noteworthy that endoplasmic reticulum stress can be adopted and feedback by astrocyte function through activating the NR4As pathway. In response to ER stress, astrocytes play a role in adopting inflammation by producing inflammatory mediators. This can reduce trophic support and transmit the adopted ER stress to other cells [89].

Arginine, Leucine, and Proline are involved in morphine and are important for adopting immune functions, maintaining heart and brain health under strong conditions.

Myeloid cells are major players in exploiting the regulators of arginine metabolism (for proline synthesis) to mediate diverse immune responses while protecting the stability of tRNA synthesis and signal transmission activities. The regulators of arginine metabolism can elicit dichotomous innate and adaptive immune responses [90].

Special attention has been paid to the group of branched-chain amino acids (BCAA), including leucine, isoleucine, and valine, as their plasma values are frequently found in high concentrations in individuals with CVD risk. Nevertheless, dietary BCAA, especially leucine, has been associated with improved indicators of atherosclerosis [91]

Leucine, isoleucine, and valine often appear in high concentrations in individuals with cardiovascular disease (CVD) due to dysfunction in arginine and tryptophan metabolic functions, which result from a deficiency in proline. This deficiency can lead to a reduction in tRNAs, contributing to hypertension and the accumulation of valine, leucine, and other important branched-chain amino acids in the body

{{AGG Arginine Arg R < ¬ ¬ > C C T Proline}}

And,

CCA _Proline <¬¬>tryptophan TGG}}

Proline is essential for tRNA synthesis and gene signal transmission. It has been reported that a conserved proline triplet in Val-tRNA synthetase plays a critical role in ValS activity and the origin of elongation factor P [92]. The absence of proline can result in decreased tRNA synthesis and the accumulation of valine, leucine, and isoleucine. Isoleucine is particularly characterized for tyrosine synthesis, while the other two triplets of isoleucine (ATT, ATC) are for termination. The absence of arginine and tryptophan can lead to a deficiency in proline and their necessary tRNA, resulting in increased tyrosine and hypertension in CVD.

Furthermore, it's been reported that proline metabolism impacts beneficial tissue regeneration but can also contribute to the progression of devastating pathologies such as fibrosis and metastatic cancer. Salivary proline-rich peptides, which can neutralize microbe attacks, could help prevent dental caries and infectious diseases [93].

This explains why arginine and proline are found in hemorphin composition, such as hemorphin-5, which comprises nine essential amino acids: Leu_Val_Val_Tyr, Pro_Pro_Thr_Gln, and Arg. Deficiency in arginine leads to a deficiency in proline, resulting in the accumulation of these amino acids, which can

lead to hypertension and CVD, along with a severe deficiency in serotonin and melatonin.

The biosynthesis of proline is crucial to sustain protein synthesis, support mitochondrial function, and nucleotide biosynthesis [94].

In conclusion, a decrease in arginine and tryptophan, followed by a decrease in proline, can lead to a decrease in lymphocyte functions, a reduction in antioxidative function, an accumulation of IL2 and IL6, and a decrease in mitochondrial OPA1 function. Morphine synthesis is of great importance for strengthening the immune system to protect the heart, brain, and overall immune functions against disease progression. Proline is essential for immune function, as the Glu/Gln cycle plays a vital role in leucine and proline synthesis and its availability by intestinal cells [95].

Mitochondrial disorders due to a deficiency in proline, leucine, and Sirt1, followed by a deficiency in Nrf2, can exacerbate white matter damage.

Firstly, we previously discussed the importance of proline synthesis from tryptophan, which is essential for mitochondrial OPA1 repair and the continued activation of the serotonin syndrome and NR4As Productive Pathway functions.

Coenzyme Q10 deficiency can be either primary or secondary to other inherited neurogenetic disorders. There are 30 primary disorders of Q10 biosynthesis that can be classified into four main groups:

1. An encephalopathic form presenting with myoglobinuria, encephalopathy, and ragged red fibers on muscle biopsy.
2. A cerebellar form with prominent cerebellar atrophy on brain MRI.
3. An infantile form with encephalopathy and steroid-unresponsive nephrotic syndrome.
4. A pure myopathic form with elevated creatine kinase and ragged red fibers. A muscle biopsy may be necessary for a reliable diagnosis of coenzyme Q10 deficiency.

The reason for observing "ragged red fibers" on muscle biopsy is likely due to a deficiency in leucine, which reflects a deficiency in tyrosine amino acids and in tyrosine kinase synthesis. The deficiency of tyrosine kinases, indicated by the TTA "Leu" <¬¬> AAT "Tyr" mutation, results in a decrease in serotonin and dopamine production in that tissue. Tyrosine kinases are necessary for ATPase function, which is essential for dopamine production. This deficiency can further lead to a decrease in Glu Gln cycles, followed by reductions in B-adrenergic, oxytocin, and Nrf2 functions, resulting in a deficiency in Nrf2, which exacerbates white matter damage and affects microglia/macrophage levels.

Additionally, there is the Isolated Mitochondrial Myopathy Associated with Muscle Coenzyme Q10 Deficiency [96].

A deficiency in valorphin results in decreased levels of leucine, arginine, and proline, which are essential for regulating and modulating Sirt1. Sirt1 is critical for preventing mitochondrial dysfunction and metabolic disorders. Research has shown that leucine, a component of valorphin, when supplemented, can increase SIRT1 expression and prevent mitochondrial dysfunction and metabolic disorders [97]. Leucine also plays a role in modulating mitochondrial biogenesis and SIRT1-AMPK [98], and the activation of Sirt1 and Sirt3 has been found to improve cardiac function in diabetic rats through the modulation of mitochondrial function [99].

Furthermore, mutations in mitochondrial OPA1 can be primarily caused by mutations in mTORC1 and in S6K, resulting from a deficiency in serine phosphorylation, followed by mitochondrial dysfunction, which can manifest as mutations in COQ4. Primary coenzyme Q10 deficiency-7 (COQ10D7) is a rare mitochondrial disease caused by biallelic mutations in COQ4 [100].

CoQ10 deficiency can also result in decreased activities of Sirt1 and Sirt3 deacetylases. We will explain later how deficiencies in threonine, tryptophan, tyrosine, cysteine, and leucine can lead to decreased or inhibited expression of Sirts and a reduction in CoQ10 expression, subsequently causing a decrease in oxytocin and Nrf2 expressions. Sirts play a key role in activating Nrf2, and leucine is the primary activator for both, making them important determinants of health span.

Furthermore, Nur77 enhances SIRT1 functionality and stability, and both Nur77 and Sirt1 reduce oxidative stress [101]. Sirt1 synthesis is crucial for Nrf2 production [102]. Valorphin activates serotonin and dopamine production first, followed by melatonin production, which activates the NR4As productive pathway, primarily Nur77. This activation subsequently leads to B-adrenergic and oxytocin production, followed by Sirt1 production, which stimulates Nrf2 productive functions for anti-inflammatory growth and processes.

Nur77 stimulates SIRT1 production, mediated by leucine and tyrosine functions, which are necessary for increasing Sirt1 production. This is further facilitated by B-adrenergic and oxytocin, followed by Nrf2 production. Research has shown that leucine significantly increases the mRNA levels of mitochondrial-related genes and that 0.25% leucine supplementation promotes enzymatic and non-enzymatic antioxidant capacity, mitochondrial biogenesis, and function [103]. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids [104]. Therefore, leucine modulates mitochondrial biogenesis, SIRT1-AMPK, and is necessary for stimulating proper Nur77 for Sirt1 production.

The NR4A nuclear receptors sub-family, including Nur77, Nurr1, and NOR-1, are emerging as important keys in cardiac stress responses and adaptations. Nur77 appears to be a promising target in heart failure characterization and therapy [105]. It is clear that leucine and tyrosine are necessary for increasing amino acids, which are essential for valorphin production. Valorphin activates both serotonin and boosts dopamine production, followed by melatonin synthesis, mediated by activating mitochondrial OPA1 functions. This activation triggers the NR4As functional pathway, which plays a significant role in oxidative processes and improves the antioxidative progressive pathway. It also facilitates the synthesis of oxytocin and Nrf2, mediated by B-adrenergic and Sirt1 synthesis. The NR4As pathway initially promotes GCs-beta synthesis, followed by IFN-beta and B-arrestins synthesis, and then Nrf2 production, which stimulates ACE functions for Ang2-AT2 synthesis and VEGF-A production, necessary for anti-inflammatory growth and the regulation of cardiac constriction and functions [106].

It's worth noting that Sirt1 is initially activated by leucine and tyrosine functions and later by B-adrenergic and oxytocin, which modulate Nrf2 expressions via the NR4As pathway. Research has shown that Q10 modulates the expression of NFκB, IκB, Nrf2, and HO-1 during exercise training, indicating an anti-inflammatory effect of Q10 and emphasizing its role in antioxidant defense [107].

Tyrosine and leucine are necessary for activating coenzyme Q10, which is the main component of the OPA1 membrane.

Firstly, tyrosine is crucial for CoQ10 synthesis. The coenzyme B6 is required for the conversion of tyrosine to p-hydroxybenzoic acid. Deficiency in coenzyme B6 can cause dysfunctions, potentially affecting the formation of vitamin Q10 and DNA [108]. Mutational analysis of 13 conserved residues of Coq10 revealed that two hydrophobic amino acid residues, leucine 63 (L63) and tryptophan 104 (W104), play an important role in Coq10 binding to CoQ. An L63A/W104A double mutant of Coq10 exhibited lower CoQ-binding activity [109].

CoQ-10 is located in the inner mitochondrial membrane and is a cofactor for at least three mitochondrial enzymes that play a vital role in oxidative phosphorylation. The mitochondrial inner membrane is a complex environment where multiple bioenergetic pathways converge, and CoQ appears as an essential component [110]. Therefore, threonine, tyrosine, and leucine, which are main components of valorphin, are necessary for CoQ10 synthesis and functions, a critical component of the mitochondrial membrane.

Cerebellar degeneration can result from inherited genetic mutations related to mitochondrial disorders. This degeneration can be attributed to a deficiency in tryptophan, tyrosine, and leucine, subsequently causing a deficiency in Sirt1. Leucine supplementation has been shown to increase SIRT1 expression and prevent mitochondrial dysfunction and metabolic disorders. Mitochondrial disorders can reflect deficiencies in both leucine and tyrosine. Isoleucine and valine are necessary for tyrosine production, which is essential for OPA1 function. Gln and Glu are necessary for leucine synthesis, which is crucial for OPA1 function. Mitochondrial diseases can manifest as multi-organ disorders, often involving neurological dysfunction. Cerebellar ataxia, either in isolation or combined with other features, can result from mitochondrial diseases [111]. The deficiency in Sirt1 can result from mitochondrial dysfunction and metabolic disorders, often due to deficiencies in tyrosine and leucine, leading to an abnormal production of specific proteins critical for the survival of neurons.

Tyr, Arg, and Proline, which are known for their protein-rich properties and are regulated in hamster parotid glands, play a crucial role in modulating mitochondrial function, necessary for immune maintenance, particularly through the SIRPα1 CD47 axis functions. This modulation helps prevent the accumulation of PD-L1 in hypoxic conditions and can aid in preventing heart failure.

Estrogen synthesis is associated with a reduction in the accumulation of PD-1 and PD-L1, which indicates proper mitochondrial function. This reduction in PD-1 and PD-L1 accumulation is a positive sign of mitochondrial health, helping to prevent inflammatory build-up and improving IL17 production. IL17 activates GCs-beta production via the NR4As pathway, which also regulates Nrf2 expression, leading to anti-inflammatory growth and the prevention of various pathogenic issues.

GCs-beta production, modulated by OPA1 synthase, is necessary for activating both oxytocin and Nrf2 synthesis via the NR4As pathway [112].

SAM (S-adenosylmethionine) is essential for tyrosine kinase synthesis, which is critical for OPA1 repairs. Methionine has an important role in activating Tyr kinases production, contributing significantly to increased mitochondrial function. Methionine supplementation has been shown to enhance mitochondrial function [113].

Interferon-gamma (IFNγ) induces the expression of MHC class II (MHCII) on various cell types, leading to antigen presentation to CD4+ T cells and immune activation [114].

IFN-gamma induces IFN-beta production, which in turn supports MHC class II synthesis. This process is followed by alpha phosphorylation to induce TLR4 and SIRPα1, which are controlled by CD14 and activated by synthase enzymes. As mentioned earlier, Arg, Pro, and Trp play important roles in activating lymphocytic functions mediated by mitochondrial function. Lymphatic endothelial cells promote MHC class II and intratumoral regulatory T cell-suppressive functions [115].

The activation of Tyr03 plays a role in activating mitochondrial synthase P function, which can prevent the accumulation of PD-1. TYRO3 induces anti-PD-1/PD-L1 therapy [116].

The expression of programmed death-ligand 1 (PD-L1) on myeloid-derived suppressor cells, dendritic cells (DCs), and pro-tumor macrophage type 2 (M2) is induced by hypoxia [117].

Inhibition in Proline functions due to Arg and Trp dysfunctions can lead to a decrease in tRNA, which may result in hypertension and hypoxia. Studies have indicated that when blood serotonin levels are high, the organism becomes more resistant to hypoxia [118].

Dietary arginine has been shown to attenuate hypoxia-induced HIF (hypoxia-inducible factor) expression, metabolic responses, and oxidative stress [119].

Serotonin, along with its regulator Trp, and Arg, serve as strong inhibitors of hypoxia and hypertension through their pathway of initially activating Proline. Proline, in turn, activates proper mitochondrial function and the necessary tRNAs for increasing the oxidative areas through Nrf2 expressions.

L-arginine has been found to improve the symptoms of strokelike episodes in patients with MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) [120]. Arginine is necessary to activate Proline synthesis, which in turn activates SIRT1, leading to improved mitochondrial function [121].

Proline has shown the ability to improve cardiac remodeling following myocardial infarction and attenuate cardiomyocyte apoptosis through redox regulation [122].

SIRT1, controlled by Proline, ameliorates oxidative stress-induced neural cell death and is down-regulated in Parkinson's disease [123].

Activation of Tph and Arg leads to the activation of Sirt1, which promotes mitochondrial activities. This activation results in the production of serotonin mediated by IL17. IL17 activates GCs-beta through NR4As pathway, leading to Nrf2 production.

Nrf2 controls PD-L1 expression and helps prevent PD-1 accumulation. It has been reported that chemical inhibition of Nrf2 with Brusatol and Luteolin reduces Nrf2 and PD-L1 mRNA expression, indicating that Nrf2 positively controls PD-L1 expression [124].

Estrogen expression, indicative of proper activation of mitochondrial OPA1 function, is carried out by activating both Arg and Trp, which further activate Proline functions and Sirt1. Estrogen plays a significant role in improving PD-L1 expression. Estrogen has been shown to ameliorate the immune microenvironment represented by PD-L1 expression, particularly in the absence of Nrf2 [125].

In summary, a deficiency or inhibition in Tyr and Leu, and consequently in estrogen synthesis, may lead to improved diabetes, white matter hyperintensity (along with hypertension), severe CoQ10 deficiency, and an increase in PD-1 accumulation, potentially resulting in heart failure.

Increased production of IL17 indicates the proper activities of OPA1 synthase, which prevents the accumulation of IL2, IL6, and PD-L1. IL17 synthesis, regulated by synthase, activates glucocorticoid-beta synthesis via NR4As pathway, followed by oxitocin and Nrf2 production. This helps adopt oxidative processes and activate heme oxygenase and Ang2-AT2 and VEGF-A, which are necessary for anti-inflammatory growth. IL17 synthesis reduces the ratio of programmed cell death accumulation. Increased Th17 counts of IL-17 levels, correlated with a high neutrophil-to-lymphocyte ratio and programmed cell death expression, are potential biomarkers for poor prognosis in diseases like ovarian cancer [126].

Proper mitochondrial OPA1 functions prevent the accumulation of inflammatory cytokines and pro-inflammation, such as PD-1 and MHC class I, by modulating IL17 and CD47 productions, which are essential for immune maintenance through SIRPα1/CD47 axis functions [127].

Estrogen can modify the effects of GC (glucocorticoid), enhancing Th2 cell survival and type 2 cytokine production, especially in severe asthma [128].

Inhibition of Leu and Tyr will inhibit both Nrf2 and oxitocin, leading to the promotion of PD-L1 accumulation and mitochondrial OPA1 dysfunction. This can lead to PD-L1 being improved to mutated PD-L2 in cases of OPA1 dysfunctions.

Proline-rich insert is required for the efficient activation of the Mitogen-activated Protein Kinases ERK1 and ERK2 in mammalian cells [129].

The activation of ERK1/2 and MHC class II production is regulated by Proline function, along with Arg and tryptophan [130].

MHC class II transactivator (CIITA) requires conserved leucine-charged domains for its function [131].

Nlrc5−/− splenocytes and bone marrow-derived macrophages can up-regulate MHC-I in response to IFN-γ, and MHC class I is regulated by Nucleotide-binding Domain, Leucine-rich Repeat-containing (NLR) Proteins [132]

In conclusion, Proline and Leucine are necessary for MHC class I and class II, especially upon IFN-gamma response, and they play a crucial role in activating the proper SIRPα1/CD47 axis required for immune maintenance [133].

Deficiency or inhibition in Proline, Leucine, and Tryptophan can lead to mitochondrial dysfunctions, resulting in the inhibition of CD47 production, which, in turn, can cause the accumulation of PD-1, SIRPα1, and MHC class I, leading to pro-inflammation.

Serotonin has roles in anti-inflammatory cytokine functions in some cells of the innate immune system. Alterations in the 5-HT/5-HTRs axis can impact tumor progression [134].

White Matter Hyperintensity in Cerebral Small Vessel Disease is connected to diabetes and inhibition of OPA1 functions, often caused by a deficiency or inhibition in Leucine synthesis, which is necessary for mitochondrial OPA1 fusion. This inhibition can affect B-adrenergic and Nrf2 production and, consequently, Ang2-AT2 and VEGF-A production, leading to a reduction in heme oxygenase. Patients with White Matter Hyperintensity in Cerebral Small Vessel Disease may have high oxidative processes, unadopted heart constriction, and an association with diabetes.

Hypertension, which is a classical risk factor in White Matter Hyperintensity, may be initiated by the inhibition of Ser phosphorylation, leading to a reduction in mTORC1 production, which is essential for astrocyte survival. This reduction can subsequently lead to a decrease in tryptophan and, consequently, a reduction in Proline, along with other necessary amino acid synthesis, due to a deficiency in OPA1 synthase. The result is an increase in pro-inflammation, a decrease in estrogen production, a decrease in glucocorticoid-beta, and a decrease in the NR4As pathway. The inhibition of glucocorticoid-beta production is linked to the inhibition of mitochondrial OPA1 synthase enzymes, where synthase enzymes promote IL17 productions and prevent the accumulation of pro-inflammatory molecules. IL17 is responsible for activating glucocorticoid-beta synthesis, followed by B-arrestins and the synthesis of both oxitocin and Nrf2. This promotes Ang2-AT2 synthesis, regulated by ACE, and VEGF-A synthesis, ultimately adopting myocardial constriction.

Hypertension in white matter hyperintensity, due to a severe decrease in tryptophan followed by a decrease in proline (which regulates tRNAs production), is followed by the accumulation of proinflammatory subunits. OPA1 dysfunction in white matter hyperintensity is associated with the inhibition of estrogen synthesis and inhibition in glucocorticoids-beta production (via NR4As pathway). It is also associated with severe decreasing in tRNAs production, which is regulated by proline, formed by tryptophan, and followed by astrocyte damage, heart failure, and stroke [135].

Mitochondrial OPA1 disease, caused by a decrease or inhibition in tryptophan and proline, is associated with inhibition in hydrophobic amino acids synthesis, including deficiency in serine, proline, leucine, tyrosine (tryptophan synthesis), and cysteine. Consequently, this reflects a deficiency in estrogen synthesis (due to deficiency in synthase enzymes), followed by a deficiency in glucocorticoid-beta synthesis, a deficiency in both oxytocin and Nrf2 production, and a severe decrease in tRNAs synthesis, which causes the accumulation of molecules like protein leucine-rich, isoleucine-rich, and valine-rich protein in cardiovascular diseases [136].

Serine phosphorylation is necessary for improving mTORC1 production, which is necessary for estrogen synthesis, regulated

by synthase enzymes. This is essential for astrocyte survival and proteostasis. MTOCR1 controls proteostasis after brain ischemia, and estradiol plays an important regulatory role for mTORC1 activity [136].

Hypertension, which is the classical risk factor for white matter hyperintensity, and diabetes mellitus, is associated with white matter hyperintensity progression [137]. This is due to severe decreasing in tRNAs synthesis. The main reasons for an increase in hypertension in white matter hyperintensity are due to a reduction in tRNAs synthesis (due to the reduction in proline, which is due to a reduction in tryptophan), followed by a reduction in OPA1 enzyme (synthase enzyme) functions associated with reductions in mTORC1 and a reduction in proper S6K (which can cause a mutation in OPA1 membrane). This reduction is also associated with a reduction in estrogen synthesis with increasing accumulation in pro-inflammations.

Type 2 diabetes is closely related to cerebral small vessel diseases, just as mitochondrial OPA1 dysfunction is associated with cerebral small vessel disease and an increase in hypertension. Some causes can have tRNAs production originated from arginine, which will reduce the accumulation of molecules but will not activate both the serotonin and NR4As pathway necessary for astrocyte functions [138].

The deficiency of Nrf2 exacerbates white matter damage due to the severe decrease in tryptophan and proline, which are necessary for promoting serotonin, tRNAs, and NR4As pathways, respectively. It has been reported that the deficiency of Nrf2 exacerbates white matter damage and microglia/macrophage levels in a mouse model of vascular cognitive impairment [139].

It has also been reported that the association of white matter hyperintensities and cardiovascular disease leads to the loss of adequate small vessel functions. This results in clinical manifestations, including chest pain, dyspnea, heart failure, lacunar ischemia, white matter hyperintensities, cognitive impairment, and dementia [140].

Due to the activation of the NR4As pathway, intranasal oxytocin attenuates cognitive impairment, β-amyloid burden, and tau deposition. This is mediated primarily by the activation of OPA1 function [141]. Oxytocin treatment has the function of activating Nrf2 synthesis by activating leucine synthesis, which will also activate Ang2-AT2 and VEGF-A synthesis, adopting myocardial constriction and activating both heme oxygenase and anti-inflammatory growth. Oxytocin treatment also has the roles of reactivating tyrosine kinases, which activate mitochondrial OPA1 function in the availability of tryptophan, proline, and leucine functions for activating proper mTORC1 and S6K production, which protects astrocytes' functional survival.

Arginine and proline are involved in morphine and are strongly important for adopting and strengthening the immune system to protect the heart, brain, and overall immune system in strong, healthy functions.

Special attention has been paid to the group of branched-chain amino acids (BCAA), leucine, isoleucine, and valine, since their plasma values are frequently found in high concentrations in individuals with CVD risk. Nevertheless, dietary BCAA, particularly leucine, have been associated with improved indicators of atherosclerosis [142].

Leucine, isoleucine, and valine often have high plasma concentrations in individuals with CVD risk due to dysfunction in arginine and tryptophan metabolic functions. This dysfunction results from a deficiency in proline, which regulates tRNAs production. Proline is necessary for tRNAs synthesis and for genes migrations. It has been reported that a conserved proline triplet in Val-tRNA synthetase is crucial for ValS activity, which may explain why bacterial cells co-evolved the EF-P rescue system [143].

The absence of proline, whose synthesis is tryptophan-dependent, results in a decrease in tRNAs, a decrease in the NR4As pathway, and an accumulation of valine, leucine, and isoleucine proteins. Isoleucine is characterized for tyrosine synthesis. The absence of arginine results in a deficiency in proline, leading to a decrease in tRNA synthesis and signals transmission. Similarly, the absence of tryptophan results in a decrease in proline and a reduction in tRNAs production, as well as a decrease in the NR4As pathway, which leads to a decrease in glucocorticoids-beta, oxytocin, and Nrf2 production. This accumulation of pro-inflammatory factors can cause an increase in hypertension in white matter hyperintensity [142].

It has been reported that proline metabolism impacts beneficial tissue regeneration but can also contribute to the progression of devastating pathologies such as fibrosis and metastatic cancer. Salivary proline-rich peptides, which can neutralize microbe attacks, could contribute to avoiding the development of dental caries and infectious diseases [144]. Other studies have reported that proline-rich proteins are necessary for controlling T cell antigen receptor expression [145].

This clarifies why arginine and proline are strongly found in hemorphin composition, as they stabilize and maintain tRNAs synthesis and protect signal migration, preventing the accumulation of tyrosine (which can cause hypertension), leucine, and valine. The presence of threonine in hemorphin promotes tryptophan synthesis, which, in turn, promotes proline synthesis and the serotonin synthesis and NR4As Productive Pathway, including glucocorticoids-beta synthesis, oxytocin, and Nrf2 synthesis. Hemorphin-5 consists of nine essential amino acids: Leu, Val, Val, Tyr, Pro, Pro, Thr, Gln, and Arg. Deficiency in arginine and tryptophan synthase results in a deficiency in proline synthesis, leading to a decrease in tRNAs synthesis and the accumulation of leucine, valine, proteins, causing an increase in hypertension and severe deficiency in serotonin and melatonin [142].

The biosynthesis of proline is key to sustaining protein synthesis, supporting mitochondrial function, and nucleotide biosynthesis [146].

In conclusion, a decrease in arginine and tryptophan (Tph) is followed by a decrease in proline, which results in a decrease in lymphocytes' functions, a decrease in antioxidative function, and an accumulation of IL2 and IL6. This is associated with a decrease in mitochondrial OPA1 function and can be a strong sign of cardiovascular disease (CVD) characterized by the accumulation of leucine, valine, and isoleucine (due to a decrease in tRNAs). Morphine plays a crucial role in adopting and strengthening the immune system and protecting heart, brain, and overall immune function [142].

Notice: Myeloid cells are major players that exploit the

regulators of arginine metabolism for proline synthesis to mediate diverse and adopt immunity. The regulators of arginine metabolism can elicit dichotomous innate and adaptive immune responses [147].

As for your question, the increasing in GFAP produced by astrocyte cells dysfunction during neurodegenerative diseases (NDGD) can be related to mTOR/S6K promoting astrocyte survival through mitochondrial OPA1 regulations.

Neurodegenerative diseases (NDGD) are characterized by a decrease in mitochondrial OPA1 function and consequently, dysfunction in astrocytes and the NR4As pathway [148]. If astrocytes are indeed the source of GFAP production, then how do these cells fail to work properly in NDGD [148]? It's worth noting that another source is responsible for creating GFAP protein, and it has been proven that the mTOR/S6K phosphorylated pathway is responsible for producing GFAP [148]. Defects in the AKT/mTOR pathway have been associated with altered translational control in Mecp2 mutant neurons [148]. Additionally, PTEN and NF1 (neurofibromin) are involved in glial growth regulation through TSC/Rheb (Ras homolog enriched in the brain) control of mTOR function [149]. An increase in cell size has been associated with protein kinase B/Akt hyperactivation [150]. Lithium has been reported to decrease the activation of the transcription factor STAT3, a regulator of GFAP transcription and astroglia genesis [151]. Neurofibromin has been found to regulate actin cytoskeleton dynamics and cell proliferation through an mTOR/Rac1-dependent signaling pathway, with NPM being a critical mTOR effector in Nf1-deficient astrocytes [152].

GFAP regulated by mTOR kinases activates astrocytes through OPA1 regulation, initially activating IL17 from IL4 and IL6, regulated by synthase function, which, in turn, activates glucocorticoid-beta production via the NR4As pathway. This is followed by B-arrestins, oxytocin, and Nrf2 synthesis, where oxytocin and Nrf2 are responsible for producing glutathione. They also activate heme oxygenase, Ang2-AT2, and VEGF-A production [148]. The increasing in GFAP regulated by the mTOR/S6K pathway, along with severe dysfunction in astrocytes or mitochondrial OPA1 function, characterizes Alzheimer's disease and other neurodegenerative diseases. These conditions involve a decrease in the NR4As productive pathway and, consequently, a decrease in oxytocin and Nrf2, resulting in decreased glutathione production [148].

In chronic neuroinflammatory conditions, such as PMS, and neurodegenerative diseases, the levels of GFAP in the blood are expected to increase with accumulating astrogliosis [153]. In ischemic stroke, the greater the damage to neurons and neuroglia, the higher the serum GFAP levels will be [154]. The accumulation of GFAP in damaged neurons and neuroglia characterizes neurodegenerative diseases [153]. Neurodegenerative diseases and stroke are characterized by continuous GFAP production regulated by the mTOR/S6K activated pathway, with dysfunction in astrocytes, which may be due to dysfunction in mitochondrial OPA1 function, reversing the decrease or inhibition in the NR4As productive pathway, mainly regulated by OPA1 functions. This reversal results in a severe decrease in oxytocin and Nrf2 functions, reflecting a decrease in glutathione production [154].

CoQ10 has an effective therapeutic role in age-related neurodegenerative disorders [155]. Previous work has indicated that neurodegenerative disorders result from dysfunction in mitochondrial OPA1 activities, and CoQ10 has the role of recovering mitochondrial OPA1 function to activate astrocytes by activating the NR4As pathway, which is dependent on mitochondrial OPA1 functions [155].

Glutathione is highly expressed by astrocytes and is formed through the binding of cysteine (the main composition of oxytocin) with glutamine to initiate leucine synthesis for activating Nrf2. γ-glutamate cysteine ligase (also known as γ-glutamylcysteine synthase) and glutathione synthase are highly expressed in astrocytes [156]. Glutathione appears to be activated by Nrf2 functions but is mainly handled by oxytocin cooperative functions. A plethora of specific targets, including those involved in thioredoxin (TRX) and glutathione (GSH) systems, are activated by Nrf2 [157]. Cysteine and glutamine are specific steps necessary for leucine synthesis, which promotes Nrf2 production via the NR4As pathway and is necessary for activating glutathione expressed by astrocytes [157]. These two works indicate the formation of oxytocin in astrocytes, which promotes Nrf2 production necessary for activating thioredoxin (TRX) and glutathione (GSH) systems by astrocytes [157].

Additionally, tyrosine kinases have been found to regulate astrocyte cytoskeletal rearrangement [158].

Activation of tyrosine (which is included with cysteine in oxytocin composition) and MAP kinases by swelling is a critical step in the opening of volume-sensitive Cl^- channels in astrocytes [159].

The role of the mTOR/S6 Kinase Pathway is not just a contribution but is necessary for astrocyte function and survival [160]. The mTOR/S6K pathway initiates the activation of serotonin and dopamine, which are regulated by tyrosine kinases. This activation is followed by the activation of the NR4As pathway in astrocytes, primarily by producing glucocorticoid-beta, followed by oxytocin and Nrf2 synthesis, mediated by B-adrenergic receptors. This is followed by Ang2-AT2 and VEGF-A synthesis [160]. It should be noted that S6K is produced by the mTOR pathway, not by astrocytes, but it is necessary for activating astrocytes and contributing to their active survival [160]. Activation of S6 kinase activity in astrocytes has been reported [161].

Astrocytes are a target for stress and glucocorticoids and are a promising target for the treatment of stress-dependent depression [162]. IL17, activated by OPA1 synthase function, promotes glucocorticoid-beta synthesis via the NR4As pathway. Additionally, the mTOR S6K pathway stimulates dendritic cells (DCs) to produce IL2, which enhances OPA1 synthase functions for producing IL4 and IL6, followed by IL17, which activates glucocorticoid-beta production, a promising target for the treatment of stress-dependent depression by astrocytes via activating the NR4As pathway [162]. A decrease or inhibition in mitochondrial OPA1 function promotes the accumulation of Interleukin-2, IL4, and IL6, which can promote mutated heterogeneity and inhibit pyrimidine biosynthesis [162].

Tryptophan is necessary for activating proline synthesis, which is necessary for mitochondrial OPA1 function. In cases of increasing inflammation, Tryptophan will follow the

pathway of proline synthesis necessary for activating OPA1 function, improving IL17 synthesis and necessary for tRNA production to prevent toxicity and improve immune functions [163]. Amyloid toxicity-induced interleukin-4 (IL4) promotes NSC proliferation and neurogenesis by suppressing tryptophan metabolism and reducing the production of serotonin [163]. Melatonin, an endogenous hormone, modulates Th17 cells via reactive oxygen species [164].

Tryptophan synthesis (Tph TGG) regulates serotonin synthesis, which activates melatonin synthesis, followed by IL17 production, regulated by OPA1 synthase function. This prevents the accumulation of IL4 and IL6, whereas OPA1 dysfunctions (due to Tph & Pro dysfunctions) will cause the accumulation of pro-inflammatory cytokines characterizing amyloid toxicity. The activation of IL17 production is followed by activating glucocorticoid-beta via the NR4As productive pathway for activating oxytocin and Nrf2 production for antioxidative function [163].

It is clear that mTORC1 S6K and tyrosine kinases activate GFAP, followed by stimulating IL2 production (by dendritic cells "DCs" function), then followed by activating serotonin, followed by activating astrocytes started by activating IL17 (regulated by OPA1 synthase functions), which activate glucocorticoid-beta via the NR4As pathway, followed by B-Adrenergic production, which activates oxytocin and Nrf2 synthesis responsible for glutathione production and adopting antioxidative stress, heme oxygenase, and anti-inflammatory growth [163].

Both OPA1 function and CoQ10 are strongly regulated by Arg, Pro, Glu, Asp, tyrosine, and leucine functions, which are necessary for regulating glucocorticoids-beta (mediated by IL17 production) via the NR4As pathway, followed by B-arrestins, B-adrenergic, and Nrf2 production. This activates ACE, necessary for Ang2-AT2 and VEGF-A synthesis, which is necessary for adopting myocardial contractions and functions [163]. CoQ10 supports patients with Coronary Artery Disease by directly activating myocardial cells [165].

OPA1 modulates CoQ10 functions, and vice versa, to prevent Acute Ischemic by modulating IL17 production, which activates glucocorticoid-beta (promoting mineralocorticoid for binding with Na and K cation salts and discarding by the kidney), followed by B-arrestins and B-adrenergic production. This is followed by oxytocin and Nrf2 production in myocardial cells' functions, a pathway that can be contributed to by astrocytes for protecting myocardial functions and brain functional activities [165]. Serotonin production (promoted by Tph synthesis, activated by OPA1 synthase and dependent on mTOR kinases pathway) prevents Acute Ischemic via activating the NR4A2 pathway [165].

It has been reported that mitochondrial enzyme 17βHSD10 modulates Ischemic and Amyloid-β-Induced Stress in Primary Mouse Astrocytes [166].

White Matter Hyperintensities linked to mitochondrial OPA1 dysfunction and tryptophan deficiency:

Firstly, tryptophan modulates Proline synthesis, and Arg modulates Proline synthesis. Proline is essential for activating mitochondrial OPA1 function and tRNA production.

Research has shown that IL-17/CXCL5 signaling within the oligovascular niche mediates white matter injury in both humans and mice [167]. Additionally, astrocytes in white matter affected by multiple sclerosis (MS) appear to be deficient in β2 adrenergic receptors (Reference 168). Moreover, the absence of Nrf2 exacerbates white matter pathology and microgliosis following cerebral hypoperfusion [169].

From previous studies, it can be concluded that the absence of leucine, tyrosine, cysteine, glycine, and GTPase may result from dysfunction in modulating IL17 production due to inhibition or dysfunction in mitochondrial OPA1 fusion. IL17 is necessary for activating glucocorticoid-beta (GCs-beta), regulated by OPA1 synthase enzyme. This dysfunction can exacerbate white matter hyperintensity. The absence of IL17 due to mitochondrial OPA1 dysfunction leads to the inhibition or reduction of glucocorticoid-beta synthesis, oxitocin, and Nrf2 production.

Leucine is important for mitochondrial OPA1 fusion, as it regulates OPA1-mediated mitochondrial fusion (Reference 170). Src is also necessary to control mitochondrial dynamics [171]. Oxidation/nitrosation of functional cysteines on mitochondrial proteins serves to modulate protein activity, localization, and complexation in response to cellular stress [172].

It's important to note that glycine and N-Acetylcysteine supplementation in mice can increase their lifespan by correcting glutathione deficiency, reducing oxidative stress, mitigating mitochondrial dysfunction, and addressing abnormalities in mitophagy [173].

Threonine, leucine, tyrosine, and cysteine, which are key components of valorphin, play roles in maintaining OPA1 function and the synthesis of serotonin, melatonin, GCs-beta, oxitocin, and Nrf2, respectively. Valorphin is necessary for regulating mitochondrial OPA1 fusion, glucocorticoids-beta, B-Adrenergic production, oxitocin, and Nrf2 synthesis. These processes protect and improve white matter hyperintensity while preventing an increase in GFAP production.

Brain cancer is connected to leucine and tyrosine dysfunction, which are necessary for activating OPA1 repairs and functions:

Glioblastoma (GBM), the most common malignant brain cancer, is associated with a deficiency in Ser phosphorylation, which leads to a reduction in mTORC1 and subsequently a reduction in VEGF-A, resulting in decreased pericyte proliferation. This reduction in leucine and tyrosine functions, as well as OPA1 synthase, leads to an increase in cholesterol and a decrease in GCs-beta. This, in turn, results in reduced levels of both oxitocin and Nrf2, affecting their functional stability.

The synthesis of GCs-beta via the NR4As pathway is necessary for Ang2-AT2 and VEGF-A synthesis, which are crucial for the biosynthesis of new cells.

Pericytes, which are activated by VEGF-A, play a critical role in stroke-induced angiogenesis and the formation of tight junctions (TJ) in newly formed vessels. Treatment with glucocorticoids (GC) has been shown to improve the tightness of the blood-brain barrier (BBB) [174]. Additionally, P-glycoprotein is thought to act as an intermediate between the brain and periphery by controlling the transport of corticosteroids at the BBB [175].

GC-beta promotes the synthesis of Ang2-AT2 via the NR4As pathway, which activates pericyte components in vascular barrier genesis crucial for BBB integrity [176]. VEGF priming enhances pericyte proliferation [177]. Therefore, the synthesis

of Ang2-AT2 and VEGF-A via the NR4As pathway, mediated by IL17 production that activates GCs-beta production, is essential for the proliferation of new cells and the removal of toxic and dead cells after a stroke.

mTORC1, primarily regulated by Ser phosphorylation, controls the production of glial fibrillary acidic protein (GFAP). GFAP promotes Schwann cell function and is retained in non-myelin-forming Schwann cells [178]. Rapamycin has been shown to preserve neural tissue, promote Schwann cell myelination, and reduce glial scar formation after spinal cord injury [179].

mTORC1 activation, regulated mainly by Ser phosphorylation, leads to the synthesis of hydrophobic amino acids, including tryptophan (Trp), which is essential for GTPase synthesis and for the synthesis of both serotonin and melatonin. Dysfunction in serotonin mirrors GTPase dysfunction and dysfunction in pyrimidine synthesis regulated by OPA1 synthetase enzymes. The synthesis of melatonin is regulated by serotonin (which is in turn regulated by Trp) and OPA1 function. Trp is crucial for reactivating OPA1 function, which is necessary for preventing the accumulation of pro-inflammatory cytokines by activating and improving IL17 production, followed by activating GCs-beta via the NR4As pathway.

Defects in melatonin can be detrimental in the context of chronic neuro-inflammation, and down-regulating melatonin may be beneficial in activating the innate immune response in the context of tumor-mediated immune suppression [180]. However, down-regulating melatonin is not beneficial for initiating the immune response in the context of tumor-mediated immune suppression. Trp, which regulates both serotonin and melatonin, is essential for activating OPA1 function, particularly OPA1 synthase, needed to remove the accumulation of proinflammatory molecules by improving IL17, which, in turn, activates GCs-beta, B-arrestins, B-adrenergic, oxytocin, and Nrf2 production, respectively.

Nrf2 signaling deficits can disrupt the blood-brain barrier in diabetic cases, and down-regulated melatonin functions reflect down-regulated glycoprotein necessary for controlling the transport of corticosteroids at the BBB, as previously mentioned. Blood-brain barrier disruption in diabetic mice has been linked to Nrf2 signaling deficits [181].

In summary, a deficiency in tryptophan synthesis, regulated by threonine and glycine, along with deficiencies in tyrosine and leucine, results in a deficiency in serotonin and defects in melatonin, reflecting a deficiency in mitochondrial repair and function. This leads to an increase in the accumulation of pro-inflammatory molecules, a decrease in both IL17 and GCs-beta (critical for BBB transport control), a decrease in oxytocin, and a decrease in Nrf2, which is vital for protecting against ischemic injury and preserving the blood-brain barrier [182].

Conclusion

Valine and isoleucine are essential for Tyr kinase production, while threonine, proline, and cysteine play a role in stabilizing tryptophan biosynthesis, which is necessary for mitochondrial OPA1 repair, serotonin and melatonin biosynthesis, IL17 production, and the activation of the GCs-beta synthesis pathway via the NR4As pathway. This, in turn, reactivates beta-arrestins, which are crucial for myocardial functions, as well as beta-adrenergic receptors, oxytocin, and Nrf2 biosynthesis. These processes help protect against chronic hypertension, white matter hyperintensity (WMH), CoQ10 deficiency, and elevated GFAP levels.

Tryptophan, tyrosine, and leucine are significant players in activating mitochondrial OPA1 repair and promoting CoQ10 synthesis. Tryptophan, particularly the "TGG" codon, is essential for proline synthesis, OPA1 function, tRNA production, IL17 production, and GCs-beta synthesis via the NR4As pathway, supporting antioxidative functions, heart and brain activities.

Tyrosine codons (TAT and TAC) are critical for mitochondrial OPA1 function, while the Glu/Gln cycle is necessary for leucine synthesis, which, in turn, supports the production of leucine pentapeptides. Methionine, regulated by tyrosine TAC codon, plays a role in brain function by activating met pentapeptides in enkephalin tissue, safeguarding antioxidative functions in the brain and preserving lymphocyte functions.

The treatment with L-cysteine significantly improves brain edema, enhances neurobehavioral functions, and reduces neuronal cell death by activating oxytocin and Nrf2 production. This promotes Ang2-AT2 and VEGF-A synthesis, leading to heart constriction, heme oxygenase activation, and anti-inflammatory processes, ultimately protecting astrocyte functions and ameliorating brain edema.

Threonine, arginine, and proline are commonly found in hemorphin composition. Threonine is crucial for regulating tryptophan synthesis, which, in turn, activates proline and the NR4As pathway. Proline plays a role in stabilizing and maintaining tRNA biosynthesis, ensuring proper cellular signal transmission. Proline, derived from tryptophan, contributes to mitochondrial OPA1 function, tRNA biosynthesis, and the NR4As pathway. Proper NR4As activation can help prevent cardiovascular diseases by regulating serotonin synthesis, IL17 production, and GCs-beta synthesis. This is especially important in preventing the accumulation of tyrosine, leucine, and valine and maintaining proper tRNA synthesis.

In summary, a decrease in tryptophan levels can result in reduced proline synthesis, leading to decreased lymphocyte function, reduced antioxidative capacity, and the accumulation of IL2 and IL6. Additionally, it can lead to a decrease in mitochondrial OPA1 function, serving as a sign of cardiovascular disease with the accumulation of leucine, valine, and isoleucine. On the other hand, a decrease in arginine can affect tRNA production, potentially causing hypertension but not activating serotonin or the NR4As pathway.

Tryptophan is a precursor for coenzymes and neuromodulators like NAD/NADP(H), crucial for modulating Sirt2 and improving hepatic mitochondrial function, cellular metabolism, and preventing chronic hypertension associated with WMH. Threonine, tryptophan, proline, and glycine play vital roles in improving hepatic mitochondrial function, regulating normal T-cell function, activating serotonin synthesis, and supporting tRNA synthesis to prevent the accumulation of pro-inflammatory molecules and hypertension in WMH.

Morphine is essential for strengthening immune effectiveness against disease progression by preserving normal astrocyte functions and supporting heart and brain functions. Reduced serotonin levels, reflecting a decrease in proline, can lead to diminished mitochondrial function, tRNA levels, megakaryocyte proliferation, hematopoiesis reduction, and white matter hyperintensity.

It's important to note that the use of atypical antidepressants

and selective serotonin reuptake inhibitors, which inhibit serotonin function, may not be the ideal approach. This can lead to white matter hyperintensity and increase the risk of cardiovascular disease and stroke.

Your question pertains to improving the molecular composition of valorphin by adding tryptophan and glycine to enhance hemorphin (valorphin) molecules. This may potentially lead to more effective treatment of various diseases, strengthen immunity, and reduce side effects, protecting against cerebral arrest and heart failure.

The recommended improved valorphin molecular structure, which should be thoroughly examined through deep research, could be:

Structure 1: Thr, Tyr, Trp, Leu, Ile, Gly, Tyr, Trp, Pro, Val, Val, Arg, Gln

Or an alternative structure:

Structure 2: Thr, Tyr, Trp, Gly, Leu, Trp, Ile, Val, Val, Gln, Arg, Trp, Pro.

Highlights

Leucine synthesis, activated by the Glu/Gln circuit and isoleucine, is essential for mitochondrial OPA1 fusion. This fusion process is necessary to promote the NR4As pathway, which, in turn, activates the β-adrenergic, oxytocin, and Nrf2 pathways. This activation is mediated by a reduction in pro-inflammatory molecules and an improvement in IL-17 production. These processes collectively contribute to the improvement of antioxidative stress and anti-inflammatory growth.

Chronic hypertension can result from deficiencies in Arginine (Arg), Tryptophan (Trp), and Proline, which can lead to tRNA deficiencies. This, in turn, may cause a reduction in Coenzyme Q10 (CoQ10). Additionally, a decrease in the activities of Proline (Pro), Tryptophan hydroxylase (Tph), Leucine (Leu), and Tyrosine (Tyr) kinases may lead to an increase in Plasma Glial Fibrillary Acidic Protein (GFAP), which is regulated by mTORC1/S6K signaling. This increase in GFAP can result from a reduction in blood flow and decreased oxygen supply to the brain, leading to neuronal damage and impairing the function of sodium and potassium channels and antioxidant mechanisms.

White Matter Hyperintensity in Cerebral Small Vessel Disease can be attributed to deficiencies or inhibitions in both mTORC1 and Leucine Biosynthesis. These deficiencies can result in a lack of Tyrosine (Tyr) and Cysteine (Cys), both of which are essential for oxytocin synthesis. Additionally, this may lead to a decrease or inhibition in Nrf2 production. Subsequently, there is a decrease in both Angiotensin II Receptor Type 2 (AT2) and Vascular Endothelial Growth Factor-A (VEGF-A) synthesis. This decrease or inhibition can be linked to reduced heme oxygenase activity, resulting in a decrease in anti-inflammatory growth.

Autoimmune diseases are often characterized by the inhibition or decrease in the function of tryptophan (Trp) and are connected to mitochondrial dysfunction. Tryptophan hydroxylase (Tph) plays a crucial role in promoting GTPase, and Rho-GTPases are essential for regulating T lymphocytes. The proline-rich structure is necessary for controlling T cell antigen receptor expression.

Both Valine (Val) and Isoleucine (Ile) are important for the production of Tyrosine kinases. Additionally, Threonine (Thr), Proline (Pro), and Cysteine (Cys) play roles in stabilizing Trp biosynthesis. This is necessary for mitochondrial OPA1 repair, as well as for the biosynthesis of serotonin and melatonin. This biosynthesis is further essential for the regulation of IL-17 production, which is necessary for activating GCs-beta synthesis via the NR4As pathway. This process is followed by the reactivation and stabilization of both B-arrestins (critical for myocardial function) and B-adrenergic signaling, oxytocin production, and Nrf2 biosynthesis. Oxytocin and Nrf2 play vital roles in adopting antioxidative stress, regulating anxiety, myocardial contractions, and activating both astrocytes and lymphocytes. These processes are mediated by Angiotensin II Receptor Type 2 (AT2) and Vascular Endothelial Growth Factor-A (VEGF-A) production, followed by heme oxygenase activity and anti-inflammatory growth, all of which are involved in the activation of normal T-cell functions.

Nrf2 dysfunction, which is connected to NR4As dysfunction, plays a significant role in the pathogenesis of Vascular Cognitive Impairment and Dementia (VCID).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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