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DPP4 valorphin activate NR4As pathway and OPA1 that protect from CoQ10 deficiency from OPA1 dysfunctions and from WMH

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Cases reports

1st _ The higher value of Plasma glial fibrillary acidic protein (GFAP) serum level, the higher value for National Institutional Health Stroke Scale (NIHSS) and correlated with stroke severity and extent of brain damage in ischemic stroke patients.

2nd_Primary coenzyme Q10 (CoQ10) deficiency usually associated with multisystem involvement, including neurologic manifestations such as fatal neonatal encephalopathy with hypotonia a late-onset slowly progressive multiple-system atrophy-like phenotype (neurodegeneration with autonomic failure and various combinations of parkinsonism.

3d_White Matter Hyperintensity "WMH" in Cerebral Small Vessel Disease is associated with diabetes, hypertension, decreasing in brain function and Coronary disease.

4th_Parkinson's-associated leucine-rich repeat kinase 2 (LRRK2)-p. R1441H impairs axonal autophagosomal transport.

5th _ Metastatic brain tumors represent 20% to 40% of all intracranial neoplasms are found most frequently in association with lung cancer (50%) and breast cancer (12%). Although brain metastases occur in <4% of all tumors of the gastrointestinal (GI) tract, the incidence of GI brain metastasis is rising in part due to more effective systemic treatments and prolonged survival of patients with GI cancer.

High light

leucine synthesis (activated by Glu/Gln circuit and isoleucine) necessary for mitochondrial OPA1 fusion which necessary for promoting NR4As pathway for activating each of B-adrenergic, oxytocin, and Nrf2 (mediated by reduction in pro-inflammatory molecules and improving IL17 productions) for improvement antioxidative stress and improving anti-inflammatory growth. Chronic hypertension result of Arg, Trp, and Proline deficiency which followed by tRNAs deficiency followed by.

Decreasing in CoQ10, where reduction in Pro, Tph, Leu & Tyr kinases will reflect increasing in Plasma Glial Fibrillary Acidic Protein "GFAP" (regulated by mTORC1 /S6K) that will be result of decreasing in blood flow to the brain, reduction in oxygen supply to the brain, and resulting of neuronal damage with decreasing in adopting Na and K channel and decreasing in anti-oxidative function.

White matter Hyperintensity in Cerebral Small Vessel Disease is due to Deficiency or inhibition in both of mTORC1 and Leucine Biosynthesis that reflect deficiency in Tyr and in Cys which involved in oxytocin composition and reflect decreasing or inhibition in Nrf2 production followed by decreasing in both Ang2AT2 and VEGF-A synthesis that reflect decreasing or inhibition in heme oxygenase and decreasing in anti-inflammatory growth.

-Autoimmune diseases are highly characterized by inhibition or decreasing in tryptophan (TGG) functions, and connected to mitochondrial dysfunction, where Tph has important role for promoting GTPase, that Rho-GTPases has important role to regulate T lymphocytes, where The proline-rich necessary to controls T cell antigen receptor expression.

Val and Île are imp for Tyr kinases production, while all of The, Pro, and Cys are having the role of stabilize Trp Biosynthesis which necessary for both mitochondrial OPA1 repairs, and for both serotonin and melatonin Biosynthesis followed by for running IL17 productions which necessary for activating GCsbeta synthesis via NR4As pathway followed by reactivating (stabilize and readopt) both of B-arrestins (which necessary for adopting myocardial functions) and B-adrenergic followed by oxytocin and Nrf2 Biosynthesis (where both are adopting antioxidative stress, anxiety adopting myocardial constrictions , and activate with adoption both astrocytes and lymphocytes functions mediated by Ang2-AT2 and VEGFA productions followed by both of heme oxygenase and anti-inflammatory growth "and processes which included activating normal T-cells functions"). Nrf2 dysfunction (which connected to NR4As

dysfunction plays a significant role in Vascular cognitive impairment and dementia (VCID) pathogenesis.

Keywords: 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

Deficiency in The, Tph (TGG), Glu, Gln (cycle) and Leucine due to increasing in the polarizability in mTORC1 and in S6K genes and subunits can cause disorders or deficiency in OPA1 repair that can be the result of Primary coenzyme Q10 (CoQ10) deficiency disease that characterized by damage in the inner mitochondrial membrane which is necessary for activating glucocorticoids receptor GCR Synthesis.

Mitochondrial damage or disorder can lead to accumulation in pro-inflammation which can cause mutations in subunit and protein.

The reduction in tryptophan, in Gly (which considered as the mirror of tryptophan triplets), and in Arg will cause reductions in Proline synthesis and consequently reductions in tRNAs, followed by reduction in mitochondrial OPA1 repairs and functions (due to reduction in GTPase), followed by reduction in IL17 synthesis and accumulation of proinflammatory molecules that followed by reduction in serotonin synthesis and in all of GC-beta, oxytocin, and Nrf2 production, that will be followed by decreasing in megakaryocytes proliferation and followed by reduction in haematopoiesis which associated to white matter hyperintensity .

Opioid receptors produce powerful analgesia that is effective in participating in the function of the immune cells, and effective for modulating acquired immune responses (include modulating lymphocytes functions). While tryptophan (and both leucine and Tyr kinases) is necessary to activate both serotonin and lymphocytes functions, the reduction in tryptophan, in Tyr, and in Leu will be result in decreasing in serotonin and in Nrf2 followed by reduction in platelets production, reduction in lymphocytes functions and reductions in hematopoietic cells functions that will be result of cerebral small vessel disease, and white matter hyperintensity. Serotonin (5-hydroxytryptamine; 5-HT) is a growth factor for hematopoietic cells promote the megakaryocytes (MKs) proliferation which produces platelets, where reduction in serotonin result of decreasing in megakaryocytes proliferation followed by reduction in haematopoiesis which associated with white matter microstructure. The availability of threonine amino acids is necessary for tryptophan synthesis by translations processes which included GTPase production (where Tph is the main source for regulating serotonin and melatonin synthesis and for GTPase synthesis):

Thr ¬¬>Tph + Cys (TGG, TGC, TGA) ¬>>melatonin ¬>> that at the same time both Thr & Tph are important to activate ATPase and GTPase production, where GTPase are playing important roles in mitochondrial OPA1 repair ¬>> where activating OPA1 repairs processes reflect activating synthase enzyme which activate the Interleukin-6 "IL6" for producing IL17 which considered as imp activator for Glucocorticoids-beta synthesis via NR4As pathway (and prevent accumulated cholesterol and pro-inflammatory cytokines), followed by activating B-arrestins and both of B-adrenergic and Nrf2 synthesis followed by activating Ang2-AT2 and VEGF-A which are necessary for activating proper anti-inflammatory growth. Glial Fibrillary Acidic Protein (GFAP) can be used as Neuroinflammation Biomarker in Acute Ischemic Stroke, that increasing in GFAP can increased gradually till will show increasing in neuronal damage.

Where the increasing in plasma glial fibrillary acidic protein (GFAP) can be adopted by activating serotonin followed by activating glucocorticoid-beta synthesis via NR4As pathway (mediated by IL17 synthesis). That the increasing in glial fibrillary acidic protein can be result of increasing in polarization due to increasing in +ve cations (related to cations-anions binding ratio) that will increase cations anions binding interactions which lead to decreasing in the free active anions functional activities (which anions represented Tyr kinases and both Leu and Trp which necessary for mitochondrial oxidative functions). The decreasing in the free -ve anions (increasing in cations binding functions) will lead to decreasing in IL17 production & reflect decreasing in GTPase productive functions, that will lead to decreasing in blood flow in brain, reducing oxygen supply in brain with increasing in accumulated cholesterol and proinflammatory cytokines, & then'll be the main for increasing in GFAP (which regulated by mTORC1 and S6K).

Tryptophan, tyrosine, and leucine are having important role in activating mitochondrial OPA1 repairs which activate the CoQ10 synthesis, while Trp "TGG" are basically necessary for activating Proline followed by activating both OPA1 function and activating tRNAs productions, followed by IL17 and activating NR4As pathway which included the activation of GCs-beta, oxitocin, and Nrf2 synthesis respectively. Cytotoxic edema results from unchecked accumulated or

uncompensated influx of cations mainly sodium Na+. Cytotoxic edema due to high of K & Na binding toxicity which is reason for coagulation & decreasing in ATPase & in GTPase that'll begin by decreasing in CoQ10 synthesis & increasing in Plasma glial fibrillary acidic protein...that will reflect decreasing in mineralocorticoid. The increasing in sodium and potassium (cations binding) related to decreasing in anions binding functions in biological molecules can be the result of decreasing in GTPase and in OPA1 function (where OPA1 function represent anions functions) that will be the result of Primary coenzyme Q10 (CoQ10) deficiency, and will be result of increasing in Plasma glial fibrillary acidic protein which elevated in cognitively normal older adults at risk of Alzheimer's disease .

The characteristics. Primary coenzyme Q10 (CoQ10) deficiency is usually associated with multisystem involvement, including neurologic manifestations such as fatal neonatal encephalopathy with hypoxia; a late-onset slowly progressive multiple-system atrophy-like phenotype (neurodegeneration with autonomic failure and various combinations of parkinsonism and cerebellar ataxia, and pyramidal dysfunction); and dystonia, spasticity, seizures, and intellectual disability. Autoimmune disease and skin inflammatory disorders are inflammatory diseases can begin due to increasing in k and Na cations binding toxicity, where their binding toxicity will reduce ATPase and GTPase functions (where both ATPase and GTPase represent -ve anions functions), that inflammatory diseases characterized by decreasing or Deficiency in proper GTPase productive functions followed by reduction in mitochondrial OPA1 function and deficiency in GCs-beta synthesis via NR4As pathway.

Glial Fibrillary Acidic Protein (GFAP) is important Neuroinflammation Biomarker where the increasing in GFAP will reflect OPA1 dysfunction and decreasing in CoQ10 that reflect increasing Neuroinflammation and reduction in NR4As productive pathway (upon reduction in anions functions which represent ATPase & GTPase & OPA1 function). The increasing in GFAP in Acute Ischemic Stroke can begin by increasing in cations bind to anions (with reduction in free anions -ve ratio functions) followed by increasing in energy stability and decreasing in tRNAs production (tRNAs synthesis are Proline dependent) and decreasing in GTPase which necessary for mitochondrial oxidative functions that will be the result of decreasing in IL17 production with increasing in pro-inflammation and in IL2 and may IL6, that will lead to decreasing in blood flow to the brain (due to decreasing in phosphorylation processes by ATPase and GTPase) , reducing oxygen supply to brain (due to decreasing in heme oxygenase which activated by Nrf2) , and will increase the neuronal damage.

Decreasing in Hemorphin "valorphin" reflect the decreasing of lymphocytes functions and loos of choline-containing phospholipids (CCPLs), where valorphin contains tyrosine necessary for kinases production that necessary for choline kinases synthesis, and necessary for activating all of tRNAs, serotonin, oxitocin and Nrf2 via NR4As pathway which are necessary for activating lymphocytes functions, and anti-inflammatory growth. The Nrf2 dysfunction which connected to NR4As dysfunction and connected to oxytocin dysfunction plays a significant role in Vascular cognitive impairment and dementia (VCID) pathogenesis.

1. Introduction

The Increasing in GFAP can be due to increasing in cations in some cellular tissues ¬¬> lead to increase in cations + anions interaction ¬¬> decreasing in free anions which can lead to in decreasing in mitochondrial OPA1 functions due decreasing in GTPase (which due to decreasing in Tph activity which followed by decreasing in Proline, where Proline synthesis regulated by tryptophan CCA <¬¬> Tph TGG). Also, Deficiency in Threonine (Thr) amino acids will reflect Deficiency in Tph amino acids (and reflect Deficiency in Pro & in Cys which necessary for oxitocin) that will be followed by Deficiency in Serotonin and in tRNAs synthesis (where tryptophan considered as important amino acids for generating energy that is important for activating GTPase synthesis which necessary for OPA1 repairs, which activate heart and brain functions) then followed by Deficiency In Nrf2 productions via NR4As pathway. Alsop Serotonin hormone (5-HT) is regulated by Tph that is a neurotransmitter used for regulatory cycles chains in human brain, that serotonin is involved in many physiological functions such as saving memories growth, sleep, pain, modulating mood and is the precursor to melatonin. The, depleted serotonin (or deficiency in serotonin synthesis due to Deficiency in Tph) causes cognitive impairments, with reports including deficits in verbal reasoning, episodic, and working memory, while conversely tryptophan (TGG) supplementation has positive effects on attention and memory (due to its role in activating GTPase and stimulating Glu/Gln circuit which necessary for leucine synthesis which activate brain functions). Also, The Tph is necessary for GTPase synthesis which is important for activating OPA1 repairs and consequently necessary for activating synthase and phospholipase functions which necessary for growth pathway, where decreasing in Tph TGG, and in Val GTP will reflect decreasing in GTPase followed by decreasing in OPA1 repair and followed by decreasing in tRNAs production, then followed by accumulation in inflammations including cholesterol.

2. Methods and results

Opioid receptors and their ligands produce powerful analgesia that is effective in pre-operative chronic pain managements. That Opioids not only participating in the function of the immune cells, but also in modulating and innate acquired immune responses [01]. Autoimmune disease and skin inflammatory disorders are inflammatory diseases that characterized by Deficiency in GTPase productive functions followed by deficiency in NR4As productive pathway. Autoimmune diseases characterized by decreasing in tryptophan, decreasing in both serotonin and

melatonin, followed by decreasing in OPA1 functions and and in T-cells maintenance. That it has been reported that: CD28, p21, MT1A, and MT1B mRNA were highly expressed in the presence of melatonin [2]. Melatonin regulated by serotonin synthesis and is highly effective in modulating T-cell activation and differentiation, especially for Th17 and Treg cells, and also memory T cells [3]. But it's imp to note that Proline rich protein control T-cells development, that Proline Rich 7 (Prr7) Develop the normal Function of T Cells [4].

So, melatonin regulates normal functions of T-cells and also Proline regulate the same normal functions of T-cells (that later I'll clarify that Trp is important for improving OPA1 repairs and tRNAs production that all together are necessary for activating normal T-cells functions via NR4As pathway). So, activating Proline by Trp will activate T-cells development (Trp TGG <¬¬> CCA Pro <¬> Gly GGT). Where, Glycine stimulates the production of serotonin [5]. So again, glycine plays so imp functions for regulating both serotonin and T-cells normal functions via Activating Trp followed by activating tRNAs production, then followed by activating IL17 productions which activate GCs-beta synthesis via NR4As pathway. And, melatonin plays an important role in T cell-mediated immune responses against cancer, infections, and the development of many autoimmune diseases [6].

So, all of glycine, tryptophan, Proline and then serotonin are playing so important functions in regulating T cell-mediated immune responses against cancer, infections, and the immune development of many autoimmune diseases. That we can consider and describe glycine as a mirror of tryptophan triplets (Trp TGG <¬> GGT Gly) that can ensure and stabilize Tph functions. Also, threonine is so necessary for tryptophan TGG synthesis which necessary for serotonin synthesis ACC "Thr" <¬¬>TGG "Trp" That the Deficiency in Thr, and in the essential Tph (TGG) (may the deficiency due to increasing in polarizability) can reflect Deficiency in serotonin and can reflect decreasing in melatonin and in modulating T-cell activation and differentiation, and can cause decreasing in GTPase followed by decreasing in NR4As pathway (with accumulation in pro-inflammation) that will be main reason for causing disorders and deficiency in OPA1 repair and will cause damage in the inner mitochondrial membrane which cause decreasing in CoQ10 production, and decreasing in tRNAs (regulated by both Trp and Pro).

Notice, as a result of the accumulation of pro-inflammatory molecules and as the result of increasing and decreasing in the generation of energy from phosphorylation, the mutated genes, subunits, and molecules will be formed that can be the result of mitochondrial disorder. The role of Trp "TGG" regulated by Thr "ACC", and Proline in treatment autoimmune disease Firstly, the main composition of valorphin (known as VV-hemorphin-5) is nine essential amino acids: Leu_Val_Val_Tyr, _Pro _Pro _Thr_ Gln_& Arg Threonine amino acids are the main source for tryptophan (Tph) synthesis (which play important role for activating mitochondrial OPA1 function, and activating both serotonin and melatonin synthesis) through translations processes Thr ACC ¬>Tph (TGG) ¬>>melatonin ¬>> activate OPA1 ¬¬>activate NR4As productive pathway, that at the same time both Thr & Tph has important role to activate GTPase which necessary to activate mitochondrial OPA1 repair which stimulate Interleukin-2, and activate IL17 productions which responsible for activating glucocorticoid beta synthesis via NR4As pathway.

Activating OPA1 repairs (regulated by Tyr, Pro, Leu, and Trp) reflect proper synthase functional activities which will activate the Interleukin-17 "IL17" upon synthase function which known as strong activator for GCs-beta productions ¬>> followed by activating B-arrestins and both B-adrenergic and both oxitocin and Nrf2 synthesis. Threonine is necessary for tryptophan TGG synthesis which necessary for serotonin synthesis and Proline production ACC "Thr" <¬¬>TGG "Trp". And, "Trp" TGG <¬activate¬> 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].

So, tryptophan and serotonin have a protective Effects in autoimmune disease While, Arginine activate Proline synthesis (just Arg necessary for activating tRNAs production but cannot promote Serotonin and NR4As pathway) "Arg" CGG <¬¬> CCG " Proline" (that Arg activate Proline like tryptophan but through different triple codons that cannot activate directly the NR4As pathway and astrocytes functions but can directly activate tRNAs productive functions). That L-Arg also acts as an inflammatory modulator in various pathologies. Arginase, being a key enzyme is involved in ammonia detoxification and regulates T cell functions [8].

My note (in previous work) that : Arg only activate Pro functions necessary for tRNAs production (which positively needed for treating malaria and preventing accumulation of Val, Leu, in CVD patient), while Tryptophan actually activate Proline like Argenine but increasingly and positively activate serotonin and melatonin which necessary for activating lymphocytes mediated by IL17 productions which by itself promote GCs-beta regulated by synthase (which activated firstly by Trp and Pro) via NR4A2 pathway followed by promoting oxytocin and Nrf2 production via the same pathways the will activate Ang2-AT2 and VEGF-A synthesis for heme oxygenase and activating anti-inflammatory, so it may indicate to me that only Trp can activate all of 1st serotonin, 2nd activate Pro functions, 3d activate OPA1 function, 4th activate NR4As productive pathway, while Arg doesn't have the Role of activating both of serotonin and NR4As productive pathway.

The branched amino acids are necessary for brain functions including Leucine which is so necessary for activating enkephalin tissue through activating Leu pentapeptides synthesis, and necessary for Nrf2 synthesis and for brain function. That it's reported that Branched-Chain Amino Acids (including Tyr, Pro, Leu, Val, Île) Enhance the Cognitive Recovery of Patients with Severe Traumatic Brain [9]. Leucine necessary for Nrf2 synthesis and cardio-protection Leucine appear to induce cardio-protection by promoting mitochondrial function via mTOR and

OPA-1 signalling [10]. And it has been reported that leucine supplementation improves glucose homeostasis [11]. And it's reported that, Nrf2 and its target genes are key components to maintain cellular redox homeostasis by attenuating oxidative stress-associated pathological processes [12].

Leucine is the main regulator amino acid for Nrf2 functions, that activated by Gln /Glu functions which are having the role of promoting hepatic glycose Homeostasis. That as Nrf2 activated as will promote Ang2-AT2 and VEGF-A productions which adopt heart constriction, activate and heme oxygenase. (regulated by Nrf2) and activate anti-inflammatory growth. Nrf2 biosynthesis activated via NR4As productive pathway which mainly Activated by serotonin Biosynthesis (which regulated by tryptophan functions) which followed by activating mitochondrial OPA1 function, and IL17 productions which necessary for activating glucocorticoids-beta synthesis, followed by mineralocorticoid and B-arrestins synthesis, then followed by oxitocin and Nrf2 production respectively. Primary coenzyme Q10 (CoQ10) deficiency due to decreasing in Leu & GTPase which can be due to decreasing in the free anion's functions. Most of Tumorigenic tissue cancers are associated with increasing in cations activities and increasing in polarizability with decreasing in anions functions with decreasing in GTPase productive functions. And most of virus's activities increased in environment of increasing in cations activities with increasing in polarization. Also sever stroke is associated with high thermal stability and increasing in polarization that molecules will reach ideal that will have inability to activate anions functions in cellular processes, that will not be able to improve inflammatory molecules accumulation and K and Na binding toxicity.

Biophysical studies indicated that Primary coenzyme Q10 (CoQ10) deficiency can be due to increasing in the polarization in mTORC1, in S6K1, and in serotonin molecules that can cause mutation or disorder in their Molecular subunits and cause inhibition in GTPase production through holding the free anions functions and cause decreasing in anions activities till deficiency in Tph, Glu, Leu,... and GTPase functions and consequently will inhibit coenzyme Q10 (CoQ10) productions. Decreasing or absence of anions functions reflect increasing in cations functions related to anions that can hold purines and pyrimidine functions and can decrease GTPase production and will be the result of mitochondrial OPA1 dysfunction. The Negative anion gap and elevated osmolar gap due to 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].

The Polarization increases with the increasing in cationic size and decreasing in anionic size (which causes enourmous distortion). Thus, the thermal stability and lattice energy increase with increasing cationic size. That in brief as the polarization increase as will show increasing in thermal stability with larger cations size and lower anions size (the decreasing in anions functions such as oxidative functions by OPA1, ATPase and GTPase). Where, the larger the anions size (decreasing in thermal stability), the weaker the cation-anion interaction [15]. Means the larger anions size (high anions functions) will show decreasing in cation-anion interaction and increasing in anions functions with increasing in proper cellular functions , but the larger cations size (larger Na, K, Ca binding) will show more cations-anions interaction with decreasing in free anions functions (OPA1 function, serotonin,… and Nrf2 functions) associated with high energy stability (as in tumor content has high energy stability). That 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.

The same in Plasma that as cations binding increases as the free anions functional activities decrease and their thermal stability will increase that the respiratory oxidative functions in Plasma will decrease with resistance to thermal degradations. Also, Divalent cations are involved in the pathogenesis of HIV-1 as well as the ability of the host to control HIV-1 replication [16]. That as Divalent cations increased with binding to Leu, Tph, Tyr… etc as the function of Trp, leucine and tyrosine kinases will be reduced and will be followed by increasing in pathogenic symptoms and increasing OPA1 dysfunctions.

So we can consider sever mitochondrial disorders, damages, and dysfunction can caused when polarization increases due to increasing yn the binding of cations with Leu Tyr, Tph and Proline, that will inhibit or decrease the Leu, Tyr, and GTPase functions, also will be the result of decreasing in tRNAs production, which can be result of the mutation in mitochondria membranes, that will show inhibition OPA1 repair (which is a GTPase dependents) , that we've to ensure there are an optimal thermal stability with proper anions percentages in active subunits through getting rid of Na and K binding (which can show increasing in cations functions with increasing in polarizability) by mineralocorticoid functions (note mineralocorticoid regulated by glucocorticoids-beta are necessary to protect heart from K and Na binding toxicity that will migrate K and Na binding molecules molecules to be discarded by kidney). The Mineralocorticoid (regulated by GCs-beta via NR4As pathway) are having the role to decrease polarization in Myocardial and epicardium layers that protect heart and brain function from binding toxicity and from accumulated subunits, and from Molecular disorder growth. The increasing in sodium binding site (which represents cations binding activities) in mTOR S6K can affect on decreasing in GTPase and in OPA1 repairs and can cause damaged astrocytes. That 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 meaning of reductions in local dynamics is the reduction in cellular functions including reduction in Myocardial functions which due to increasing in Na binding with reduction in anions functions that will cause OPA1 dysfunctions, Pro and Leu dysfunction, reduction in Tyr, and reductions in tRNAs productions (regulated by Trp and by Arg). The Cytotoxic edema results from unchecked or uncompensated influx of cations, mainly Na+, through cation channels [18].

So, binding Na+ to serotonin can reduce its transportation and reduce local dynamic activities, that K is playing the same activity as Na+ that upon increasing in their binding sites in genes will

be result of decreasing in surrounding cellular activities , and result of increasing in plasma toxicity (increasing in polarities), and damage in neuronal cells functions that can be the result of increasing In Plasma glial fibrillary acidic protein, that toxicity can be done in neuronal tissues while GFAP can still promoted and regulated by mTORC1 /S6K. Also , decreasing in oxytocin can reflect increasing in sodium and potassium-cations bind to purines and to pyrimidine in Leu, Trp, Tyr and Cys triplets, where increasing in sodium and in potassium binding will accelerate and promote antagonist characters (note : antagonist has higher energy stability) while increasing in free anions promote agonist functions, that it has been reported that antagonists promote sodium binding while agonists attenuate sodium binding [19].

The increasing in sodium binding (related to anions binding functions) will reduce surrounding passive transport and migration (reflect reduction in Proline and reduction in tRNAs). That the increase in both Na and K which their binding considered as cations +ve binding will reduce the free anions binding function that will lead to increasing in acidic binding activities that will reduce most of brain function (reduction in tRNAs synthesis), reduce heart function and reduce cellular activities, while can lead to increasing or accumulation in Plasma glial fibrillary acidic protein (regulated by mTORC1 /S6K) which considered as increase the risk of Alzheimer's disease.

Where, Glial Fibrillary Acidic Protein (GFAP) can be used as Neuroinflammation Biomarker (where, the increasing in GFAP can reflect increasing Neuroinflammation due to reduction in NR4As productive pathway upon reduction in anions functions and increasing in GFAP) in Acute Ischemic Stroke, that increasing in GFAP can be started to increase gradually till will show increasing in neuronal damage. It's clear that increasing in plasma glial fibrillary acidic protein (GFAP) can reflect increasing in polarization due to increasing in cations bind with tryptophan, with Leu, with Pro that will cause reductions in serotonin and cause in OPA1 repair and reduction in tRNAs and reductions in activating IL17 and in NR4As pathway). that will cause increasing in cations anions binding & interactions that will be the result of decreasing in the free active anions functional activities which represented mitochondrial oxidative functions, increasing in pro-inflammation and in IL2, that will lead to decreasing in blood flow to the brain, with reduction in oxygen supply to brain, then'll cause neuronal damage.

The Increasing in GFAP is due to increasing in cations bind to the anions necessary for activating GFAP production ¬¬> (increasing in polarization) ¬¬¬> increasing in toxicity and mutated inactive subunits (which can characterize by high thermal stability) ¬¬> decreasing in mitochondrial OPA1 function¬¬¬> increasing in astrocyte cells damage. Cysteine and Tyrosine improved by Thr and Île respectively for activating Oxytocin which improves cardiac function The arrhythmia and stroke can be due to increasing in Na and K binding (+ve cations binding) with severe decreasing in Arg, in leucine and in Trp functions, where Arg and Trp are necessary to activate Proline which necessary for tRNAs production, and necessary to activate OPA1 mitochondrial function , while Trp by itself necessary to activate both serotonin, and activate Proline production which promote tRNAs synthesis and promote mitochondrial function that pro-inflammatory cytokines will be reduced and the IL17 productions will be activated followed by activating GC-beta via NR4As pathway which included the activation of oxitocin and Nrf2 synthesis followed by activating heart, and immune functions. Serotonin and dopamine are connected to each other in their functions and Biosynthesis, that inhibition in serotonin Biosynthesis will be associated with inhibition in dopamine. that it is reported that Activation, and recycling of the serotonin 2A receptor by dopamine [20]. The tryptophan (Trp or Tph) are necessary for both serotonin and dopamine, while leucine activation will promote Nrf2 functions (mediated by activating oxitocin Biosynthesis) and {which can adopt the percentage Glial Fibrillary Acidic Protein (GFAP)}.

That, valorphin composed of nine important amino acids include' Thr, cysteine, Proline and Tyrosine, that all of them are stabilize each other for stabilizing GTPase synthesis, for stabilizing tRNAs production, for stabilizing Thr phosphorylation processes, and for stabilize both of Trp and oxitocin Biosynthesis:

Gly GGT <¬¬> Pro CCA And, Thr ACC <¬¬> Trp TGG And, Thr ACC <¬¬> Gly GGT Also, ACT "Thr" <¬¬>TGA "Cys" And, ACA "Thr" <¬¬> TGT 'Cys', ACG "Thr"<¬¬> TGC 'Cys', and Thr ACG important for Cys TGC synthesis,
Where, Val and ile are necessary for Tyr synthesis: Val ATG <¬>TAC Tyr, ÎLe ATA <¬>TAT Tyr.

So, Val and Île are imp for Tyr kinases production, where, Thr, Pro, Cys as mentioned previously having the role of stabilize Trp Biosynthesis which necessary for both OPA1 repairs and for both serotonin and melatonin biosynthesis for running IL17 productions followed by activating GCs-beta synthesis via NR4As pathway followed by reactivating (stabilize and readopt) both of B-arrestins (which necessary for adopting myocardial functions) and B-adrenergic followed by oxitocin and Nrf2 Biosynthesis (where both are adopting antioxidative stress, adopting myocardial constrictions , and activate with adoption both astrocytes and lymphocytes functions mediated by Ang2-AT2 and VEGF-A productions followed by both of heme oxygenase and anti-inflammatory growth "and processes which included activating normal Tcells functions").

Cys which included in oxytocin has the necessity for contributing in activating Trp synthesis (through activating Thr phosphorylation which will reactivate Trp synthesis : ACC "Thr" <¬¬>TGG "Trp) which imp for serotonin and melatonin production, and for re-activate OPA1 functions through activating GTPase production by which activate IL17 productions that necessary for activating GC-beta via NR4A2 pathway (regulated by synthase) followed by B-arrestins, B-adrenergic, oxytocin then Nrf2 respectively .

Tyr (TAT and TAC) are activated by Glu /Gln cycle and by methionine functions (where, methionine is necessary in brain function through activating met pentapeptides in enkephalin tissue with the formation of Leu pentapeptides for protecting

the stability of antioxidative function in brain and protect the lymphocytes activities).

That Nrf2 activator upregulated oxytocin mRNA expression and might be able to upregulate oxytocin receptor expression by interacting with MAFF (basic leucine zipper transcription factor) [21]. So, oxytocin mRNA is activating MAFF and activated by MAFF for reactivating oxytocin receptor expression which reactivate Nrf2 expressions for adopting antioxidative functions. The B-adrenergic which important for promoting oxytocin and Nrf2 expressions in NR4As productive pathway is necessary for promoting oxytocin expression which is important for protecting brain function and preventing the increasing in Glial Fibrillary Acidic Protein (GFAP).

That, activating oxytocin Biosynthesis will activate heart and brain functions mediated by Nrf2 production (via NR4As pathway), that it is reported that Oxytocin production appears to prevent stroke [22]. Through activating Leu functions by activating Glu /Gln cycles, and Thr phosphorylation, the Nrf2 will be activated via NR4As pathway followed by adopting antioxidative stress and activating heme oxygenase followed by Ang2-AT2 synthesis and VEGF-A synthesis which activate anti-inflammatory growth. The tyrosine can be activated by isoleucine and by Val which involved in valorphin composition that it's important process for protecting Tyr functional stability: ATA île <¬> TAT Tyr, And GTA Val <¬> TAC Tyr. While Arg in valorphin are necessary for activating Proline synthesis which necessary for activating tRNAs production which prevent the accumulation of Leu, Île, and Val rich protein (in CVD risk).

And oxytocin treatment (which regulated by B-arrestins, followed by B-adrenergic) improves cardiac function , reduces apoptosis and inflammation, that has important roles for re-activate Thr phosphorylation and Tph synthesis which promote Serotonin and melatonin functions mediated by activating OPA1 repairs functions which followed by reactivating IL17 productions which promote GCbeta production via NR4As pathway followed by activating B-adrenergic, and stabilize oxitocin and Nrf2 functions followed by Ang2-AT2 and VEGF-A productions which necessary for anti-inflammatory processes. That Treatment with oxytocin reduces the expression of pro-inflammatory cytokines [23]. Activating Oxytocin productions can be considered as essential to prevent Glial Fibrillary Acidic Protein (GFAP), Attenuate Early Brain Injury, and improve brain functions and neuro-behavioural function (in case of reduction in +ve binding cations toxicity such as Na and K binding toxicity).

Also, cysteine is important for activating brain functions, and help to improve chronic respiratory conditions fertility, and improve brain functions. That it has been reported that: l-cysteine treatment significantly ameliorated brain edema, improved neurobehavioral function, and attenuated neuronal cell death in the PFC; these effects were associated with a decrease in the Bax/Bcl-2 ratio [24]. So, cysteine is necessary for improving neuro-behavioural function, and attenuated neuronal cell death through activating Nrf2 synthesis (via NR4As pathway) followed by Ang2-AT2 and VEGF-A necessary for activating anti-inflammatory growth. Increasing in both K and Na binding will restrict the cysteine and tyrosine functions (cause brain edema), followed by restriction to the B-adrenergic and Nrf2 productive functions that can be the result of increasing in GFAP (which regulated by mTORC1 /S6K pathway functions), and then reduction in both of heart and brain function. Where increasing in B-adrenergic activities (more than cations binding percentage) will restrict cations binding through activating both oxytocin and Nrf2 which activate brain functions and cardiovascular functions. That it has been reported that: beta-adrenergic receptor function does accompany sympathetic activation during sodium restriction and converting enzyme inhibition [25].

And, the sodium restriction and β2-adrenergic receptor polymorphism modulate cardiovascular function in humans [26]. Also, 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]. Ser/Thr phosphorylation necessary for Tph, Cys and Tyr kinases synthesis for oxytocin synthesis to prevent mitochondrial dysfunction and the increasing in GFAP Ser /Thr phosphorylation pathway are the main key for Tph and Cys synthesis, where Tph are necessary for serotonin synthesis followed by melatonin synthesis, but Tyr and Cys are necessary for oxytocin synthesis followed by promoting Nrf2 synthesis which necessary for heme oxygenase and for activating anti-inflammatory processes and growth mediated by Ang2-AT2 and VEGF-A productions:

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

As Tryptophan Tph formed as activate both melatonin and will activate IL17 productions followed by GCs-beta, B-arrestins, and B-Adrenergic productions, then followed by oxytocin for Nrf2 synthesis and Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth and processes, (where previous pathway will prevent mitochondrial dysfunction and prevent increasing in GFAP). Ser /Thr phosphorylation has strong roles in activating mitochondrial OPA1 function through Tph, Cys, Tyr productions which promote Serotonin, oxitocin, and Nrf2 productions respectively, mediated by OPA1 and IL17 production which activate GCs-beta via NR4A2 pathway, that it has been reported that data define a role for serine in supporting mitochondrial function and cell proliferation through ceramide metabolism [28]. And, Mitochondrial ClpP serine protease-biological function and emerging target for cancer therapy [29]. Also, it is reported that mitochondrial matrix serine/threonine protein phosphatase regulates the mitochondria permeability transition pore and is essential for cellular survival and development [30]. So previous studies indicated the critical roles of both Serine and Threonine amino acids for improving Trp, Cys, Tyr Biosynthesis for improving mitochondrial OPA1 functions (where Trp has important functions for improving OPA1 function and tRNAs production through activating Proline synthesis), that Thr/ Ser phosphorylation have also their responsibility for mTORC1 productions which improve astrocytes survival, and GTPase

production through modulating Tph, Cys and tyrosine synthesis followed by Leu productions. Where the Deficiency in Ser /Thr phosphorylation followed by reduction in Tph, Tyr, Leu, amino acids that will be result of Deficiency in CoQ10 synthesis and reflect deficiency in lipid metabolism with accumulation of cholesterol and increasing in GFAP.

The tyrosine and Leucine are so imp for mitochondrial OPA1 repairs, where it has been reported that, DRP1 phosphorylation at Ser616 or dephosphorylation at Ser 637 regulates its translocation to mitochondria and mitochondria fission36. And Inhibition of DRP1 and scavenging mtROS attenuated LPS-induced VE-cadherin Y658 phosphorylation and endothelial permeability [31]. The tyrosine is playing important role in leucine synthesis, While Val imp for tyrosine synthesis, and tyrosine necessary for stabilizing Leucine productive functions:

GTA Val <¬¬> TAC Tyr TAT Tyr <¬¬> ATA île And, "Tyr"<¬¬>activate OPA1 function ¬> activate Leucine synthesis. {That Again Tyrosine, Leu, Arg, and valine are essential in valorphin composition which contain nine essential amino acids; Leu_Val_Val_Tyr, _Pro _Pro _Thr_ Gln_& Arg. So as tyrosine, Leu (and Pro essential for activating OPA1 and tRNAs will be discuss later) are so necessary for mitochondrial function as valorphin (VV-hemorphin-5) is so necessary for activating mitochondrial OPA1 functions and astrocytes survival as well through activating serotonin synthesis followed by activating NR4As pathway productive functions. Tph "TGG", Tyr, and Leucine are having important role in activating mitochondrial function and CoQ10 biosynthesis Firstly all of Tph "TGG", Tyr, and Leucine are necessary for activating mitochondrial function and for adopting antioxidative functions, where availability of sufficient of those three amino acids will prevent accumulated inflammatory molecules through activating synthase function and activating IL17 synthesis which activate GCs-beta synthesis. The Tph "TGG" synthesis promoted by threonine "ACC" that is upon ATPase will utilize GTPase which activate mitochondrial OPA1 fusion which prevent the accumulation of inflammation. That, the Kyn pathway of Trp metabolism is activated due to inflammation and stress, further skewing immune balance [32]. Tryptophan is a precursor for the biosynthesis of co-enzymes and neuromodulators, such as NAD/NADP(H), kynurenic acid, melatonin and serotonin. [33] And, stimulating the TRP-NAD+ pathway with NAD+ precursors improve hepatic mitochondrial and overall metabolic function through SIRT1 modulation [34].

So, it's clear that tryptophan necessary for activating mitochondrial functions through activating GTPase which is necessary for mitochondrial OPA1 repairs and is activated by Ser /Thr phosphorylation. Where, Mitochondrial fusion is regulated by GTPase-dependent proteins, including MFN1, MFN2, and OPA1 [35]. That also leucine has the role of activating mitochondrial fusion. Where has been reported that Leucine imparts cardioprotective effects by enhancing mTOR activity and mitochondrial fusion in a myocardial ischemia/reperfusion injury [36]. And it's necessary to note that both tyrosine and leucine are necessary for building the promoters in active genes and subunits "Tyr _ TAT, TAC Leu _TTA, TTC. For activating mitochondrial repair and functions which activate CoQ10 synthesis. That 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, and reduced tumor growth [37]. And Studies approved the necessity of Tyr with leucine for activating mitochondrial repairs "fusion" and functions, that it has been approved that Stable c-Src activation decreased the distance between the ER and outer mitochondrial membrane (OMM) [38].

Also, the GTPase synthesis (promoted and regulated by Tyr kinases functions) necessary for fusion of the outer mitochondrial membrane. That it's approved: a major component of the tethering structures between the two organelles is mitofusin 2 (Mfn2), a GTPase associated with fusion of the outer mitochondrial membrane [39]. So, tryptophan, tyrosine, and leucine are having important functions for activating mitochondrial function and CoQ10 synthesis. The importance of tyrosine in activating mitochondrial repair & functions boils down to activate CoQ10 synthesis regulated by coenzyme B6 which necessary for converting Tyr to p-hydroxybenzoic acid. The deficiency of the coenzyme B6 (which necessary for converting tyrosine to p-hydroxybenzoic acid) can cause dysfunctions, prior to the formation of vitamin Q10, to DNA [40]. Also, Human cells synthesize CoQ 10 from the Tyrosine, through eight steps which require adequate levels of vitamins [41].

And, it has been reported that: phosphorylation the protection against apoptosis and the antioxidant capacity of OXT may contribute to the observed increase in cell proliferation, and Oxytocin and OXTR appear to be fundamental for cell growth and viability of glial cells [42]. Note that: tyrosine TAT <¬¬> ATA isoleucine "Île", while Tyr TAC <¬¬>ATG _Methionine upon translation processes, where Tyr synthesis is so important for manufacturing active promotors that controls the functions of genes activities and directs them to promote their own functions for their immune system. The presence and availability of Tyr with Leu (Tyr _ TAT, TAC Leu _TTA, TTC) will form so important active promoters for their active subunits that will have the role of activating mitochondrial OPA1 fusion and repairs and will have the roles of activating their signals migration through tRNAs synthesis (where tRNAs regulated by Trp, Pro, & Arg functions). As tyrosine kinases promote CoQ10 as the decreasing in phosphorylation (by Decreasing in Tyr kinases) will reflect decreasing in CoQ10 production and will reflect decreasing in adopting sodium and potassium channel, that will lead to increasing in Na+ and K+ binding toxicity. That, it has been reported that Severe CoQ10 deficiency is associated with marked decrease of cellular ATP content [43]. And the sever decreasing in CoQ10 is mainly due to fail in reactivating OPA1 repairs and functions, where Trp "TGG" is so necessary for reactivating GTPase synthesis which necessary for activating OPA1 repairs followed by reactivating IL17 and NR4As pathway. Tyrosine kinases & leucine necessary for phosphorylation for OPA1 repairs and IL17 production for activating NR4As

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

Note the: opioid accompanied with various side effects due to its first interfere with cellular processes for Organizing and rearranging its necessary amino acids, which are essential for immunity, that is why it was mentioned that it certainly has the ability to reorganize the immune response and reconfigure the important receptors which important cell running cellular processes.

Firstly, morphine and the endogenous opioid peptides, including β-endorphin and dynorphin peptides, modulate the function of lymphocytes (which included modulating and innate acquired immune responses) [45]. Note that the Activation of tyrosine kinase (where tyrosine included in valorphin) are necessary for creating the autophosphorylation" which is mechanistically coupled to the recruitment of adaptor proteins which necessary to adopt, initiate, and activate immune. That it's approved the activation of tyrosine kinases activity results in "autophosphorylation" which is mechanistically coupled to the recruitment of adaptor proteins and conjugation of ubiquitin to RTKs [46]. And its approved Na/K-ATPase-Mediated Signal Transduction (autophosphorylation) which regulated and promoted by Src family kinases which are membrane-associated non-receptor tyrosine kinases, play essential role in the signal transduction pathways provoked by many extracellular stimuli [47]. And again, Tyrosine kinases (note tyrosine with leucine necessary for re-activating OPA1 proper functions) has necessary role for activating mitochondrial function (which necessary to adopt proper immune responses) through activating protein phosphorylation and dephosphorylation [48]. Where, Src-Tyrosine kinases considered the major agents in mitochondrial tyrosine phosphorylation [49]. And so, it's clear that the modulation of thymocytes and mature lymphocytes are promoted by tyrosine kinases through activating dopamine and serotonin followed by IL17 which necessary for glucocorticoid beta synthesis via NR4As pathway started by activating OPA1 function. That it has been reported that: 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].

And, Non-receptor-tyrosine Kinases Integrate Fast Glucocorticoid Signaling (promote fast IL17 synthesis for GCs-beta synthesis via NR4As pathway) in Hippocampal Neurons [51]. And, the promotion of wound repair by coenzyme Q10: PI3K/Akt signal activation [52]. The promotion of wound repair is running by coenzyme Q10 which activated by PI3K/Akt and regulated by mitochondrial OPA1 proper functions. Also, CoQ10 inhibits platelet integrin αIIbβ3 outside-in signalling, where That inhibitory effects are mainly mediated by upregulating cAMP/PKA pathway [53]. Thus, Src kinases (with availability of leucine functions) are necessary for activating mitochondrial OPA1 functions which necessary for activating CoQ10, followed by activating both serotonin and IL17 which necessary for activating glucocorticoid-beta Via NR4As pathway followed by activating oxytocin and Nrf2 production which necessary for astrocytes survival.

White matter hyperintensities (WMHs) reverse decreasing in tyrosine kinases and leucine that reflect decreasing in OPA1 functions, decreasing in cerebral blood flow, and decreasing in Nrf2 synthesis. White matter hyperintensities (WMHs) of presumed vascular origin are neuroimaging feature of small vessel disease (SVD), a disorder of the cerebral micro vessels. WMHs are visible on MRI as hyperintense lesions on T2-weighted and hypointense on T1-weighted sequences. Cerebral small vessel disease (SVD) is a major contributor to stroke and dementia, characterized by white matter hyperintensities (WMH) on neuroimaging. WMH are associated with reduced cerebral blood flow (CBF) [54]. Inhibition of the JAK2V617F kinase with a small molecule inhibitor leads to inhibition of proliferation of hematopoietic cells [55].

Note that Reduction in Tyr kinases synthesis revers decreasing in both Valine and isoleucine:
ATA île <¬> TAT Tyr GTA Val <¬> TAC Tyr
And: Gln /CAG<¬¬> Leu /GTC

And the reduction in Gln reverse reduction in Leu and consequently in Nrf2 functions. Where HO-1 is important for the proper function of hematopoietic stem cells "HSC" such self-renewal. That HO-1 expression in HSPC in steady-state levels is low, but increases in hematopoietic stress, such as haematopoiesis [56].

The Nrf2 transcription factor promotes the expression of HO-1 (if originated from Trp and Proline function) to remove excess of heme and protect against oxidative stress (adopt antioxidative functions) [57]. Also, the activation of D2-type dopamine receptors on HSCs and LSK cells can promote hematopoietic Reconstitution [58]. So, activation of D2-type dopamine receptors (which connected to and depend on tryptophan functions and GTPase) necessary to promote hematopoietic Reconstitution, mediated by oxitocin and Nrf2 production followed by Ang2-AT2 and VEGF-A productions which promote heme oxygenase and anti-inflammatory growth.

Where, reduction in tryptophan, in Tyr, and in Leu result in decreasing in serotonin and in both OPA1 functions and Nrf2 followed by reduction in platelets production. That serotonin (5-hydroxytryptamine; 5-HT) is a growth factor for hematopoietic cells promote the megakaryocytes (MKs) proliferation (which produces platelets) [59]. And, Users of atypical antidepressants, selective serotonin reuptake inhibitors, and depressed people displayed markers of cerebral small vessel disease. [60].

So, it's prohibiting to use atypical antidepressants, selective serotonin reuptake inhibitors which is a wrong way for activating white matter hyperintensity survival and later stroke. Where, reduction in serotonin result of decreasing in megakaryocytes proliferation followed by reduction in haematopoiesis and

associated to white matter hyperintensity That it's reported: The While Clonal haematopoiesis with DNMT3A mutation is associated with lower white matter hyperintensity volume [61]. And, Hematopoietic stem cell transplant, if performed early in metachromatic leukodystrophy, can not only stabilize but even improve cerebral white matter abnormalities [62]. So now it's necessary to declare that activating both serotonin and dopamine via Activating Tyr kinases, Trp, will promote melatonin production that will activate hematopoietic cells mediated by the expression both of Oxitocin and Nrf2 which for promoting heme oxygenase and Ang2-AT2 and VEGF-A necessary for activating hematopoietic cells functions and anti-inflammatory growth via NR4As pathway.

That dopamine receptors on HSCs and LSK cells can reflect the IL17 productions which activate glucocorticoid-beta Via NR4As pathway followed by activating B-adrenergic and oxitocin which followed by Nrf2 production which necessary for activating heme oxygenase and promote both Ang2-AT2 and VEGF-A productions which necessary for hematopoietic Reconstitution. That the inhibition in activating NR4As pathway by inhibition in both serotonin and dopamine will inhibit the hematopoietic cells functions and will reflect Inhibition or decreasing in Nrf2 production and dysfunction in the modulation of antioxidative stress and anti-inflammatory processes that will be result of the survival of white matter hyperintensity. Also, reduction in serotonin result of decreasing in megakaryocytes proliferation followed by reduction in haematopoiesis which associated with white matter microstructure affects processing speed in cerebral small vessel disease [63]. So, activating mitochondrial OPA1 function via Activating Trp and Proline (which contained in valorphin composition) has strong roles to activate lymphocytes proper functions and protect from Cerebral Small Vessel Disease, and protect heart and blood vessels from immunometabolism injuries, through activating in serotonin and megakaryocytes proliferation mediated by IL17 productions which activate GCs-beta productions via NR4As pathway followed by oxitocin and Nrf2 production necessary for heme oxygenase and for activating Ang2-AT2 and VEGF-A necessary for anti-inflammatory growth and activate lymphocytes functions.

The threonine (which activate Tph synthesis), Tyr and Leu are so important for OPA1 repairs and functions and necessary for serotonin synthesis which boost dopamine production which followed by activating NR4As pathway which regulate B-Adrenergic productions followed by activating oxytocin synthesis which regulated by Cysteine and Tyrosine which also important for improving Nrf2 synthesis. where decreasing in Cysteine will be result of decreasing in oxytocin and decreasing in Nrf2 and will lead to Alzheimer's disease and will be followed by in both Ang2-AT2 and VEGF-A which will. WMH which associated with reduction in cerebral blood flow (depending on the percentage of decreasing in Cysteine, Tyr and in Leucine followed by decreasing in NR4As productive pathway). Also, Deficiency of Nrf2 (which reflect serotonin deficiency) exacerbates white matter damage and microglia/macrophage levels in a mouse model of vascular cognitive impairment [64].

And, activating Nrf2 induce antioxidative and enhance red blood cells (RBC) started by Activating NR4As pathway and mediated by activating B-adrenergic and oxitocin which protect Nrf2 functional stability which promote heme oxygenase and anti-inflammatory growth which includes blood cells (RBC) phagocytosis which occurs by many tissues as bone marrow, spleen and by astrocytes functions [65].

And, The Nrf2 dysfunction plays a significant role in VCID pathogenesis [66]. So, activating oxytocin followed by Nrf2 via NR4As pathway (and firstly promoted by tryptophan functions which promote both serotonin and Proline) will up-regulate phagocytosis-mediating scavenger receptor CD36, that will protect from white Matter Hyperintensity in Cerebral Small Vessel Disease, and will mitigate the Vascular cognitive impairment and dementia (VCID) process. Serotonin (regulated by Src functions and by both Leucine and tryptophan) act as an inhibitor of the increasing glial fibrillary acidic protein GFAP: The increasing in binding of +ve charge cations with Threonine and Tryptophan "Tph" will hold and inhibit Their functions that will be the main reason for decreasing in serotonin and in dopamine production followed by Deficiency in OPA1 repair (due to decreasing in GTPase utilized from Tph functions) and will lead to Deficiency in CoQ10 synthesis with accumulation in IL2 and in cholesterol and result in decreasing in IL17 and in GCs-beta synthesis followed by reduction in NR4As pathway. Tph is necessary for GTPase synthesis which is important for activating OPA1 repairs and consequently necessary for activating synthase and phospholipase functions (notice deficiency in Thr will reflect Deficiency in cysteine amino acids that will lead to Deficiency in both oxytocin and Nrf2 functions). Where it has been reported that The Trp is the most complex and the most energy-consuming among all amino acids, and one of the rarest in the proteome [67]. The expression of Src resulted in PP2-sensitive increases in SERT function and expression [68].

Where, SIRT1 improves hepatic mitochondria (which adopt mTORC1 /S6K expression and GFAP expression), and Sirt3 important for Nrf2 production which necessary for antioxidative functions and activate proper astrocytes functions with adoption to GFAP expression. And, the decreasing in mitochondrial OPA1 functions followed by reduction in both serotonin and dopamine and followed by reduction in NR4As pathway can reflect increasing in glial acidic protein. That it has been reported that Serotonin may act as an inhibitor of glial fibrillary acidic protein GFAP expression either on the transcription or on the stability of the GFAP-mRNA [69].

So, it's clear that decreasing in the threonine, Cys, Leu, tyrosine and in Tph will inhibit or decrease the serotonin synthesis followed by decreasing in activating NR4As pathway followed by decreasing in IL17 and in GCs-beta and in all of B-arrestins, B-adrenergic and Nrf2 with increasing in The accumulated cholesterol and in pro-inflammatory molecules.

The Deficiency in Thr will be followed by Deficiency in cysteine and in Trp (TGG) and will be followed by the survival of fatal neonatal encephalopathy with hypotonia and reflect Deficiency

in both melatonin (which promoted by serotonin synthesis) and in oxytocin Biosynthesis where both serotonin and oxitocin considered as strongly necessary for improving both brain and heart functions through activating Nrf2 functions for activating heme oxygenase and activate both Ang2-AT2 and VEGF-A productions which necessary for anti-inflammatory growth. Both of dopamine and serotonin are connected to each other that as the activation of serotonin occur as dopamine levels will be reduced (and as dopamine activated as serotonin levels will be reduced).
That Serotonin Agonists Reduce Dopamine Synthesis in the Striatum Only when the Impulse Flow of Nigro-Striatal Neurons Is Intact [70]. And serotonin inhibits impulsive behaviour while dopamine enhances impulsive behaviour, that Serotonin neuron activation does not induce inhibition of motor behaviours [71].

Also, the dopamine is so effective for activating brain memories, That PDD patients have extensive cholinergic loss as well as dopamine (DA), that combined loss of DA and Ache could be sufficient for pathogenesis of specific cognitive deficits as Parkinson's disease dementia "PDD" [72]. Extensive cholinergic loss as well as dopamine (DA) because loss of Tyr kinases (which necessary for choline kinases and dopamine synthesis) will be result of deficits in both genes and in their productive pathway, that combined loss of DA and ACh reflect a sever loos and deficiency in tyrosine kinases (which in the main composition of valorphin), that could be sufficient for pathogenesis. The melatonin (regulated by Thr which regulate Tph synthesis) has strong roles in neuroprotection through activating NR4As pathway That melatonin level (regulated mainly by threonine which regulate tryptophan synthesis) is disturbed in some neurological conditions such as stroke, Alzheimer's disease, and Parkinson's disease, which indicates its involvement in the pathophysiology of these diseases. Its properties qualify it to be a promising potential therapeutic neuroprotective agent. [73].

Melatonin has important antimicrobial properties and can mediate activation and proliferation (through activating the full NR4As productive pathway) of intestinal mucosal immune cells [74].

And, melatonin exerts its anti-gastrointestinal cancer actions are explained, including inhibition of proliferation, invasion, metastasis, and angiogenesis, and promotion of apoptosis and cancer immunity [75]. So, the antimicrobial properties of melatonin described as its role in activating NR4As pathway mediated by activating IL17 synthesis which promote glucocorticoid-beta as a first active step in NR4As pathway followed by B-arrestins synthesis and B-Adrenergic productions which followed by oxitocin and Nrf2 production and consequently followed by Ang2-AT2 and VEGF-A productions "respectively" followed by activating heme oxygenase and anti-inflammatory growth.

it's clear that serotonin and oxytocin synthesis respectively) that will be the result of decreasing in serotonin and in dopamine that will lead to decreasing in attention and in bran memories (followed by decreasing in decreasing in oxytocin synthesis which promoted by B-adrenergic) , and decreasing in antimicrobial properties due to decreasing in melatonin which necessary for activating NR4As pathway that can lead to decreasing in oxitocin followed by decreasing in Nrf2 and in anti-inflammatory growth and processes that will be result of gastrointestinal cancer, which reflect decreasing in GC-beta and in Barrestins followed by decreasing in both B-adrenergic and in Nrf2 followed by decreasing in Ang2-AT2 and in VEGF-A synthesis and decreasing in the regulated anti-inflammatory growth respectively. Melatonin possesses an incredible variety of actions and one of the most promising is its antineoplastic effect of the (through its role in activating NR4As pathway). In particular, melatonin inhibits more than one of the cancer hallmarks due to its antiproliferative, cytostatic, antimetastatic, and proapoptotic effects against tumor cells (note: by promoting the full NR4As productive pathway) [76]. So as melatonin (which firstly regulated by Thr amino acids for Tph TGG and synthesis) has antineoplastic effect as has the role of enrolling the neoplastic molecule through activating NR4As productive pathway for activating GCs-beta followed by B-adrenergic and oxytocin for promoting Nrf2 synthesis which are necessary for anti-inflammatory growth. And so, melatonin has the role of anti-fatal neonatal encephalopathy with hypotonia through activating NR4A2 productive pathway and reactivating brain functional activities. That it has been reported that: Melatonin has diverse properties in neuroprotections include antioxidant, anti-inflammatory, and anti-apoptotic effects. that melatonin is a promising agent to improve the outcomes of infants with NE [77].

Melatonin are important for Neuroprotection through its role for activating GTPase (that its triple codons is TGG which promote GTPase synthesis) which necessary for improving OPA1 inner membranes repair which necessary for CoQ10 synthesis and activate NR4As productive pathway for activating anti-inflammatory growth which includes Neuroprotection. It has been reported that its safety and helpful to use Melatonin for Neuroprotection in Asphyxiated New-borns [78]. Also, Melatonin seems to be safe and beneficial in protecting neonatal brains from perinatal HIE [79]. That melatonin promotes Rho-family GTPases productions which is the key regulators of the actin cytoskeleton, play essential roles in orchestrating the development and remodeling of spines and synapses [80]. So, Melatonin (which activated by Trp "TGG") has the role of protecting neonatal brains and necessary for orchestrating development and remodeling of spines and synapses through promoting GTPase productive functions. So, melatonin which regulated by Trp TGG and serotonin synthesis is firstly regulated by Threonine "which involved in valorphin" has the important role for activating the NR4As productive pathway.

That melatonin synthesis is reflecting the strong role of Tph for activating GTPase synthesis which promote and activate OPA1 inner membranes repair that promote CoQ10 synthesis and prevent fatal neonatal encephalopathy and hypotonia through activating full NR4A2 productive pathway mediated by IL17 synthesis and GCs-beta synthesis followed by B-arrestins synthesis and B-Adrenergic and Nrf2 synthesis which reactivate

anti-inflammatory growth and brain functional activities. And, the importance of valine is so important for stabilize tyrosine kinases synthesis and functions (and the role of glu/Gln cycles are for stabilize valine synthesis) GTC Valine <<¬>> CAG Glutamine GTA Val <¬¬> TAC Tyr ATA_ Isoleucine <¬¬> TAT tyrosine

Notice that both valine and isoleucine are involving in valorphin composition, that it's clear that valorphin necessary for activating Tph synthesis and necessary for tyrosine kinases production necessary for serotonin and dopamine production, and also the presence of Leu is necessary for Nrf2 production. Cysteine, Tph, Leu and tyrosine kinases necessary for activating astrocytes and protect from Autoimmune: Increasing in the defective OPA1 membranes will be the result of increasing in accumulated inflammatory subunits. The mitochondrial dysfunctions can be due to severe deficiency in Trp TGG, and in Gly (and "or" in Arg), and in the necessity hydrophobic amino acids as Leu, Tyr Glu Gln, Val…etc.

Where Trp, Leu, Tyr and Gly are playing important role in mitochondrial repair and functions and consequently in activating astrocytes functions. Threonine phosphorylation are necessary for serotonin, for oxitocin and for Nrf2 synthesis :(ACT Thr ¬¬¬¬>TGA Cys ACC Thr ¬¬¬>TGG Trp which activate melatonin at night). The Glu Gln cycle are necessary for activating valine synthesis and functions which necessary for activating tyrosine synthesis, that threonine phosphorylation promote both Trp TGG and Cys synthesis where both Tyr and Cys activate oxytocin synthesis while Tph activate serotonin and melatonin synthesis. That it has been reported that Glutamatergic clock output stimulates melatonin synthesis at night [81]. So, Glu functions stimulate Trp functions for activating melatonin Biosynthesis and so is having the role of activating IL17 productions through its role in activating OPA1 functions. And, inhibition in Thr phosphorylation inhibition in Cys and Trp synthesis will inhibit or decrease all of serotonin melatonin and oxitocin synthesis. Threonine are playing necessary role in activating Cys and Trp synthesis while Glutamate can activate Leu synthesis, where glutamine can modulate melatonin synthesis through its mechanisms that started by activating leucine synthesis: GAA Glutamate ¬¬> CTT Leucine And "TTA" Leu <¬¬> activate "AAT" Tyr And "ACA" Thr <¬¬>activate "TGT" 'Cys' then followed by {ACT Thr <¬¬>TGA Cys ACA Thr<¬¬> TGT 'Cys' ACG Thr <¬¬> TGC 'Cys'} ACC - Thr <¬¬>TGG "Tph" Tryptophan which is important for serotonin and melatonin synthesis which will activate the full NR4As productive pathway, while Tyr and Cys synthesis will activate oxitocin synthesis regulated by B-adrenergic.

Glutamate stimulate leucine synthesis which enhance Tyr synthesis which will activate Tyr kinase necessary for serotonin and dopamine production followed by activating melatonin synthesis which will activate NR4As productive pathway, where the primary formation of Cys and Tyr will activate oxitocin synthesis while Leu which formed by glutamate will activate Nrf2 productive functions. Where it has been reported that glutamate modulate the pineal melatonin synthesis [82]. It's important to note that Leu and Gln are stabilizing and regulating each other throughout translation processes that (GAA) Glutamine <¬> leucine (Leu CTT) (GAG) Glutamine <¬> leucine (Leu CTC). And Thr ACT ¬¬>TGA Cys And TCA - Ser ¬¬> AGT Cys which activate ¬¬>oxytocin synthesis. That it has been reported that: L-leucine stimulates glutamate dehydrogenase activity and glutamate synthesis by regulating mTORC1[83]. So Trp TGG is necessary for activating melatonin synthesis (where leucine is necessary for Nrf2 synthesis), where melatonin is so important for activating immune cells by stimulating NR4As productive pathway for activating IL17 synthesis which necessary for GCs-beta synthesis then followed by B-arrestins pro for activating B-adrenergic which promote oxytocin synthesis for Nrf2 synthesis which necessary for activating Ang2-AT2 and VEGF-A synthesis for anti-inflammatory growth. And, the necessity of tryptophan is regulating mitochondria OPA1 repairs by activating GTPase synthesis, that any decreasing in tryptophan will cause reduction in GTPase and in brain function and cause decreasing in CoQ10 and cause autoimmune diseases (depending on the percentage of decreasing in Tph). That mitochondrial fission is primarily regulated by Tph which has the role of stimulating GTPase synthesis which necessary for OPA1 repairs [84]. Also, Tph and GTPases has strong roles in the regulation of mitochondrial dynamics in Parkinson's disease [85].

And, The ARL2 GTPase Is Required for Mitochondrial Morphology, Motility, and for Maintenance of ATP Levels [86]. Where decreasing in GTPase production will reflect decreasing in ATPase activities (decreasing in adopting ATPase activities with decreasing in adopting Na and K channels) that will increase inflammation and Na and K binding toxicity. And, GTPase synthesis are so imp for protein synthesis that breakdown of Tph will promote firstly Ser and Thr phosphorylation pathway which will promote both Cys and Tyr which activate oxytocin synthesis and complete NR4As productive for Nrf2 synthesis and both Ang2-AT2 and VEGF-A for anti-inflammatory growth. That it has been reported that: NOA1 is an essential GTPase required for mitochondrial protein synthesis, that NOA1-deficient mice exhibit midge station lethality associated with a severe developmental defect of the embryo and trophoblast [87].

Where GTPase synthesis is the initial important of steps for activating proliferation through activating glucocorticoid beta followed by B-arrestins which is essential for activating Ang2-AT2 (for adopting heart constriction) followed by activating VEGF-A synthesis for adopting anti-inflammatory growth mediated by B-adrenergic and Nrf2 synthesis via NR4As pathway, that decreasing or Deficiency in GTPase synthesis or production will lead to defect in anti-inflammatory pathways that will lead to defect in the development of embryo and trophoblast. And, Rho-GTPases is regulators of T lymphocyte [88]. The GTPase synthesis by Tph are required for OPA1 inner membrane repairs and inner membrane fusion, and the Defect in OPA1 function are fully related to GTPase Deficiency and consequently related to tryptophan Deficiency which considered as the most complex and the most energy-consuming among all amino acids and considered as the one of the rarest in the

proteome. It's important to note that Thr TCC is necessary for preventing Tph TGG synthesis, where valorphin is containing Thr TCC and Leu in its composition that valorphin has the strong Advantages for Tph synthesis and functions and for mitochondrial OPA1 repair and function.

And in brief, the Tph and Leu are so necessary for activating NR4As pathway by astrocytes cells functions started by adopting and activating mitochondrial OPA1 repairs and functions followed by serotonin and dopamine synthesis which exactly followed by activating melatonin and IL17 productions which will begin to activate GCs-beta and B-Adrenergic productive functions which will be followed by oxitocin and Nrf2 production which adopt heme oxygenase and antioxidative stress followed by Ang2-AT2 and VEGF-A synthesis which necessary for anti-inflammatory growth and TH17 production "respectively". Also note that, endoplasmic reticulum stress can be adopted and feedback by astrocytes function by activating NR4As pathway in astrocytes. That in response to ER stress, the astrocytes are having the roles to adopt inflammation through producing inflammatory mediators, that can reduce trophic support, and can transmit the adopted ER stress to other cells [89]. Arg, Leu & Proline involved in morphine That important for adopt immune functions, heart and brain in strong healthy conditions. That Myeloid cells are major players that exploit the regulators of Arginine metabolism (for proline synthesis) to mediate diverse and adopt immunity through protecting the stability of tRNAs synthesis and protecting the signals 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), leucine, isoleucine, and valine, since their plasma values are frequently found in high concentrations in individuals with CVD risk. Nevertheless, dietary BCAA, leucine in particular, have been associated with improved indicators of atherosclerosis [91]. leucine, isoleucine, and valine, since their plasma values are frequently found in high concentrations in individuals with CVD due to dysfunction in Arg and in tryptophan metabolic functions which will be result of Deficiency in Proline followed by reduction in tRNAs which will be result of hypertension and accumulated Val, Leu-protein and other imp branched amino acids protein. {{AGG Arginine Arg R<¬¬>CCT Proline}} And CCA _Proline <¬¬>tryptophan TGG}} Where Proline necessary for. TRNAs synthesis and for genes signals transmission. That it has been reported that conserved proline triplet in Val-tRNA synthetase and the origin of elongation factor P. And we suggest that the critical role of the proline triplet for ValS activity may explain why bacterial cells co-evolved the EF-P rescue system [92].

So, absence of Proline result of decreasing in tRNAs synthesis followed by accumulation in Val, Leu and île, where isoleucine is characterized for Tyr synthesis ÎLE _ ATT, ATC, ATA {{Île ATA<¬>TAT Tyr}} While the other two triplets of Ile (ATT, ATC) are for termination. So, absence of Arg and Trp will result of Deficiency in Proline and consequently in their necessity tRNA that will be result of increasing in Tyr and hypertension in CVD. also, it's reported that: proline metabolism impacts beneficial tissue regeneration, but also contributes to the progression of devastating pathologies such as fibrosis and metastatic cancer. That Salivary proline-rich peptides able to neutralize microbe attacks could contribute to avoiding the development of dental caries, and infectious disease [93]. So it is cleared why Arg and Proline are strongly found in hemorphin composition.That hemorphin-5) is nine essential amino acids: Leu_Val_Val_Tyr, _Pro _Pro _Thr_ Gln_& Arg So again deficiency in Arg result of Deficiency in Proline that will be result of accumulation of Leu_ Val_Val_Tyr, _Pro _Pro _Thr_ Gln and then will be result of hypertension and CVD with severe Deficiency in serotonin and melatonin And That the biosynthesis of proline is key to sustain protein synthesis, support mitochondrial function and nucleotide Biosynthesis [94]. So, I can strongly conclude that: Decreasing in Arg and tryptophan followed by decreasing in Proline will be result of decreasing in lymphocytes functions, decreasing in antioxidative function, and accumulation in IL2 and IL6, with decreasing in mitochondrial OPA1 function.

And the morphine synthesis is strongly important for adopt and strengthen immune for protecting heart brain and all immune functions in strong healthy functions against disease progression. As Proline is necessary for immune function as Glu /Gln cycle is playing necessary role for leucine synthesis and for proline synthesis and its availability by intestine cells [95]. Mitochondrial Disorders Due to Deficiency In Proline, Leucine and deficiency in Sirt1 followed by Deficiency of Nrf2 which exacerbates white matter damage Firstly, previously we discussed the necessity of Proline synthesis from tryptophan are so important for mitochondrial OPA1 repair and for continuing activating serotonin syndrome and NR4As Productive Pathway functions. Coenzyme Q10 deficiency can be primary, or secondary to other inherited neurogenetic disorders. 30 Primary disorders of Q10 biosynthesis fall into four main groups:1) an encephalopathic form presenting with myoglobinuria encephalopathy and ragged red fibers on the muscles biopsy; 2) a cerebellar form with prominent cerebellar atrophy on brain MRI; 3) an infantile form with encephalopathy and steroid-unresponsive nephrotic syndrome; and 4) a pure myopathic form with elevated creatine kinase and ragged red fibers. A muscle biopsy may be required to reliably diagnose coenzyme Q10 Deficiency. The understandable reasons for ragged red fibers on the muscles biopsy is that : the Deficiency In leucine which reflect Deficiency in Tyrosine amino acids and in tyrosine kinases synthesis too (TTA "Leu" <¬¬> AAT "Tyr")) that will lead to decreasing in serotonin and dopamine in that tissue (because Tyr kinases necessary for ATPase function which necessary for dopamine production, that will reflect decreasing in Glu Gln cycles), followed by decreasing in B-adrenergic, in oxitocin, and in Nrf2 functions that will be the result in deficiency in Nrf2 which exacerbates white matter damage and microglia/macrophage levels. And, the Isolated Mitochondrial Myopathy Associated With Muscle Coenzyme Q10 Deficiency [96].

The deficiency in valorphin will be result in decreasing in Leu, in arginine and in Proline which are necessary for regulating and modulating Sirt1 which necessary for preventing the

mitochondrial dysfunction and metabolic disorders.

Where it has been reported that: Leucine (which necessary in valorphin composition) supplementation increases SIRT1 expression and prevents mitochondrial dysfunction and metabolic disorders [97]. And, Leucine Modulates Mitochondrial Biogenesis and SIRT1-AMPK [98]. And Sirt1 and Sirt3 Activation Improved Cardiac Function of Diabetic Rats via Modulation of Mitochondrial Function [99]. And also, mutation in mitochondrial OPA1 can caused firstly by mutations in mTORC1 and in S6K due to Deficiency in Ser phosphorylation followed by mitochondrial dysfunction that can show mutations in COQ4. Where it has been reported that, Primary coenzyme Q10 deficiency-7 (COQ10D7) is a rare mitochondrial disease caused by biallelic mutations in COQ4 [100]. Moreover, CoQ10 deficiency can reflect decreasing in activities of Sirt1 and Sirt3 deacetylases functions , that later we will explain that Thr, Tph, Tyr, Cys, and Leu deficiency can reflect decreasing or inhibition in Sirts expression and decreasing in CoQ10 expression followed by decreasing in oxytocin and in Nrf2 expressions (note Sirts is an important key for activating Nrf2 that leucine is the main activator for both of them) believed to be key determinants of health span.

And, Nur77 increase SIRT1 functionality and stability and both Nur77 and Sirt1 decrease the oxidative stress [101]. And the Sirt1 synthesis is so important for Nrf2 production [102]. So Valorphin activate firstly Serotonin And dopamine production followed by melatonin production which activate NR4As productive (Nur77) which activate B-adrenergic and oxitocin followed by Sirt1 production which stimulate Nrf2 productive functions for activating anti-inflammatory growth and processes. Nur77 stimulate SIRT1 Production (upon leucine and tyrosine functions which necessary for increasing Sirt1 productions) mediated by B-adrenergic and oxitocin and followed by Nrf2 production. That leucine significantly increased the mRNA levels of mito- chondrial-related genes. That it has been reported that 0.25% leucine supple- mentation promoted enzymatic and non-enzymatic antioxidant capacity and mitochondrial biogenesis and function [103]. And, high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids [104]. So, Leucine Modulates Mitochondrial Biogenesis, SIRT1-AMPK, and necessary for stimulating proper Nur77 for Sirt1 Productions. That NR4A nuclear receptors sub-family (Nur77, Nurr1 and NOR-1) are emerging as important key in cardiac stress responses and adoptions Where Nur77 seems to be a promising target in HF characterization and therapy [105]. And it is clear that leucine and tyrosine are necessary for increasing amino acids protein necessary for valorphin production which activate both serotonin and boost dopamine production followed by melatonin synthesis and mediated by activating mitochondrial OPA1 functions which activate NR4As functional pathway which has strong roles of the primary adoption to the oxidative processes and improve the antioxidative progressive pathway by activating both oxitocin and Nrf2 synthesis and mediated by B-adrenergic and Sirt1 synthesis , where the NR4As pathway promote firstly GCs-beta synthesis followed by IFN-beta and B-arrestins synthesis then followed by Nrf2 production which stimulate ACE functions for Ang2-AT2 synthesis and VEGF-A necessary for anti-inflammatory growth and modulate cardiac constriction and functions [106]. Notice that Sirt1 activated firstly by leucine and tyrosine functions then by B-adrenergic and oxitocin which modulate Nrf2 expressions via NR4As pathway.

That it has been reported that: Q10 modulates the expression of NFκB, IκB, Nrf2 and HO-1 in exercise training, indicating an anti-inflammatory effect of Q10 and emphasizes its role in antioxidant defense [107]. Tyrosine and Leucine are necessary for activating coenzyme Q10 which is the main component of OPA1 membrane Firstly, tyrosine is very necessary for CoQ10 synthesis. That The coenzyme B6, required for the conversion of tyrosine to p-hydroxybenzoic acid. Where deficiency of the coenzyme B6 can cause dysfunctions, prior to the formation of vitamin Q10, to 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]. And the CoQ-10 is located in the inner mitochondrial membrane. It is a cofactor for at least three mitochondrial enzymes that plays a vital role in oxidative phosphorylation. That Mitochondrial inner membrane is a very complex environment in which many bioenergetics pathways converge, and CoQ appears as an essential component. [110].

So, Threonine, tyrosine, and Leucine which are main component of valorphin are necessary for CoQ10 synthesis (where Thr are necessary for tryptophan synthesis which necessary for GTPase synthesis) and functions which is main component of mitochondrial membrane. And Cerebellar degeneration the result of inherited genetic mutations due to mitochondrial disorders which can be due to deficiency in Tph, in tyrosine and in leucine and consequently will cause deficiency in Sirt1 (that Leucine supplementation increases SIRT1 expression and prevents mitochondrial dysfunction and metabolic disorders), and mitochondrial disorder can reflect Deficiency in both leucine and Tyrosine. Where Isoleucine and Val are necessary for tyrosine production (necessary for OPA1 function): ATA île <¬> TAT Tyr GTA Val <¬> TAC Tyr While Gln Glu necessary for Leu synthesis (which necessary for OPA1 function). That it's reported that Mitochondrial disease can manifest as multi-organ disorder, often with neurological dysfunction. Cerebellar ataxia in isolation or in combination with other features can result from mitochondrial disease. [111]. The deficiency in Sirt1 can be the result of mitochondrial dysfunction and metabolic disorders (due to Deficiency in Tyrosine and in Leucine) that alter the normal production of specific proteins that are necessary for the survival of neurons. Tyr, Arg and Proline (protein rich Proline regulated in hamster parotid glands) modulate mitochondrial function necessary for immune maintenance (upon SIRPα1 CD47 axis functions) and for preventing the accumulated PD-L1 in hypoxia and prevent heart failure As Estrogen synthesis reflect reduction in the PD-1 PD-L1 accumulation and reflect a good sign of mitochondrial proper functions that prevent inflammatory accumulation and improve the IL17 productions

which activate GCs-beta via NR4As pathway which regulate Nrf2 expressions and anti-inflammatory growth for preventing many pathogenic problems. That GCs-beta productions modulated by OPA1 synthase are necessary to activate both oxitocin and Nrf2 synthesis via NR4As pathway [112]. While, SAM is essential for tyrosine kinases synthesis (Met ATG<¬>Tyr TAC) which is necessary for OPA1 repairs the methionine has important role in activating Tyr kinases production which play imp role to increase mitochondrial function. That, Methionine supplementation increases mitochondrial functions [113]. Interferon-γ (IFNγ) which induce expression of MHC class II (MHCII) on many different cell types, leading to antigen presentation to CD4+ T cells and immune activation [114]. That IFN-gamma induce IFN-beta upon synthase function which support MHC class 2 synthesis followed by alpha phosphorylation to induce TLR4 and SIRPα1 which controlled by CD14 which activated by synthase enzymes. As mentioned before Arg, Pro and Trp are imp to activate lymphocytic functions mediated by activating mitochondrial function, that lymphatic EC promote MHC class 2 and Intratumoral Regulatory T cell– Suppressive Functions [115]. The activating Tyr03 will activate mitochondrial synthase P function which prevent PD-1 accumulation. Where, TYRO3 induces anti-PD-1/PD-L1 therapy [116]. But, The expression of programmed death-ligand 1 on myeloid-derived suppressor cell, dendritic cells (DCs) and pro-tumor macrophage type 2 (M2) is induced by hypoxia [117] So inhibition in Proline functions due to Arg and Trp dysfunctions will cause decreasing in tRNA that will be the result of hypertension and hypoxia. That Studies indicated that high initial values of blood serotonin, the organism is more resistant to hypoxia [118]. And, Dietary arginine attenuates hypoxia- induced HIF expression, metabolic responses and oxidative stress [119]. So, serotonin and it's regulator Trp, and Arg are strong inhibitor to hypoxia and hypertension through their pathway of firstly activating Proline which activate proper mitochondrial function and activate necessary tRNAs for increasing the oxidative areas with adoption through Nrf2 expressions. Notice, L-arginine improves the symptoms of strokelike episodes in MELAS je [120]. And, Arg which necessary to activate Proline synthesis which activate SIRT1 that activate mitochondrial function. That L Argenine -mediated vasoreactivity in patients with a risk of stroke [121]. While, Proline improves cardiac remodeling following myocardial infarction and attenuates cardiomyocyte apoptosis via redox regulation [122]. So, Proline in Salivary proline-rich peptides able to neutralize microbe attacks and play important role in improving cardiac remodeling following myocardial infarction and attenuates cardiomyocyte apoptosis.

The (Sirt1 which controlled by Proline) SIRT1 ameliorates oxidative stress induced neural cell death and is down-regulated in Parkinson's disease [123]. And through activating Tph and Arg the Sirt1 will be activated (promote mitochondrial activities) and serotonin will be activated mediated by IL17 productions which activate GCs-beta followed by Nrf2 production via NR4As pathway which control PD-L1 expression and prevent PD-1 accumulation. That it has been reported that Chemical inhibition of Nrf2 with Brusatol and Luteolin showed a strong reduction of Nrf2 and PD-L1 mRNA expression levels. This result supports the idea that Nrf2 positively controls the PD-L1 expression [124]. Notice, the estrogen expression which indicate proper activations of mitochondrial OPA1 function carried by activating both Arg and Trp for activating Proline functions and Sirt1, has imp functions in improving PD-L1 expression. That it's reported that estrogen ameliorates the immune microenvironment represented by PD-L1 expression and enhances its effect in the absence of Nrf2 [125]. And it's Important to conclude that Deficiency or inhibition in Tyr, in Leu and consequently in estrogen synthesis will improve diabetes, white matter hyperintensity (with hypertension), and will show sever CoQ10 deficiency followed by increasing in the PD-1 accumulation and heart failure The increasing in production of IL17 indicate the proper activities of OPA1 synthase which prevent accumulation of IL2, IL6, and PD-L1 through IL17 synthesis (regulated by synthase) which activate glucocorticoid-beta synthesis via NR4As pathway followed by oxitocin and Nrf2 production which adopt oxidative processes and activat heme oxygenase and Ang2-AT2 and VEGF-A necessary for anti-inflammatory growth.

Where IL17 synthesis reduce or inhibit the ratio of the accumulated programmed cell death. That it has been reported the increased Th17 counts IL-17 level, which correlated with high neutrophil-to lymphocyte ratio and programmed cell death expression, are potential biomarkers for poor prognosis in ovarian cancer and likely indications for application of programmed cell death 1 ligand 1 pathway inhibitors [126]. That increased Th17 counts IL-17 level, which correlated with high neutrophil-to-lymphocyte ratio and programmed cell death expression. The proper functions of mitochondrial OPA1 prevent the accumulation of inflammatory cytokines and pro-inflammation (PD-1, MHC class l) by modulating IL17 and CD47 productions which has the role of immune maintenance upon SIRPα1 /CD47 axis functions. And, IL-17-activated PCs (regulated by OPA1 function, and consequently by Pro, Leu, Tph) can modulate neutrophil functions within the perivascular tissue space [127]. And, Estrogen modifying the effects of GC, enhancing Th2 cell survival and type 2 cytokine production in severe asthma [128]. That, the estrogen synthesis reflect proper OPA1 functions which prevent androgen accumulation through activating Estrogen synthesis which modulate (followed by) glucocorticoid-beta synthesis and Barrestins synthesis which followed by Nrf2 production. So, inhibition in Leu, Tyr, will inhibit both Nrf2 and oxitocin which will be main reason for promoting PD-L1 accumulation and promote mitochondrial OPA1 dysfunction (that PD-L1 can be improved to mutated PDL2 in cause of OPA1 dysfunctions). Proline-rich Insert Is Required for Efficient Activation of the Mitogen-activated Protein Kinases ERK1 and ERK2 in Mammalian Cells [129].

Where, Mitogen-activated Protein Kinase ERK1/2 Regulates the Class II Trans activator [130]. So, Proline function (and consequently Arg and tryptophan) required for (regulate) ERK1/2 and for MHC class ll production. Where, MHC class II trans activator (CIITA) requires conserved leucine charged domains [131]. And, Nlrc5−/− splenocytes and bone marrow-derived macrophages were able to up-regulate MHC-I in

response to IFN-γ; that MHC class l regulated by Nucleotide-binding Domain, Leucine-rich Repeat containing (NLR) Proteins [132]. So, in conclusion Proline and leucine are necessary for MHC class l and class Il (upon IFN-gamma response) and are necessary to activate proper SIRPα1 / CD47 axis that required for immune maintenance [133]. Where the absence of rich-Proline, rich-Leucine, Tryptophan will cause the mitochondrial dysfunctions that will cause inhibition to CD47 production that will cause accumulation of PD-1, SIRPα1 and MHC class l (accumulation of pro-inflammation). That, serotonin has the roles of anti-inflammatory cytokine functions by some cells of the innate immune system. And 5-HT/5-HTRs axis-mediated alterations in the tumor progression [134].

White Matter Hyperintensity in Cerebral Small Vessel Disease is connected to diabetes and inhibition in OPA1 functions followed by reduction in tRNAs synthesis The White Matter Hyperintensity in Cerebral Small Vessel Disease due to Deficiency or inhibition in Leu synthesis (which necessary for mitochondrial OPA1 fusion) that will inhibit B-adrenergic or Nrf2 production and consequently will inhibit both Ang2-AT2 and VEGF-A production followed by inhibition in heme oxygenase So Patient with White Matter Hyperintensity in Cerebral Small Vessel associated are having high oxidative processes and unadopted heart constriction and associated with diabetes. The hypertension, which is the classical risk factor in WMH is started by inhibition in Ser phosphorylation (that will be result of decreasing in mTORC1 production which necessary for astrocytes survival) followed by reduction in tryptophan and consequently reduction in Pro with reductions in necessary amino acids synthesis (due to Deficiency In OPA1 synthase), that will be results of increasing in pro-inflammation with decreasing in estrogen production, decreasing in glucocorticoids-beta and decreasing in NR4As pathway. The inhibition in glucocorticoids-beta production is due to inhibition in mitochondrial OPA1 synthase enzymes where synthase enzymes promote IL17 productions and prevent the accumulation of proinflammatory molecules, that IL17 responsible for activating glucocorticoid-beta synthesis followed by Barrestins and both oxitocin and Nrf2 synthesis which promote Ang2-AT2 synthesis (regulated by ACE) and VEGF-A synthesis that adopt myocardial constriction. So, hypertension in white matter hyperintensity due to severe decreasing in tryptophan followed by decreasing in Proline (which regulate tRNAs production) followed by accumulation of proinflammatory subunits the OPA1 dysfunction in white matter hyperintensity will be associated with inhibition estrogen synthesis and inhibition in glucocorticoids-beta production (via NR4As pathway) , and associated with sever decreasing in tRNAs production (regulated by Pro which formed by tryptophan), the followed by astrocyte damages, HF and stroke. That it has been reported that: White Matter is involvement in mitochondrial diseases [135].

That mitochondrial OPA1 disease (caused due to decreasing or inhibition in tryptophan and Proline) are associated with inhibition in hydrophobic amino acids synthesis that include Deficiency in Ser, Pro, Leu, Tyr, (Trp synthesis) and Cys, and consequently reflect Deficiency in estrogen synthesis (due to Deficiency In synthase enzymes) , followed by deficiency in glucocorticoid-beta synthesis, deficiency in both oxitocin and Nrf2 production, and followed by sever decreasing in tRNAs synthesis which cause the accumulation of molecules as protein Leu rich protein, Île rich protein, and Val rich protein in CVD. The Ser phosphorylation is necessary for improving mTORC1 production which necessary for Estrogen synthesis (regulated by synthase enzymes) which necessary for astrocytes survival and for proteostasis. That mTORC1 Control Proteostasis after Brain Ischemia. And estradiol shows an important regulatory role for the mTORC1 activity [136] So, hypertension, which is the classical risk factor for WMH, and diabetes mellitus is associated with WMH progression [137], is due to severe decreasing in tRNAs synthesis.

The main reasons for increasing in the hypertension in WMH are due to reduction in tRNAs synthesis (which due to the reduction in Pro which due to reduction in Trp) , followed by reduction in OPA1 enzymes (synthase enzyme) functions that associated with reductions in mTORC1 and reduction in proper S6K (which can cause mutation in OPA1 membrane) , that also associated with reduction in Estrogen synthesis with increasing and accumulation in pro-inflammations. It has been reported that type 2 diabetes is closely related to cerebral small vessel diseases [138]. As type 2 diabetes is closely related to cerebral small vessel disease as the mitochondrial OPA1 dysfunction is associated with the cerebral small vessel disease and also associated with the increasing in hypertension (except some causes can have tRNAs production originated from Arg, that will reduce the accumulation of molecules but will not activate both serotonin and NR4As pathway necessary for astrocyte functions). The Deficiency of Nrf2 exacerbates white matter damage due to the sever decreasing in tryptophan and in Proline which are necessary for promoting Serotonin, tRNAs, and NR4As pathway respectively. That 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].

And it has been reported that: Association of White Matter Hyperintensities and Cardiovascular Disease with loss of adequate small vessel functions leading to clinical manifestations including chest pain, dyspnea, heart failure, lacunar ischemia, WMH, cognitive impairment, and dementia [140]. Due to the activation of NR4As pathway, the Intranasal Oxytocin Attenuates Cognitive Impairment, βAmyloid Burden and Tau Deposition, but mediated firstly by the activation of OPA1 function [141]. So, oxitocin treatment has the function of activating Nrf2 synthesis by activating Leu synthesis which as well will activate Ang2-AT2 and VEGF-A synthesis that adopt myocardial constriction and activate both heme oxygenase and anti-inflammatory growth.

Also, oxitocin treatment has the roles of re-activating Tyr kinases which activate mitochondrial OPA1 function in the availability of Trp, Pro, and Leu functions for activating proper mTORC1 and S6K production which protect astrocytes functional survival. Arg & Proline involved in morphine which are strongly important

for adopt, and strength immune for protecting heart brain and immune 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, leucine in particular, have been associated with improved indicators of atherosclerosis [142]. leucine, isoleucine, and valine, since their plasma values are frequently found in high concentrations in individuals with CVD risk due to dysfunction in Arg and in tryptophan metabolic functions which will be result of Deficiency in Proline (which regulate tRNAs production).

{{AGG Arginine Arg R<¬¬>CCT Proline}}
And,
CCA _Proline <¬¬>tryptophan TGG}}

Where Proline necessary for TRNAs synthesis, and for genes migrations. That it has been reported that conserved proline triplet in Val-tRNA synthetase and the origin of elongation factor P. And we suggest that the critical role of the proline triplet for ValS activity may explain why bacterial cells co-evolved the EF-P rescue system [143]. So, absence of Proline (that its synthesis is Trp dependent) result of decreasing in tRNAs, decreasing in NR4As pathway, and accumulation in Val, Leu and île proteins. Where isoleucine is characterized for Tyr synthesis

ÎLE _ ATT, ATC, ATA
{{Île ATA<¬>TAT Tyr}}

While the other two triplets of Ile (ATT, ATC) are for termination. So absence of Arg will result of Deficiency in Proline and consequently will be result of decreasing in tRNA synthesis and decreasing in signals transmission, while the absence in tryptophan will be the result of decreasing in Proline followed by reduction in tRNAs production and decreasing in NR4As pathway which reflect decreasing in all of GCs-beta, in oxitocin and in Nrf2 production, that will be result of accumulation in pro-inflammation (which can included the accumulation of Val, Leu, & île protein in the case CVD) that will cause the increasing in hypertension in WMH. also, it's reported that: proline metabolism impacts beneficial tissue regeneration, but also contributes to the progression of devastating pathologies such as fibrosis and metastatic cancer. That Salivary proline-rich peptides able to neutralize microbe attacks could contribute to avoiding the development of dental caries, and infectious disease [144].

And, other Studies reported that proline-rich protein necessary for controlling T cell antigen receptor expression [145]. So now it is very clear why Arg and Proline are strongly found in hemorphin composition that for stabilizing and maintaining tRNAs synthesis and protect the signals migration for keeping running cellular functional activities and prevent accumulation of Tyr (cause hypertension) , Leu and Val, while the availability of threonine in Hemorphin is to promote tryptophan synthesis which promote Proline synthesis and promote both Serotonin synthesis and NR4As Productive Pathway which include GCs-beta synthesis, oxitocin, and Nrf2 synthesis. The hemorphin-5) is nine essential amino acids: Leu_Val_Val_Tyr, _Pro _Pro _ Thr_ Gln_& Arg.

So again, deficiency in Arg, and in tryptophan synthase will be result of Deficiency in Proline synthesis that will be result of decreasing in tRNAs synthesis that will cause the accumulation of Leu, Val, proteins then will be result of increasing in hypertension (and accumulation of Val, Leu, and île protein in cases of CVD) with severe Deficiency in serotonin and melatonin. And the biosynthesis of proline is key to sustain protein synthesis, support mitochondrial function and nucleotide Biosynthesis [146]. So, I can strongly conclude that Decreasing in Arg and in tryptophan Tph will be followed by decreasing in Proline that will be result of decreasing in lymphocytes functions, decreasing in antioxidative function, and accumulation in IL2 and IL6, with decreasing in mitochondrial OPA1 function, and will be a strong sign of cardiovascular disease "CVD" which show accumulation of Leu, Val, and île (due to decreasing in tRNAs) . And the morphine is strongly important for adopt, for strengthen immune, and for protecting heart brain and immune in strong healthy functions.
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]. Is the increasing in GFAP produced by astrocyte cells dysfunction during neurodegenerative diseases (NDGD)? That mTOR/S6K promote astrocyte survival by mitochondrial OPA1 regulations: That NDG-diseases is characterized by decreasing in mitochondrial OPA1 function and consequently dysfunction in astrocytes and in NR4As pathway. If astrocytes are indeed the source of GFAP production, then how, those cells characterized failed to work properly in neurodegenerative diseases (NDGD).

Indeed, there are another source that responsible for creating those GFAP protein for activating astrocytes regulated by mitochondrial OPA1 function, that it has been proven that mTOR S6K phosphorylated pathway is responsible for producing GFAP. indicate that defects in the AKT/mTOR pathway are responsible for the altered translational control in Mecp2 mutant neurons and disclosed a novel putative biomarker of the pathological process [148]. And, PTEN and NF1 (neurofibromin) glial growth regulation requires TSC/Rheba (Ras homolog enriched in brain) control of mTOR function [149]. And, increase in cell size associated with protein kinase B/Akt hyperactivation, which occurs independent of phosphatidylinositol 3-kinase activation. [150]. And, lithium has also been reported to decrease activation of the transcription factor STAT3, which is a regulator of GFAP transcription and astroglia genesis [151]. And, neurofibromin regulates actin cytoskeleton dynamics and cell proliferation through a mTOR/Rac1dependent signaling pathway and identify NPM as a critical mTOR effector mediating these biological properties in Nf1-deficient astrocytes [152]. The GFAP regulated by mTOR kinases will activate astrocytes through the OPA1 regulation by activating NR4As pathway that activate firstly IL17 from IL4 and IL6 regulated by synthase function which activate glucocorticoid-beta production via NR4As pathway,

followed by B-arrestins, oxitocin and Nrf2 synthesis, where oxytocin and Nrf2 are responsible for producing glutathione .and activate heme oxygenase followed by Ang2-AT2 and VEGF-A productions. That the increasing in GFAP regulated by mTOR /S6K pathway with sever decreasing or inhibition in astrocyte functions or decreasing or inhibition in mitochondrial OPA1 function, is characterized the Alzheimer's disease and neurodegenerative diseases which included decreasing or inhibition in NR4As productive pathway and consequently decreasing in oxytocin and in Nrf2 followed by decreasing in glutathione production.

And, in chronic neuroinflammatory (for example, PMS) and neurodegenerative diseases, the levels of GFAP in the blood are expected to increase with accumulating astrogliosis [153]. And, ischemic stroke, the greater the damage to neurons and neuroglia, the serum GFAP levels will increase [154]. So, the accumulation of GFAP in the damaged neurons and neuroglia will characterized neurodegenerative diseases. So, neurodegenerative diseases and stroke are characterized by continuing GFAP production regulated by mTOR /S6K activated pathway, with dysfunction in astrocytes (may due to dysfunction in mitochondrial OPA1 function) which reverse decreasing or inhibition in NR4As productive pathway (which mainly regulated by OPA1 functions) that reverse sever decreasing in oxytocin and in Nrf2 functions, and consequently reflect decreasing in glutathione production. Notice, CoQ10 has an effective therapeutic role in age-related neurodegenerative disorders [155]. So previous work indicated that the neurodegenerative disorders due to dysfunction in mitochondrial OPA1 activities, where CoQ10 has the roles of recover mitochondrial OPA1 function to proceed the function for activating astrocytes by activating NR4As pathway which is dependent on mitochondrial OPA1 functions.

The glutathione is highly expressed by astrocytes, Firstly, formed through the binding of cysteine (which is the main composition of oxitocin) with glutamine for firstly leucine synthesis for activating Nrf2. The γ-glutamate cysteine ligase (also known as γ-glutamyl cysteine synthase) and glutathione synthase, are highly expressed in astrocytes [156]. But it looks that glutathione activated by Nrf2 functions but mainly are handled by oxitocin cooperative functions. That A plethora of specific targets, including those involved in thioredoxin (TRX) and glutathione (GSH) systems, are activated by Nrf2 [157]. So, cysteine and glutamine id specific step necessary for Leucine synthesis which promote Nrf2 production via NR4As pathway which necessary for activating glutathione expressed by astrocytes. And notice that previous two works indicate the formation of oxitocin in astrocyte which promote Nrf2 production necessary for activating thioredoxin (TRX) and glutathione (GSH) systems by astrocytes. Also, the tyrosine kinases regulate astrocyte cytoskeletal rearrangement [158]. And, activation of tyrosine (where tyrosine included with cysteine in oxitocin composition) and MAP kinases by swelling is a critical step in the opening of volume-sensitive Cl^- channels in astrocytes [159]. And, the role of mTOR/S6 Kinase Pathway Contributes to Astrocyte Survival during Ischemia [160]. Where the role of mTOR/S6 Kinase Pathway is necessary (not only contribute) for Astrocyte functions Survival that mTOR S6K start to activate serotonin and dopamine which regulated by Tyr kinases then followed by activating NR4As pathway in astrocyte firstly by producing glucocorticoid-beta followed by oxitocin and Nrf2 synthesis and mediated by B-adrenergic then followed by Ang2-AT2 and VEGF-A synthesis. Where S6K is produced by mTOR pathway not by astrocytes but necessary for activating astrocytes and contribute their active survival. Where it has been reported that Activation of S6 kinase activity in astrocytes [161]. And it has been reported that Astrocytes, being a target for stress and glucocorticoids, are a promising target for the treatment of stress-dependent depression [162]. That as IL17 activated by OPA1 synthase function as will promote glucocorticoid-beta synthesis via NR4As pathway Also, mTOR S6K pathway stimulate DCs function to produce IL2 which enhance OPA1 synthase functions for producing IL4, IL6 then followed by IL17 which activate glucocorticoid-beta production which promising target for the treatment of stress-dependent depression by astrocytes via Activating NR4As pathway. The decreasing or inhibition in mitochondrial OPA1 function will promote the accumulated Interleukin-2, IL4 and IL6 that can promote mutated heterogeneity and will show inhibition in Biosynthesis of pyrimidine.

Note that tryptophan necessary for activating Proline synthesis which necessary for mitochondrial OPA1 function, that in cases of increasing in pro-inflammation the Tph will follow the passway of proline synthesis necessary for activating OPA1 function that will improve IL17 synthesis, and necessary for tRNA production for prevent toxicity followed by improving immune functions. It has been found that: amyloid toxicity-induced interleukin-4 (IL4 promotes NSC proliferation and neurogenesis by suppressing the tryptophan metabolism and reducing the production of serotonin [163]. That also Melatonin is endogenous hormone, modulates Th17 cells via the reactive-oxygen species [164]. The tryptophan (Tph TGG) synthesis (Tph has imp role for activating Proline synthesis which necessary for activating OPA1 function) regulate serotonin synthesis which activate melatonin synthesis that followed by IL17 productions (regulated by OPA1 synthase function) which prevent IL4 and IL6 accumulation, where OPA1 dysfunctions (due to Tph & Pro dysfunctions) will cause accumulation of pro-inflammatory cytokines which characterize amyloid toxicity. But The activation of IL17 production will be followed by activating glucocorticoid-beta Via NR4As productive pathway for activating oxitocin and Nrf2 production (antioxidative function. So it's clear that mTORC1 S6K and tyrosine kinases activate GFAP followed by stimulate IL2 productions (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 NR4As pathway followed by B-Adrenergic productions which activate oxytocin and Nrf2 synthesis responsible for glutathione production and responsible for adopting antioxidative stress, for heme oxygenase, and anti-inflammatory growth. 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 productions) production via NR4As

pathway followed by B-arrestins, B-adrenergic, and Nrf2 production which activate ACE necessary for Ang2-AT2 and VEGF-A synthesis which necessary for adopting myocardial constrictions and functions. CoQ10 support patients with Coronary Artery Disease by activating directly on myocardial cells [165]. While OPA1 modulate CoQ10 functions (and vise versa) will prevent Acute Ischemic through modulating. IL17 productions which activate glucocorticoid-beta (which promote mineralocorticoid for binding with Na and K cations salts and discard by kidney) followed by B-arrestins and B-Adrenergic productions which followed by oxitocin and Nrf2 production in Myocardial cells functions where that pathway adopt myocardial constriction and promote Ang2-AT2 and VEGF-A necessary for heme oxygenase and anti-inflammatory growth (via NR4As pathway), and that pathway can be contributed by astrocytes for protecting myocardial functions and brain functional activities.

Note that Serotonin productions (which promoted by Tph synthesis which activated by OPA1 synthase and dependent on mTOR kinases pathway) prevent Acute Ischemic via Activating NR4A2 pathway.

Where 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 to tryptophan deficiency Firstly, tryptophan modulates Proline synthesis Arg modulate Proline synthesis, where Proline are so necessary for activating mitochondrial OPA1 function and for activating tRNA production. IL-17/CXCL5 signaling within the oligovascular niche mediates human and mouse white matter injury [167]. Astrocytes in MS white matter appear to be deficient in β2 adrenergic receptors [168]. Also it has been reported that: absence of Nrf2 exacerbates white matter pathology and microgliosis following cerebral hypoperfusion [169].

Now from previous studies we can conclude that absence of leucine, tyrosine, Cys, glycine and GTPase will be the result of dysfunction in modulating IL17 production due to inhibition or dysfunction in mitochondrial OPA1 fusion (IL17 necessary for activating glucocorticoid beta "GCs-beta" and regulated by OPA1 synthase enz.) that can exacerbates white matter hyperintensity, so absence of IL17 due to mitochondrial OPA1 dysfunction will be followed by inhibition or decreasing in glucocorticoid-beta synthesis and inhibition in oxitocin and Nrf2 productions. So white matter hyperintensity is connected to OPA1 mitochondrial dysfunction, that will be the result of inhibition in NR4As pathway that consequently will inhibit glucocorticoid-beta synthesis and inhibition in oxitocin and in Nrf2 synthesis. Where, leucine is important for mitochondrial OPA1 fusion, that leucine zipper/EF-hand-containing transmembrane protein-1 Regulate OPA1-mediated mitochondrial fusion [170]. And Src necessary to control mitochondrial dynamics [171]. And, Oxidation/nitrosation of functional cysteines on mitochondrial proteins serves to modulate protein activity, localization, and complexation in response to cellular stress [172]. And it's necessary to note that Glycine and N-Acetylcysteine) Supplementation in Mice Increases Length of Life by Correcting Glutathione Deficiency, Oxidative Stress , Mitochondrial Dysfunction , Abnormalities in Mitophagy [173] So threonine, leucine, tyrosine, and cysteine which are in the main composition of valorphin are having the roles for maintaining OPA1 function and having the role of the formation all of serotonin, melatonin, GCs-beta, oxitocin and Nrf2 synthesis respectively.

The necessity of valorphin in regulating mitochondrial OPA1 fusion and regulating glucocorticoids-beta, and B-Adrenergic productions followed by oxitocin and Nrf2 synthesis that protect and improve white matter hyperintensity, that also prevent and adopt the increasing in GFAP productions. Brain cancer connect to Leu and Tyr dysfunction which necessary for activating OPA1 repairs and functions Glioblastoma (GBM) is the most common malignant brain cancer is connected to Deficiency in Ser phosphorylation (reduction in mTORC1 followed by reduction in VEGF-A & consequently in pericyte proliferation) , reduction in Leu and Tyr dysfunctions, and reduction in OPA1 synthase which reflect increasing in cholesterol and decreasing in GCs-beta followed by decreasing in both oxitocin and Nrf2 functional stability. The GCs-beta synthesis via NR4As pathway are necessary for Ang2-AT2 and VEGF-A synthesis which are necessary for new cells Biosynthesis. Where pericytes activated by VEGF-A that play a key role in stroke-induced angiogenesis and TJ formation in the newly formed vessels. GC treatment has been demonstrated to improve the tightness of the BBB [174]. And, P-glycoprotein may play a crucial role as an intermediate between brain and periphery by controlling transport of corticosteroids at the BBB [175]. Where The GC-beta promote Ang2-AT2 synthesis via NR4As pathway which activate Pericyte component in vascular barrier genesis which vital to BBB integrity, that pericytes play a key role in stroke-induced angiogenesis and TJ formation in the newly formed vessels [176]. While VEGF (vascular endothelial growth factor) priming enhances pericyte proliferation [177]. So, the Ang2-AT2 and VEGF-A synthesis via NR4As pathway mediated by IL17 productions which activate GCs-beta productions are necessary for the proliferation new cells and for cleaning the toxicity and died cells after stroke. MTORC1 as mentioned previously promote glial fibrillary acidic protein (GFAP). That GFAP promote Schwann cell function. That GFAP is suppressed in cells that form myelin but retained in non-myelin-forming Schwann cells [178]. And, Rapamycin Preserves Neural Tissue, Promotes Schwann Cell Myelination and Reduces Glial Scar Formation After Hemi-Contusion Spinal Cord Injury [179]. So mTORC1 Control the GFAP production which necessary for activating astrocytes to perform NR4As pathway for activating heme oxygenase and anti-inflammatory growth associated with activating BBB after injury for discard damaged cells and genes.

While mTORC1 activated (regulated mainly by Ser phosphorylation) will activate hydrophobic amino acids. While mTORC1 activated (regulated mainly by Ser phosphorylation) will activate hydrophobic amino acids synthesis which concluded tryptophan (TGG) as necessary amino acid for GTPase synthesis and for both serotonin and melatonin synthesis. As serotonin dysfunction occure as a mirror of GTPase dysfunction and dysfunction in pyrimidine synthesis which regulated by OPA1

synthetase enzymes. The melatonin synthesis is regulated by serotonin (which regulated by Trp), and regulated by OPA1 function, that Trp (as mentioned previously is so imp for reactivating OPA1 function which necessary for preventing the accumulation of pro-inflammatory cytokines through activating and improving IL17 productions followed by activating GCs-beta via NR4As pathway. Where it has been reported that: defect in melatonin may be detrimental in the setting of chronic neuroinflammation, downregulating melatonin may be beneficial in activating innate immune response in the context of tumor-mediated immune suppression [180].

Actually the down-regulation of melatonin will not beneficial to initiate immune in the context of tumor mediate immune suppression, because Trp (which regulate both serotonin and melatonin) is so necessary for activating OPA1 function specifically synthase which needed for removing the accumulation of proinflammatory molecules through improving IL17 which activate GCs-beta followed by B-arrestins, B-adrenergic, oxytocin, and Nrf2 production "respectively", where, the Nrf2 signaling deficits disrupt blood brain barrier (in diabetic cases), and down-regulated melatonin functions reflect down-regulated glycoprotein which necessary to control transport of corticosteroids at the BBB (as mentioned previously). The Nrf2 dysfunctions via NR4As dysfunctions (which is the mirror of Deficiency in OPA1 synthase function and increasing in diabetes type 2 as mentioned previously) will be the mirror of inhibition in VEGF-A synthesis that will be result of inhibition in pericyte proliferation and in BBB. That it has reported that Blood-brain barrier disruption in diabetic mice is linked to Nrf2 signaling deficits [181]. So in brief, deficiency in tryptophan synthesis (regulated by Thr and Gly) and deficiency in Tyr and in Leu will be result of deficiency in serotonin and defects in melatonin which reflect Deficiency in mitochondrial repair and functions , followed by increasing in the accumulation of pro-inflammatory molecules, followed by decreasing in both IL17 and in GCs-beta (which necessary for controlling transport of blood brain barrier), followed by decreasing in both oxytocin and in Nrf2 which necessary to protects against ischemic injury and preserves the blood-brain barrier [182].

3. Conclusion

Val and île are imp for Tyr kinases production, while all of Thr, Pro, and Cys are having the role of stabilize tryptophan Biosynthesis which necessary for both mitochondrial OPA1 repairs, and for both serotonin and melatonin Biosynthesis followed by for running IL17 productions which necessary for activating GCs-beta synthesis via NR4As pathway followed by reactivating (stabilize and readopt) both of B-arrestins (which necessary for adopting myocardial functions) and B-adrenergic followed by oxitocin and Nrf2 Biosynthesis (where both are adopting antioxidative stress, anxiety adopting myocardial constrictions , and activate with adoption both astrocytes and lymphocytes functions mediated by Ang2AT2 and VEGF-A productions followed by activating both of heme oxygenase and anti-inflammatory growth, that will protect from Chronic hypertension which associated with WMH, and protect from CoQ10 deficiency, and from increasing in GFAP.

Actually, Tryptophan, tyrosine, and leucine are having the important roles in activating mitochondrial OPA1 repairs, and promoting with adoption to the CoQ10 synthesis , while Trp "TGG" are basically necessary for activating Proline synthesis followed by activating both of OPA1 function and tRNAs production, followed by activating IL17 productions which necessary for activating GCs-beta synthesis via NR4As pathway, followed by oxytocin , and Nrf2 biosynthesis Respectively which necessary for adopting antioxidative functions and necessary for adopting both of heart and brain functional activities. Both of Tyrosine triplets (TAT and TAC) are necessary for mitochondrial OPA1 function, while Glu /Gln cycle are necessary for Leu synthesis which necessary for activating Leu pentapeptides synthesis, while methionine "ATG "(regulated by Tyr TAC) are necessary in brain function through activating met pentapeptides in enkephalin tissue for protecting the stability of antioxidative functions in brain and protect the lymphocytes functional activities. L-cysteine treatment significantly ameliorated brain edema, improved neurobehavioral functions, and attenuated neuronal cell death through activating oxytocin followed by Nrf2 production which promote Ang2-AT2 and VEGF-A synthesis necessary for adopting heart constriction, necessary for activating heme oxygenase, and necessary for activating anti-inflammatory processes and activate normal lymphocytes functions. So, oxytocin and Nrf2 are having significant role in protecting astrocytes functions and treating ameliorate brain edema.

it is very clear why threonine, Arg and Proline are strongly found in Hemorphin composition that firstly threonine necessary to regulate Trp synthesis which activate both Pro and NR4As pathway, where Pro are necessary for stabilizing and maintaining tRNAs biosynthesis and protect cellular signals transmission for keeping their proper functional activities , where Proline originated from Trp are necessary for contributing the mitochondrial OPA1 function, necessary for activating tRNAs Biosynthesis , and necessary for activating NR4As pathway which regulate the oxytocin and Nrf2 productions , that activating proper NR4As will prevent cardiovascular disease (note that CVD has sign of the accumulation of Tyr , Leu and Val due to decreasing in tRNAs synthesis, that tRNAs synthesis which are Trp dependent are more necessary to prevent CVD and prevent accumulation of Val, Île and Leu, mediated by activating serotonin synthesis followed by activating IL17 and NR4As pathway, than the tRNAs which are Arg dependent that will not activate serotonin nor NR4As pathway), adopt heart constriction, activate heme oxygenase, activate lymphocytes functions, and activate anti-inflammatory processes and growth.

That we can strongly conclude that Decreasing in tryptophan Tph will be followed by decreasing in Proline synthesis, that will be result of decreasing in lymphocytes functions, decreasing in antioxidative function, and accumulation in IL2 and IL6, with decreasing in mitochondrial OPA1 function, and will be a strong sign of cardiovascular disease "CVD" which show accumulation of Leu, Val, and île (due to decreasing in tRNA which is Trp /Proline dependent). While, decreasing in Arg will reflect decreasing in tRNAs production and reflect accumulations

in molecules and will cause increasing in hypertension but will not activate serotonin, and will not activate NR4As pathway. Tryptophan (which modulate Proline Biosynthesis functions which modulate OPA1 function) is a precursor for the biosynthesis of co-enzymes and neuromodulators, such as NAD/NADP(H), which necessary to modulate Sirt2 Which necessary for improving hepatic mitochondrial, improving necessary cellular metabolic function, and necessary to prevent chronic hypertension which can be associated with WMH.

All of Thr, Trp, Pro, and Gly (which is the mirror of Trp triplets) are necessary for improving hepatic mitochondrial functions, necessary for regulating normal T-cells functions, necessary for activating serotonin synthesis, and necessary to activate the synthesis of tRNAs which is so necessary for preventing the accumulation of Pro-inflammatory molecules and prevent the increasing in hypertension in WMH. Strongly, morphine is important to adopt, and for strengthen immune effectiveness against diseases progression through protecting normal astrocytes functions and activating both of heart brain functions. The reduction in serotonin (reflect reduction in Pro) will be result of (reflect) decreasing in both of mitochondrial functions and tRNAs, followed by decreasing in megakaryocytes proliferation, followed by reduction in haematopoiesis and associated to white matter hyperintensity. And, my important note is: it's prohibit to use atypical antidepressants, selective serotonin reuptake inhibitors which have the role of inhibiting serotonin function, that it is wrong way and steps which activate white matter hyper-intensity survival followed by CVD and stroke.

My question now is : can we reduce the various side effects by improving valorphin Molecular composition by adding tryptophan (which already formed directly by threonine and Pro, & indirectly by Leu, Val, Glu/Gln, and île) and Gly directly to improve Hemorphin (valorphin) molecules that will lead to a rapid and proper strong effect in getting rid of those aforementioned diseases , while quickly restrengthening the patient's immunity, with reduction in its various side effects, to protect against cerebral arrest and heart failure?. We need another quick research work to record quick results immediately, and I strongly expect strong success in developing the structure of the basic morphine molecules. The recommended new improved valorphin Molecular structure that must be checked by deep research work (through its effect on oxidative 6, on WMH treatment, on adopting myocardial functions, & on activating astrocytes functions): Thr, Tyr, Trp, Leu, Île, Gly, Tyr, Trp, Pro, Val, Val, Arg, Gln Or, and Thr, Tyr, Trp, Gly, leu, Trp, île, Val, Val, Gln Arg, Trp, Pro.

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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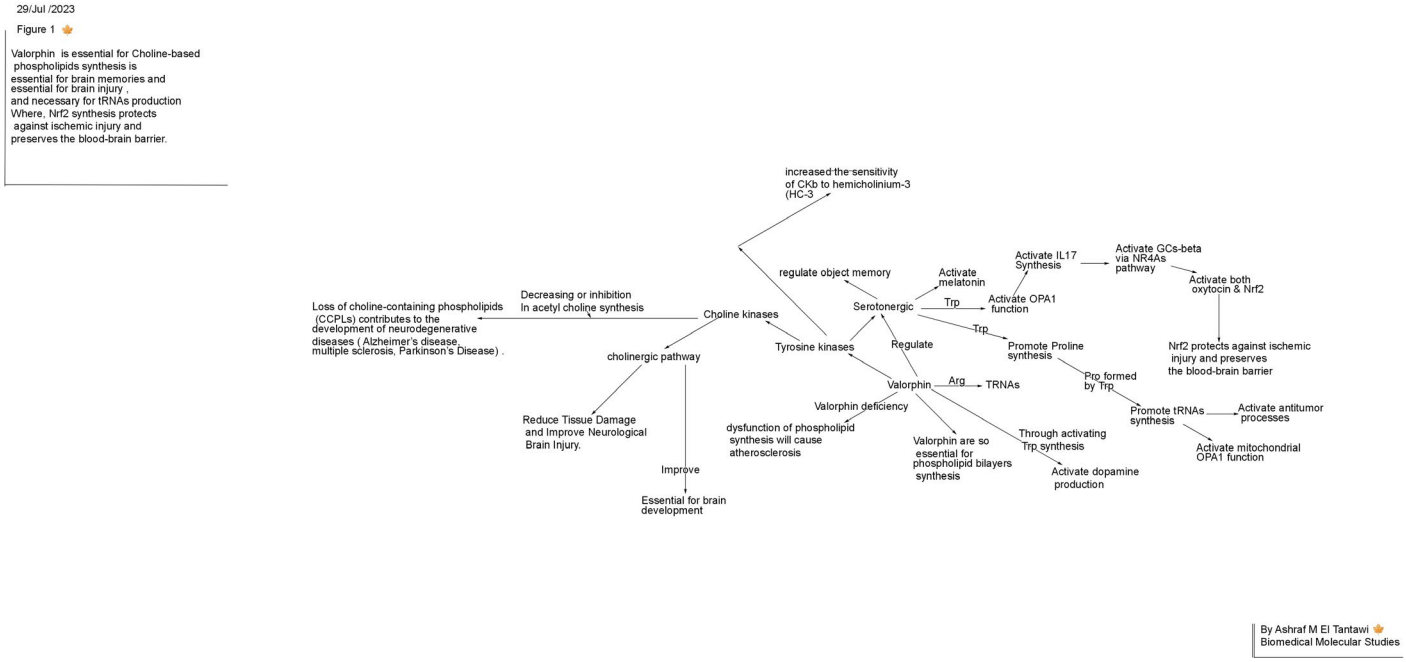

Figure 1

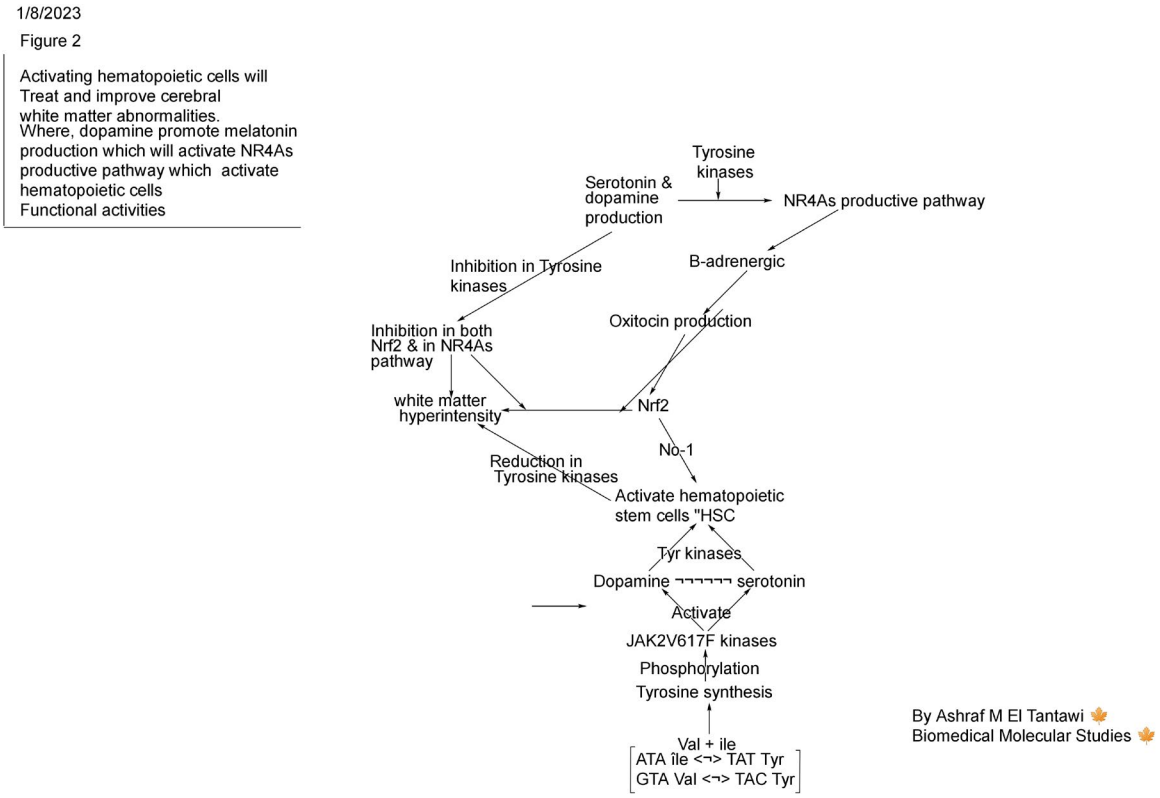

Figure 2

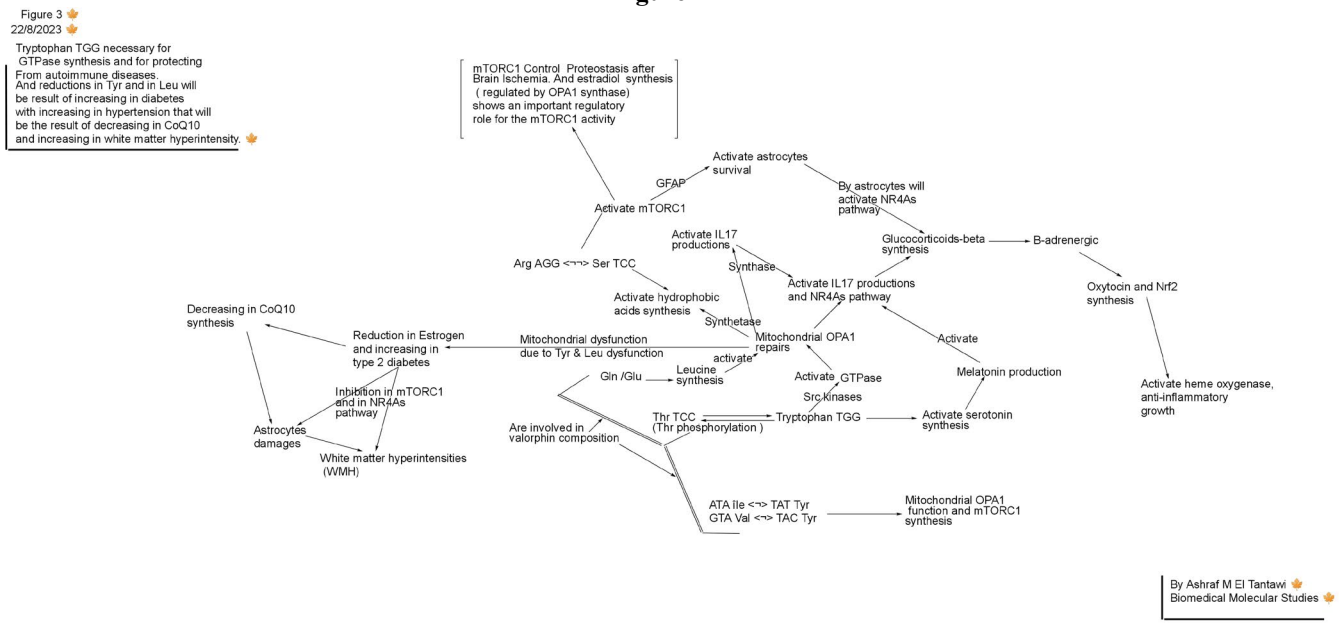

Figure 3

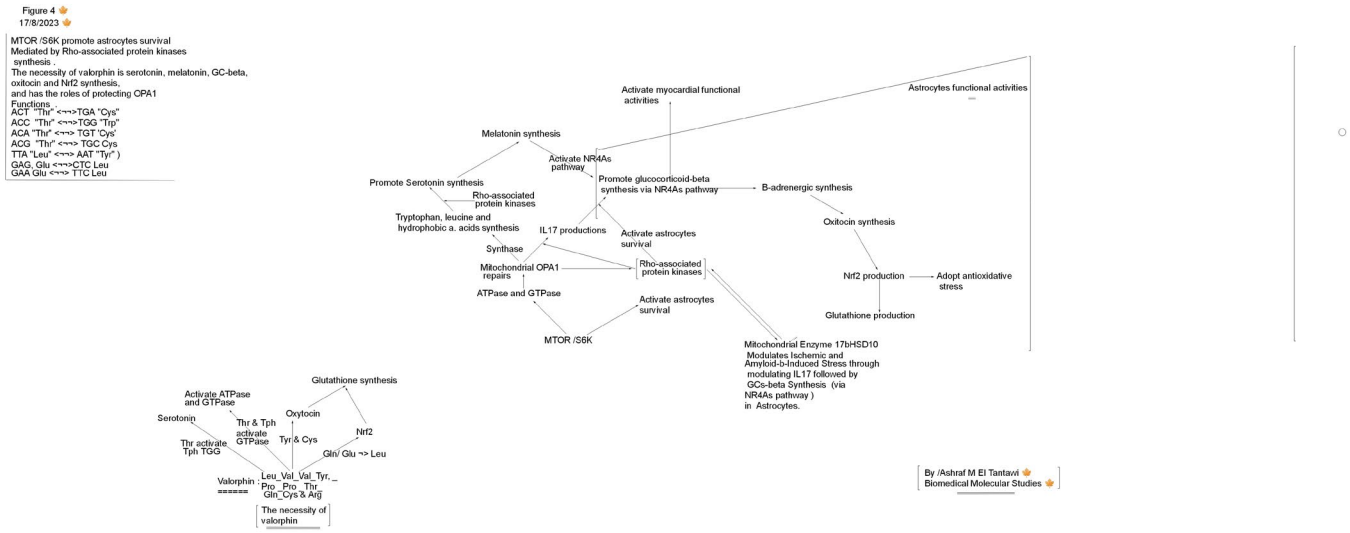

Figure 4

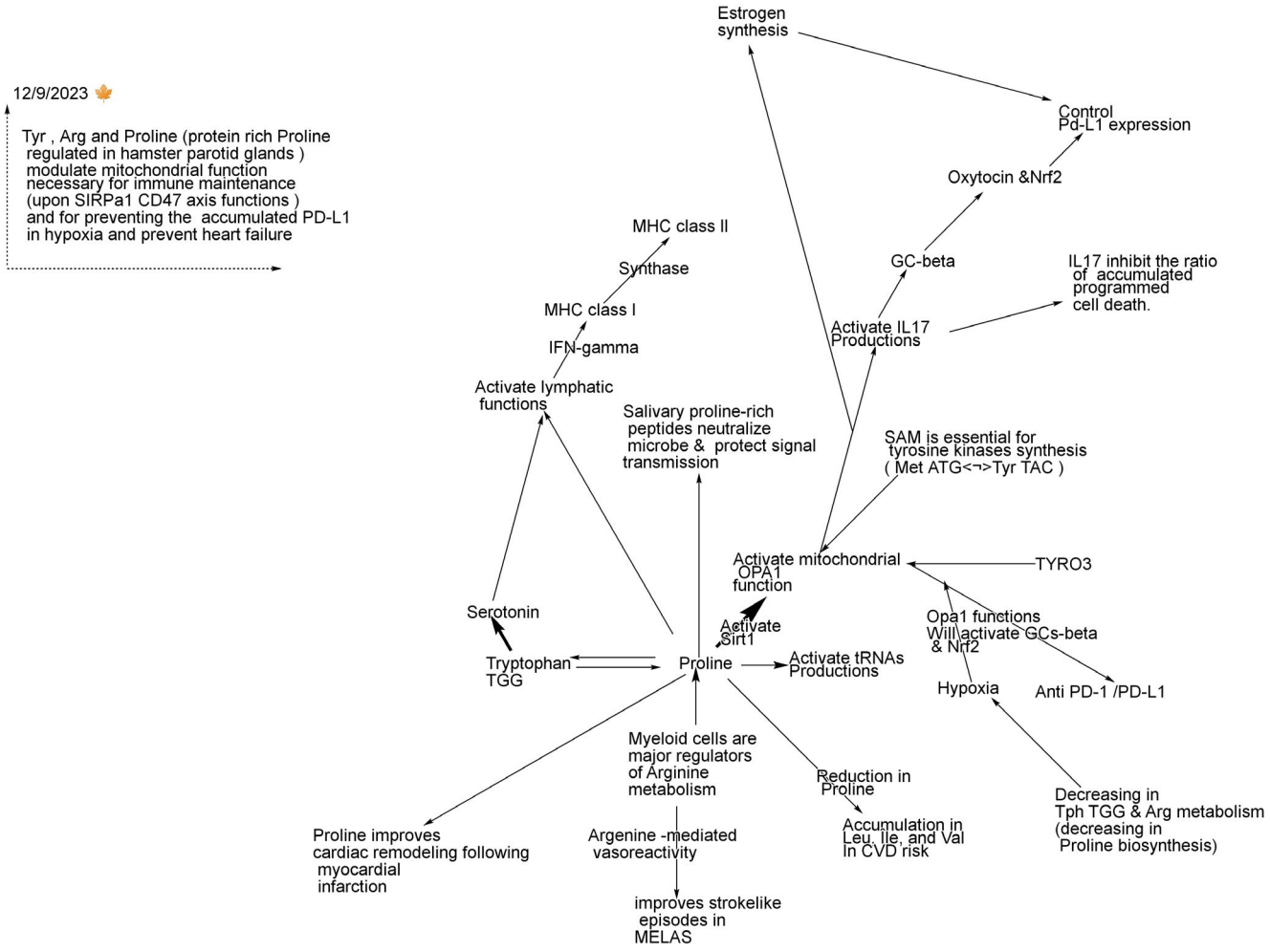

Figure 5

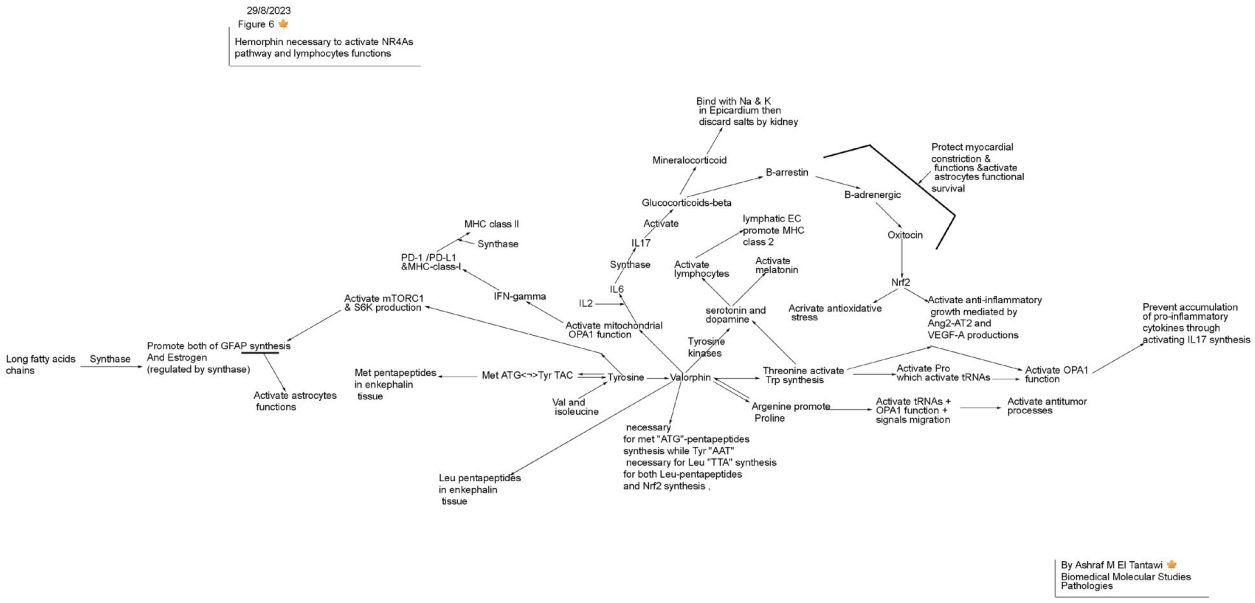

Figure 6

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