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Review

Interferon-gamma – Inducible Inflammation: Contribution to Aging and Aging-Associated Psychiatric Disorders

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ABSTRACT: Aging is associated with the chronic, low grade, Th-1 type inflammation. The key Th-1 type, pro-inflammatory cytokine, interferon-gamma (IFNG), transcriptionally induces the rate-limiting enzyme of tryptophan (TRY) – kynurenine (KYN) pathway, indoleamine 2,3- dioxygenase (IDO). Activation of IDO shunts TRY metabolism from production of serotonin (substrate of antidepressant effect) and its derivatives: N-acetylserotonin (an agonist to the receptors of brain derived neurotropic factor), and melatonin (regulator of sleep and other circadian rhythms), towards production of KYN and its derivatives (anxiogenic, neurotoxic and pro-oxidant factors). Some of kynurenines up-regulate nitric oxide synthase (NOS). Concurrently with activation of IDO, IFNG induces guanosine triphosphate cyclohydrolase I (GTPCH), the rate limiting enzyme of GTP conversion into BH2 (and increases formation of a stable derivative of BH2, neopterin, at the expense of production of BH4, the mandatory co-factor of NOS). Combination of increased NOS activity (by kynurenines) with decreased formation of BH4 leads to the uncoupling of NOS with consequent shift of arginine metabolism from biosynthesis of NO to formation of superoxide anion and other free radicals, and exacerbation of depression, anxiety and cognitive impairment caused by kynurenines. Polymorphism of IFNG (+874) T/A gene, that encodes production of IFNG protein, impacts the IDO and GTPCH activity that might be assessed in humans by KYN/TRY ratio and neopterin concentrations in biological fluids (e.g., blood, urine and spinal fluid). The hypothesis of IFNG inducible IDO/GTPCH inflammation cascade helps to understand the increased association between aging, inflammation and aging-associated psychiatric and medical (insulin resistance, obesity) disorders. Evaluation of markers of IFNG-inducible inflammation cascade might be used to assess the severity of corresponding behavioral and cognitive changes and the efficacy of pharmacological interventions (e.g., IDO inhibitors).

Key words: Interferon-gamma, Aging, Inflammation, Neopterin, Kynurenines, Depression, Insulin resistance, Obesity, Metabolic syndrome

Aging and IFNG-induced inflammation

Recent evidences suggest that aging is associated with a chronic low grade inflammation triggered by a shift from the homeostatic balance of pro- and anti-inflammatory mediators to a pro-inflammatory Th-1 (cellular) type state (1); and by increased reactivity upon immune stimulation due to priming of brain microglial cells and peripheral macrophages. Activation of macrophages and microglia requires both a "priming" stimulus (i.e., interferon-gamma, IFNG) and a secondary "triggering" stimulus such as stress [2] or infection (e.g., gram-negative bacterial endotoxin, lipopolysaccharide (LPS) [3]. Most experimental studies of inflammation and aging focused on the role of LPS, and pro-inflammatory factors such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1b and IL-6. Only very few studies were dedicated to the role of IFNG, the key pro-inflammatory cytokine. Meanwhile, converging evidences point to the involvement of IFNG in mechanisms of aging. Thus,

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interferon-related genes have been identified among six pathways regulating senescence/immortalization: the cell cycle pRB/p53, cytoskeletal, insulin growth factor-related, MAP kinase and oxidative stress pathway [4]. Gene set analysis suggested up-regulation of IFNG in post-mortem brain tissue samples from Brodmann Area 10 in the prefrontal cortex from psychotropic drug-free persons, with the history of depression [5]. Prolonged treatment with IFNG induces cellular senescence in human vascular endothelial cells via up-regulation of senescence-associated genes [6]. Age-dependent increases in IFNG production have been reported in *in vitro* and *in vivo* studies, with minor changes in the remaining evaluated cytokines in senescence-accelerated mice [7]. The frequency of A (low producer) alleles of IFNG(+874) gene that encodes the production of IFNG protein, (see below) increased with aging in line with the other evidences that centenarians are characterized by a higher frequency of genetic markers associated with better control of inflammation [8]. Down's syndrome, a condition representing an accelerated aging, was associated with higher percentages of IFNG-producing cell in comparison with mentally retarded and healthy controls [2].

Interferones might exert their effects via activation of hundreds of genes [10]. This review focuses only on IFNG-induced concurrent transcriptional activation of indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of kynurenine (KYN) pathway of tryptophan (TRY) metabolism, and of guanosine triphosphate cyclohydrolase (GTPCH), the rate-limiting enzyme of tetrahydrobiopterin (BH4) formation from guanosine triphosphate (GTP) [11]. Present review of literature and our data suggests that IFNG-induced concurrent activation of the rate-limiting enzymes of TRY and GTP metabolism is one of the mechanisms responsible for the increased association between aging and aging-associated psychiatric conditions such as depression, anxiety, insomnia, and cognitive impairment (e.g., vascular cognitive impairment, post-operative cognitive decline, and Alzheimer's type dementia).

TRY – KYN metabolism

TRY is an essential amino acid (for humans) with two non-protein metabolic pathways: methoxyindoles and kynurenines, competing for the same substrate, TRY (Fig.1).

Under physiological conditions, about 95% of TRY is metabolized by TRY – KYN pathway. It involves the cleavage of the indole ring of TRY resulted in the formation of N-formylkynurenine followed by KYN in an ensuing step [12] (Fig.1). The rate-limiting enzyme of KYN formation from TRY is IDO, that is ubiquitously (except the liver) distributed in mammals, in neurons, astrocytes, microglia, microvascular endothelial cells and macrophages [13]. Blood KYN/TRY ratio is used as a marker of IDO activity in human studies. Approximately 40% of the kynurenine in brain is synthesized there, the remainder having come from plasma [12].

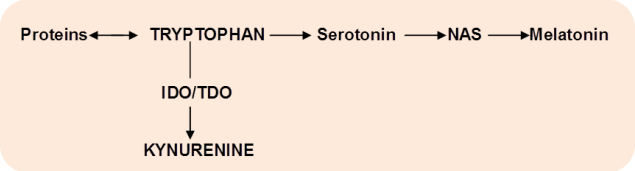

Figure 1. Major pathways of tryptophan metabolism. NAS – N-acetylserotonin, IDO - indoleamine 2,3-dioxygenase; TDO – tryptophan 2,3-dioxygenase

TRY 2,3-dioxygenase (TDO) is the other enzyme (besides IDO) that catalyzes TRY conversion into kynurenine. TDO is found in the bacteria and liver, kidney and brain of the mammals [14]. In difference with IDO, TDO is activated by stress hormones but not by pro-inflammatory cytokines. However, cortisol and dexamethasone "super-induce" IDO in IFNG- primed human astrocytoma cells and native human astrocytes [15]. Since aging is characterized by elevated cortisol production due to dis-inhibition of the HPA axis [16-19], and by increased IFNG production [7], activation of both IDO and TDO might contribute to high risk of depression in the elderly [20]. On the other hand, decrease of TDO activity during an immune response in human astrocytoma cells and in native human astrocytes occurs concomitantly with IDO induction, suggesting a coordinate shift in TRY metabolism from the liver to extrahepatic tissues [21]. Aging-associated elevation of cortisol might affect life span via up-regulation of TRY - KYN metabolism. We found that life span of Drosophila Melanogaster mutants with deficient TDO (vermillion) or impaired transmembrane transport of TRY (white) was two-fold longer that the life span of wild flies [22].

Post-KYN metabolism

KYN is a substrate for competitive post-KYN metabolic routes: KYN – nicotinamide adenine dinucleotide (NAD), and KYN – kynurenic acid (KYNA), and 3-hydroxyKYN – xanthurenic acid (XA) (Fig.2).

The end product of KYN – NAD pathway is NAD. Among the intermediate metabolites of KYN – NAD pathway are N-methyl-D-aspartate (NMDA) agonists (quinolinic and picolinic acids), free radical generator, 3-hydroxyanthranilic acid, and inducers of T-cell apoptosis and lipid peroxydation (KYN and 3-hydroxyKYN) [23]. One of the major metabolite of this pathway, 3-

hydroxyKYN, is a potential neurotoxin in several neurodegenerative disorders [24]. Quinolinic and picolinic acids exerted anxiogenic effects in animal models (25,26), probably, due to effect on benzodiazepines receptors [28].

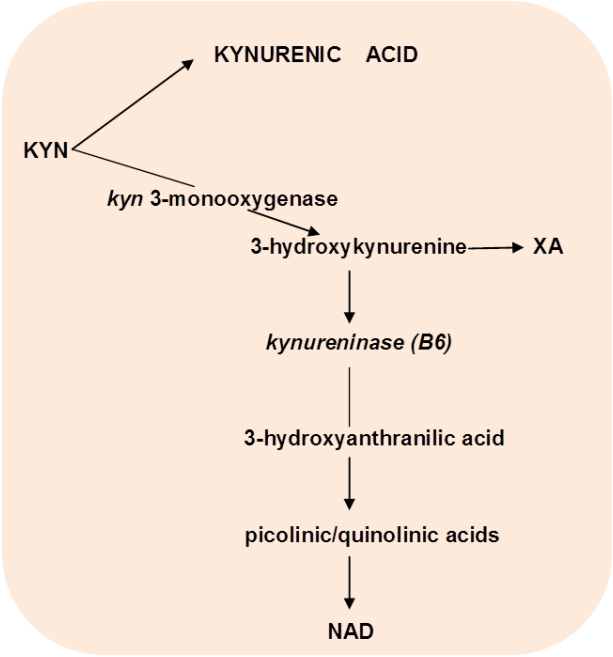

Figure 2. Competitive pathways of post-kynurenine metabolism
Abbreviations: KYNA – kynureninc acid; XA – xanthurenic acid; NAD - nicotinamide adenine dinucleotide, B6 -vitamin B6

The end product of KYN – KYNA pathway is KYNA, the only known endogenous antagonist to alpha 7 nicotinic acetylcholine (alpha7nACh) and NMDA receptors [23]. KYNA, as alpha7nACh antagonist, might contribute to cognitive impairment observed in depression, schizophrenia, dementia, and Down's, Crohn's, Huntington's and Parkinson's diseases and in obesity and hypertension.

The end product of 3-hydroxyKYN – XA pathway is xanthurenic acid (XA) from KYN derivative, 3-hydroxyKYN. Pyridoxal-5'-phosphate (PLP) is a co-factor of kynureninase, the enzyme of the next step converting 3-hydroxyKYN into antranilic acid. Inflammation-associated PLP deficiency inhibits kynureninase, and, consequently shifts 3-hydroxyKYN from formation of antranilic acid towards increased production of XA, that might contribute to the development of insulin resistance [28]. XA reacts with insulin with formation of a complex antigenetically indistinguishable from insulin [29, 30]. Formation of insulin/xanthurenic acid complex might result in decreased sensitivity to insulin rather than in decreased concentrations of insulin, i.e., with insulin resistance [31].

Since IDO inhibitors block the IFNG-induced activation of NOS one might suggest that IFNG effect on NOS is mediated by derivatives of KYN. In fact, two KYN derivatives, quinolinic and picolinic acids are transcriptional inducers of NOS [32, 33].

TRY – methoxyindoles metabolism

Methoxyindoles pathway leads to formation of serotonin (5-HT), N-acetylserotonin (NAS) and melatonin. Under physiological conditions only about 1 - 5% of TRY is metabolized to 5-HT [12]. Up-regulation of TRY – KYN metabolism affects not only TRY – KYN but methoxyindoles pathway as well due to competition for the availability of TRY as a common substrate for both pathways. The rate-limiting enzyme of the 5-HT biosynthesis is TRY-hydroxylase that catalyzes formation of 5-hydroxytryptophan from TRY. The subsequent decarboxylation results in the formation of 5-HT (mainly in the brain raphe nuclei and the gut's enterochromafin tissues).

5-HT is a substrate of NAS and melatonin biosynthesis that takes place, mostly, in the pineal gland. Our post-mortem studies of human pineal confirmed observation from animal research that NAS biosynthesis depends on the availability of 5-HT (as an initial substrate) and up-regulation of beta-adrenoreceptors that mediates noradrenalin-induced stimulation of N-acetyltransferase (NAT), enzyme converting serotonin into NAS. NAS undergoes O-methylation with the formation of 5-methoxy-N-acetyltryptamine (melatonin) [34, 35].

Interferons are transcriptionally induced IDO in a variety of immune cells (e.g., monocyte-derived macrophages, microglia and 5-HT neurons [13]. IFNG is the strongest among interferones inducer of IDO [14].

TNF-alpha stimulates IDO activity and enhances (up to 300%) IFNG-induced IDO expression [14]. Other proinflammatory molecules such as IL-1, IL-12, Il-18, and PGE_2 synergistically with IFNG induce IDO activity [13]. However, the induction of IDO by the bacterial endotoxin LPS might be IFNG-independent [36].

Cross-talk between the methoxyindole and kynurenine pathways

The main impact of IFNG-induced activation of IDO is up-regulation of TRY – KYN pathways and down-regulation of methoxyindoles biosynthesis due to shunt of TRY from 5-HT formation towards KYN pathway. TRY – KYN shunt in depression was originally

suggested by Lapin & Oxenkrug [37, 20]. Additionally, increased production of KYN and its derivatives might contribute to down-regulation of methoxyindoles pathway because of KYN ability to inhibit TRY passage via blood-brain-barrier, and to activate IDO and 5-HT transmembrane transport [12, 38, 26]. NMDA agonists stimulate while NMDA antagonist inhibits NAT. Besides IDO, IFNG stimulates both key enzymes of KYN – NAD pathway, kynurenine mono-oxygenase and kynureninase macrophages [39]. Finally, the increased utilization of PLP by IFNG-induced up-regulation of KYN pathways might decrease availability of PLP as a co-factor for 5-HTP and DOPA decarboxylases, and, therefore, inhibit 5-HT and dopamine biosynthesis.

IFNG-induced changes in guanosine triphosphate metabolism

IFNG transcriptionally activates GTPCH, the rate limiting enzyme of biosynthesis of BH4, the obligatory cofactor of NOS [11] (Fig.3).

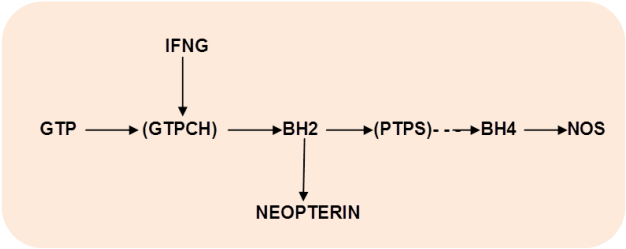

Figure 3. Interferon-gamma and GTP – BH4 pathway. Abbreviations: IFNG – interferon-gamma; GTP – guanosine triphosphate; GTPCH – GTPcyclohydrolase 1; BH2 - 7,8-dihydroneopterin; PTPS – pyruvoyl tetrahydropterin synthase; .BH4 – tetrahydrobiopterin; NOS – nitric oxide synthase.

GTPCH catalyzes GTP conversion into 7,8-dihydroneopterin (BH2). Regulation of GTPCH might be tissues and species specific. In wild-type male and female animals the highest levels of GTPCH mRNA expression were observed within 5-HT neurons, followed by noradrenaline and then dopamine neurons. Wild-type female animals were found to express lower levels of GTPCH mRNA in each cell type when compared with levels seen in wild-type males. [40].

In humans, IFNG-induced stimulation of GTPCH does not result in correspondent up-regulation of pyruvoyl tetrahydropterin synthase (PTPS) that becomes the rate-limiting step of pteridines biosynthesis with consequent accumulation of BH2 and its stable metabolite, neopterin [41]. Importantly, IL-1 beta, in difference with IFNG, activates, mainly, PTPS, and partly GTPCH. As a result, IL-1beta increases the amount of BH4 (+40%) but concomitantly reduced the accumulation of BH2 (and neopterin) whereas IFNF-induced stimulation of GTPCH results in accumulation of BH2 (and neopterin) at the expense of BH4 formation [11]. Therefore, elevated neopterin levels in body fluids like cerebrospinal fluid, blood and urine closely reflect activation of GTPCH inducible by IFNG (but not by other pro-inflammatory factors, e.g., TNF-alpha and IL-1beta [42]. Neopterin reflects IFNG-inducible pro-inflammatory immune status and serves as a marker of cellular immune system activation in clinical studies [43]. In addition to its role as a marker of GTPCH activation and IFNG activity, neopterin (as some other pteridines), might modulate oxidative stress [44].

IFNG inducible IDO/GTHCH-inflammation cascade

We suggested that IFNG-induced concurrent up-regulation of production of kynurenines and BH2 leads to formation of an inflammation cascade that combines up-regulated activity of NOS (by kynurenines) with deficient availability of BH4 as NOS cofactor [45]. Such a combination results in an uncoupling of NOS and, consequently, in shifting of arginine metabolism away from the formation of NO and towards production of reactive oxygen species (ROS) such as superoxide anion [46] and hydrogen peroxide [47]. Superoxide is a substrate for formation of one of the most aggressive free radicals, peroxynitrite. Peroxynitrite (as well as 3-hydroxyKYN and 3-hydroxyanthranilic acids, and neopterin and other pteridines), triggers phospholipase A2 – arachidonic acid – cyclooxygenase 2 - arachidonate 5-lipoxygenase metabolic pathway resulting in the increased production of inflammatory factors: prostaglandins, via activation of cycloxygenase (COX) and leucotrienes, via activation of arachidonate 5-lipoxygenase (5-LOX) [48]. The pathway of the inflammatory enzyme, 5-LOX, was suggested as a putative common mechanism that is affected by aging and may link depression and atherosclerosis [49].

IFNG (+874) T/A gene polymorphism and IDO/GTPCH-inflammation cascade

Single-nucleotide polymorphisms (SNPs) in regulatory regions of cytokine genes have affect the levels of expression of some cytokines. IFNG protein production is encoded by polymorphic IFNG (+874) T/A gene [50]. The T to A polymorphism located at position +874 of the intron 1 of IFNG gene (+874 IFNG) directly influences the level of IFNG production associated with the CA microsatellite marker (50). Three possible genotypes are generated by analyzing the sequence mutation for +874 IFNG (either T or A), the A/A, T/A and T/T genotypes,

which confer three different phenotypes: low, intermediate and high producers of IFNG respectively [51, 52]. In humans, T (high producer) allele (TA + TT genotypes) is associated with higher IFNG mRNA expression (53) and higher blood levels of IFNG, baseline and released by stimulated peripheral blood mononuclear cells, than AA genotypes [54].

Since IFNG induces IDO activity one might suggest that high producer alleles would be associated with higher IDO activity than low producer alleles. Indeed, in healthy women in Finland high producer T allele of IFNG (+874) gene was associated with increased IDO activity (i.e. elevated plasma KYN/TRY ratios) in comparison with the presence of low producer A allele [55]. This finding indicates that TRY – KYN metabolism is genetically controlled by the IFNG gene via regulation of IDO activity.

We could not find reports on the association of IFNG (+874) T/A genotypes and GTPCH activity. Our study of 174 American Caucasian reveals association of increased GTPCH activity (evaluated by plasma neopterin levels) with IFNG (+874) TT (high producers alleles) in comparison with AA and AT genotypes [56]. Our finding suggests that GTP – BH4 metabolism might be genetically controlled by the IFNG gene via regulation of GTPCH activity.

Therefore, literature and our data suggest that polymorphisms of IFNG (+874) T/A gene might impact the activity of the key enzymes of the IFNG inducible IDO/GTPCH inflammation cascade.

IFNG might be involved in epigenetic regulation of immune response by augmentation of the development of Th-1 cells from Th-17 cells via DNA methylation [57] and of O(2)(-)-generating system via histone modifications [58]. Methylation of IFNG was significantly associated with seniority in shift workers [59].

Psychiatric symptoms associated with IFNG inducible IDO/GTPCH inflammation cascade

Depression- and aging-associated inflammation is associated with behavioral and cognitive impairment. Many of the known biochemical disturbances associated with certain psychiatric conditions might be related to the up-regulated IFNG inducible IDO/GTPCH inflammation cascade.

IFNG inducible IDO/GTPCH inflammation cascade might be clinically characterized by three major markers: IFNG (+874) T/A polymorphism, KYN/TRY ratio (IDO activity), neopterin concentrations (or BH4/neopterin ratio (GTPCH activity) and indexes of NOS uncoupling (e.g., levels of BH4, NO and O_2^-).

Psychiatric symptoms associated with IFNG (+874) T/A *gene polymorphism*

We are not aware of studies of IFNG gene polymorphisms associated with depression. Majority of information on inflammation-associated depression came from the studies of depression developed in 30 - 50% patients during IFN-alpha treatment of hepatitis C virus (HCV) and malignant melanoma [60]. IFN-alpha treatment of HCV patients a) increased the severity of depression and anxiety assessed by a Montgomery–Asberg Depression Rating Scale and HAM-A scores; b). increased blood kynurenine/TRY ratio, indicator of increased IDO activity, and c) reduced plasma TRY and serum serotonin concentrations. There were significant relationships between the IFN-alpha induced changes in the MADRS score and serum KYN (positive) and serotonin (negative) concentrations [60].

The causative role of the elevated IDO activity in mediation of co-morbid depression in inflammatory disorders could be further supported by studies of a depressive-like behavioral syndrome induced in mice by LPS-induced activation of IDO. Blockade of IDO activation by anti-inflammatory tetracycline derivative minocycline [61] or IDO inhibitor, L-methyltryptophan (L-MT), prevented the development of depressive-like symptoms [62]. Administration of KYN to naive mice dose dependently induces depressive-like behavior. These results implicate IDO as a critical molecular mediator of inflammation-induced depressive-like behavior [62]. Systemically administrated IFN-alpha passes the blood–brain barrier and reaches effective concentrations acting on microglial cells as well as macrophage receptors. IFN-alpha has much weaker direct IDO stimulating effect than IFNG but might increase IDO activity by stimulating the production of IFNG and TNF- alpha [14]. Polymorphisms of genes related to 5-HT, IL-6 and IFN-alpha receptors were studied in HCV patients treated with IFN-alpha [60, 62]. However, we found no studies of genetic polymorphisms of IFNG gene that encodes IFNG production. In our retrospective study of 180 HCV patients treated in the past with IFN-alpha we found less frequent A (low producer) allele and more frequent T (high producer) allele among patients who developed depression during treatment with IFN-alpha in comparison with HCV patients who did not experience depression during treatment with IFN-alpha [63]. Our results suggest that T (high producer) allele of IFNG (+874) gene might be a risk factor for the development of depression triggered by interferon-induced inflammation.

Psychiatric symptoms associated with IFNG-induced activation of IDO

Up-regulation of IDO leads to decreased 5-HT, NAS and melatonin production and increased formation of kynurenines due to shunt of TRY metabolism from methoxyindoles toward KYN pathway [37, 20].

"Kynurenine shunt" decreases the availability of TRY as a substrate to biosynthesis of 5-HT, the substrate of depression [37]. IFN-alpha significantly reduces serotonin in the frontal cortex, midbrain, and striatum of rats [13]

Depression and dementia are the symptoms of pellagra, the diet-induced TRY deficiency [64]. TRY depletion has been associated with the induction of depressive relapse in vulnerable patients. Key factors in depression are low levels of 5-HT and its metabolites as well as a reduced sensitivity to 5-HT receptor [65].

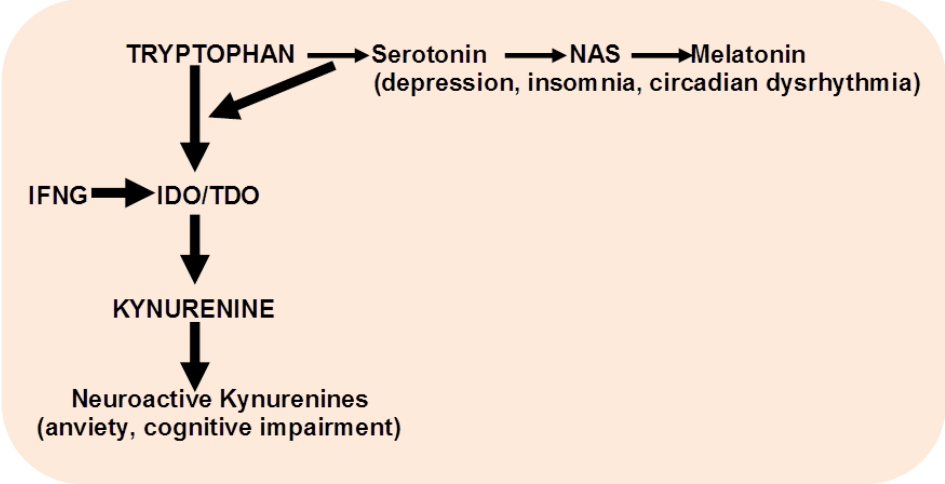

Figure 4. Shift of tryptophan metabolism in depression (Lapin, Oxenkrug, 1969; Oxenkrug, 2010). IFNG – interferon-gamma; NAS – N-acetylserotonin, IDO-indoleamine 2,3-dioxygenase; TDO – tryptophan 2,3- dioxygenase

IFNG-induced IDO activation leads to deficient production of 5-HT, the substrate of melatonin biosynthesis. Deficiency of melatonin contributes to primary and depression-associated insomnia and circadian rhythms disturbances, especially in elderly population [66].

IDO up-regulation increases production of kynurenine, quinolinic acid and 3-hydroxykynurenine. These kynurenine derivatives exerted an anxiogenic activity in the standard animal models of anxiety [67]. Kynurenine**,** in its turn, activates IDO, and, thus, a "vicious circle" is formed that supports an elevated level of kynurenines for prolong time [25, 26]. Increased KYN levels were found in patients with anxiety and depression [68] suggesting that aging-associated up-regulation of kynurenines production might contribute to aging-associated increase of anxiety (69).

Depression in elderly is often associated with psychotic features. IDO up-regulation might result in increased production of KYNA, the only known endogenous NMDA antagonist. KYNA activates midbrain dopaminergic neurons similar to the effect of ketamine and MK-801, the exogenous NMDA antagonists and psychotomimetics [39]. KYNA role as psychotomimetic is further stressed by the findings of increased KYNA in brains and CSF in schizophrenia and its ability to inhibit prepulse inhibition (animal model of schizophrenia) [70, 71].

Impaired production of brain derived neurotropic factor (BDNF) is associated with IFN-alpha-induced depression in HCV patients [67]. IFNG-induced IDO activation might lead to decreased formation of BDNF receptors agonists via deficient production of 5-HT and, consequently, of NAS. The general consensus limits NAS role to the intermediate product of melatonin formation from 5-HT. However, recent studies revealed that NAS (but not 5-HT or melatonin) is a specific agonist of BDNF (TrkB) receptors [72]. Neurogenesis is essential for antidepressant effect [73], and BDNF levels were reduced during depressive episodes and recover after treatment [74]. Ability of NAS to stimulate BDNF receptors might explain our observations of anti-aging [75], anti-inflammatory [76], memory-enhancing [77] and anti-hypertensive [78,79,80] effects of NAS and its derivatives. Electroconvulsive shock elevated pineal NAS [81]. Antidepressant-like effect of NAS in mouse

tail-suspension test [82], and force swimming test [72] might be mediated (in addition to Trkb receptors) via quinone reductase (QR)/melatonin 2 binding sites [83]. Therefore, NAS deficiency associated with aging [84] and inflammation might contribute to related behavioral and cognitive psychiatric changes.

KYNA antagonism to alpha-7-nicotinic acetylcholine receptors might contribute to impairment of executive function (working memory) in response to IFN-alpha therapy [85]. Increased production of KYNA was observed in Alzheimer's disease, Down syndrome and Crohn's disease [9], and aging. While inflammation of white matter microvessels might be one of the causative factor in vascular dementia, it might contribute to cognitive impairment at the late studies of the Alxheimer's type dementia since beta-amyloid stimulates IFNG production [9, 86,87].

Pro-inflammatory cytokines, including IFNG, might contribute to postoperative cognitive dysfunction that occurs after surgery and can persist long after physical recovery in elderly patients [88].

Psychiatric symptoms associated with IFNG-induced activation of GTPCH

NOS uncoupling (and subsequent activation of lipid peroxidation and arachidonic acid cascade) is a major consequence of the upregulation of IFNG-inducible cascade. Accordingly, baseline levels of both plasma NO and platelet NOS activity were significantly lower in depressed subjects compared to healthy controls [89]. Treatment with paroxetine, selective 5-HT uptake inhibitor, considered a standard for prevention of IFN-alpha induced depression [60] increased plasma NO levels as well [89].

COX-2 activity might contribute to depression while 5-LO activity was suggested with a link depression and atherosclerosis [90].

Interestingly, inflammatory markers, including both IDO (TRY/KYN ratio) and GTPCH (neopterin concentrations) were found to be increased in obese rats [91] and obese subjects [60]. However, only neopterin and KYN/TRY ratios did not normalized after the bariatric surgery and weight loss [92, 93]. These studies suggest that IFNG-induced IDO and GTPCH activities have unique role as the trait (vs state) inflammatory markers in obesity.

Recent analysis of behavior and cognitive changes associated with aging indicated that increased KYNU/TRY ratio was associated with depressive symptoms of lassitude, reduced motivation, anorexia and pessimism while neopterin (and other markers of GTPCH activity were associated with neurovegetative symptoms such as digestive symptoms, fatique, sickness and sleep disturbances [85]. These results suggest that IDO component of IFNG-inducible inflammation cascade is related more to the development of psychiatric symptoms while GTPCH component is related more to the development of medical problems.

Aging and IFNG inducible IDO/GTPCH inflammation cascade

The frequency of A (low producer) alleles of IFNG(+874) gene that encodes the production of IFNG protein, increased with aging [8]. Microglia-derived IFNG was shown to stimulate astrocytes via IFNG receptor in the injured hippocampus of SAMR1 mice [94].

Down's syndrome, a condition representing an accelerated aging, was associated with higher percentages of IFNG-producing cell in comparison with mentally retarded and healthy controls consistent with observation of an increased KYNA levels in Down's syndrome patients [9].

Animal and human data suggest the increased activities of IDO and GTPCH with aging. Increased formation of KYN derivative, KYNA, was observed in aged rat brain [95, 96] and in human serum [97]. KYN/TRY ratio positively correlated with increased aging in humans of the three age groups (34-60, 61-71, and 72-93 years) [98] and nonagenarians in comparison with 45 years old subjects [99]. The higher rate of TRY conversion into KYN at the entry into the study was predictive of higher mortality in 10-year prospective study of nonagenarians [100].

Increased plasma levels of neopterin (but not other 33 independent immune parameters) separated the aged and a healthy younger group [101]. Neopterin levels increased with age [44, 102] with no gender differences [42] while age-associated increase of IDO was more prominent in women than in men [55].

Medical diseases associated with IFNG-induced activation of IDO

Elevation of neopterin, as a consequence of up-regulation of IFNG production, has been shown to correlate with several components of inflammation-associated metabolic syndrome, aging, and total and disease-specific mortality in populations of European ancestry [103, 104]. We assessed neopterin correlations with clinical markers of metabolic syndrome and mortality risk in population with a different genetic background, i.e., Puerto Ricans residents of Boston (592 subjects (45 - 75 years of age). Neopterin concentrations correlated with abdominal obesity (waist circumference, $r=0.085$, $p<0.038$), HDL cholesterol ($r= - 0.15$,

p<0.0001), and insulin resistance (HOMA-IR, r=0.08, P<0.03). Neopterin concentrations of >16 nmol/L at baseline were associated with the dramatically increased risk of mortality in 113 subjects followed for 6 years [105]. These results together with previously reported data in European subjects suggest a similar pattern of neopterin correlations with metabolic syndrome and mortality risk in population with different genetic backgrounds.

Since inflammation is associated with PLP deficiency [106, 107], we assessed correlations of neopterin with PLP. Neopterin concentrations correlated with plasma (PLP (r= - 0.13, P=0.002) [105]. Our observation is in line with the previously reported decreased serum PLP and increased serum neopterin levels in patients with coronary heart disease (108)". Since PLP deficiency is associated with the increased production of diabetogenic kynurenine derivative, xanthurenic acid [28], our results suggest that up-regulation of IFNG inducible IDO/GTPCH inflammation cascade, i.e, combination of increased formation of KYN from TRY (e.g., in depression) with PLP deficiency (e.g., in aging-associated inflammation) might contribute to the development of insulin resistance [108], and to increased incidence of diabetes in depressed patients [109]. It is noteworthy that increased uncoupling of NOS (the major consequence of IFNG inducible IDO/GTPCH inflammation cascade) was found to associate with aging and diabetes [110].

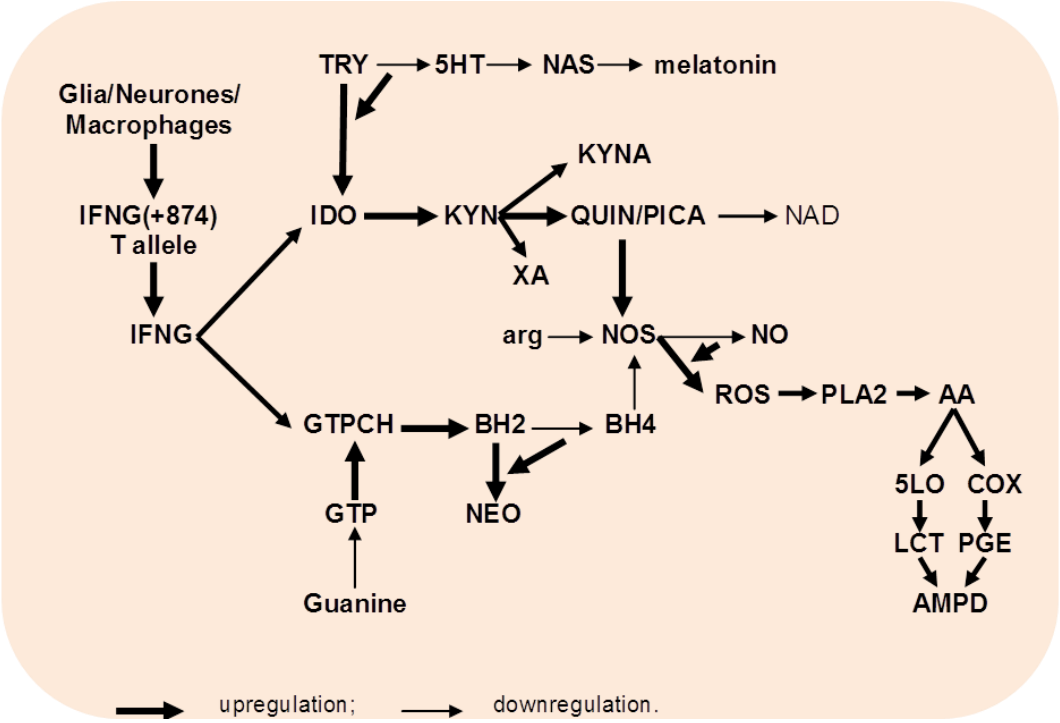

Fig. 5. IFNG-inducible activation of TRY – KYN and GTP – BH4 metabolism in aging and associated medical and psychiatric disorders.

Abbreviations: IFNG – interferon-gamma; TRY- tryptophan; 5HT – serotonin; NAS – N-acetylserotonin; IDO- indoleamine 2,3-dioxygenase; KYN – kynurenine; QUIN/PICA – quinolinic/picolinic acids; XA – xanthurenic acid; NAD - nicotinamide adenine dinucleotide; GTPCH – guanosine triphosphate cyclohydrolase 1; BH2 - 7,8-dihydroneopterin; BH4 – tetrahydrobiopterin; NEO – neopterin; NOS – nitric oxide synthase; arg - arginine; ROS - superoxide anion, hydrogen peroxide**;** PLA – phospholipase A2; AA – arachidonic acid; COX – cyclooxygenase 2; 5-LO – arachidonate 5-lipoxygenase; PGE – prostaglandins; LCT – leucotriens; AMPD – aging-associated medical and psychiatric disorders

Conclusion

The hypothesis of IFNG inducible IDO/GTPCH inflammation cascade helps to understand the increased association between aging, inflammation and aging-associated psychiatric and medical (insulin resistance, obesity) disorders. Evaluation of markers of IFNG-inducible inflammation cascade might be used to assess the severity of corresponding behavioral and cognitive changes and the efficacy of pharmacological interventions (e.g., IDO inhibitors) [61].

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