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Serotonin – kynurenine hypothesis of depression: historical overview and recent developments

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Abstract

In the late 60th - early 70th of the last century Prof. IP Lapin (June 26, 1930 – August 23, 2012) suggested that “intensification of central serotonergic processes is a determinant of the thymoleptic (mood elevating) component” while “activation of noradrenergic processes is responsible for psychoenergetic and motor-stimulating component of the clinical antidepressant effect”. He suggested that in depression cortisol-inducible activation of liver enzyme, tryptophan 2,3-dioxygenase (TDO), shunted “metabolism of tryptophan away from serotonin production towards kynurenine production” leading to serotonin deficiency. He was the first to suggest and discover that kynurenine and its metabolites affect brain functions, and propose the role of neurokynurenines in pathogenesis of depression and action mechanisms of antidepressant effect. Further major developments of serotonin-kynurenine hypothesis include the discovery of antidepressant and cognition-enhancing effects of post-serotonin metabolite, N-acetylserotonin, an agonist to tyrosine kinase B(TrkB) receptors of brain derived neurotrophic factor. The discovery of indoleamine 2,3-dioxygenase (IDO), another rate-limiting enzyme of TRY – KYN metabolism, located in brain and inducible by pro-inflammatory cytokines, suggested the link between depression and aging/aging-associated medical (e.g., insulin resistance, obesity, cardiovascular), psychiatric (e.g., vascular cognitive impairment) and other disorders associated with chronic inflammation (e.g., hepatitis virus C, psoriasis) disorders.

A. Historical perspective

A1. Serotonin hypothesis

The discovery of the tricyclic antidepressants by R. Kuhn [1] in 1958 stimulated the research of the biological causes of depression and action mechanisms of antidepressant effect. Most researchers by the 1960s considered the noradrenaline involvement in both pathogenesis of depression and action mechanisms of antidepressants proposed in 1965 [2,3]. The serotonin hypothesis of depression was championed only by very few psychiatrists, such as A. Coppen in England. He originally suggested that “low” serotonin (but not noradrenaline) causes depression while clinical antidepressant effect is mediated by the increase of serotonin (but not of noradrenaline) [4].

I. Lapin and his co-workers were the first to demonstrate that imipramine potentiated the central effects of serotonin (but not of noradrenaline) injected into the amygdala of cats [5,6]. To further investigate the role of serotonin in the effects of antidepressants, I. Lapin used frog (whose brain contains mostly serotonin but not noradrenaline) to observe behavioral effects specific for serotonin (in rodents serotonin effects are “masked” by noradrenaline). He found that behavioral effects of serotonin in frog were potentiated by tertiary

(predominantly serotonin uptake inhibitors) (e.g., imipramine) but not by secondary (predominantly noradrenaline uptake inhibitors) (e.g., desipramine) tricyclic antidepressants [7,8]. Considering that predominant clinical effect of tertiary tricyclic antidepressants is improvement of mood while that of secondary tricyclics is psychomotor stimulation, I. Lapin suggested that “intensification of central serotonergic processes is a determinant of the thymoleptic (mood elevating) component” while “activation of noradrenergic processes is responsible for psychoenergetic and motor-stimulating component of the clinical antidepressant effect” [9]. A. Carlsson and his research team arrived to the same conclusion based on their finding that tertiary (but not secondary) tricyclic antidepressants attenuated the depletion of intraneuronal brain serotonin stores caused by 4-methyl-alpha-ethyl-meta-tyramine [10].

A.2. Tryptophan shunt towards formation of kynurenines as a cause of serotonin deficiency

As to the role of serotonin in the pathogenesis of depression, Prof. Lapin proposed that serotonin deficiency in depression was caused by the “shunt” of tryptophan (TRP) metabolism from formation of serotonin (along the methoxyindole pathway of TRP metabolism) towards production of kynurenine (KYN). The shunt was suggested to be caused by the activation of the rate-limiting enzyme of TRP – KYN pathway, TRP 2,3-dioxygenase (TDO), activated by cortisol. Since production of cortisol by adrenal gland is inhibited by serotonin in brain (“amygdaloid complex”), it was proposed that serotonin deficiency resulted in disinhibition of brain-adrenal axis, and, consequently, in increased production of cortisol, the super-induction of TDO, and shifting of TRP metabolism from serotonin to KYN pathways, i.e., “vicious cycle” sustaining serotonin deficiency [9]. (This 1969 Lancet paper was recognized as a Citation Classic).

A.3. Kynurenine hypothesis

I. Lapin formulated a new, “kynurenine”, hypothesis of depression [11]. The “kynurenine” hypothesis (in difference with “serotonin” hypotheses) [4,9,10] concentrated on the role of elevated KYN and its derivatives for pathogenesis of depression and action mechanisms of antidepressive effect. He suggested that KYN and its derivatives [that were in late 60th considered only as intermediate products of nicotinamide adenine dinucleotide (NAD) formation from TRP] have their own biological activity [11]. I. Lapin discovered that KYN and its derivatives participate in regulation of blood pressure [12,13], body temperature [11], seizure activity [14 – 19], and anxiety [20, 21]. He introduced the term “neurokynurenines” (NEKY) and suggested that NEKY are the “participants of depression” and the “common neurochemical links of stress and anxiety” [11, 22].

It is noteworthy that I. Lapin found that kynurenine, quinolinic acid and 3-hydroxykynurenine exerted an anxiogenic while KYNA exerted anxiolytic activity in the standard animal models of anxiety [21]. He discovered the antagonistic relationships (e.g., pro-convulsive VS anti-convulsive and anxiogenic VS anxiolytic) between kynurenic acid (KYNA) and major N-methyl-D-aspartate (NMDA) agonists (e.g., quinolinic and picolinic acids [21]). (According to current understanding, KYNA is NMDA and alpha7nACh antagonist while most of the rest of KYN derivatives are NMDA agonists [23]. Since KYN attenuated serotonin effects (including activation of serotonin uptake by blood platelets), I. Lapin suggested that increased formation of NEKY might contribute to the mechanisms of resistance to antidepressants [24].

Thus, the studies of I. Lapin and his research team initiated in the late 60-th – early 70-th of the last century established 1). Association of serotonin with mood elevating (thymoleptic) component of clinical antidepressant effect [9]; 2). Shunt of TRP metabolism towards

formation of KYN causing deficiency of serotonin [9]; and 3). Role of NEKY in pathogenesis of depression and anxiety and action mechanisms of antidepressants [11,22].

B. Recent developments

B1. "N-acetylation" of serotonin hypothesis

B1a. Biological activities of N-acetylserotonin—Under physiological conditions only about 1 – 5% of TRY is metabolized to 5-HT [25]. Up-regulation of TRY – KYN metabolism affects not only TRP – KYN but methoxyindoles pathway as well due to competition for TRP as a common substrate for both pathways. The first steps of the methoxyindoles pathway of TRP metabolism includes formation of serotonin that served as a substrate for melatonin biosynthesis via formation of N-acetylserotonin (NAS). Therefore, deficiency of serotonin caused by TRP shunt to KYN production might impact not only the functions of serotonin receptors but formation of NAS and melatonin. Melatonin biosynthesis follows circadian pattern in many species [26], including humans [27,28], and its deficiency contributes to disturbances of sleep and circadian rhythms in depression [29]. The first step of melatonin biosynthesis from serotonin is formation of NAS catalyzed by serotonin-N-acetyltransferase (SNAT) [30]. For many years NAS was considered only as an intermediate product (and immediate precursor) of melatonin biosynthesis from serotonin. G. Brown and his team were the first to suggest that NAS may have a role in the central nervous system distinct from that of being a precursor for melatonin. This hypothesis was based on the immunohistochemical identification of NAS in specific brain areas separate from melatonin and serotonin (e.g., brain stem, cerebellum and hippocampus, and within the reticular formation nuclei and motor nuclei of the brain stem); on the inhibitory action of NAS on glutamate induced firing of pyramidal cells; and on its analgesic effect (separate from melatonin and serotonin) [31–34].

B1b. NAS and antidepressant effect—We were the first to observe antidepressant-like effect of NAS in a mice tail-suspension test [35]. NAS antidepressant-like effect was confirmed in a rat forced swim test [36]. Literature data and our studies revealed NAS involvement in action mechanisms of antidepressants. Selective tricyclic antidepressants and serotonin uptake inhibitors increased SNAT mRNA expression [37]. Our *in vivo* and *in vitro* experiments revealed that acute administration of irreversible (clorgyline) and reversible (brofaromine, beflaxotone, moclobemide) selective monoamine oxidase (MAO) type A inhibitors (but not of highly selective MAO-B inhibitors) suppressed MAO-A activity and stimulated pineal NAS biosynthesis. The effect of MAO-A inhibitors is strain (spontaneously hypertensive rats > Fisher 344N > Wistar Kyoto > Sprague-Dawley) and gender (male > female) dependent. Considering that MAO-A but not MAO-B inhibitors exert a clinically antidepressant effect, we suggested that stimulation of NAS biosynthesis contributes to the antidepressant effect of MAO-A inhibitors. Antidepressant and selective MAO-A inhibitor, clorgyline, stimulates rat pineal NAS biosynthesis by preserving MAO-A substrates (serotonin and NA) from deamination. Reversible MAO-A inhibitors, brofaromine and beflaxotone, stimulated pineal NAS production as well [38 – 41]. We reported that antidepressant, methylene blue, and other blue dyes, the selective MAO-A inhibitors [42] stimulate pineal NAS production [43]. Acute administration of MAO-B type inhibitor, deprenyl (not exerting an antidepressant effect), did not stimulate rat pineal NAS biosynthesis. However, chronic (6 months) injections of low dose of deprenyl, an irreversible MAO-B inhibitor, inhibits MAO-A and stimulated pineal NAS production but only during the dark phase [44,45].

The role of MAO inhibition in NAS metabolism might be further supported by the study of the effect of bioprecursor of MAO inhibitor on rat pineal NAS. Serotonin conversion into NAS (and melatonin) occurs mostly (but not exclusively) in the pineal gland located in the

brain but outside of blood brain barrier (BBB). The bioprecursor amino acid (MDL 72394) is converted into the irreversible selective MAO-A inhibitor (MDL 72392) by aromatic L-amino acid decarboxylase (AADC). Pretreatment with carbidopa, a peripheral AADC inhibitor, which does not penetrate BBB, prevents the liberation of the MAO-A inhibitor outside the BBB and results in exclusive inhibition of brain MAO-A. We found that systemic administration of MDL 72394 (0.5 mg/kg) stimulated rat pineal NAS and melatonin biosynthesis. Carbidopa, in a dose-dependent manner, attenuated or completely prevented MDL-induced stimulation of NAS and melatonin biosynthesis in the pineal gland located outside of BBB [46].

B1c. Possible mechanisms of the antidepressant effect of NAS

B1c1. NAS and QR2/MT3: Melatonin 3 type (MT-3) receptor has higher affinity to NAS than to melatonin, and was identified as the same protein as quinone reductase 2 (QR2) detoxifying and antioxidant enzyme [47]. We found that QR2/MT3 agonist 5-methoxycarbonylamino-*N*-acetyltryptamine (5MCA-NAT) decreased, while the QR2/MT3 antagonist prazosin increased the duration of immobility in the tail suspension test in C57BL/6 mice. Prazosin, in a dose that did not affect the duration of immobility, attenuated the antidepressant-like effect of NAS and 5MCA-NAT [48]. It is noteworthy that QR2/MT3 mediated effects appeared to be specific for antidepressant-like action of NAS since 5MCA-NAT did not affect NAS-induced protection against LPS toxicity [49].

B1c2. NAS as agonist to TrkB receptors: The most important step in establishing NAS biological activity independent from serotonin and melatonin is a recent discovery that NAS (but not serotonin or melatonin) is an agonist to tyrosine kinase B (TrkB) (but not TrkA or TrkC) receptors of brain derived neurotrophic factor (BDNF) [36,50]. Recent review indicates that activation of TrkB by NAS might contribute to antidepressant effects of NAS (and MAO-A inhibitors) [50]. Discovery of the TrkB-mediated antidepressant effect of NAS is in line with the hypothesis that loss of BDNF is directly involved in the pathophysiology of depression, and that its restoration may underlie the therapeutic efficacy of antidepressant treatment [51]. NAS-induced TrkB stimulation might be involved in several other than antidepressant effects of NAS reported by our team: cognition-enhancing [52], antihypertensive [53], prolongation of life span [54, 55], prevention of pathological opening of the mitochondrial permeability transition pores [56], protection from beta-amyloid toxicity [52] and inhibition of lipid peroxidation [57–59].

B1d. NAS and “memory peptide”—Cognitive impairment is a common feature of depression. The involvement of NAS in cognition-enhancing effects was described by Satake & Morton [60] but went mostly underappreciated [61]. The idea that memories could be transferred from one organism to another by administration of a “trained” donor brain to a naive recipient seized both scientific and public attention in the 1960's and early 1970's [62]. One of the “memory peptide” candidates was identified in the brain extracts of rats trained with shock to avoid dark (hence, “scotophobin”) [63]. Scotophobin was found to be an effective inhibitor (KI50, 6×10^{-7} M) of purified bovine HIOMT, the enzyme, converting NAS into melatonin. The finding that scotophobin inhibits HIOMT suggested that NAS is a mediator of the memory-enhancing effect of scotophobin. Further experiments confirmed that scotophobin action required intact pineal, and that NAS induced dark avoidance in goldfish, as did S-adenosyl-homocysteine, another HIOMT inhibitor [60].

Therefore, the significance of TRP shunt towards KYN production and away from serotonin formation proposed by I. Lapin in 1969 for pathogenesis of depression might not be limited to a creating of serotonin deficiency but resulting in deficiency of NAS as well [64].

B2. Kynurenine pathway

B2a. Tryptophan – kynurenine metabolism—The major non-protein route of TRP metabolism is formation of N-formyl-kynurenine with ensuing production of KYN, catalyzed by rate-limiting enzymes: inflammation-inducible *indoleamine 2,3-dioxygenase* (IDO) or stress and/or substrate-inducible *TRP 2,3-dioxygenase* (TDO) [25].

KYN, in its turn, serves as a substrate for two post-KYN pathways: 1). formation of KYNA, catalyzed by rate-limiting enzyme, *KYN aminotransferase* (KAT). and 2). formation of 3-hydroxyKYN (3-HK) catalyzed by *KYN 3-monoxygenase* (KMO) (Fig.2) [23].

The first step of 3-HK – NAD pathway, formation of 3-hydroxyanthranilic acid, is catalyzed by *kynureninase*. Among the intermediate metabolites of KYN – NAD pathway are NMDA agonists (quinolinic and picolinic acids), free radical generator, 3-hydroxyanthranilic acid, and inducers of T-cell apoptosis and lipid peroxidation (KYN and 3-HK) [23]. One of the major metabolite of this pathway, 3-HK, is a potential neurotoxin in several neurodegenerative disorders [65]. Quinolinic and picolinic acids exerted anxiogenic effects in animal models [11, 21] probably, due to effect on benzodiazepines receptors [66].

B2b. Kynurenines and chronic inflammation—One of the limitations of serotonin – kynurenine hypothesis proposed by Lapin was the notion of TDO exclusive location in the liver excluding the possibility of formation of NEKY in the brain. (Recently TDO was found in the brain and suggested to be involved in the pathogenesis of schizophrenia [23]). The question was whether NEKY can penetrate BBB (some but not all, e.g., KYNA, do). The major breakthrough was achieved by the discovery of another enzyme converting TRP into KYN, indoleamine 2,3-dioxygenase, IDO [67]. IDO is located in brain (including micro- and astro-glia and dendrites), macrophages, kidney but not in liver; and has a broader substrate specificity than TDO [23].

Discovery of IDO contributed to the understanding of pathogenesis of depression as a side-effect of IFNG treatment of melanoma and hepatitis C virus patients [68]. Clinical and experimental studies revealed that development of depression (clinically almost identical to major depressive disorder) during the IFN-alpha treatment was mediated by IFN-induced up-regulated formation of NEKY [68]. Predisposition to the development of such a depression was associated with the presence of high producer allele (T) of IFNG (+874) T/A polymorphic gene that encodes the formation of IFNG protein (i.e., pro-inflammatory cytokine - inducer of IDO) [69].

B2c. TRP – KYN pathway as a link between depression and aging/aging-associated disorders—We suggested that up-regulation of TRP – KYN pathway is one of the mechanisms common for aging and aging-associated medical and psychiatric disorders (AAMPD) [70–72].

B2c1. Depression as aging-associated disorder: Aging is associated with up-regulation of TRP – KYN metabolism.[73].The increased di-oxygenation of mitochondrial TRP to N-formylKYN was consistently present among conserved biomarkers across ageing models in five species [74]. Literature and our studies indicate that genetically or pharmacologically induced inhibition of KYN formation from TRP prolonged life span in *Drosophila* model[75–79]. There are, at least, two possible mechanisms of aging-associated up-regulation of KYN formation from TRP: 1). Increase of cortisol production that induces TDO [73, 80]; and 2). Activation of IDO induced by pro-inflammatory cytokines (e.g., IFNG) due to aging-associated chronic inflammation [81].It is noteworthy that, besides IDO, IFNG stimulates key enzymes of KYN – NAD pathway, kynurenine mono-oxygenase and kynureninase macrophages involved in formation of NMDA agonists [23, 25].Aging-

associated increase of incidence of depression and anxiety might be mediated by increased formation of NEKY and serotonin/NAS deficiency. Therefore, TRP–KYN is a common pathway for mediating genetic and environmental impacts in aging and major depressive disorder [82]

B2c2. Depression and insulin resistance: Many studies reported the association between insulin resistance (IR) (or diabetes type 2) and depression [83]. Some of these studies suggested that depression leads to diabetes. Thus, the prospective study of depressed patients without diabetes at the entry of the study observed the 65% increased risk of development of diabetes (mostly type 2) in clinically depressed patients [84]. The major diabetogenic derivative of KYN is xanthurenic acid (XA) formed from 3-HK. XA is further converted into diabetogenic 8-Hydroxyquinaldic acid (8-HQ) [85] (Fig.2). KYNA is further converted into diabetogenic quinaldic acid (QA) [86]. Diabetogenic effects of XA, KYNA, QA and 8-HQ was demonstrated in clinical and experimental studies: XA induced experimental diabetes in rats; urine XA concentrations were higher in type 2 diabetes patients than in healthy subjects; XA may contribute to the development of IR by formation of chelate complexes with insulin (XA-In) with 49% lower activity in comparison with pure insulin; and XA may exert a toxic effect in isolated pancreatic islets because of formation of complexes with Zn⁺⁺-ions in β -cells [87–91].

XA, KYNA and their derivatives, QA and 8-HQ, inhibit pro-insulin synthesis in isolated rat pancreatic islets [92], and insulin release from rat pancreas [93].

The key enzymes of post-KYN metabolism, *KAT* and *kynureninase* require pyridoxal 5'-phosphate (P5P) (an active metabolite of vitamin B6). The latter enzyme is particularly sensitive to dietary vitamin B-6 restriction [94]. P5P deficiency-induced inhibition of kynureninase, induced by P5P deficiency, blocks 3-HK – NAD pathway and shifts 3-HK metabolism from production of NAD to production of XA (Fig.3) [94].

Depression is characterized by up-regulated production of XA [95] and P5P deficiency [96]. Thus, P5P deficiency might shift up-regulated TRP – KYN metabolism from formation of NAD to formation of diabetogenic KYN derivatives (e.g. XA and KYNA). Increased formation of diabetogenic KYN derivatives might contribute to increased incidence of IR (and type 2 diabetes) in depressed patients.

B2d. Kynurenines and oxidative stress—The major pro-inflammatory cytokine, IFNG, activates nitric oxide synthase (NOS), the key enzyme of NO biosynthesis from arginine. It was reported that this effect is mediated by kynurenines, quinolinic and picolinic acids [97]. Concurrently with IDO activation, IDO transcriptionally induces guanine triphosphate cyclohydrolase (GTPCH), the key enzyme of pteridines biosynthesis, that results in increased formation of BH₂ (and its stable metabolite, neopterin) and in decreased production of BH₄, the obligatory cofactor of NOS [98]. Neopterin plasma concentrations strongly ($r=0.65$) and highly significantly ($p=0.001$) positively correlate with plasma KYN [99], and (negatively) with plasma P5P and IR [100]. 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 [70,71]. 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 and hydrogen peroxide [101,102]. Superoxide is a substrate for formation of one of the most aggressive free radicals, peroxynitrite (70,71). Therefore, up-regulation of TRP – KYN metabolism contributes to formation of both ROS and reactive nitrogen species, the major propagators of oxidative stress,

Peroxynitrite (as well as 3-HK 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 cyclooxygenase (COX) and leucotrienes, via activation of arachidonate 5-lipoxygenase (5-LOX) [103]. 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 [104].

Conclusions: Serotonin-kynurenine hypothesis of depression and action mechanisms of antidepressant effect proposed by I. Lapin dramatically improved our understanding of pathogenesis of depression and links between depression and medical conditions associated with chronic inflammation (including aging). KYN pathway of TRP metabolism could be considered as a new target for prevention and treatment of depression, and aging/aging-associated medical (e.g., IR, obesity, cardiovascular), psychiatric (e.g., vascular cognitive impairment) and other disorders associated with chronic inflammation (e.g., HCV infection [68, 69, 105], psoriasis [106, 107]) disorders.

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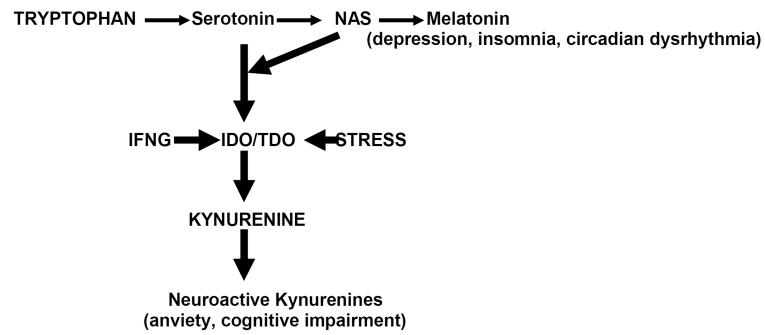


Fig.1. Non-protein pathways of tryptophan metabolism and shunt to kynurenine formation in depression.
NAS – N-acetylserotonin; IFNG – interferon-gamma; IDO – indoleamine 2,3-dioxygenase; TDO – 2,3-dioxygenase tryptophan

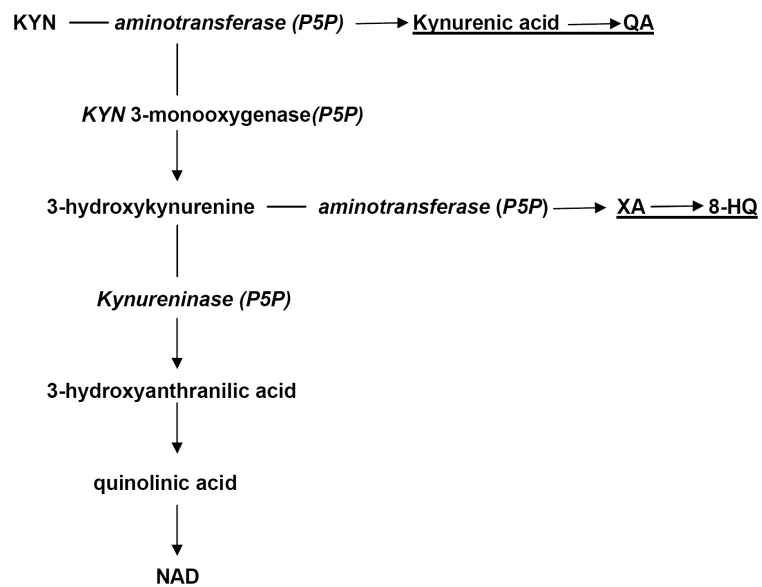
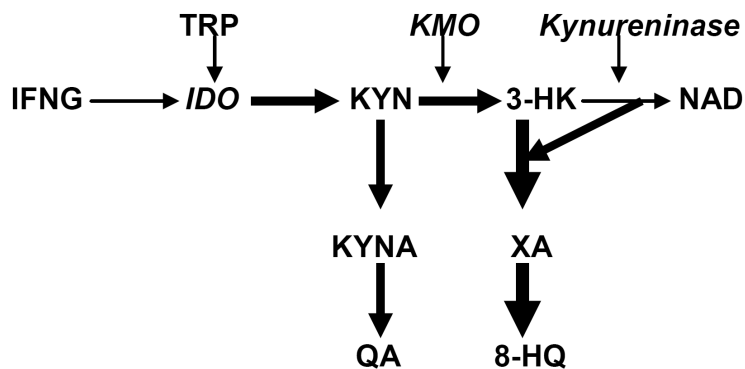


Fig. 2.
 Post-kynurenine metabolism and diabetogenic KYN derivatives.
 Abbreviations: KYNA – kynureninc acid; XA – xanthurenic acid; P5P - pyridoxal 5'-phosphate; 8-HQ - 8-Hydroxyquinaldic acid; QA - quinaldic acid; NAD - nicotinamide adenine dinucleotide.

**Fig.3.**

Vitamin B6 deficiency-induced shift of post-KYN metabolism towards formation of diabetogenic KYN derivatives..

Abbreviations. TRP – tryptophan; IDO – indoleamine 2,3,-dioxygenase; KMO- KYN 3-monooxygenase; P5P - pyridoxal 5'-phosphate; KYN – kynurenine; 3OHKYN – 3-hydroxyKYN; QUIN – quinolinic acid; XA – xanthurenic acid; 3-HAA - 3-hydroxyanthranilic acid; NAD - nicotinamide adenine dinucleotide.