Tryptophan–Kynurenine Metabolism as a Common Mediator of Genetic and Environmental Impacts in Major Depressive Disorder: The Serotonin Hypothesis Revisited 40 Years Later

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ABSTRACT

The original 1969 Lancet paper proposed, "in depression the activity of liver tryptophan-pyrrolase is stimulated by raised blood corticosteroids levels, and metabolism of tryptophan is shunted away from serotonin production, and towards kynurenine production." Discovery of neurotropic activity of kynurenines suggested that up-regulation of the tryptophan-kynurenine pathway not only augmented serotonin deficiency but also underlined depression-associated anxiety, psychosis and cognitive decline.

The present review of genetic and hormonal factors regulating kynurenine pathway of tryptophan metabolism suggests that this pathway mediates both genetic and environmental mechanisms of depression. Rate-limiting enzymes of kynurenine formation, tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) are activated by stress hormones (TDO) and/or by pro-inflammatory cytokines (IDO). Simultaneous presence of high producers alleles of pro-inflammatory cytokines genes (e.g., interferon-gamma and tumor necrosis factor-alpha) determines the genetic predisposition to depression via up-regulation of IDO while impact of environmental stresses is mediated via hormonal activation of TDO. Tryptophan-kynurenine pathway represents a major meeting point of gene-environment interaction in depression and a new target for pharmacological intervention.

Although often referred to as "serotonin hypothesis," the 1969 Lancet paper proposed the disturbances of tryptophan (TRY) metabolism, i.e., the shunt of TRY from serotonin (5-HT) synthesis to kynurenine (KYN) formation, as a major etiological factor of depression (1). It suggested the formation of "vicious cycle" perpetuating the increase of KYN and decrease of 5-HT production in depression due to a) stress hormones – induced activation of tryptophan 2,3-dioxygenase (TDO), the rate-limiting enzyme of TRY – KYN pathway; b) diminished availability of TRY as an initial substrate of 5-HT biosynthesis due to increased formation of KYN from TRY; and c) increased production of cortisol due to weakening of 5-HT inhibitory effect on amygdaloidal complex (2) (Fig. 1).

Figure 1. *Shunt of TRY metabolism from 5-HT to KYN production in depression (1)*
Abbreviations: TRY – tryptophan; 5-HT – serotonin; TDO – tryptophan 2,3-dioxygenase
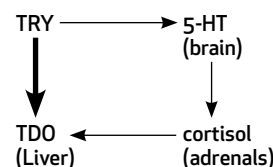
5-HT deficiency was thought as a major consequence of the shift of TRY metabolism to KYN formation, and "intensification of the central 5-HT-ergic processes" was suggested as "a possible determinant of the thymoleptic (mood-elevating) effect" (1). Introduction and wide

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use of selective 5-HT uptake inhibitors as antidepressant drugs contributed to almost 40 years of continued interest in the "serotonin hypothesis."

Another important consequence of so-called "serotonin hypothesis" was stimulation of research of biological and neurotropic activity of KYN and its derivatives (summarily called "kynurenines") (3-7) and of factors regulating KYN pathway of TRY metabolism (8). This review offers analysis of the current status of the serotonin hypothesis with special consideration of the discovery of indoleamine 2,3-dioxygenase (IDO) (9), the other rate-limiting enzyme of TRY - KYN pathway, different from TDO in substrate specificity, localization and regulatory mechanisms.

TRYPTOPHAN METABOLISM

In humans TRY is an essential amino acid with two non-protein metabolic pathways: methoxyindoles and KYN (Fig. 2).

THE METHOXYINDOLES PATHWAY

Availability of TRY as a substrate is one of the rate-limiting factors of methoxyindoles pathway of 5-HT biosynthesis since less than 5% of TRY metabolized along this pathway (10). The other rate-limiting step is hydroxylation of TRY catalyzed by TRY-hydroxylase with the formation of 5-hydroxytryptophan. The subsequent decarboxylation results in the formation of 5-HT, a substrate for melatonin synthesis. The rate-limiting step of melatonin synthesis is 5-HT-N-acetylation resulting in the formation of N-acetyl-serotonin (NAS) with subsequent O-methylation into 5-methoxy-N-acetyltryptamine (melatonin) (11) (Fig. 2).

5-HT (not competitively) and NAS and melatonin (competitively) inhibit liver TDO (12). Deficient production of 5-HT, NAS and melatonin contribute to depressed mood (13), and disturbances of sleep (14) and circadian rhythms (15).
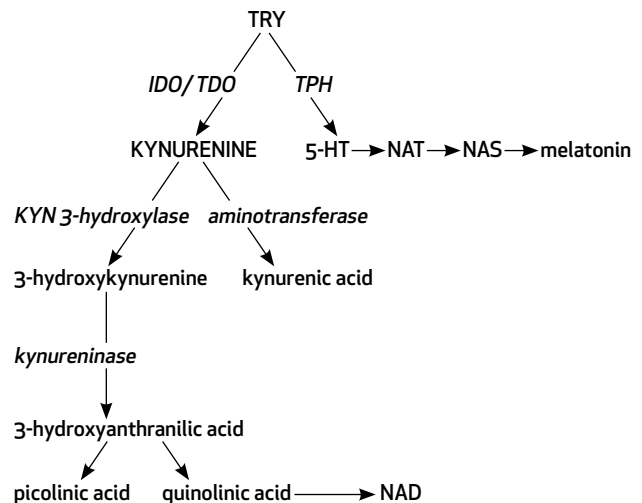
THE KYNURENINE PATHWAY

About 95% of TRY is metabolized via the KYN pathway (10, 16). There are two steps of the TRY–KYN pathway: a) formation of KYN from TRY, and b) post-KYN metabolism via two routes competing for KYN as their initial substrate.

a. Tryptophan conversion into Kynurenine

Unlike the methoxyindoles pathway that does not affect

Figure 2. *Methoxyindoles and kynurenine pathways of tryptophan metabolism*
Abbreviations: TRY – tryptophan; IDO – indoleamine 2,3-dioxygenase; TDO- tryptophan 2,3-dioxygenase; TPH – tryptophan hydroxylase; 5-HT – serotonin; NAT – N-acetyltransferase; NAS – N-acetylserotonin; NAD - nicotinamide adenine dinucleotide

the indole ring of TRY, the KYN pathway begins by the cleavage of the indole ring of TRY which results in the formation of N-formylkynurenine followed by kynurenine in an ensuing step (10). The rate-limiting enzymes of KYN formation from TRY are IDO (9) in astrocytes, microglia, microvascular endothelial cells and macrophages and TDO in liver, kidney and brain (10).

KYN inhibits TRY transport via the blood-brain barrier (4), stimulates IDO activity (10), and exerts anxiogenic activity in animal models of anxiety (4).

b. Post-Kynurenine metabolism

Kynurenine is further metabolized along the two distinct routes competing for KYN as a substrate: KYN–kynurenic acid (KYNA) pathway, and KYN–nicotinamide adenine dinucleotide (NAD) pathway.

b1. The KYN –KYNA pathway

The KYN-KYNA pathway is regulated by KYN aminotransferases, the major biosynthetic enzymes of KYNA formation in the brain (17).

KYNA, the only known endogenous antagonist to N-methyl-D-aspartate (NMDA) receptors, might, similarly to the exogenous NMDA antagonists, ketamine and MK-801, exert antidepressant (18) and psychotomimetic (19) effects. KYNA may contribute to cross

talk between the melatonin and kynurenine pathways by inhibiting 5-HT-N-acetylation, the rate-limiting step of melatonin biosynthesis (20).

KYNA has higher affinity to alpha-7-nicotinic acetylcholine than to NMDA receptors, and as such might contribute to cognitive impairment observed in depression, schizophrenia, dementia, and Down's and Crohn's syndromes (21, 22).

b2. The KYN-NAD pathway
The KYN–NAD pathway produces NMDA agonists (quinolinic and picolinic acids) and free radical generators (3-hydroxykynurenine and 3-hydroxyanthranilic acid) (16). Increased formation of NMDA agonists might result in hyperglutamatergic status suggested to be associated with depression (21).

Quinolinic and picolinic acids exerted an anxiogenic effect in experimental models (4). Quinolinic and picolinic acids stimulate inducible nitric oxide synthase (iNOS) and together with 3-hydroxykynurenine and 3-hydroxyanthranilic acids might increase lipid peroxidation, and trigger arachidonic acid cascade resulting in the increased production of inflammatory factors: prostaglandines, via activation of cycloxygenase (COX) and leucotrienes, via activation of arachidonate 5-lipoxygenase (5-LO) (16, 23, 24). COX-2 is of particular interest since its inhibitors blocked KYNA production (25) and exerted antidepressant and antipsychotics effects (21) while 5-LO was suggested as a link between depression and atherosclerosis (26-28) (Fig. 3).

Figure 3. *Kynurenines and psychiatric and vascular complications*
Abbreviations: TRY – tryptophan; IDO – indoleamine 2,3-dioxygenase; TDO – tryptophan 2,3-dioxygenase; BBB – blood brain barrier; KYN - kynurenine, 3HKYN - 3-hydroxyKYN; KYNA – kynurenic acid; QUIN – quinolinic acid; iNOS – inducible nitric oxide synthase; NO - nitric oxide; PLA – phospholipase; AA – arachidonic acid; COX - cycloxygenase; 5-LO - arachidonate 5-lipoxygenase; PGE – prostaglandines.
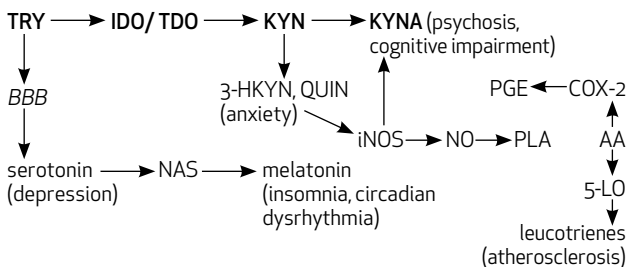
REGULATION OF RATE-LIMITING ENZYMES OF KYN PATHWAY.
REGULATION OF TDO
a. *Substrate activation.* TDO is activated by its substrate (TRY) (10). Because KYN competes for cerebral transport and cellular uptake of TRY, and because of substrate inhibition on TRY hydroxylase, the rate-limiting enzyme of 5-HT biosynthesis, excessive TRY doses may decrease 5-HT production (29).

b. *Hormonal activation.* Cortisol activates TDO and increased KYN production (30). Literature data regarding the effect of estrogens and testosterone on TDO are controversial: both adrenalectomy and ovariectomy reduced TDO activity in homogenates of liver from mature rats. However, administration of estrogens and testosterone had no effect on TDO (31, 32).

Hormonal activation of TDO and consequent shift of TRY metabolism from 5-HT to KYN formation was suggested as an etiological factor in depression (1) (Fig.1).

REGULATION OF IDO
a. Cytokines and IDO
a1. IFN-gamma. Pro-inflammatory cytokines (including, most notably, interferons) transcriptionally induce IDO in a variety of immune cells (e.g., monocyte-derived macrophages and microglia) (33). IFNG is the strongest known inducer of IDO (34). Therefore, the shift of TRY metabolism from 5-HT to KYN formation

Figure 4. *Cytokines and regulation of IDO*
Abbreviations: IFNG – interferone-gamma; IFN-alpha – interferone-alpha; TNF-alpha – tumor necrosis factor-alpha; IDO – indoleamine 2, 3-oxygenase
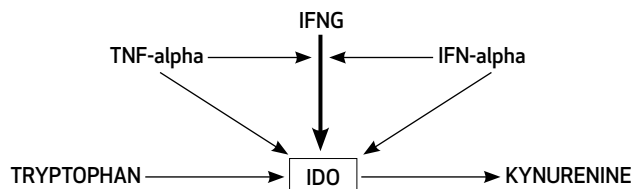
might be caused not only by TDO activation by cortisol but by IFNG-induced IDO activation as well. The shift of TRY towards formation of kynurenines might be further augmented by IFNG-induced stimulation of the enzymes of KYN – NAD route: 3-hydroxylase and kynureninase (35).

a2. IFN-alpha. Systemically administrated IFN-alpha

passes the blood-brain barrier and reaches effective concentrations acting on microglial cells as well as macrophage receptors (36). 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 (37) (Fig. 4). Administration of IFN-alpha to patients with hepatitis C is associated with depression attributed to increased formation of kynurenines (38-40).

a3. TNF-alpha. TNF-alpha stimulates IDO activity and enhances (up to 300%) IFNG-induced IDO expression (41). The induction of IDO by the bacterial endotoxin lipopolysaccharide was IFNG-independent and might be mediated by toll-like receptors (42).

a4. Other proinflammatory molecules such as IL-1, IL-12, Il-18, PGE_2 synergistically with IFNG induce IDO activity (43, 44).

Experimental and clinical data demonstrated that IFNG and TNF-alpha trigger depression (and depressive-like symptoms) via stimulation of IDO and consequent increase of kynurenines formation from TRY (39, 45).

CYTOKINE GENE POLYMORPHISM AND IDO

Cytokine genes are polymorphic and certain SNPs located within coding/regulatory regions affect the overall expression and secretion of cytokines (46).

IFNG production is encoded by polymorphic IFNG (+874) gene with high (T) and low (A) producer alleles (46). Mean concentration of IFNG cytokine released by stimulated peripheral blood mononuclear cells was higher in healthy carriers of T than in carriers A allele (47). High producer T allele was associated with increased IDO activity (i.e., elevated plasma kynurenine levels and kynurenine/tryptophan ratios) in healthy females (48). These results suggest that IFNG genotype influences TRY catabolism via regulation of IDO activity.

TNF-alpha production is encoded by the TNF-alpha (-308 A/G) polymorphic gene. Since TNF-alpha stimulates IDO and potentiates IFNG-induced stimulation of IDO (see above), a (TNF-alpha (−308) high producer (A) allele might strength the association between IFNG (+874) high producer (T) and IDO up-regulation (16). Increased frequency of the TNF-alpha -308A allele (high producer) was reported in Korean subjects with major depression (49), in Korean bipolar I patients (50), and in Polish subjects with bipolar affective disorder and positive family history (51). It suggested that (−308) TNF-alpha gene polymorphism might be involved in genetic susceptibility to mood disorders.

IDO−TDO INTERACTION

a. Hormonal activation of IDO. Although IDO is mainly induced by cytokines, experimental data suggested that expression of IFNG gene may be subject to direct hormonal control since receptors of prolactin and IFNG share their structure and signal transduction pathway. Prolactin by itself has little or no effect on IDO but potentiates INFG-induced IDO activation in CD14-positive cells (52). 17beta-estradiol increased the activity of the IFNG promoter in lymphoid cells (53).

Hydrocortisone and dexamethasone induced IDO in human astrocytoma cells and in native human astrocytes (54).

b. Cytokines and the HPA axis. Proinflammatory cytokines may cause hypothalamic-pituitary-axis (HPA) hyperactivity (that is frequently observed in depression) by disturbing the negative feedback inhibition of circulating corticosteroids on the HPA axis (55, 56).
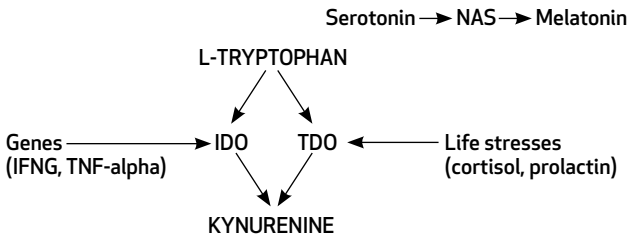
c. Aging as a merging point of IDO-TDO interaction. Aging is characterized by elevated cortisol production due to disinhibition of the HPA axis (57-59), and by increased IFNG and TNF-alpha production (60). It is noteworthy that high producer allele (T) of the IFNG +874 gene (61) and high IDO activity predicted high lethality in elderly subjects (62). In the same vein, Drosophila Melanogaster mutants with impaired KYN production have longer life span than wild type flies (63). These results suggest that activation of both IDO and TDO might contribute to high risk of depression in the elderly.

HYPOTHESIS

The original 1969 hypothesis of up-regulation of the KYN pathway of TRY metabolism as an etiological factor in depression suggested that "in depression the activity of liver TRY-pyrrolase (TDO) is stimulated by raised blood corticosteroids levels" that resulted in 5-HT deficiency due to the shift of TRY metabolism from 5-HT to KYN formation (1). The discovery of neurotropic activity of kynurenines (37) emphasized the increased formation of kynurenines as etiological factor in depression (in addition to 5-HT deficiency) (39). IDO, the other enzyme catalyzing TRY conversion into KYN, is transcriptionally activated by pro-inflammatory cytokines (mainly, IFNG and TNF-alpha). The polymorphisms of genes impacting the production of pro-inflammatory cytokines provides

Figure 5. *Genetic and environmental impacts on tryptophan metabolism*
Abbreviations: NAS – N-acetylserotonin; IFNG – interferone; TNF – tumor necrosis factor; IDO – indoleamine 2,3-dioxygenase; TDO – tryptophan 2,3-dioxygenase.

Serotonin → NAS → Melatonin

L-TRYPTOPHAN

Genes (IFNG, TNF-alpha) → IDO   TDO ← Life stresses (cortisol, prolactin)

KYNURENINE

further insight in the etiological role of upregulated TRY – KYN metabolism in depression.

This review suggests that genetic and/or environmental (life stresses) factors trigger depression by up-regulation of TRY-KYN metabolism. Effect of genetic factors (such as high producer alleles of pro-inflammatory genes) is mediated by cytokine-induced up-regulation of IDO. Combination of high producer alleles of IFNG (+874) and TNF-alpha (-308) genes might result in high production of these cytokines, and trigger the "super-induction" of IDO. The effect of life stressors might be mediated by hormonal activation of TDO. Cytokine–induced stimulation of cortisol production and augmentation of IFNG-induced activation of IDO by stress hormones suggest that the TRY-KYN pathway might be the converging point of gene-environmental interaction (e.g., like in aging) (Fig. 5).

LIMITATIONS

Some major limitations should be mentioned with the hope to stimulate further evaluation of the proposed hypothesis.

The present hypothesis predicts higher frequency of carriers of high producer alleles of pro-inflammatory genes in subjects with mood disorders. While some studies of TNF-alpha genotypes support this suggestion (49-51), no publications regarding IFNG (or other pro-inflammatory cytokines) were found in the available sources.

The present hypothesis is based on the assumption that carriers of high producer alleles of cytokine genes have higher production of cytokines than carriers of low promoter alleles. These relationships were reported for healthy volunteers but were not studied in depressed patients. Similarly, the association between high producer alleles for the IFNG (+874) gene and high IDO

activity was observed in healthy volunteers but no studies done in depressed patients.

TRY–KYN METABOLISM AS A NEW TARGET FOR PREVENTION AND TREATMENT OF MDD AND PSYCHIATRIC COMPLICATIONS OF IFN-ALPHA TREATMENTS

Genotype assessment might help identify subjects-at-risk of developing depression in response to environmental stressors and/or to IFN-alpha therapy of hepatitis C, cancer, amyotrophic lateral sclerosis and multiple sclerosis.

Potential pharmacological interventions in identified subjects may include:

a) inhibition of cytokine production by antibodies to TNF-alpha (e.g., etanercept, infiximab) and IFNG (64), and/or more careful selection of antidepressants. While both selective 5-HT uptake inhibitor, fluoxetine (65) and the dopamine enhancer, wellbrutin (66) inhibit cytokine production, the latter might be of advantage considering the impaired 5-HT synthesis as a result of IDO activation.

b) inhibition of IDO activity by MAO inhibitors (67-69), minocycline (70) and 1-methyl-L-TRY (71).

d) administration of methoxyindoles that might modulate the TRY-KYN pathway due to their inhibitory effect on cortisol (72) and proinflammatory cytokines (73-75) production. Methoxyindoles (melatonin, in particular) might attenuate excitatory, glutamate-mediated responses triggered by KYN pathway metabolites (76, 77).

References

1. Lapin IP, Oxenkrug GF. Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. Lancet 1969; 1: 32-39.

2. Rubin RT, Mandell AJ, Crandall PH. Corticosteroid responses to limbic stimulation in man: Localization of stimulus sites. Science 1966;153:767-768.

3. Lapin IP. Convulsions and tremor in immature rats after intraperitoneal injection of kynurenine and its metabolites. Pharmacol Res Comm 1978;10: 81–84.

4. Lapin IP. Neurokynurenines (NEKY) as common neurochemical links of stress and anxiety. Adv Exp Med Biol 2003; 527:121-125.

5. Oxenkrug G F, Lapin IP. Kynurenine pathway of the metabolism of tryptophan and its possible neuropharmacologic role. In: Yakovelev V, editor. Chemistry and pharmacology of indole compounds. Kishinev: Stinza, 1975: pp. 5-18.

6. Lapin IP. Antagonism of kynurenic acid to anxiogens in mice. Life Sci 1998; 63:PL231-236.

7. Lapin IP. Kynurenines and anxiety. Adv Exp Med Biol 1996; 398:191-194.

8. Schwarcz R, Pellicciari R. Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther 2002; 303:1-10.

9. Hayaishi O. Properties and function of indoleamine 2,3-dioxygenase. J Biochem (Tokyo) 1976;79:13P-21P.

10. Gál EM, Sherman AD. L-kynurenine: Its synthesis and possible regulatory function in brain. Neurochem Res 1980; 5:223-239.

11. Kopin IJ, Pare CB, Axelrod J, H Weissbach. The fate of melatonin in animals. J Biol Chem 1961; 236:3072-3075.

12. Walsh HA, Daya S. Inhibition of hepatic tryptophan-2,3-dioxygenase: Superior potency of melatonin over serotonin. J Pineal Res 1997; 23:20-23.

13. Lewy AJ, Wehr TA, Goodwin FK, et al. Light suppresses melatonin secretion in humans. Science 1980; 210:1267-1269.

14. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, et al. Effects of exogenous melatonin on sleep: A meta-analysis. Sleep Med Rev 2005; 9:41-50.

15. Oxenkrug GF, Requintina PJ. Melatonin and jet lag syndrome: Experimental model and clinical implications. CNS Spectrums 2003; 8:139-148.

16. Oxenkrug GF. Genetic and hormonal regulation of the kynurenine pathway of tryptophan metabolism: New target for clinical intervention in vascular dementia, depression and aging. Ann NY Acad Sci 2007; 1122: 35-49.

17. Guidetti P, Amori L, Sapko MT, et al. Mitochondrial aspartate aminotransferase: A third kynurenate-producing enzyme in the mammalian brain. J Neurochem 2007;102:103-111.

18. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol Psychiatry 2005;57:430-432.

19. Krystal JH, Karper LP, Seibyl, JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51:199-214.

20. Zawilska JB, Rosiak J, Senderecka M, Nowak JZ. Suppressive effect of NMDA receptor antagonist MK-801 on nocturnal serotonin N-acetyltransferase activity in the rat pineal gland. Pol J Pharmacol 1997; 49: 479-483.

21. Müller N, Schwarz M. A psychoneuroimmunological perspective to Emil Kraepelins dichotomy: Schizophrenia and major depression as inflammatory CNS disorders. Eur Arch Psychiatry Clin Neurosci 2008; 258:97-106.

22. Oxenkrug GF. Tryptophan metabolism as a new target for the treatment of schizophrenia. US Psychiatry Review 2007 (Touch Briefings): pp. 38-39.

23. Oxenkrug GF. Antioxidant effects of N-acetylserotonin: Possible mechanisms and clinical implications. Ann NY Acad Sci 2005;1053: 334-347.

24. Melillo G, Cox DW, Biragyn A, Sheffler LA. Regulation of nitric-oxide synthase mRNA expression by interferon-gamma and picolinic acid. J Biol Chem 1994; 269: 8128-8133.

25. Schwieler L, Erhardt S, Nilsson L, et al. Effects of COX-1 and COX-2 inhibitors on the firing of rat midbrain dopaminergic neurons - possible involvement of endogenous kynurenic acid. Synapse 2006 ; 59:290-298.

26. Manev G, Manev R. 5-lipoxygenase as a possible biological link between depressive symptoms and atherosclerosis. Arch Gen Psychiatry 2007; 64:1333.

27. Oxenkrug GF. Metabolic syndrome, age-associated neuroendocrine disorders and dysregulation of tryptophan - kynurenine pathway metabolism. Ann NY Acad Sci; 2009 (in press).

28. Oxenkrug GF. Antidepressant effect of N-acetylserotonin in relation to aging, hypertension and cancer. In: Berstein L, editor. Hormones, age and cancer. St. Petersburg: Nauka, 2005: pp. 140-158.

29. Forrest CM, Mackay GM, Stoy N, Egerton M, Christofides J, Stone TW, Darlington LG. Tryptophan loading induces oxidative stress. Free Radic Res 2004;38:1167-1171.

30. Rubin RT. Adrenal cortical activity changes in manic-depressive illness. Influence on intermediary metabolism of tryptophan. Arch Gen Psychiatry 1967;17:671-679.

31. Bender DA, Laing AE, Vale JA, et al. The effects of oestrogen administration on tryptophan metabolism in rats and in menopausal women receiving hormone replacement therapy. Biochem Pharmacol 1983; 32: 843-848.

32. Shibata K, Toda S. Effects of sex hormones on the metabolism of tryptophan to niacin and to serotonin in male rats. Biosci Biotechnol Biochem 1997; 61:1200-1202.

33. Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. FASEB J 1991; 5:2516-2522.

34. Widner B, Ledochowski M, Fuchs D. Interferon-gamma-induced tryptophan degradation: Neuropsychiatric and immunological consequences. Curr Drug Metab 2000;1:193-204.

35. Alberati-Giani D, Ricciardi-Castagnoli P, Köhler C, Cesura AM. Regulation of the kynurenine metabolic pathway by interferon-gamma in murine cloned macrophages and microglial cells. J Neurochem 1996; 66:996-1004.

36. Sweeten TL, Ferris M, McDougle CJ, et al. Induction of indoleamine 2,3-dioxygenase in vivo by IFN-con1. J Interferon Cytokine Res 2001 ;21:631-633.

37. Taylor JL, Grossberg SE. The effects of interferon-alpha on the production and action of other cytokines. Semin Oncol 1998;25:23-29.

38. Capuron L, Miller AH. Cytokines and psychopathology: Lessons from interferon-alpha. Biol Psychiatry 2004; 56: 819-824.

39. Wichers MC, Koek GH, Robaeys G, Verkerk R, Scharpé S, Maes M. IDO and interferon-alpha-induced depressive symptoms: A shift in hypothesis from tryptophan depletion to neurotoxicity. Mol Psychiatry 2005;10:538-544.

40. Bonaccorso S, Meltzer HY, Maes M. Psychological and behavioral effects of interferons. Curr Opin Psychiatry 2000; 13:673-677.

41. Robinson CM, Hale PT, Carlin JM. The role of IFN-gamma and TNF-alpha-responsive regulatory elements in the synergistic induction of indoleamine dioxygenase. J Interferon Cytokine Res 2005;25:20-30.

42. Wilson AG, de Vries N, Pociot F, et al. An allelic polymorphism within the human tumor necrosis factor-alpha promoter region is strongly associated with HLA A1, B8, and DR3 alleles. J Exp Med 1993; 177:557-560.

43. Liebau C, Baltzer A W, Schmidt S, et al. Interleukin-12 and interleukin-18 induce indoleamine 2,3-dioxygenase (IDO) activity in human osteosarcoma cell lines independently from interferon-gamma. Anticancer Res 2002; 22: 931-936.

44. Kwidzinski E, Bunse J, Aktas O, et al. Indolamine 2,3-dioxygenase is expressed in the CNS and down-regulates autoimmune inflammation. FASEB J 2005; 19:1347-1349.

45. O'Connor JC, André C, Wang Y, Lawson MA, Szegedi SS, Lestage J, Castanon N, Kelley KW, Dantzer R. Interferon-gamma and tumor necrosis factor-alpha mediate the up-regulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. J Neurosci 2009;29:4200-4209.

46. Pravica V, Perrey C, Stevens A, et al. A single nucleotide polymorphism in the first intron of the human INFG gene: Absolute correlation with a polymorphic CA micro marker of high INFG gene. Hum Immunol 2000; 61: 8333-8366.

47. Anuradha B, Rakh SS, Ishaq M, et al. Interferon-gamma Low producer genotype +874 overrepresented in Bacillus Calmette-Guerin nonresponding children. Pediatr Infect Dis J 2008; 27:325-329.

48. Raitala A., Pertovaara M, Karjalainen J, et al. Association of interferon-gamma+874(T/A) single nucleotide polymorphism with the rate of tryptophan catabolism in healthy individuals. Scand J Immunol 2005; 61: 387-39046.

49. Jun TY, Pae CU, Hoon-Han, Chae JH, Bahk WM, Kim KS, Serretti A. Possible association between -G308A tumour necrosis factor-alpha gene polymorphism and major depressive disorder in the Korean population. Psychiatr Genet 2003;13:179-181.

50. Pae CU, Lee KU, Han H, et al. Tumor necrosis factor alpha gene-G308A polymorphism associated with bipolar I disorder in the Korean population. Psychiatry Res 2004;125:65-68.

51. Czerski PM, Rybakowski F, Kapelski P, et al. Association of tumor necrosis factor -308G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. Neuropsychobiology 2008; 57:88-94.

52. Kawaguchi R, Ozawa-Kondo M, Ohta-Misaki I, et al. Prolactin (PRL) up-regulates indoleamine 2,3-dioxygenase (IDO) expression in CD14+ cells. Nihon Rinsho Meneki Gakkai Kaishi 2005; 228:407-412.

53. Fox HS, Bond BL, Parslow TG, et al. Estrogen regulates the IFN-gamma promoter. J Immunol 1991; 146: 4362-4367.

54. Ozaki Y, Edelstein MP, Duch DS. The actions of interferon and antiinflammatory agents of induction of indoleamine 2,3-dioxygenase in human peripheral blood monocytes. Biochem Biophys Res Commun 1987; 144: 1147-1153.

55. Leonard BE. The HPA and immune axes in stress: The involvement of the serotoninergic system. Eur Psychiatry 2005; 20: S302-S306.

56. Leonard BE, Myint A. The psychoneuroimmunology of depression. Hum Psychopharmacol 2009;24:165-175.

57. Dilman VM, Lapin IP, Oxenkrug GF. Serotonin and aging. In: Essman W, editor. Serotonin in Health and Disease. New York, London: Spectrum, 1979; vol. 5: pp. 111-123.

58. Oxenkrug GF, McIntyre I M, Gershon S, et al. Dexamethasone suppression test: Experimental model in rats and effect of age. Biol Psychiat 1984; 19: 413-416.

59. Oxenkrug GF, Pomara N, McIntyre I, et al. Aging and cortisol resistance to suppression by dexamethasone: A positive correlation. Psychiatry Res 1983; 10: 125-130.

60. Rodríguez MI, Escames G, López LC, et al. Chronic melatonin treatment reduces the age-dependent inflammatory process in senescence-accelerated mice. J Pineal Res 2007; 42:272-279.

61. Lio D, Scola L, Crivello A, et al. Allele frequencies of +874T-A single nucleotide polymorphism at the first intron of interferon-gamma gene in a group of Italian centenarians. Exp Gerontol 2002, 37: 315-319.

62. Pertovaara M, Raitala A, Lehtimaki T, et al. Indoleamine 2,3-dioxygenase activity in nonagenarians is markedly increased and predicts mortality. Mech Ageing Dev 2006; 127:497-499.

63. Oxenkrug GF. The extended life span of Drosophila melanogaster eye-color (white and vermilion) mutants with impaired formation of kynurenine. J Neural Transm 2010; 117: 23 -26.

64. Skurkovich B, Skurkovich S. Inhibition of IFN-gamma as a method of treatment of various autoimmune diseases, including skin diseases. Ernst Schering Res Found Workshop 2006;56:1-27.

65. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. Int J Neuropsychopharmacol 2002; 5:401-412.

66. Brustolim D, Ribeiro-dos-Santos R, Kast RE, et al. A new chapter opens in anti-inflammatory treatments: The antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. Int Immunopharmacol 2006; 6:903-907.

67. Samsonova ML, Oxenkrug GF. Inhibition of substrate induction of TRY-pyrrolase in liver and increase in the content in 5-HT in brain under action of inhibitors of MAO. Vopr Med Khim 1972; 17: 198-201.

68. Oxenkrug GF. The acute effect of monoamine oxidase inhibitors on serotonin conversion to melatonin. In: Sandler M, Coppen A, Harnett S, editors. 5-hydroxytryptamine in psychiatry: A spectrum of ideas. Oxford, New York, Tokyo: Oxford University, 1991: pp: 98-109.

69. Sono M, Cady SG. Enzyme kinetic and spectroscopic studies of inhibitor and effector interactions with indoleamine 2,3-dioxygenase. 1. Norharman and 4-phenylimidazole binding to the enzyme as inhibitors and heme ligands. Biochemistry 1989; 28:5392-5399.

70. Ryu J K, Choi H B, McLarnon J G. Combined minocycline plus pyruvate treatment enhances effects of each agent to inhibit inflammation, oxidative damage, and neuronal loss in an excitotoxic animal model of Huntington's disease. Neuroscience 2006;141:1835-1848.

71. Cady SG, Sono M. 1-Methyl-DL-tryptophan, beta-(3-benzofuranyl)-DL-alanine (the oxygen analog of tryptophan), and beta-[3-benzo(b)thienyl]-DL-alanine (the sulfur analog of tryptophan) are competitive inhibitors for indoleamine 2,3-dioxygenase. Arch Biochem Biophys 1991;291:326-333.

72. Oxenkrug GF, McIntyre IM, Gershon S. Effects of pinealectomy and aging on the serum corticosterone circadian rhythm in rats. J Pineal Res 1984; 1:181-185.

73. Perianayagam MC, Oxenkrug GF, Jaber B. Immune modulating effects of melatonin, N-acetyl Serotonin and N-acetyl Dopamine. Ann NY Acad Sci 2005; 1053:386-393.

74. Requintina PJ, Oxenkrug GF. Differential effects of lipopolysaccharide on lipid peroxidation in F344N, SHR rats and BALB/C mice and protection of melatonin and NAS against its toxicity. Ann NY Acad Sci 2003; 993:325-333.

75. Bachurin S, Oxenkrug G, Lermontova N, et al. N-acetylserotonin, melatonin and their derivatives improve cognition and protect against beta-amyloid-induced neurotoxicity. Ann NY Acad Sci 1999; 890:155-166.

76. Lapin IP, Mirzaev SM, Oxenkrug GF, et al. Anticonvulsant activity of melatonin against seizures induced by quinolinate, kainate, glutamate, NMDA and pentylenetetrazole in mice. J Pineal Res 1998; 24: 215-218.

77. Prakhie IV, Oxenkrug GF. The effect of nifedipine, Ca++ antagonist, on activity of MAO inhibitors, N-acetylserotonin and melatonin in the mouse tail suspension test. Intern J Neuropsychopharmacol 1998; 1:35-40.