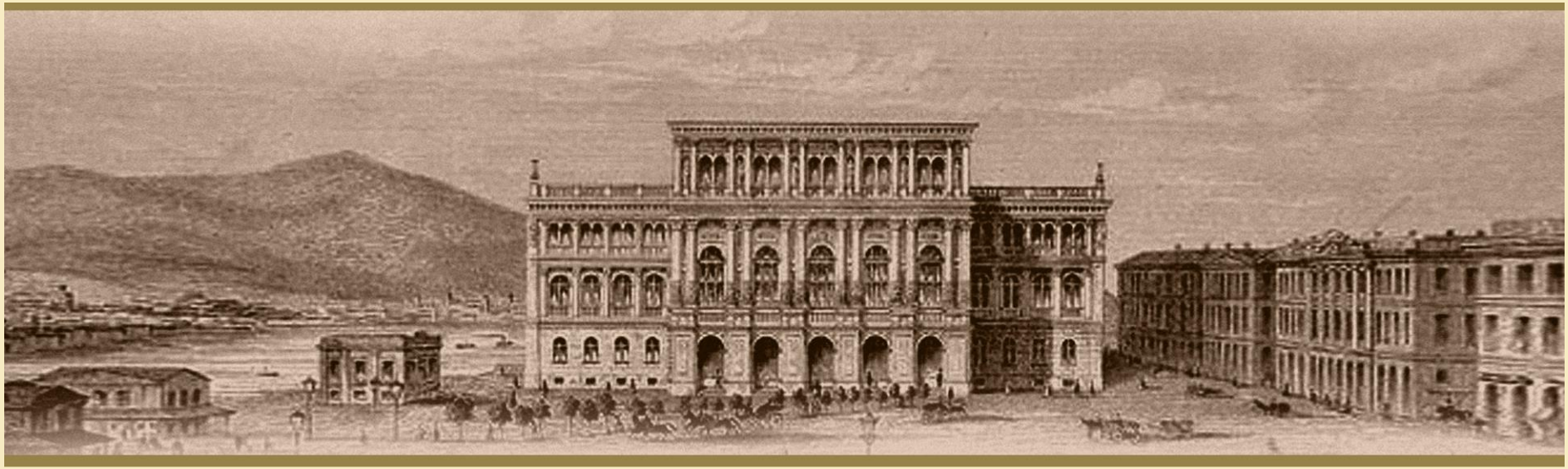
A MAGYAR TUDOMÁNYOS AKADÉMIA



187. KÖZGYŰLÉSE

2016. május 2–3.

Stressz és kinureninek: új stressz molekulák és klinikai lehetőségek

(Stess and kynurenines: New stress mediators, with clinical implications)

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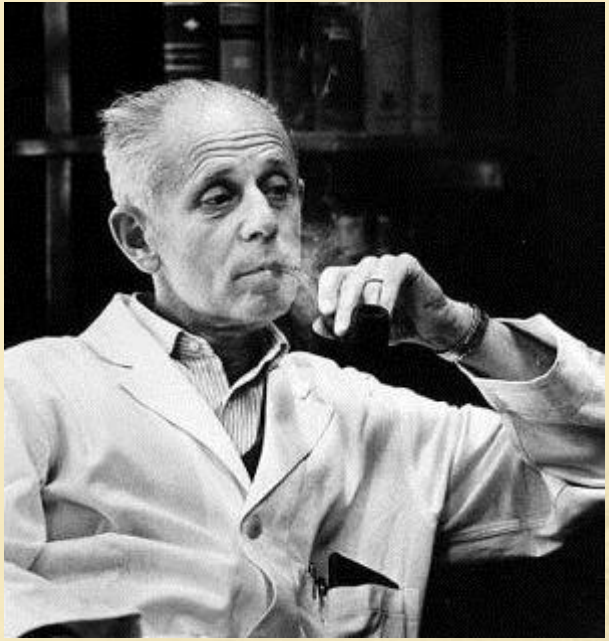


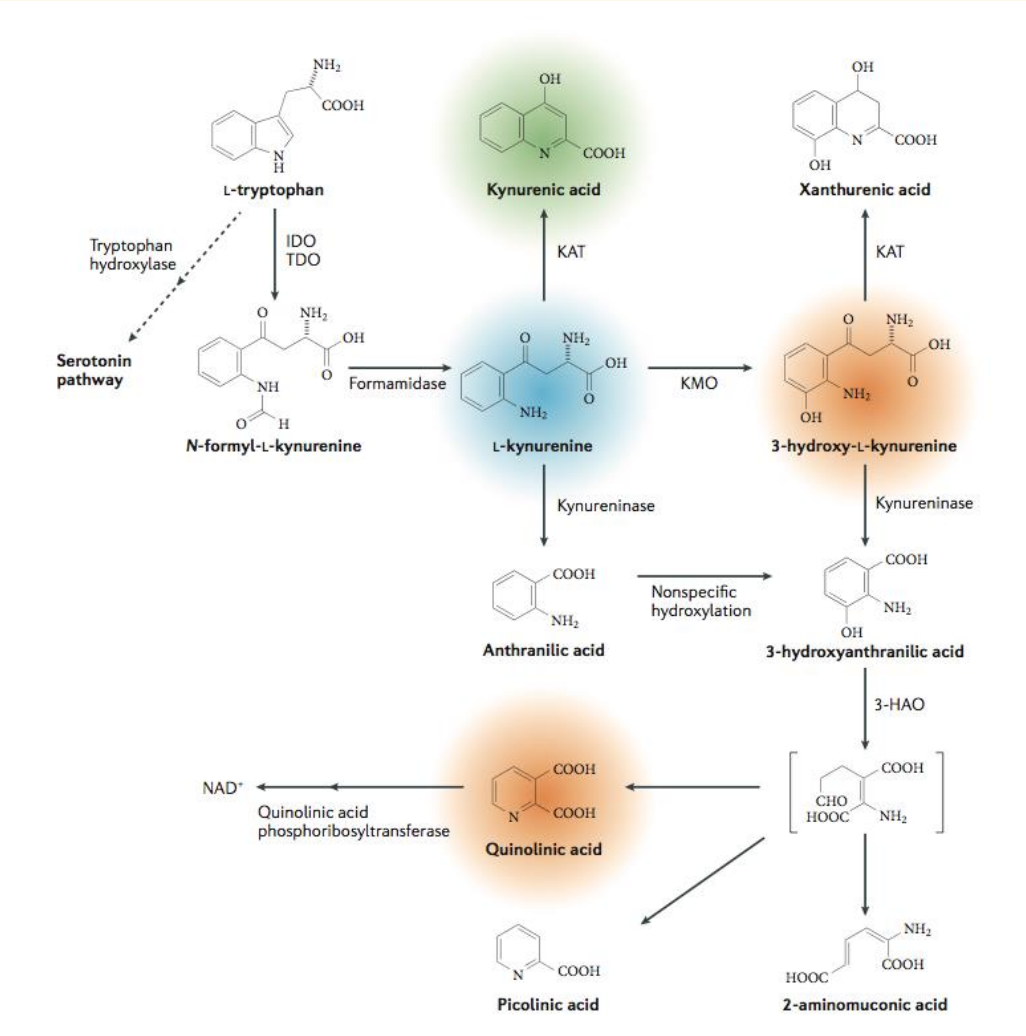
- Crucial role of adrenal cortex–hypophysis axis in the stress response.
- both negative and positive stressors elicit virtually identical corticoid/catecholamine responses.

Selye H, Szabo S.: Experimental model for production of perforating duodenal ulcers by cysteamine in the rat. Nature. 1973 Aug 17;244(5416):458-9.

- Evoke duodenal ulcus - stress model,
- Acetanilide, 3,4 -toluenediamine, 3,4-toluenedithiol, propionitril
- Cysteamin, only naturally-occuring ulcerogan agent, ulcus + adrenocortical necrosis
  - Increased gastric acid output,
  - Delayed gastric emptying
  - Elevetad serum gastrin level

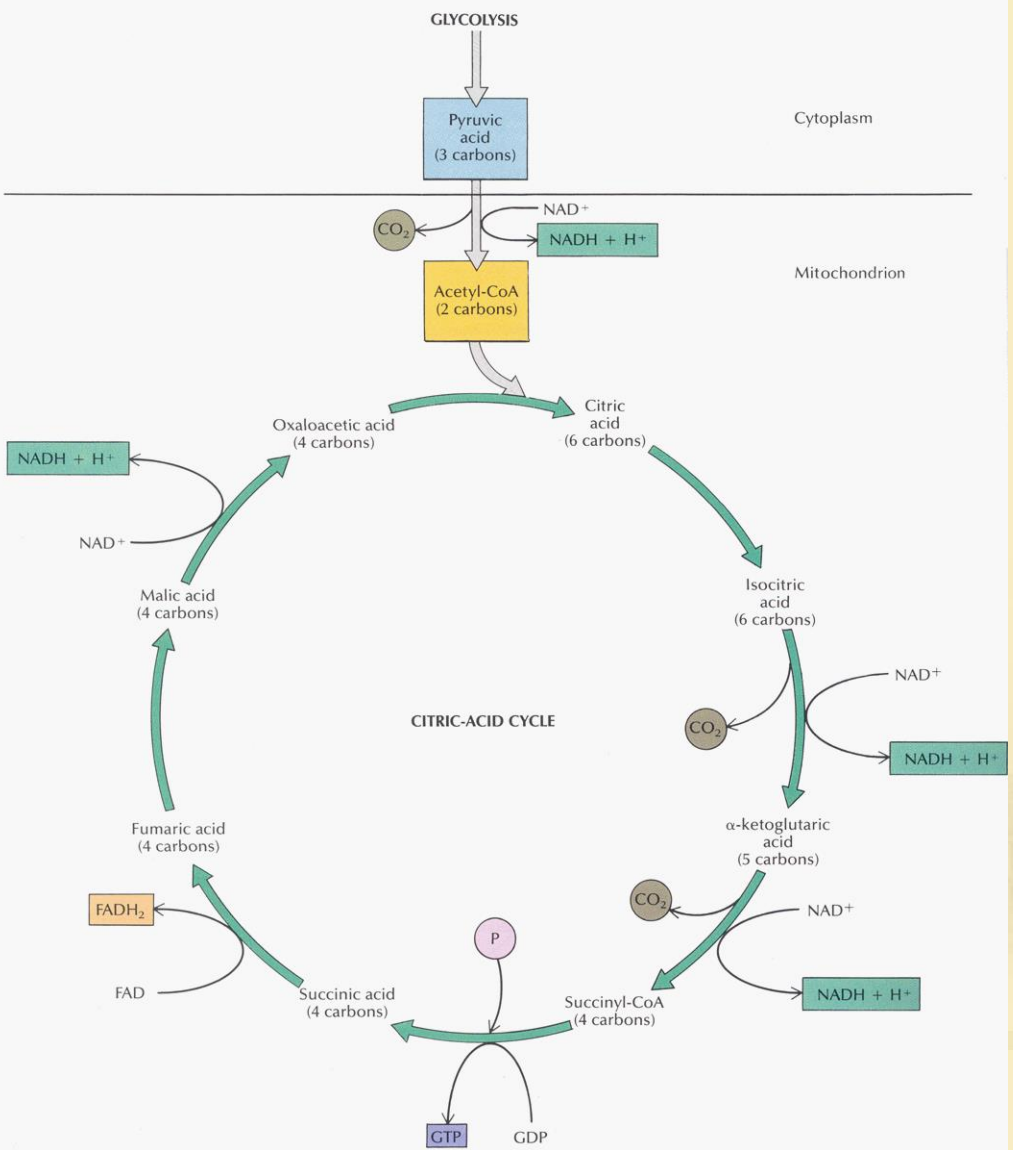
  BUT the duodenal ulcus and adrenal lesion suggest the central / periferal nervous system and neuroendocrin system interaction also.

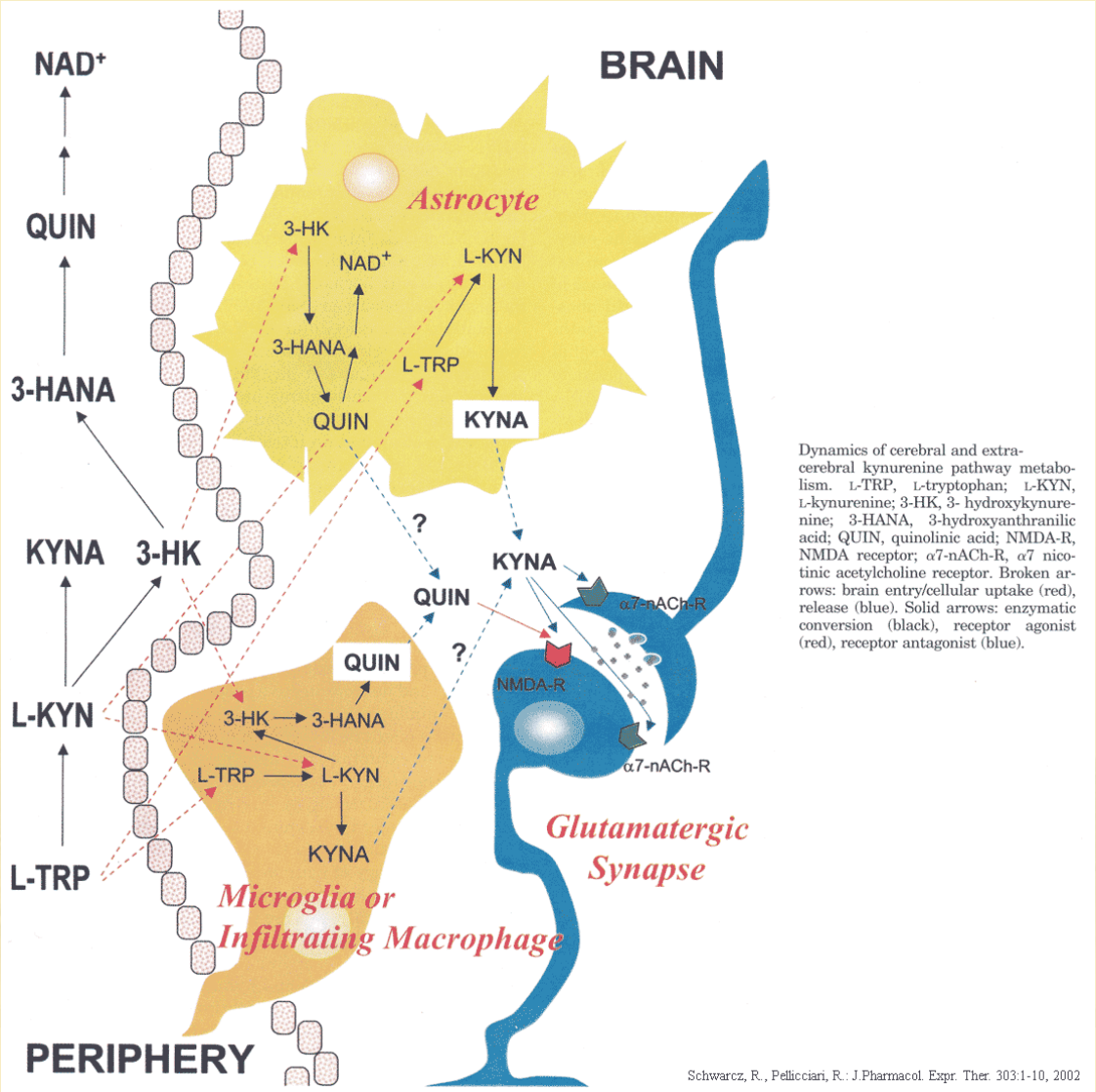
A potential new neuroendocrine molecule: kynurenic acid



Nat Rev Drug Discov. 2013 Jan;12(1):64-82.

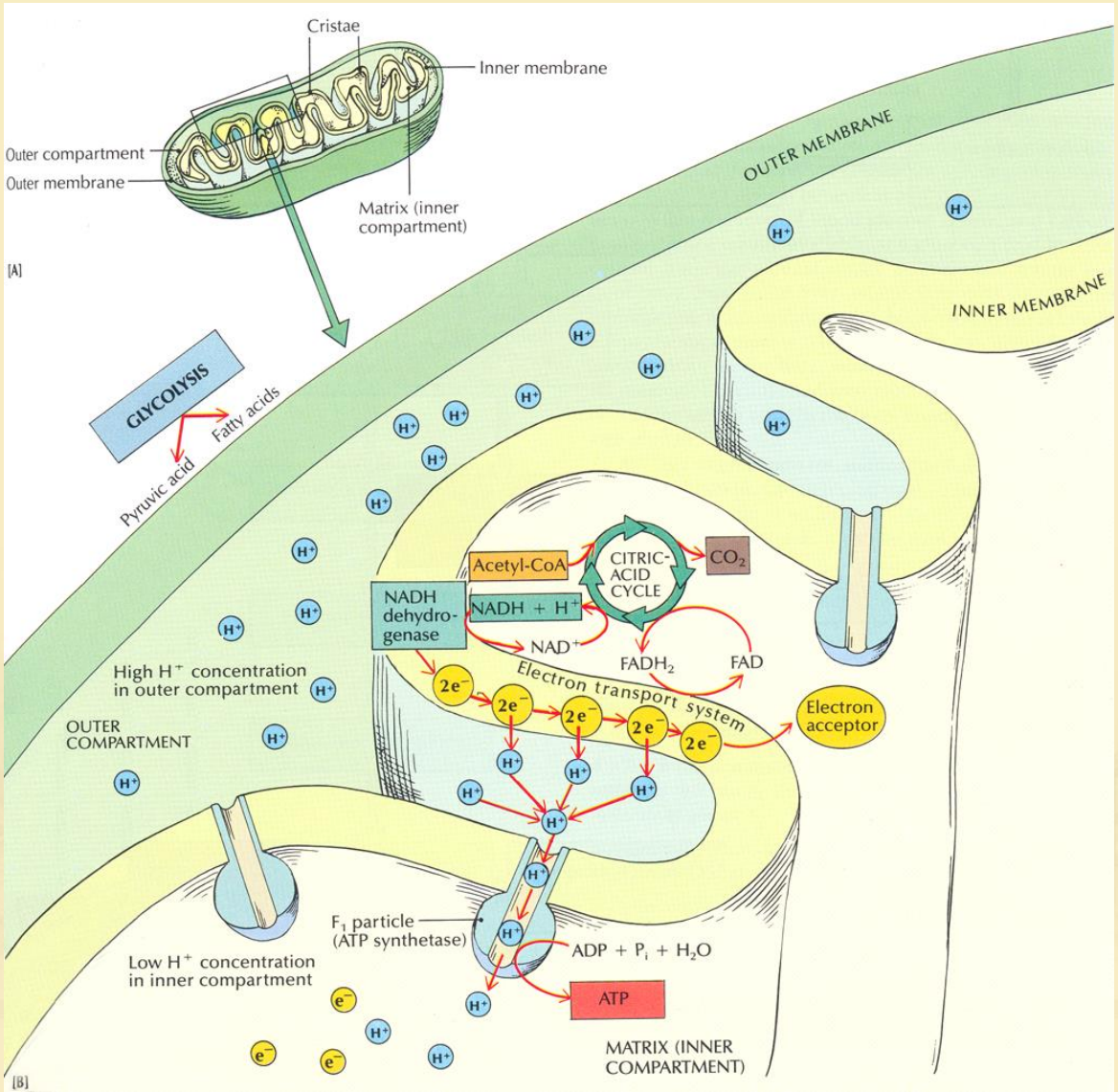
(B) Simplified version of the citric-acid cycle.



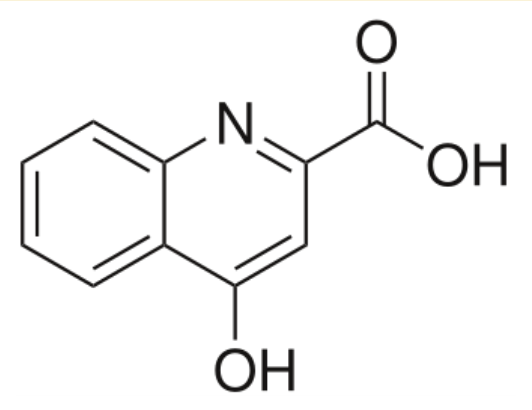


Dynamics of cerebral and extracerebral kynurenine pathway metabolism. L-TRP, L-tryptophan; L-KYN, L-kynurenine; 3-HK, 3- hydroxykynurenine; 3-HANA, 3-hydroxyanthranilic acid; QUIN, quinolinic acid; NMDA-R, NMDA receptor; α7-nACh-R, α7 nicotinic acetylcholine receptor. Broken arrows: brain entry/cellular uptake (red), release (blue). Solid arrows: enzymatic conversion (black), receptor agonist (red), receptor antagonist (blue).

Schwarcz, R., Pellicciari, R.: J.Pharmacol. Expr. Ther. 303:1-10, 2002


Cristae
Inner membrane
Outer compartment
Outer membrane
Matrix (inner compartment)
[A]
OUTER MEMBRANE
INNER MEMBRANE
GLYCOLYSIS
Fatty acids
Pyruvic acid
Acetyl-CoA
CITRIC-ACID CYCLE
CO_2
NADH dehydro-genase
NADH + H^+
NAD^+
$FADH_2$
FAD
Electron transport system
Electron acceptor
High H^+ concentration in outer compartment
OUTER COMPARTMENT
F_1 particle (ATP synthetase)
ADP + P_i + H_2O
ATP
Low H^+ concentration in inner compartment
MATRIX (INNER COMPARTMENT)
[B]

Kynurenic acid = KYNA



It acts as an antiexcitotoxic – neuroprotective compound by antagonism of excitatory amino acid (EAA) receptors.

Targets of KYNA :

1.) ionotropic AMPA, NMDA and Kainate glutamate receptors - antagonist

2.) glycine site of the NMDA receptor - noncompetitive antagonist

3.) α7 nicotinic acetylcholine receptor - antagonist

4.) orphan G protein-coupled receptor GPR35 - ligand

Role of KYNA in neurological diseases:

HD, PD, migraine, MS, schizophrenia, tick-borne encephalitis, ALS, stroke, epilepsy

KYNA in endocrine/neuroendocrine aspects

1. Individual islets from rat pancreas

3-Hydroxykynurenine and 3-hydroxyanthranilic acid were inhibitors at concentrations below 10 mM whereas tryptophan, kynurenine, kynurenic acid, xanthurenic acid, and anthranilic acid were ineffective inhibitors at concentrations up to 10 mM on leucine-stimulated release of insulin.

(Rogers KS, Evangelista SJ. Proc Soc Exp Biol Med. 1985;178(2):275-8.)

2. Ovariectomized, estradiol-primed rats

Intracisternal administration of QUIN, as a potent agonist at NMDA-preferring EAA receptors, resulted in an acute, dose-dependent increase of serum LH concentrations, which was blocked by KYNA.

(Johnson MD, Whetsell WO Jr, Crowley WR. Exp Brain Res. 1985;59(1):57-61.)

3. Regulation of hypothalamic-pituitary-adrenal axis – in vitro – by EAA transmitters

Significantly decreased CRH release by agonists.

Significantly increased AVP release by L-Aspartate (ASP) and NMDA as well as decreased by Kainic acid and Quisqualic acid.

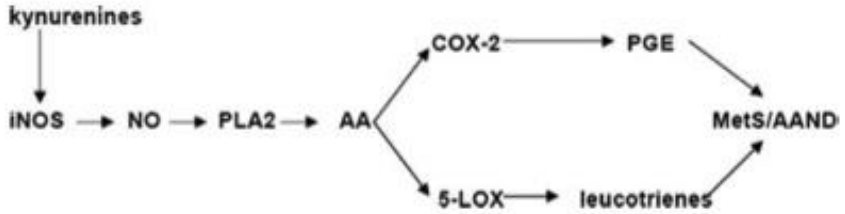
KYNA completely abolished the ASP effects on CRH and AVP release in vitro.

(*Vladimir K. Patchev, Katia Karalis, George P. Chrousos.* Brain Research 633 (1994) 312-316).

KYN-pathway
4. Metabolic syndromes (MetS) - Age-associated neuroendocrine disorders (AAND)

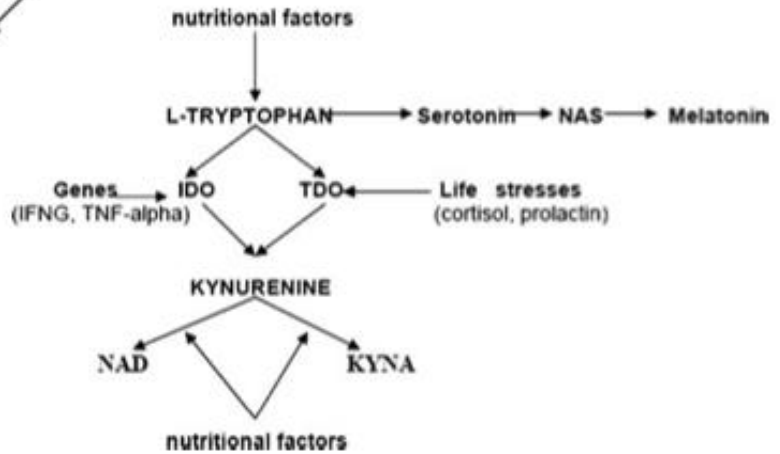
Transcriptional induction of **indoleamine 2,3-dioxygenase (IDO)** by pro-inflammatory cytokines (PIC) - development of MetS/AAND.

Activation of IDO shifts TRY metabolism from serotonin synthesis to formation of “kynurenines” – MetS/AAND via apoptotic, neurotoxic and pro-oxidative effects.



The combined presence of high producers of alleles of polymorphic PIC genes (e.g., IFY, TNFα) might account for the genetic predisposition to high levels of PIC production, leading to “superinduction” of IDO.

(Gregory F. Oxenkrug, Ann N Y Acad Sci. 2010;1199:1-14.)

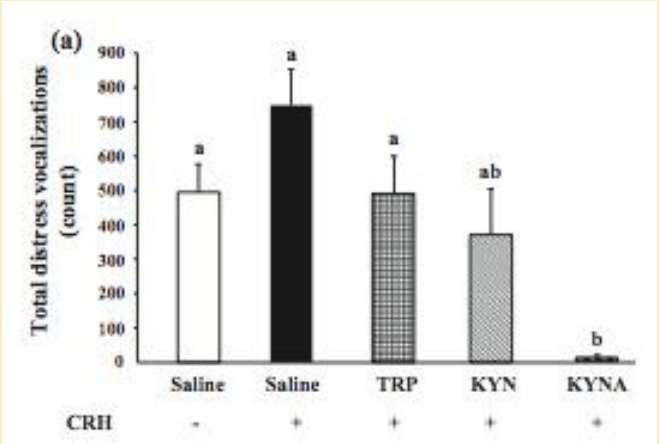


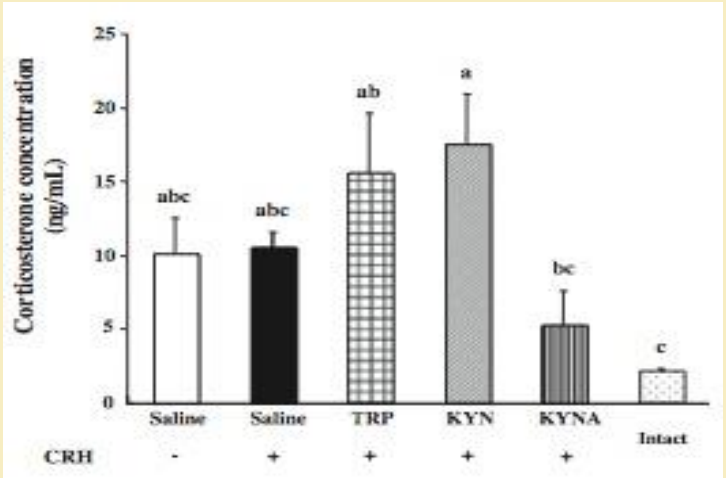
5. Anxiolytic effect of KYNA

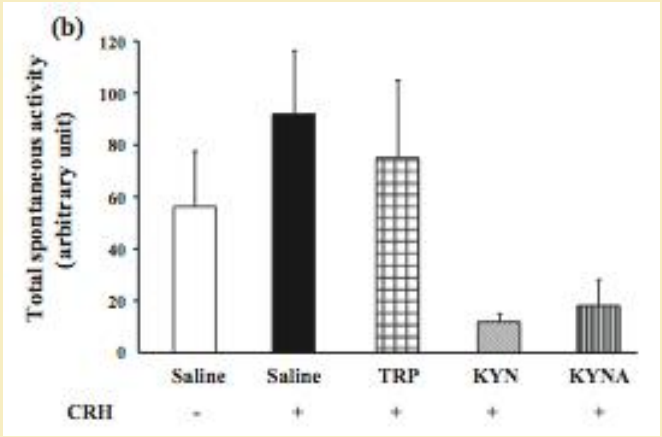
- Neonatal chicks
- Social isolation induced stress model and the i.c.v. injected CRH-augmented stress response

- KYNA can more effectively:
- decrease the distress vocalization and the active wakefulness
- increase the time of sleeping position
- depress the plasma corticosterone concentration compared to the TRP.

Yoshida J, Tomonaga S, Ogino Y, Nagasawa M, Kurata K, Furuse M. Neuroscience. 2012;220:142-8.







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Research Article

Acute Psychological Stress Modulates the Expression of Enzymes Involved in the Kynurenine Pathway throughout Corticolimbic Circuits in Adult Male Rats

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Tryptophan is an essential dietary amino acid that is necessary for protein synthesis, but also serves as the precursor for serotonin. However, in addition to these biological functions, tryptophan also serves as a precursor for the kynurenine pathway, which has neurotoxic (quinolinic acid) and neuroprotective (kynurenic acid) metabolites. Glucocorticoid hormones and inflammatory mediators, both of which are increased by stress, have been shown to bias tryptophan along the kynurenine pathway and away from serotonin synthesis; however, to date, there is no published data regarding the effects of stress on enzymes regulating the kynurenine pathway in a regional manner throughout the brain. Herein, we examined the effects of an acute psychological stress (120 min restraint) on gene expression patterns of enzymes along the kynurenine pathway over a protracted time-course (1–24 h post-stress termination) within the amygdala, hippocampus, hypothalamus, and medial prefrontal cortex. Time-dependent changes in differential enzymes along the kynurenine metabolism pathway, particularly those involved in the production of quinolinic acid, were found within the amygdala, hypothalamus, and medial prefrontal cortex, with no changes seen in the hippocampus. These regional differences acutely may provide mechanistic insight into processes that become dysregulated chronically in stress-associated disorders.

These data present the first investigation of the effects of acute stress on regional changes in mRNA expression of enzymes regulating the kynurenine pathway. Specifically, we found changes in enzymes along the QUIN neurotoxic arm of the kynurenine pathway are increased within the amygdala, while a downregulation of mRNA expression of these enzymes was seen in the medial prefrontal cortex, following exposure to acute stress (Figure 1).

These changes are a consequence of increased inflammatory mediators in discrete brain regions and could provide a mechanistic pathway linking stress-induced inflammation to alterations in cellular integrity within the brain.

Acute stress-induced changes in the gene expression of enzymes leading to kynurenine metabolites that alter excitatory signalling, may may provide insight into processes that can become dysregulated during chronic stress conditions, which could, in turn, contribute to some of the neuropathological effects documented following stress or inflammatory-related illnesses, particularly major depression.

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Social isolation rearing in rats alters plasma tryptophan metabolism and is reversed by sub-chronic clozapine treatment

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Kynurenic acid
Anti-inflammatory
Antioxidant

ABSTRACT

Schizophrenia is associated with increased oxidative stress, although the source of this redox disequilibrium requires further study. Altered tryptophan metabolism has been described in schizophrenia, possibly linked to inflammation and glutamate-directed excitotoxicity. Social isolation rearing (SIR) in rats induces various behavioural manifestations akin to schizophrenia, as well as altered frontal cortical glutamate N-methyl-D-aspartate (NMDA) receptor binding and increased oxidative stress, all reversed by antipsychotic treatment. Tryptophan is catabolized via the kynurenine pathway to kynurenine, 3-hydroxykynurenine, quinolinic acid (QA), kynurenic acid (KYNA), anthranilic acid and 3-hydroxyanthranilic acid (3-OHAA), ultimately contributing to neuronal integrity and redox balance in the brain. We studied tryptophan metabolism and neuroprotective-neurodegenerative balance in postnatal SIR rats, and its response to clozapine treatment. Male Sprague-Dawley (SD) rats (10 rats/group) were exposed to SIR or social rearing for 8 weeks, whereupon they received either sub-chronic vehicle or clozapine (5 mg/kg i.p) treatment. Plasma tryptophan metabolites were analysed by liquid-chromatography electrospray ionization tandem mass spectrometry. Plasma tryptophan, kynurenine, anthranilic acid, 3-OHAA and QA were significantly elevated in SIR vs. socially housed rats. KYNA and the neuroprotective ratio were significantly decreased. The latter implies a decrease in KYNA (neuroprotective) but an increase in QA (neurodegenerative) directed components of the pathway. Clozapine significantly reversed all the above alterations in SIR animals. Concluding, SIR in rats significantly disrupts tryptophan metabolism via the kynurenine pathway with increased risk for neurodegenerative changes in the brain. These changes are reversed by clozapine, emphasising the importance of these findings for the neurobiology and treatment of schizophrenia.

Köszönöm a figyelmet!