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UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Centro Interdipartimentale Grandi Strumenti CINQUANTA

# Analisi quantitativa target HPLC-MS della via metabolica delle chinurenine: eziopatogenesi e cura delle malattie umane

Prof. Silvia Alboni Dipartimento di Scienze della Vita

Modena, 6/11/2024

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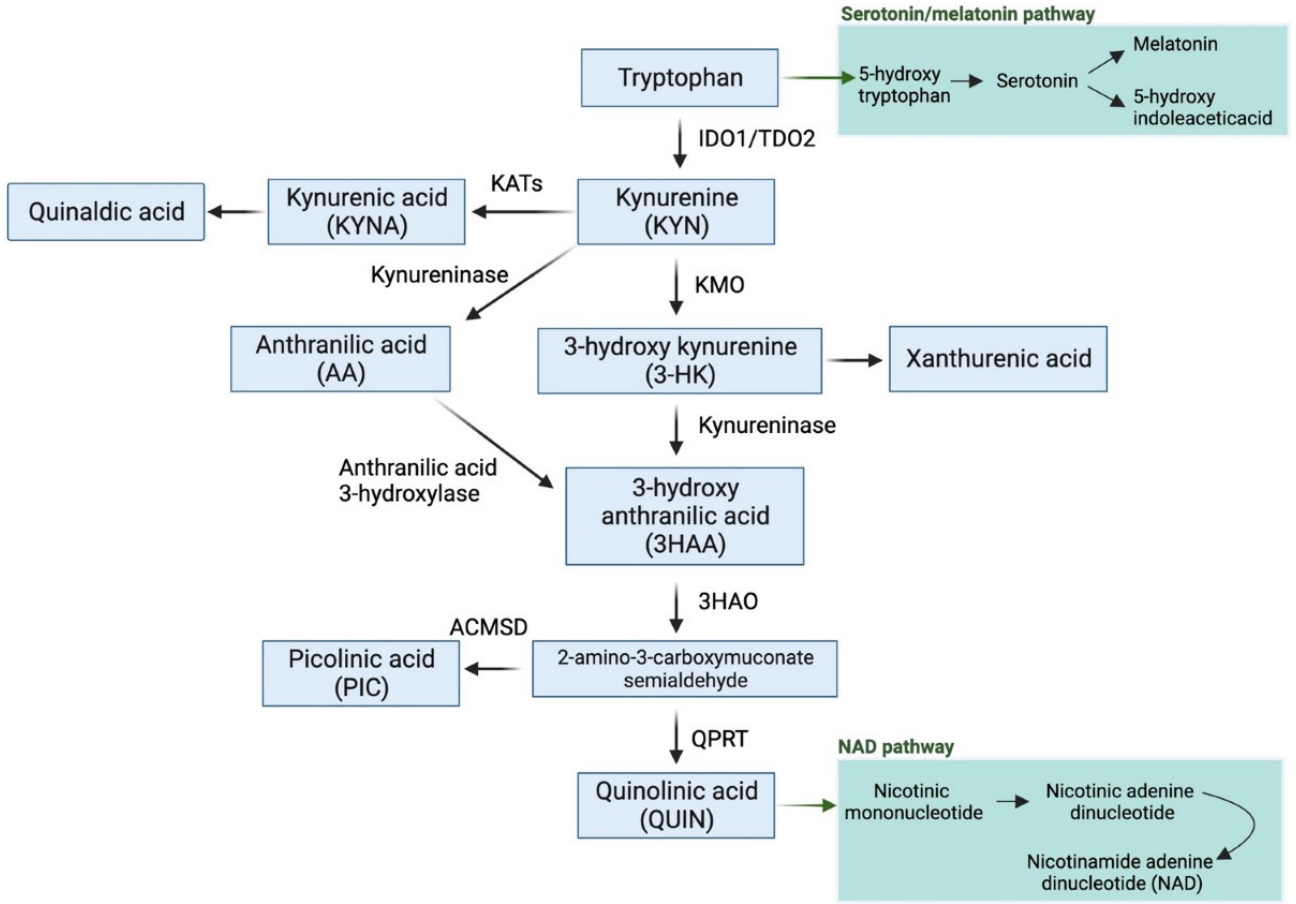
Dr. Paolo Giudetti

Prof. Giuseppe Cannazza

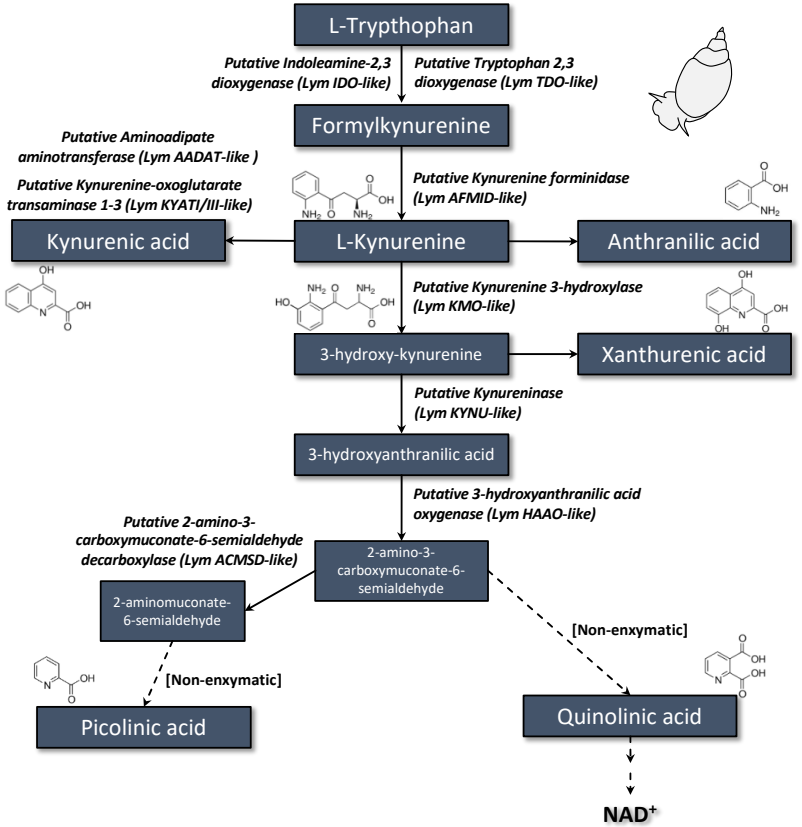
# VIA METABOLICA DELLE CHINURENINE

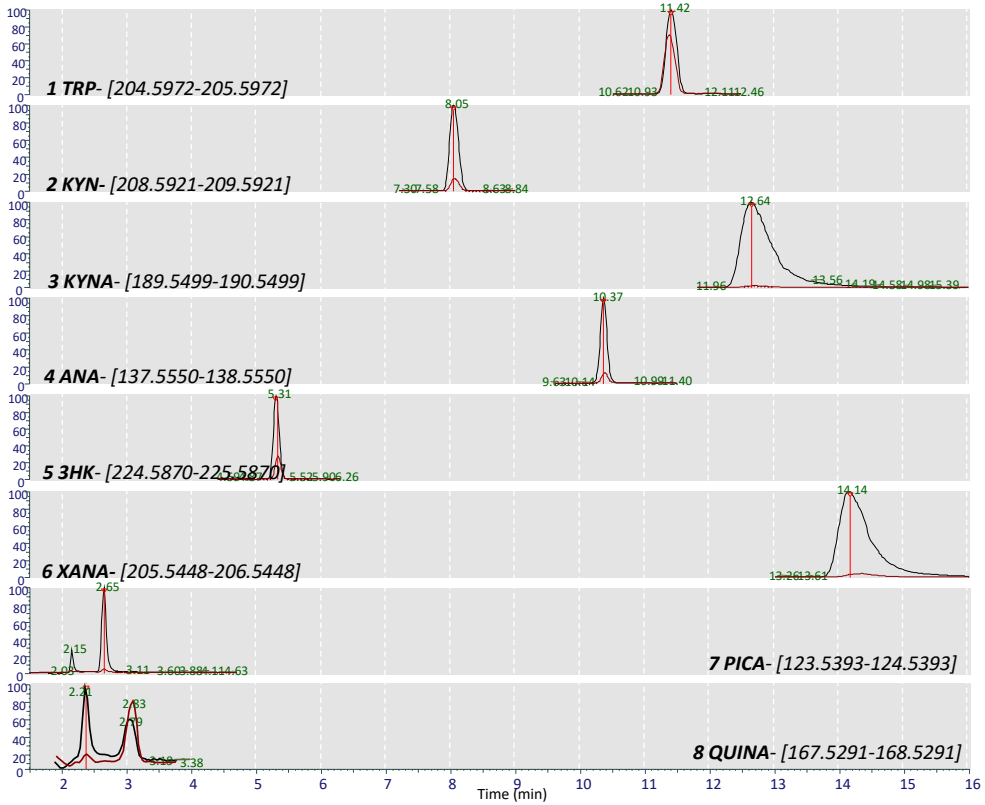



*Dehhaghi et al., 2004*

The kynurenine pathway (*KP*) and its derivative pathways. *IDO*-1: Indoleamine-pyrrole 2,3-dioxygenase; *TDO*2: Tryptophan 2,3-dioxygenase; *KATs*: Kynurenine aminotransferase; *KMO*: Kynurenine 3-monooxygenase; *HAAO*: 3-hydroxyanthranilate 3,4-dioxygenase; *QPRT*: Quinolinate phosphoribosyl transferase; *ACMSD*: Aminocarboxymuconate-semialdehyde decarboxylase. Created with biorender.com

# VIA METABOLICA DELLE CHINURENINE




BIOLOGICAL REVIEWS
Cambridge Philosophical Society

Original Article | Open Access

## What can we teach *Lymnaea* and what can *Lymnaea* teach us?

Veronica Rivi, Cristina Benatti, Ken Lukowiak, Chiara Colliva, Silvia Alboni, Fabio Tascedda, Johanna M.C. Blom

# VIA METABOLICA DELLE CHINURENINE

Journal of Pharmaceutical and Biomedical Analysis 211 (2022) 114636

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.journals.elsevier.com/journal-of-pharmaceutical-and-biomedical-analysis

## Kynurenine and kynurenic acid: Two human neuromodulators found in *Cannabis sativa* L.

Fabiana Russo [a,b,1], Francesco Tolomeo [c,1], Maria Angela Vandelli [d], Giuseppe Biagini [b], Roberta Paris [e], Flavia Fulvio [e], Aldo Laganà [f], Anna Laura Capriotti [f], Luigi Carbone [c], Giuseppe Gigli [c], Giuseppe Cannazza [d,*], Cinzia Citti [c,*]

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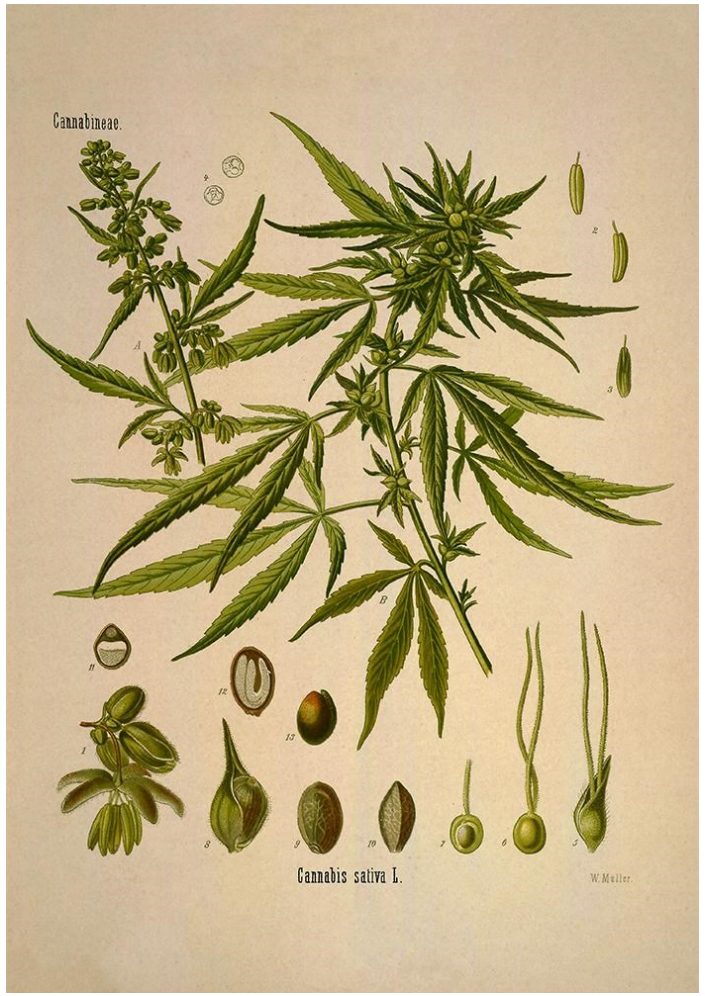
ARTICLE INFO

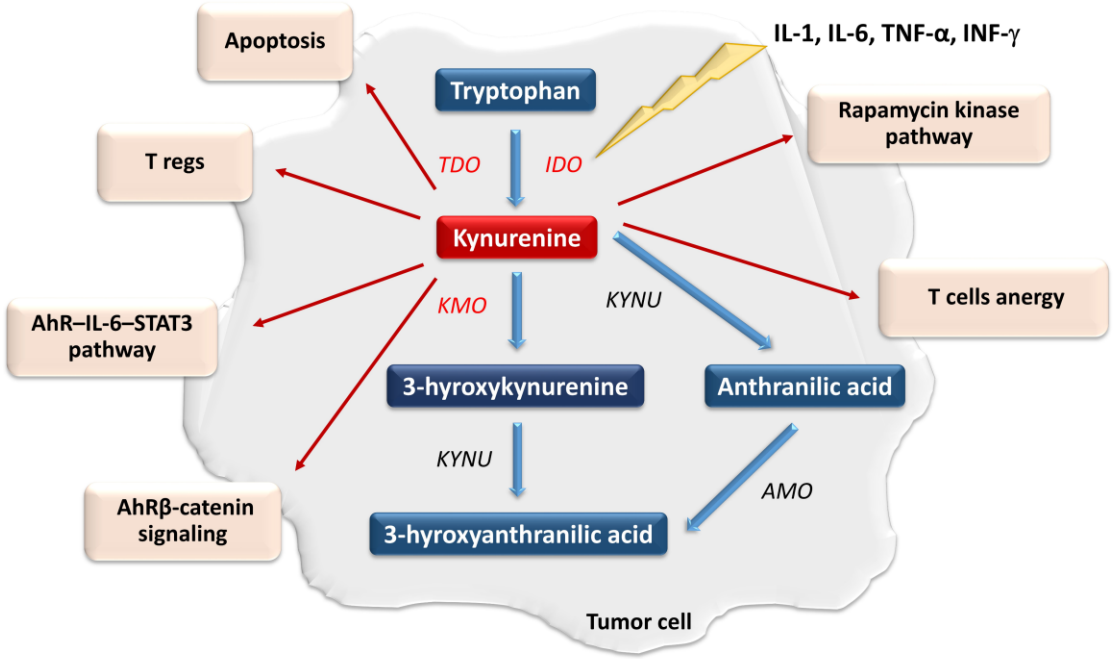
*Keywords:*
Cannabis sativa
Tryptophan
Kynurenine
Kynurenic acid
Liquid chromatography
High-resolution mass spectrometry

ABSTRACT

L-Kynurenine (KYN) and kynurenic acid (KYNA) are products of the metabolism of L-tryptophan (TRP) in the central nervous system of animals, but they are not commonly found in plants. In particular, KYNA is known for its interesting pharmacological properties (anti-oxidative, anti-inflammatory, hypolipidemic, and neuro-protective), which suggest a potential functional food ingredient role. The three compounds were identified in samples of *Cannabis sativa* L. by means of high-performance liquid chromatography coupled to high-resolution mass spectrometry using an untargeted metabolomics approach. Their concentrations were evaluated using a targeted metabolomics method in three organs of the plant (roots, stem, and leaves) in soil at two different growth stages and in hydroponics conditions. The distribution of TRP, KYN and KYNA was found tendentially higher in leaves compared to stem and roots and changed over time. Moreover, the levels of KYNA found in this study are unprecedentedly high compared to those found so far in other plant species, suggesting that *Cannabis sativa* L. could be a promising alternative source of this metabolite.



# VIA METABOLICA DELLE CHINURENINE & CANCER




**Kynurenines as a Novel Target for the Treatment of Malignancies**

*Mor A et al., 2021*

## Indoleamine 2, 3-Dioxygenase 1 Mediates Survival Signals in Chronic Lymphocytic Leukemia *via* Kynurenine/Aryl Hydrocarbon Receptor-Mediated MCL1 Modulation

*Claudio Giacinto Atene[1], Stefania Fiorcari[1], Nicolò Mesini[1], Silvia Alboni[2,3], Silvia Martinelli[1,4], Monica Maccaferri[4], Giovanna Leonardi[4], Leonardo Potenza[1,4], Mario Luppi[1,4], Rossana Maffei[4†] and Roberto Marasca[1,4*†]*

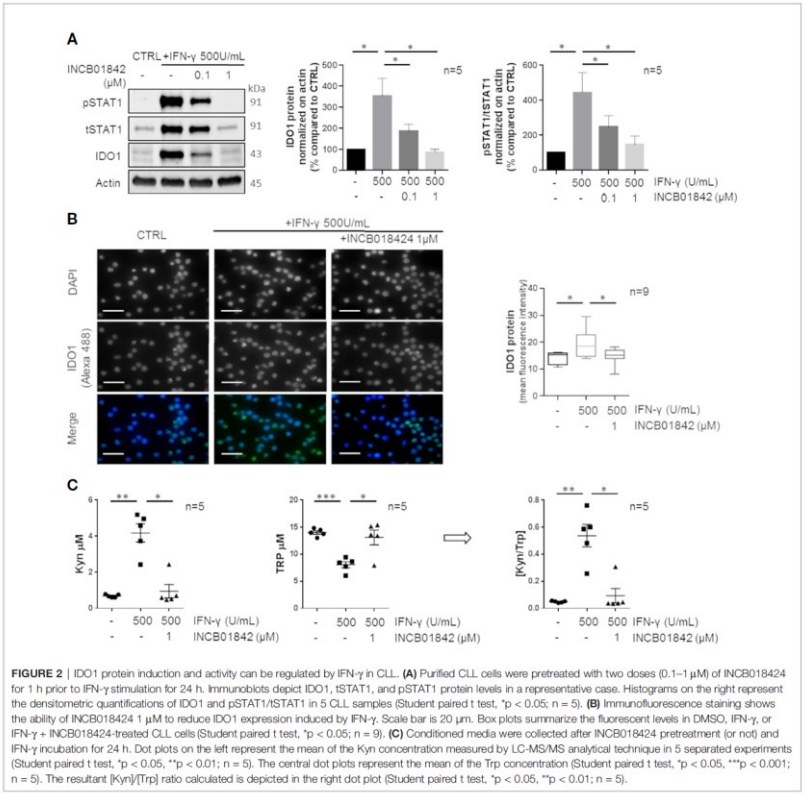



**FIGURE 2** | IDO1 protein induction and activity can be regulated by IFN-γ in CLL. **(A)** Purified CLL cells were pretreated with two doses (0.1–1 μM) of INCB018424 for 1 h prior to IFN-γ stimulation for 24 h. Immunoblots depict IDO1, tSTAT1, and pSTAT1 protein levels in a representative case. Histograms on the right represent the densitometric quantifications of IDO1 and pSTAT1/tSTAT1 in 5 CLL samples (Student paired t test, *p < 0.05; n = 5). **(B)** Immunofluorescence staining shows the ability of INCB018424 1 μM to reduce IDO1 expression induced by IFN-γ. Scale bar is 20 μm. Box plots summarize the fluorescent levels in DMSO, IFN-γ, or IFN-γ + INCB018424-treated CLL cells (Student paired t test, *p < 0.05; n = 9). **(C)** Conditioned media were collected after INCB018424 pretreatment (or not) and IFN-γ incubation for 24 h. Dot plots on the left represent the mean of the Kyn concentration measured by LC-MS/MS analytical technique in 5 separated experiments (Student paired t test, *p < 0.05, **p < 0.01; n = 5). The central dot plots represent the mean of the Trp concentration (Student paired t test, *p < 0.05, **p < 0.001; n = 5). The resultant [Kyn]/[Trp] ratio calculated is depicted in the right dot plot (Student paired t test, *p < 0.05, **p < 0.01; n = 5).

# VIA METABOLICA DELLE CHINURENINE & CNS diseases

Molecular Psychiatry (2020) 25:131–147
https://doi.org/10.1038/s41380-019-0414-4

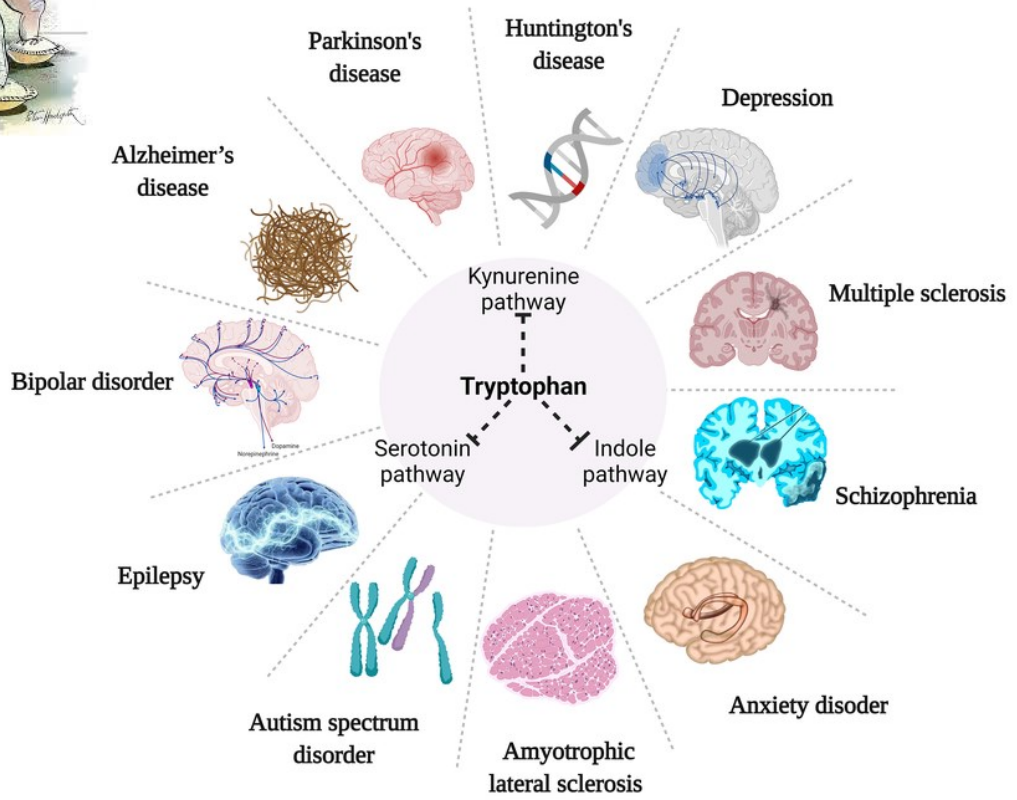
EXPERT REVIEW

## The kynurenine pathway: a finger in every pie

Jonathan Savitz[1,2]

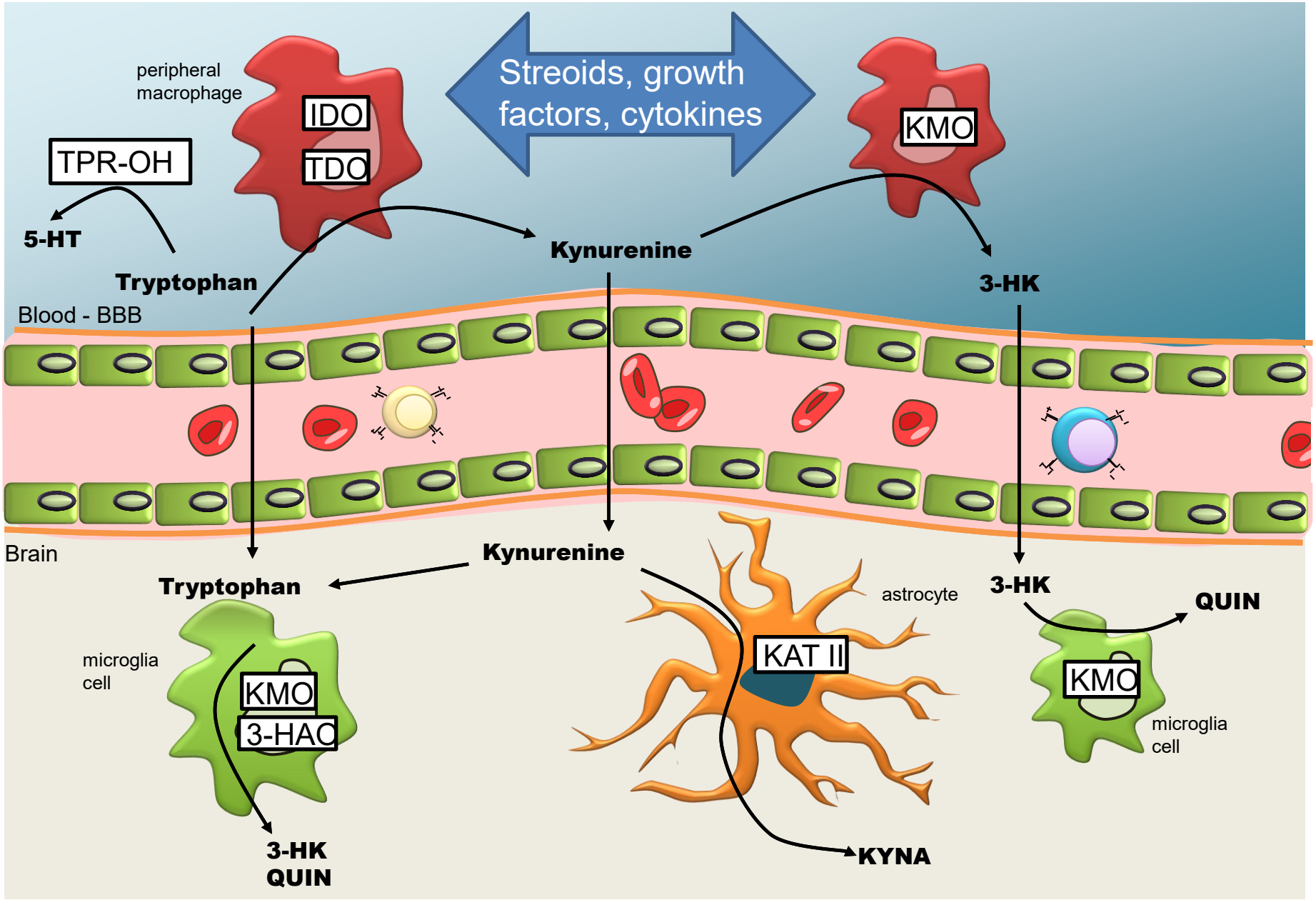
Received: 21 October 2018 / Revised: 18 March 2019 / Accepted: 22 March 2019 / Published online: 12 April 2019


**Abstract**
The kynurenine pathway (KP) plays a critical role in generating cellular energy in the form of nicotinamide adenine dinucleotide (NAD+). Because energy requirements are substantially increased during an immune response, the KP is a key regulator of the immune system. Perhaps more importantly in the context of psychiatry, many kynurenines are neuroactive, modulating neuroplasticity and/or exerting neurotoxic effects in part through their effects on NMDA receptor signaling and glutamatergic neurotransmission. As such, it is not surprising that the kynurenines have been implicated in psychiatric illness in the context of inflammation. However, because of their neuromodulatory properties, the kynurenines are not just additional members of a list of inflammatory mediators linked with psychiatric illness, but in preclinical studies have been shown to be necessary components of the behavioral analogs of depression and schizophrenia-like cognitive deficits. Further, as the title suggests, the KP is regulated by, and in turn regulates multiple other physiological systems that are commonly disrupted in psychiatric disorders, including endocrine, metabolic, and hormonal systems. This review provides a broad overview of the mechanistic pathways through which the kynurenines interact with these systems, thus impacting emotion, cognition, pain, metabolic function, and aging, and in so doing potentially increasing the risk of developing psychiatric disorders. Novel therapeutic approaches targeting the KP are discussed. Moreover, electroconvulsive therapy, ketamine, physical exercise, and certain non-steroidal anti-inflammatories have been shown to alter kynurenine metabolism, raising the possibility that kynurenine metabolites may have utility as treatment response or therapeutic monitoring biomarkers.

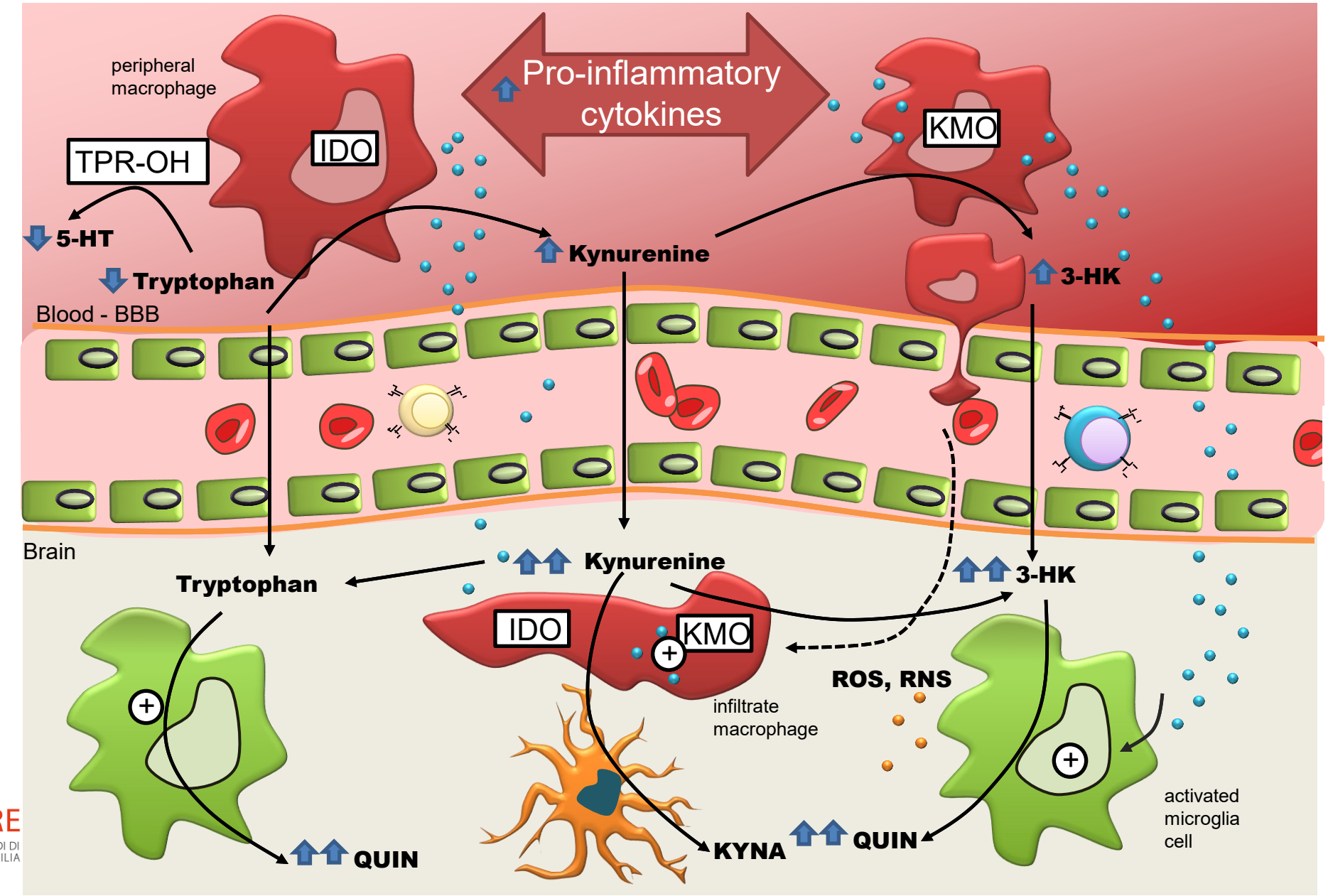



*Li D. et al., 2022*

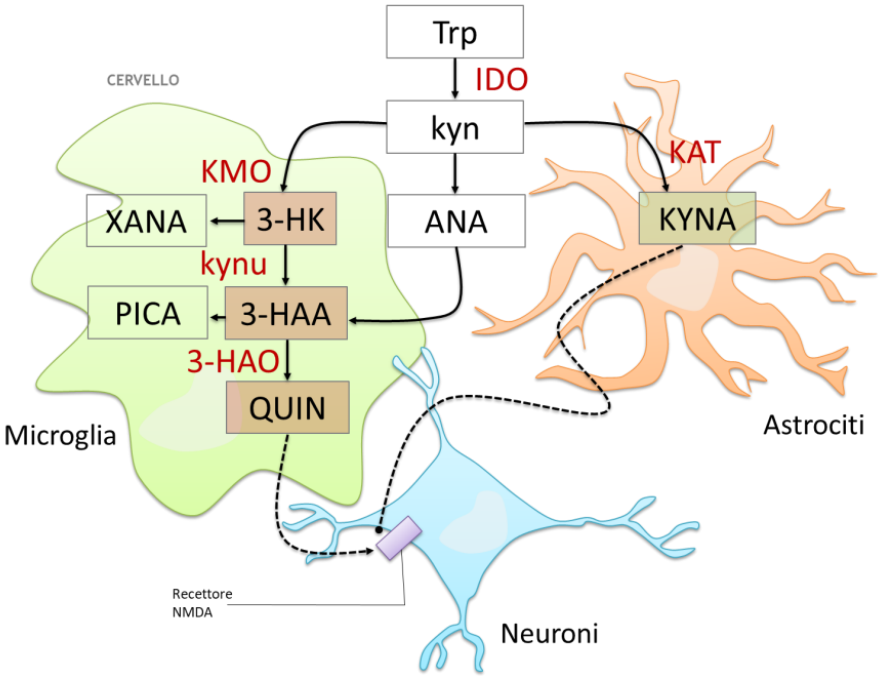
# VIA METABOLICA DELLE CHINURENINE & MDD

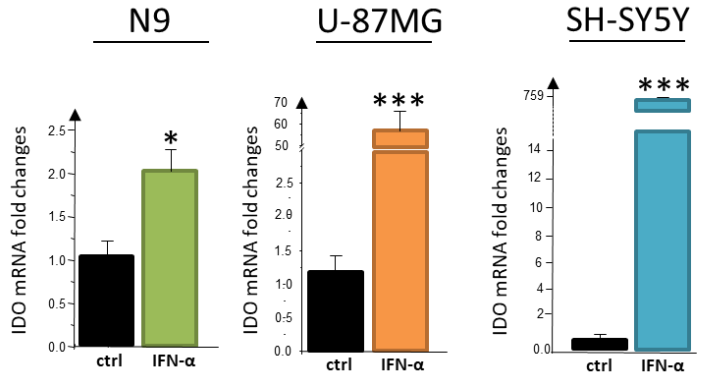


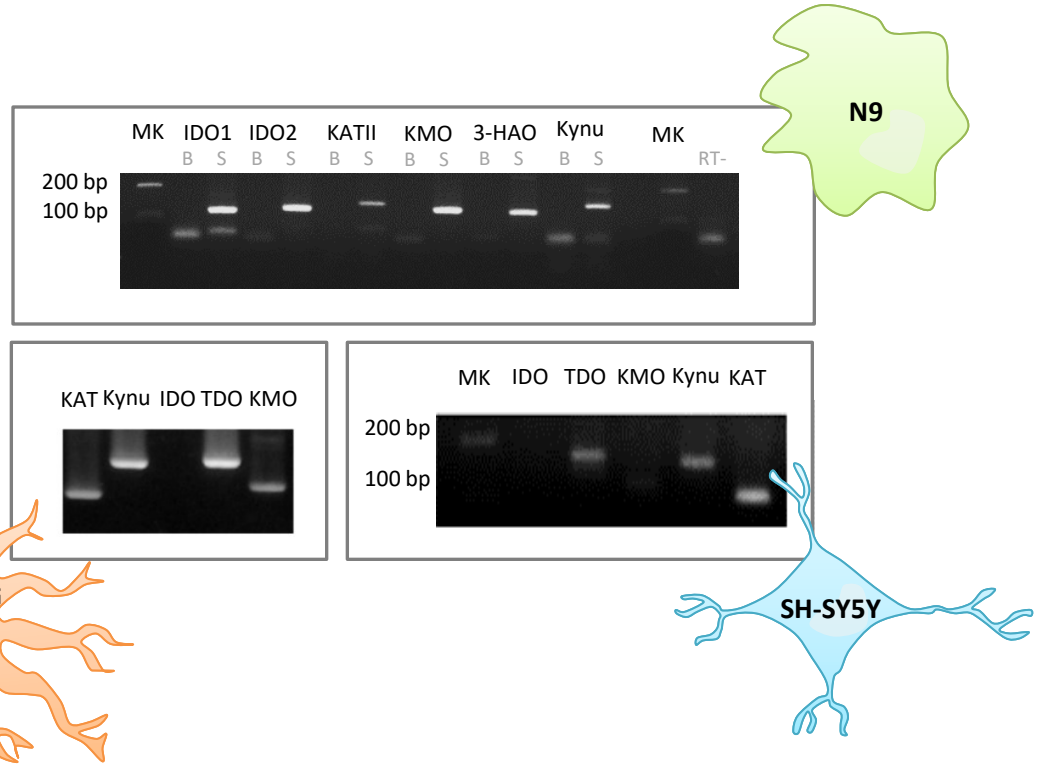
# VIA METABOLICA DELLE CHINURENINE & MDD



# I neuroni producono metaboliti della KP? E la loro produzione è stimolata?

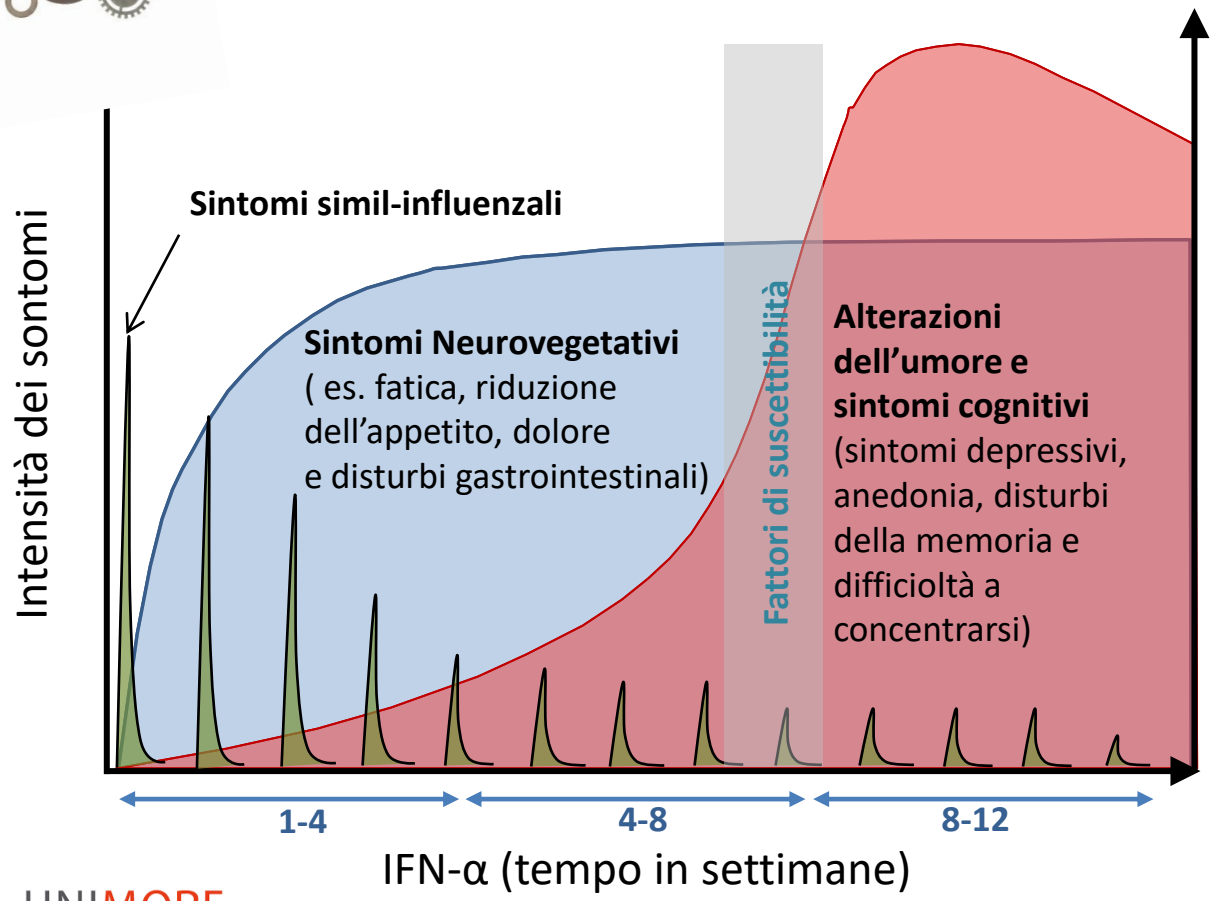


# La terapia con IFN-α induce sintomi depressivi

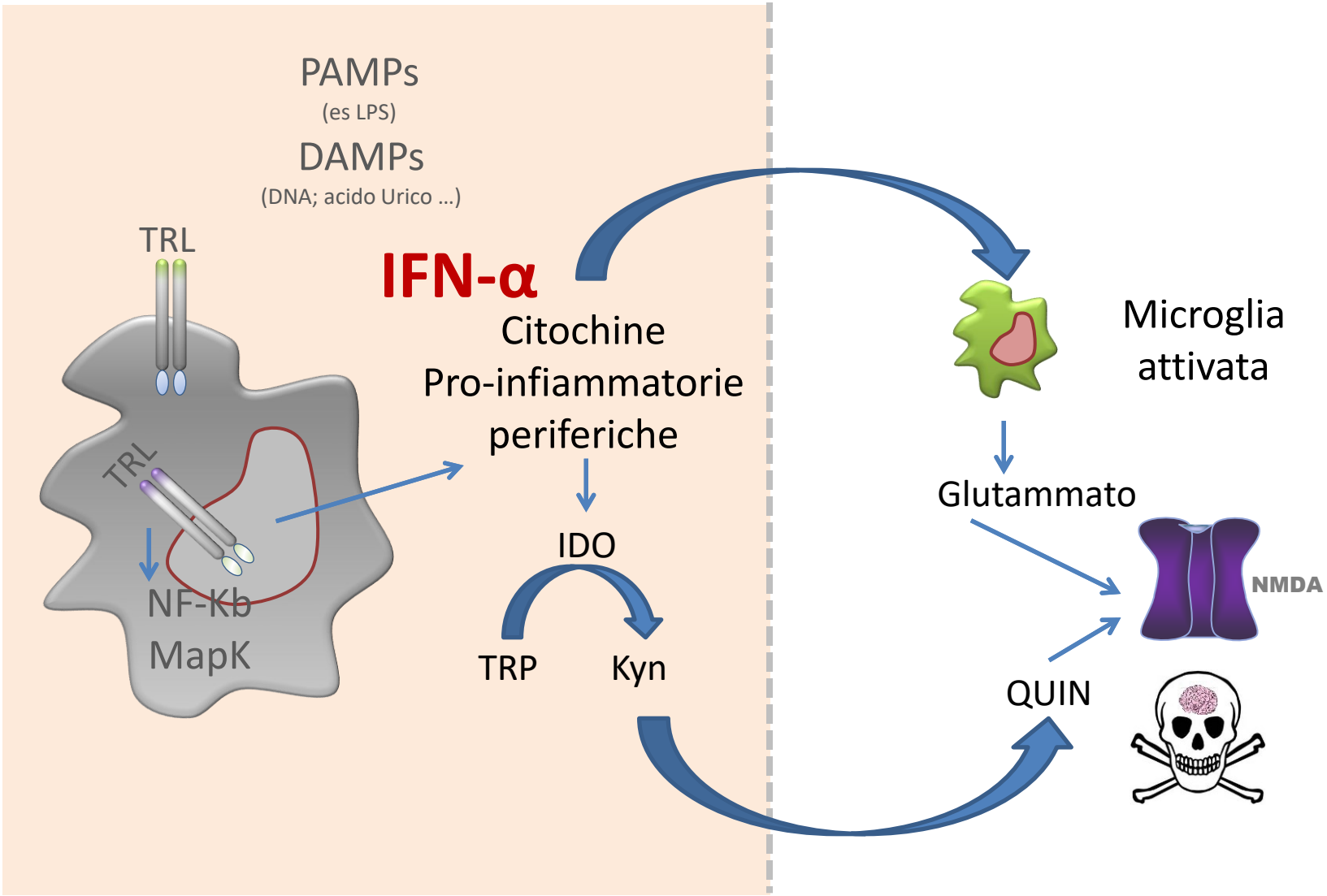
Meccanismi dell'associazione?



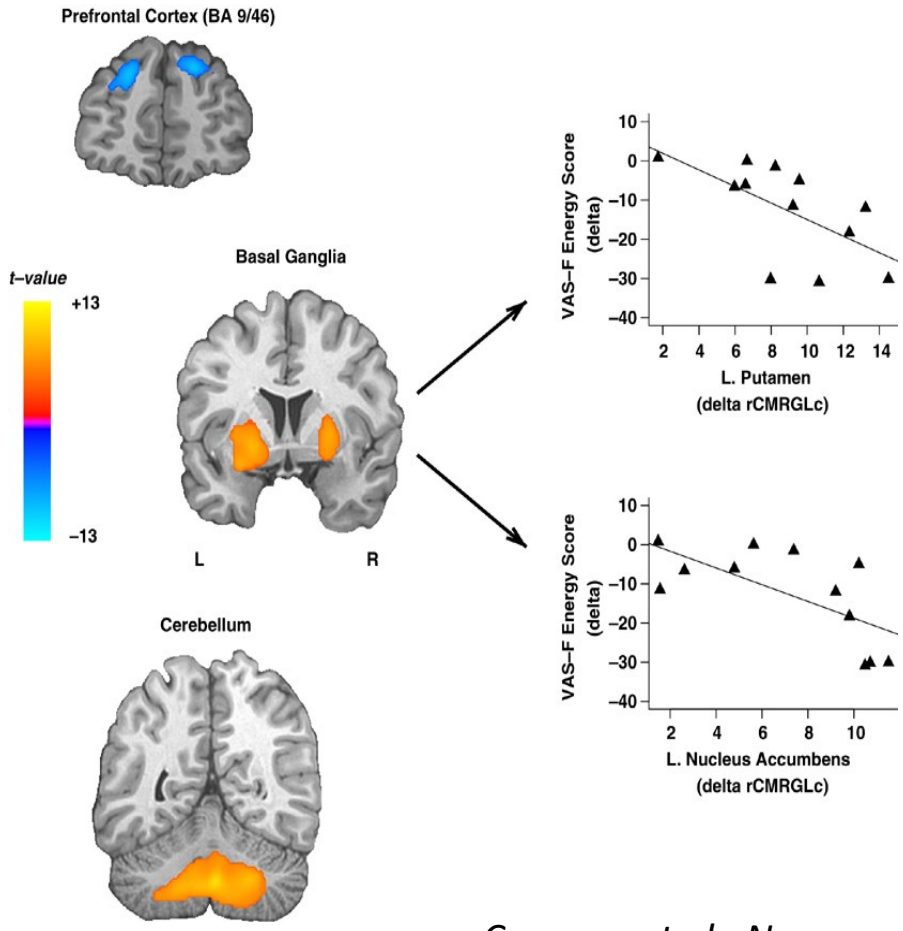

| Effetto collaterale | Prevalenza (%) |
|---|---|
| Fatica | 39-80 |
| Disturbi del sonno | 18-45 |
| Irritabilità | 16-50 |
| Ansia | 11-45 |
| Disturbi cognitivi | 2-30 |
| Mania | 0-3,2 |
| Psicosi | 0-0,6 |
| Pensieri e ideazioni suicidarie | 3,5-10% |
| Suicidio o tentati suicidi | 0-0,2% |

*Capuron & Miller, Pharmacol Therap. 2011*

# Patofisilogia della depressione indotta da stimoli infiammatori (IFN-α)



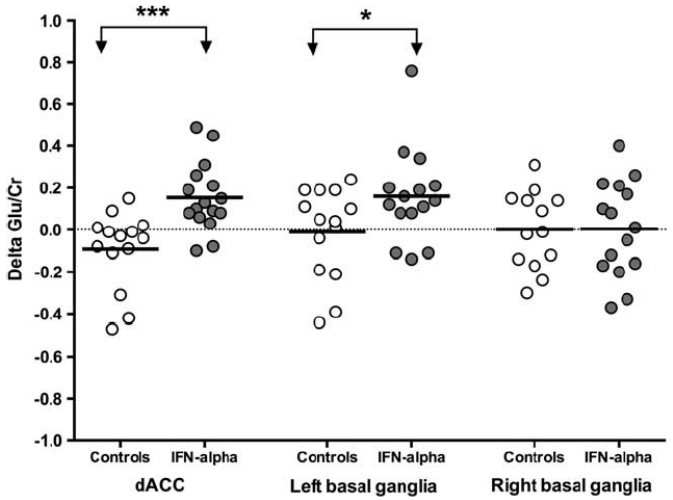
# IFN-α aumenta l'attività metabolica nei gangli della base e diminuisce quella della corteccia prefrontale



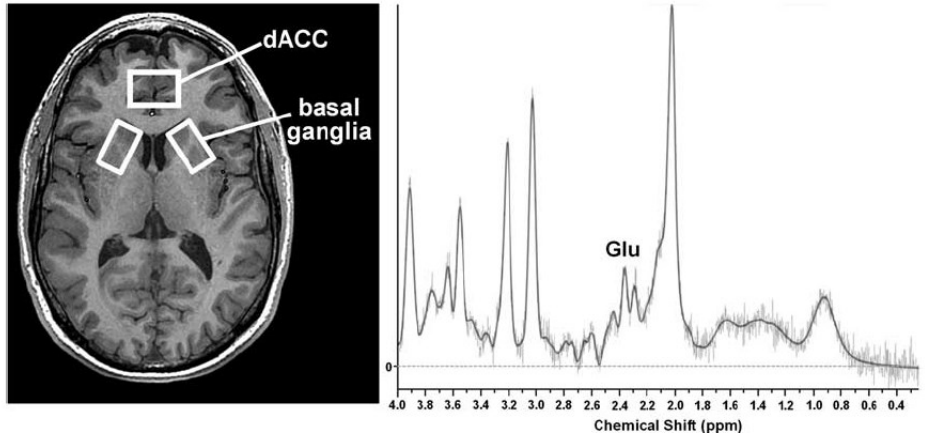

12 patients with malignant melanoma
4 weeks IFNα IV, TEP $^{18}$FDG

*Capuron et al., Neuropsychopharmacology 2007*

# IFN-α aumenta il glutammato nella corteccia dei cingoli anteriore dorsale e nei gangli della base

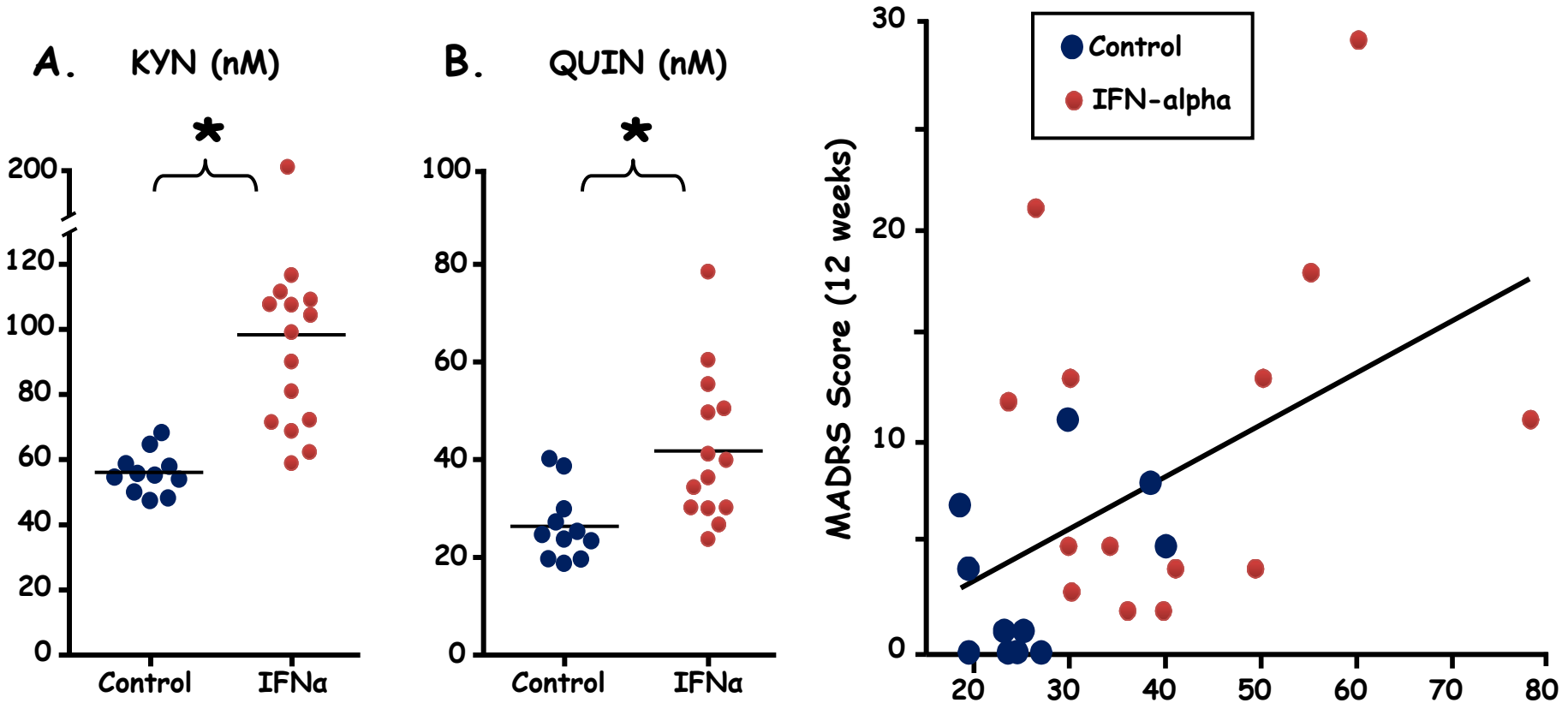



31 HCV-positive patients (17 IFN-α treated ; 14 controls)
Visit 1: before and visit 2 during (about 1 month later) IFN- α treatment.



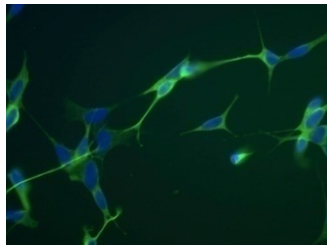

*Haroon E et al., Neuropsychipharmacology 2014*

# Aumentati livelli di chinurenie (KYN) e acido chinolinico (QUIN) nel fluido cerebro spinale di soggetti HCV positivi trattati con IFN-α per 12 settimane

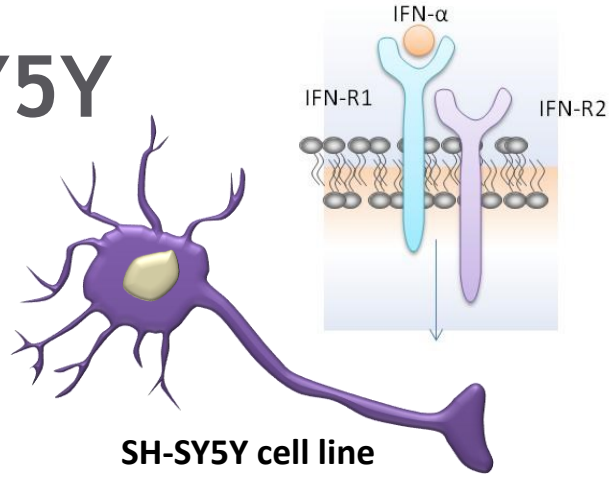


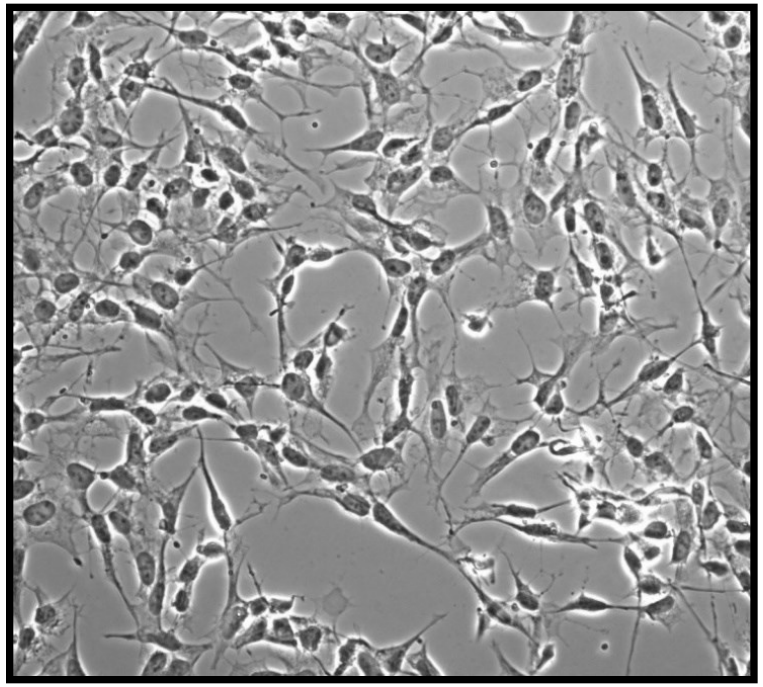

*Raison et al., Mol Psychiat 2010*

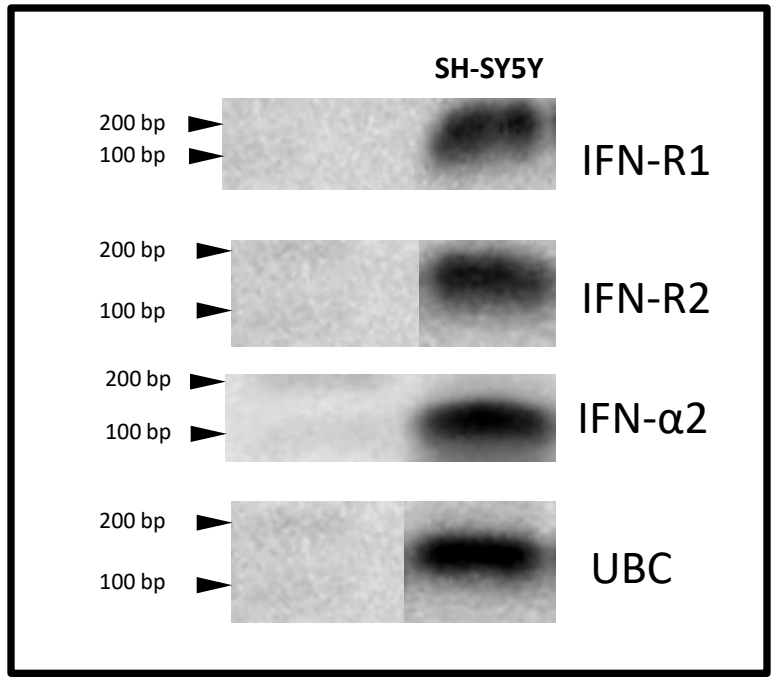
# Modello sperimentale: SH-SY5Y



DAPI - beta tub III

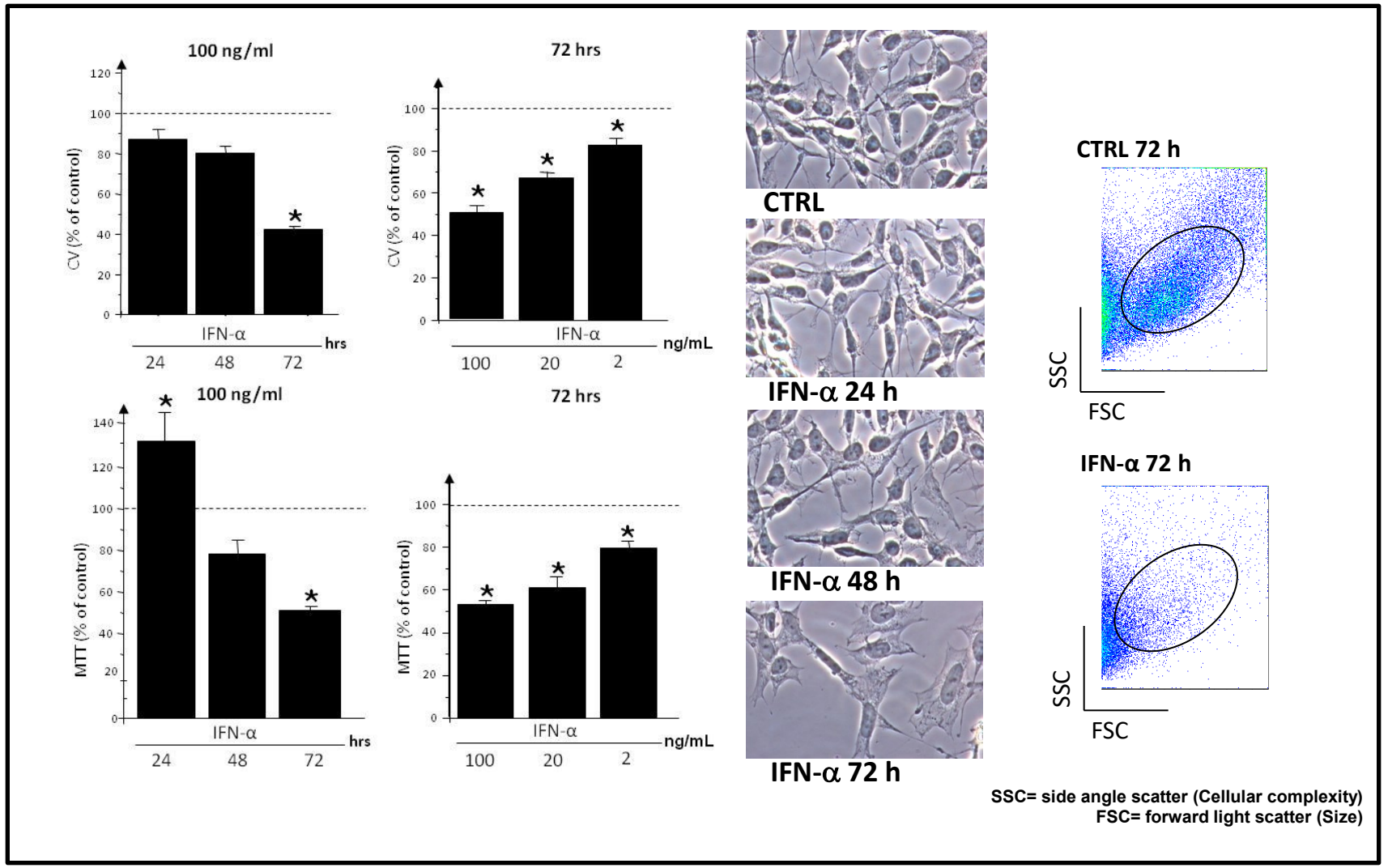




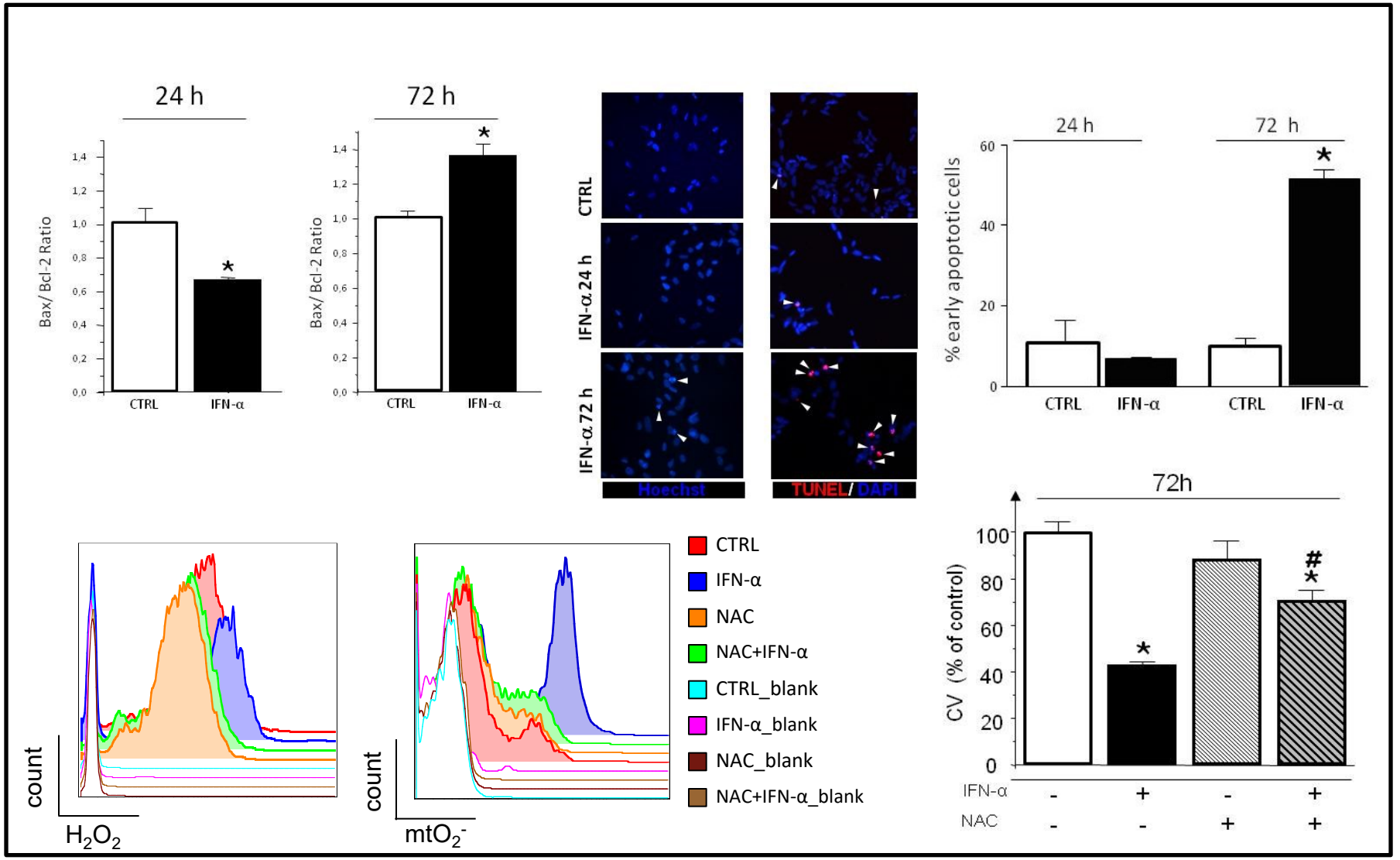

Cellule SH-SY5Y sono sensibili all'IFN-α?

# IFN-α induce effetti citotossici nel nostro modello di neuroni umani

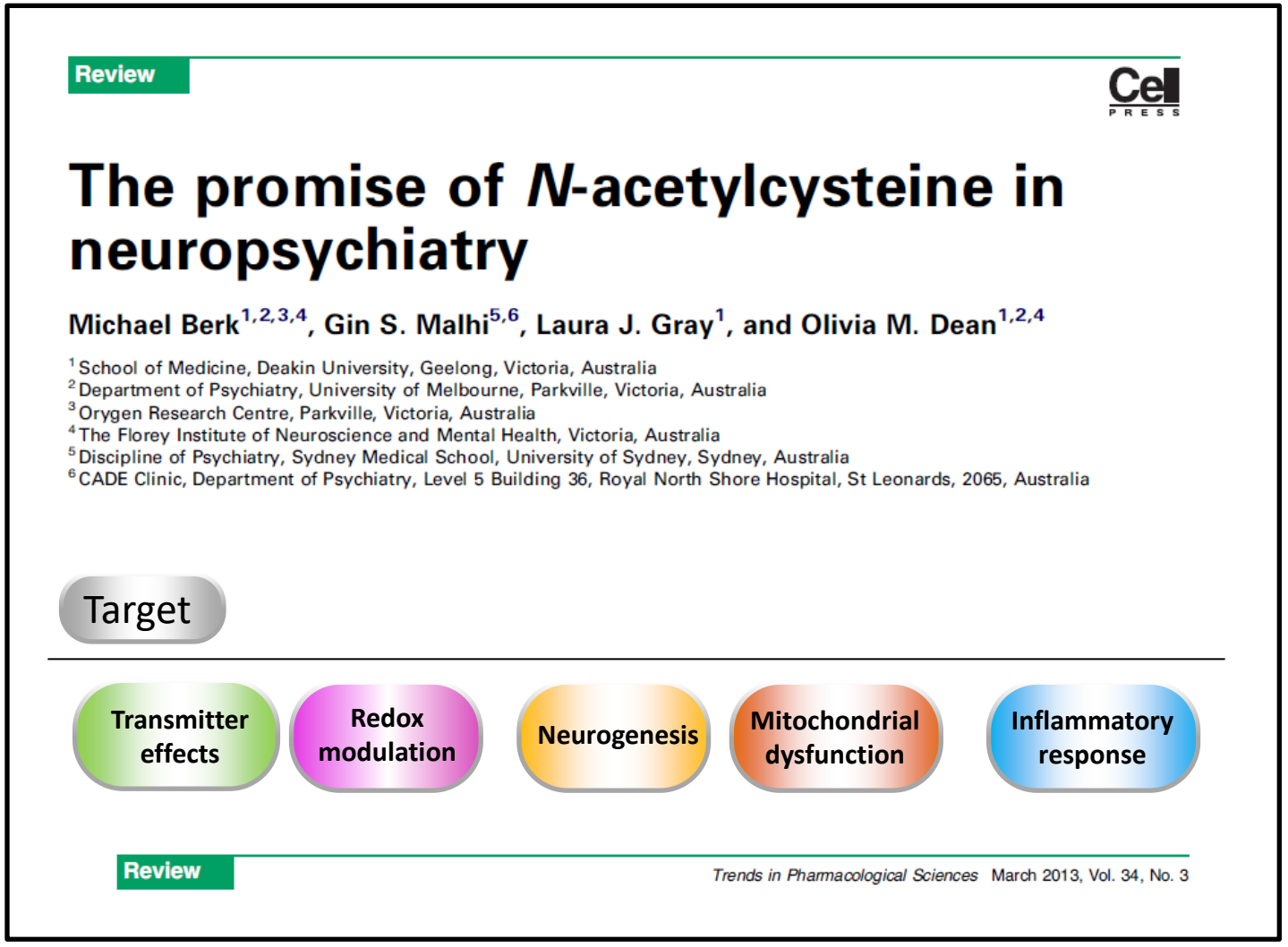



*Alboni S et al.; 2013 International Journal of Neuropsychopharmacology*

# IFN-α induce stress ossidativo e apoptosi



# N-Acetlil-Cisteine protegge le SH-SY5Y dagli effetti dell'IFN-α



Review

Cell PRESS

## The promise of *N*-acetylcysteine in neuropsychiatry

Michael Berk[1,2,3,4], Gin S. Malhi[5,6], Laura J. Gray[1], and Olivia M. Dean[1,2,4]

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Target

Transmitter effects | Redox modulation | Neurogenesis | Mitochondrial dysfunction | Inflammatory response

CNS Drugs (2022) 36:451–482
https://doi.org/10.1007/s40263-022-00907-3

REVIEW ARTICLE

# The Potential of *N*-Acetyl-L-Cysteine (NAC) in the Treatment of Psychiatric Disorders

Richard C. J. Bradlow[1] · Michael Berk[2,3,4,8] · Peter W. Kalivas[5,6] · Sudie E. Back[6,7] · Richard A. Kanaan[4,8]

Accepted: 17 February 2022 / Published online: 22 March 2022


**Abstract**

*N*-acetyl-L-cysteine (NAC) is a compound of increasing interest in the treatment of psychiatric disorders. Primarily through its antioxidant, anti-inflammatory, and glutamate modulation activity, NAC has been investigated in the treatment of neurodevelopmental disorders, schizophrenia spectrum disorders, bipolar-related disorders, depressive disorders, anxiety disorders, obsessive compulsive-related disorders, substance-use disorders, neurocognitive disorders, and chronic pain. Whilst there is ample preclinical evidence and theoretical justification for the use of NAC in the treatment of multiple psychiatric disorders, clinical trials in most disorders have yielded mixed results. However, most studies have been underpowered and perhaps too brief, with some evidence of benefit only after months of treatment with NAC. Currently NAC has the most evidence of having a beneficial effect as an adjuvant agent in the negative symptoms of schizophrenia, severe autism, depression, and obsessive compulsive and related disorders. Future research with well-powered studies that are of sufficient length will be critical to better understand the utility of NAC in the treatment of psychiatric disorders.

**Key Points**

Through its antioxidant, anti-inflammatory, and glutamate modulation activity *N*-acetyl-L-cysteine may have a role in the treatment of multiple psychiatric disorders.

Whilst there have been some promising results, especially in schizophrenia, autism, depression, and obsessive compulsive and related disorders, findings have been mixed, and better powered and longer studies are needed.

✉ Richard A. Kanaan
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## 1 Introduction

*N*-acetyl-L-cysteine (NAC), the acetylated precursor of L-cysteine, is used in medicine as a mucolytic agent to treat drug toxicity or overdose, given orally, intravenously, or by inhalation [1]. Though these uses are well established, there has been much recent interest in the use of NAC in treating neuropsychiatric conditions, including schizophrenia, mood and anxiety disorders, and substance-use disorders (SUDs). In the following, we review the growing body of research



Wozniak *et al. BMC Psychiatry* (2022) 22:314
https://doi.org/10.1186/s12888-022-03943-x

BMC Psychiatry

RESEARCH Open Access

# Findings from a pilot open-label trial of N-acetylcysteine for the treatment of pediatric mania and hypomania

Janet Wozniak[1,2*], Maura DiSalvo[1], Abigail Farrell[1], Carrie Vaudreuil[1,2], Mai Uchida[1,2], T. Atilla Ceranoglu[1,2], Gagan Joshi[1,2], Emmaline Cook[1], Stephen V. Faraone[3] and Joseph Biederman[1,2]

**Abstract**

**Background:** Pediatric bipolar disorder is a highly prevalent and morbid disorder and is considered a prevalent public health concern. Currently approved treatments often pose the risk of serious side effects. Therefore, this study assessed the efficacy and tolerability of N-acetylcysteine (NAC), in children and adolescents with bipolar spectrum disorder.

**Methods:** We conducted a 12-week open-label trial of NAC for treatment of mania and hypomania in children and adolescents ages 5–17 with bipolar spectrum disorder including participants with full and subthreshold manic symptoms, accepting those with and without mixed states with co-occurring depression, and Young Mania Rating Scale scores ≥ 20 and < 40. Symptoms of mania and depression were assessed using the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), Children's Depression Rating Scale (CDRS), and Clinical Global Impression (CGI) Severity (CGI-S) and Improvement (CGI-I) scales for mania and depression.

**Results:** This study had a high drop-out rate with only 53% completing all 12 weeks. There was a significant reduction in YMRS, HDRS, and CDRS mean scores from baseline to endpoint. Of the 24 exposed participants, 54% had an anti-manic response measured by a reduction in YMRS ≥ 30% and 46% had a CGI-I mania score ≤ 2 at endpoint. Additionally, 62% of participants had an anti-depressive response measured by a reduction in HDRS ≥ 30%, 31% had an anti-depressive response measured by a reduction in CDRS ≥ 30%, and 38% had a CGI-I depression score ≤ 2 at endpoint.

**Conclusions:** These pilot open-label findings in a small sample provide preliminary data supporting the tolerability and safety of NAC in a pediatric population. The findings of this pilot scale study indicating improvement in mania and depression are promising, but require replication with a monotherapy randomized placebo controlled clinical trial and larger sample.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT02357290. First Registration 06/02/2015.

**Keywords:** Bipolar spectrum disorder, Child, N-acetylcysteine

## Background

Due to its high prevalence of 1–3% in national and international samples and morbidity, pediatric bipolar (BP) disorder represents a serious public health concern [1–4]. Pediatric BP disorder is commonly characterized by high levels of severe irritability and concurrent features of

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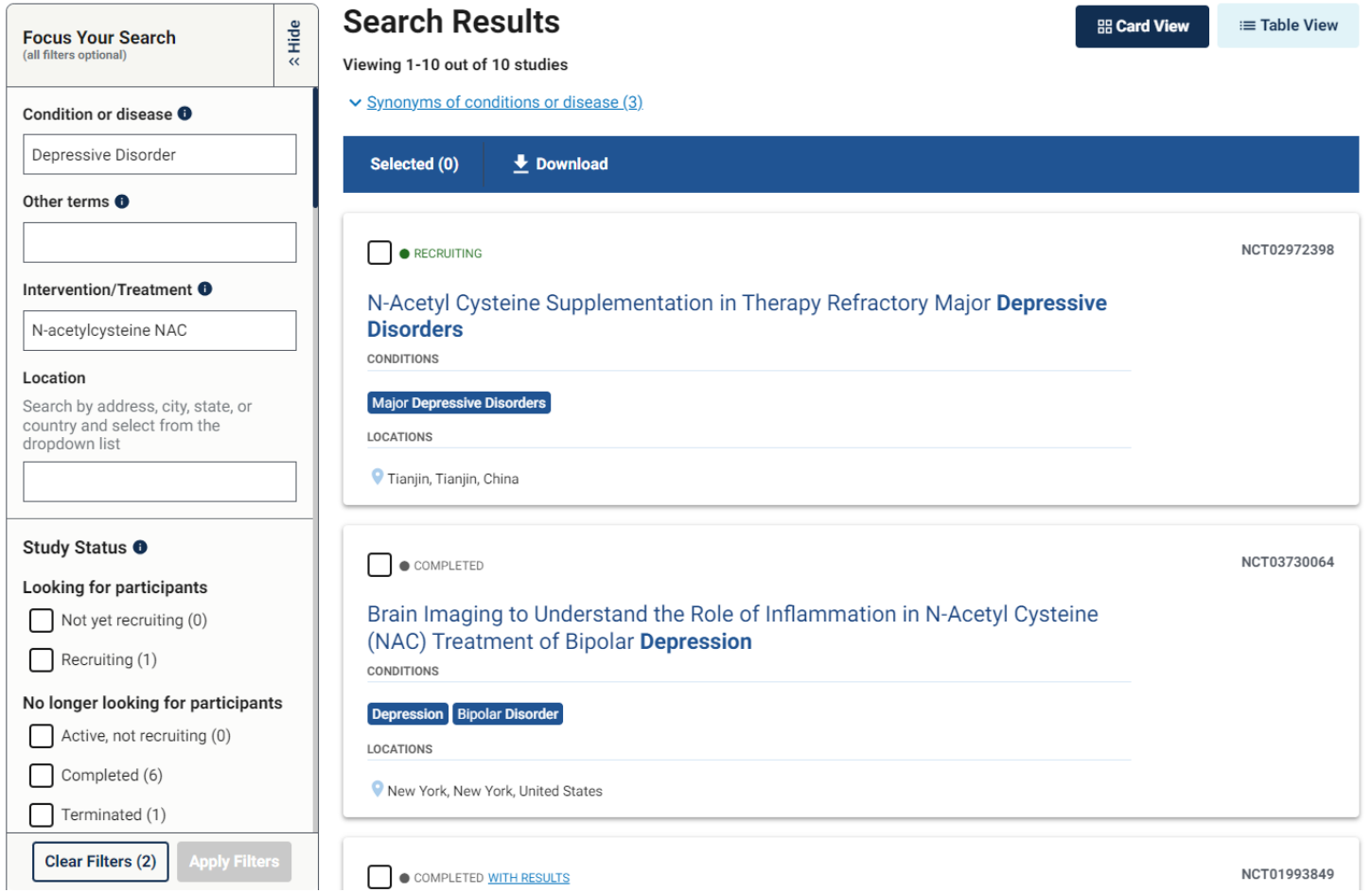
# N-Acetlil-Cisteine studi clinici

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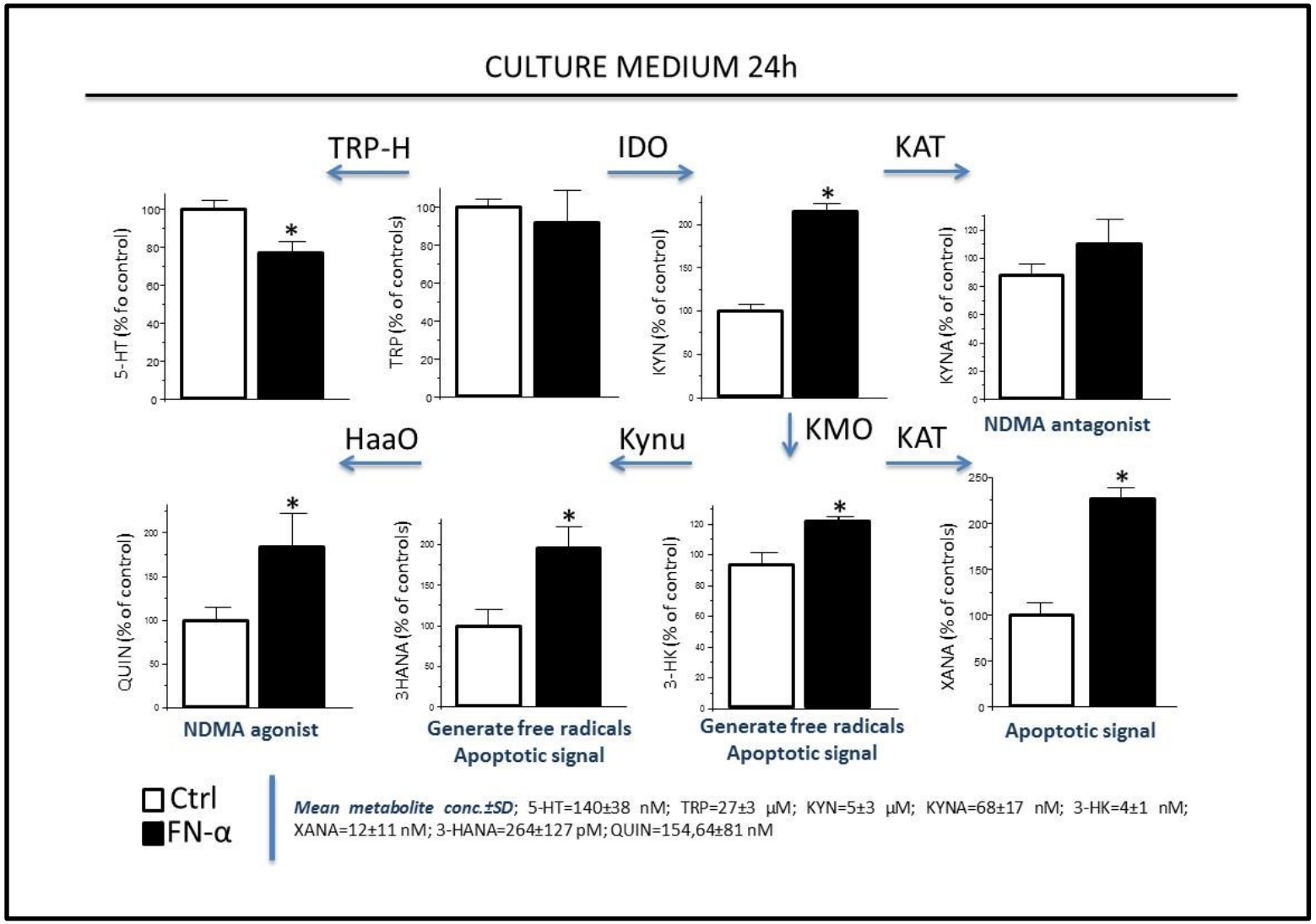
Centro Interdipartimentale Grandi Strumenti
CINQUANTA

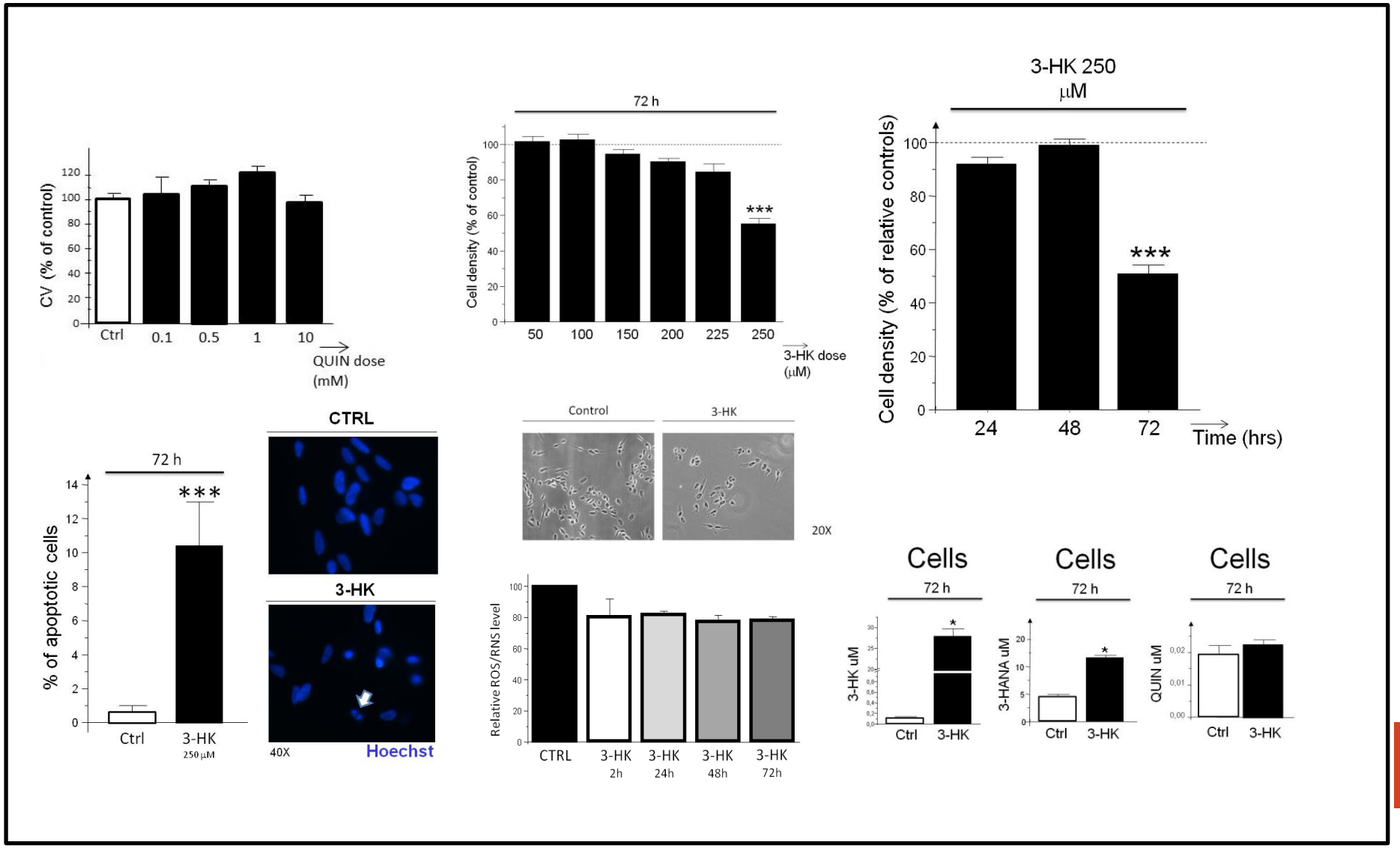
# Il trattamento con IFN-α aumenta i livelli di metaboliti della KP nel terreno di coltura di cellule SH-SY5Y




UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Centro Interdipartimentale Grandi Strumenti
CINQUANTA

# Cellule SH-SY5Y sono sensibili agli effetti tossici della 3-HK

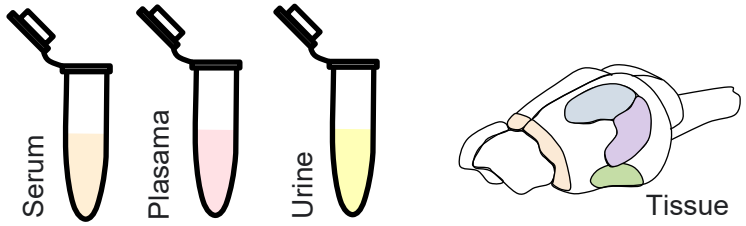


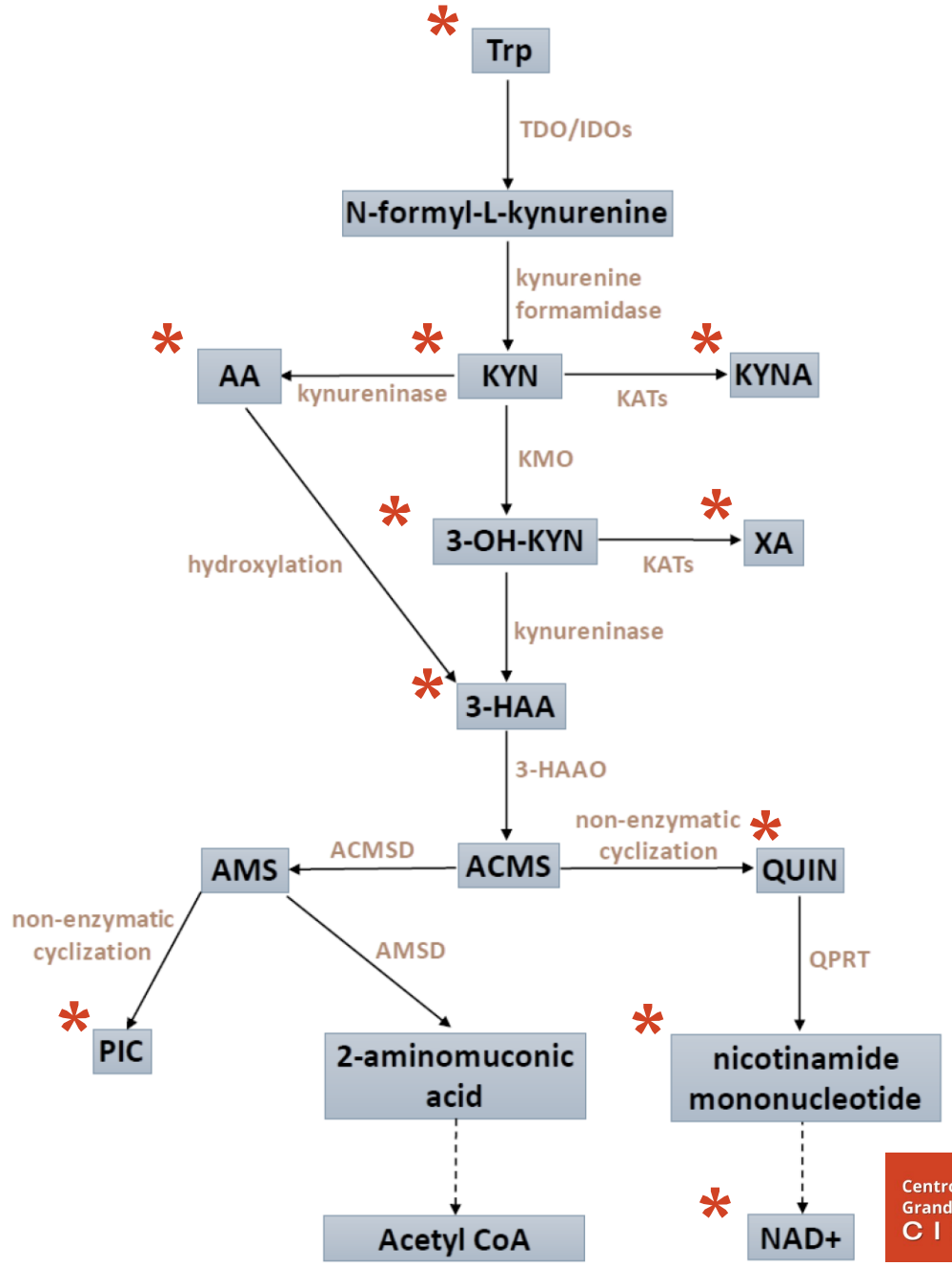
| Disease | Sample | Alteration of metabolites | Sample | Alteration of enzymes | References |
|---|---|---|---|---|---|
| Alzheimer's disease | Plasma | TRP, KYNA decreased and QUIN increased | The prefrontal cortex, hippocampal | IDO increased | (116, 117) |
| Parkinson's disease | Plasma, cerebrospinal fluid | 3-HK in plasma increased, 3-HAA and 5-HT/KYN decreased, KYNA and KYNA/KYN in cerebrospinal fluid decreased, and QUIN/KYNA increased | Plasma | KAT I and KAT II decreased | (118, 119) |
| Huntington's disease | Serum | KYN increases, KYNA/KYN decreases | Putamen | KAT I and KAT II decrease, IDO activation | (120, 121) |
| Depression | Hippocampu | Lower ratios of KYNA/KYN, KYNA/3-HK, and KYNA/QUIN | Serum, prefrontal cortex, hippocampus, and cerebral cortex | TPH2, KATII/KMO mRNA decreased, KMO, IDO-1 upregulated | (122–124) |
| Multiple sclerosis | Prefrontal cortex、Hippocampus、Spinal cord、Spleen | TRP, KYN, and KYN/TRP in the prefrontal cortex, hippocampus, spinal cord, and spleen increased; 3-HK and QUIN in the Prefrontal cortex and hippocampus increased, while KYNA decreased | Plasma | KAT I and KAT II decreased | (125, 126) |
| Schizophrenia | Plasma | TRP decreases, KYN and KYN/TRP increase | Cerebral cortex | KMO, 3-HAO reduced | (127, 128) |
| Anxiety disorder | Plasma | KYN, KYN/TRP elevated | Center seam core | TPH2 decreased | (129, 130) |
| Amyotrophic lateral sclerosis | Cerebrospinal fluid, cortical | QUIN, IDO, TRP, KYN increased | Motor cortex, spinal cord | TPH decreased, IDO increased | (131, 132) |
| Autism spectrum disorder | Serum | TRP and 5-HT increased and KYNA decreased | – | KMO expression | (133, 134) |
| Epilepsy | Plasma | TRP, KYN higher, KYNA, 3-HK, KYNA/KYN lower | – | IDO Expression | (135, 136) |
| Bipolar disorder | Serum | TRP, KYNA, PIC, QUIN/TRP, and PIC/QUIN elevated | Serum | IDO-1 expression is upregulated | (137) |

*Li D. et al., 2022*

# HPLC/MS method

## 10 µl/mg of samples



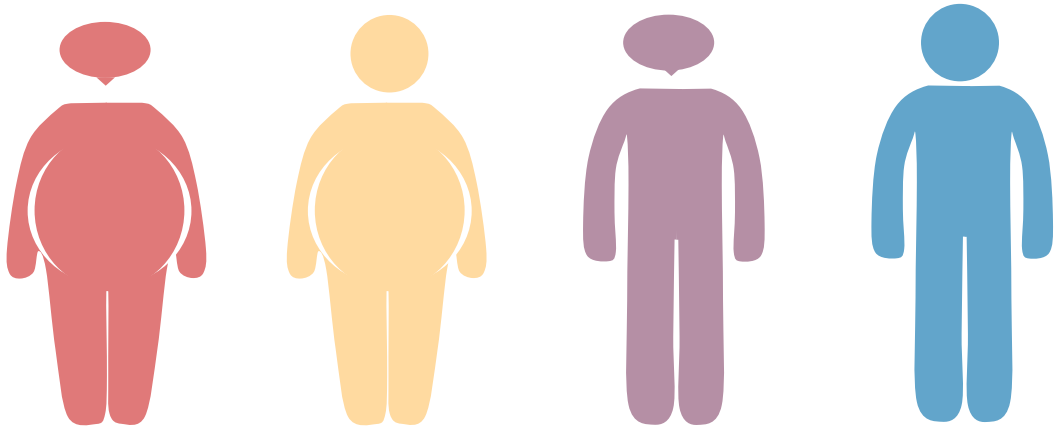
# Study design: a cross-sectional study in outpatients undergoing colonoscopy

**Outpatients (M/F)**
126 who underwent a colonscopy for non-specific abdominal symptoms
January 1st 2014 – June 1st 2021

**INCLUSION CRITERIA**
Age ≥ 40; male and female, informed consent,

**EXCLUSION CRITERIA**
Age < 40; diagnosis of non-colorectal neoplasia, advanced diseases, patients with chronic inflammatory bowel diseases

**Outpatients (M/F)**
100 patients (complete metabolic and psychometric assessments)



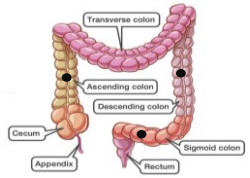

*Study protocol approved by the local Ethics Committee ( prot. No. 4396/C.E.)*

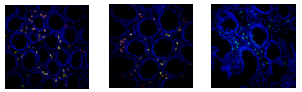
# Studio PNEI_MO

## Serum

C-HDL, C-LDL, C-VDLD, C-TOT, TRG
hs-PCR
LPS
Cytokines (IL-1β,TNFα, IFNγ, IL-6)
**Kynurenine pathway metabolites**
Glycemia

## Samples of normal colorectal mucosa

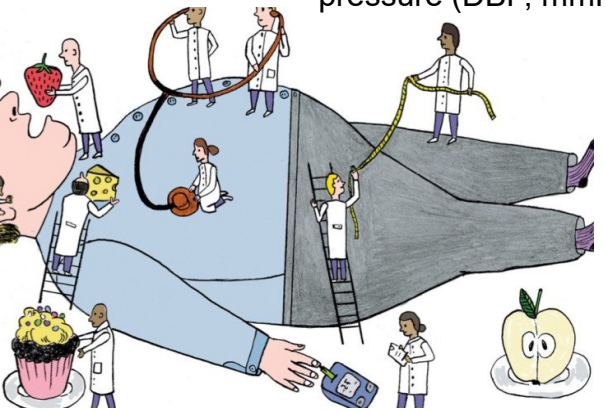


Autophagy (LC3B-II)
Inflammation (MPO)
DAPI

## Anthropometric & clinical variables

Weight (Kg), height (m) -> BMI
Waist circumferences (cm), hip circumference (cm) –> W/H
Systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg)



*For MS assessment both the ATPIII and IDF criteria were used*

## Socio-demographical & lifestyle information

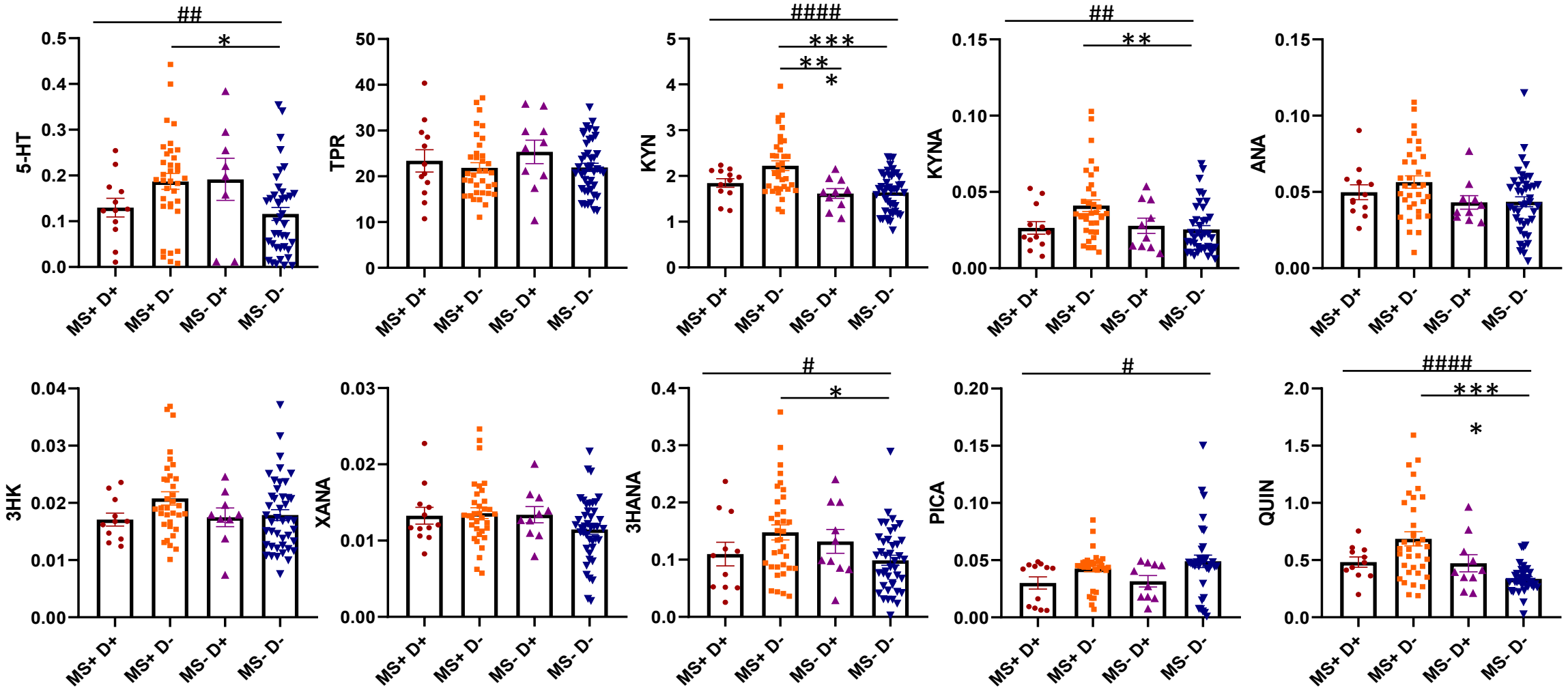
Age(years), sex
Active tabacco smoking, alcohol intake, sedentary habits
Pharmacological treatments, comorbidity (CIRS-SI)

## Psychometric assesment

HADS-A HADS-D
TCI
SF-36

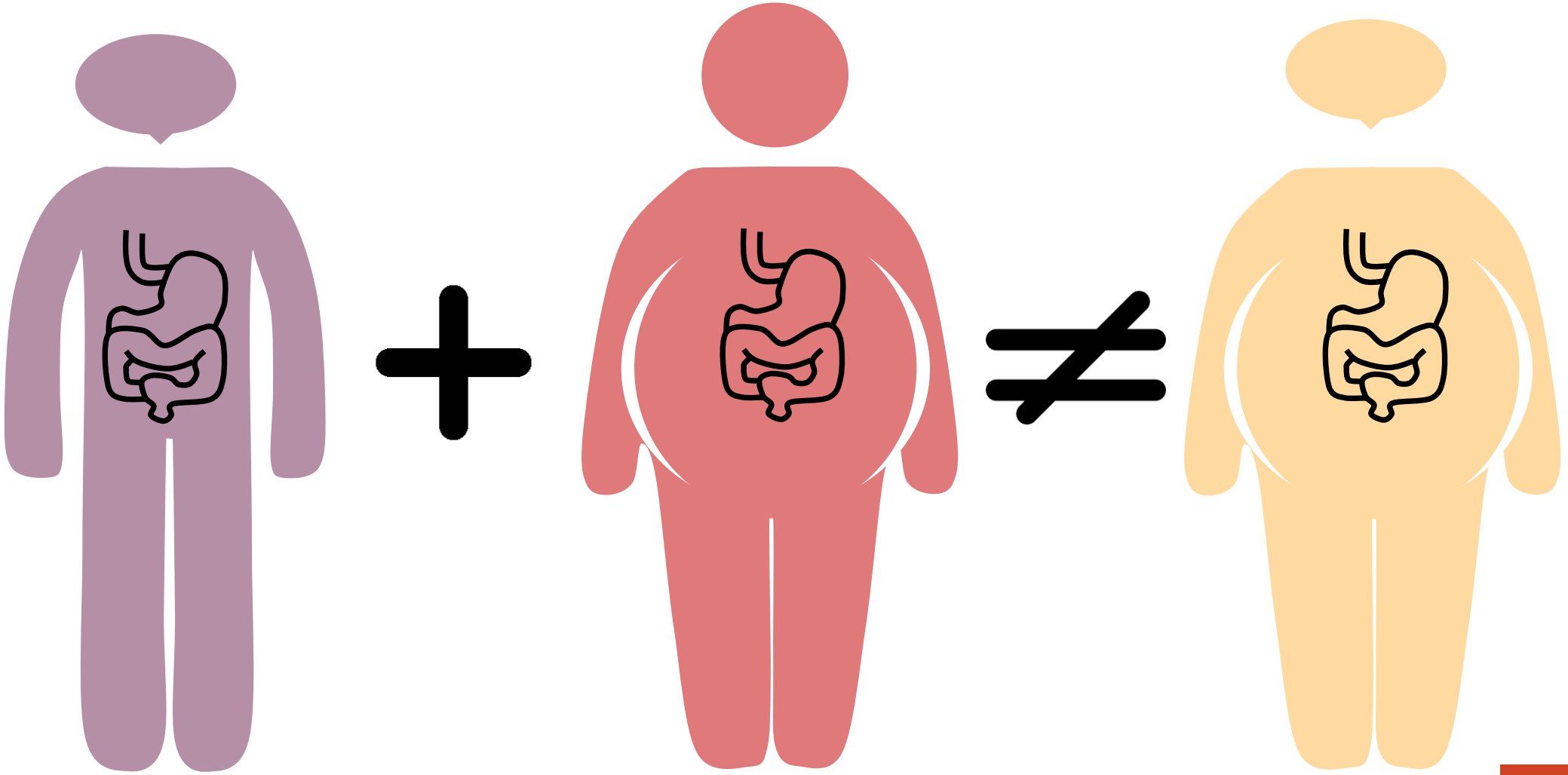
*Study protocol approved by the local Ethics Committee ( prot. No. 4396/C.E.)*

# Studio PNEI_MO

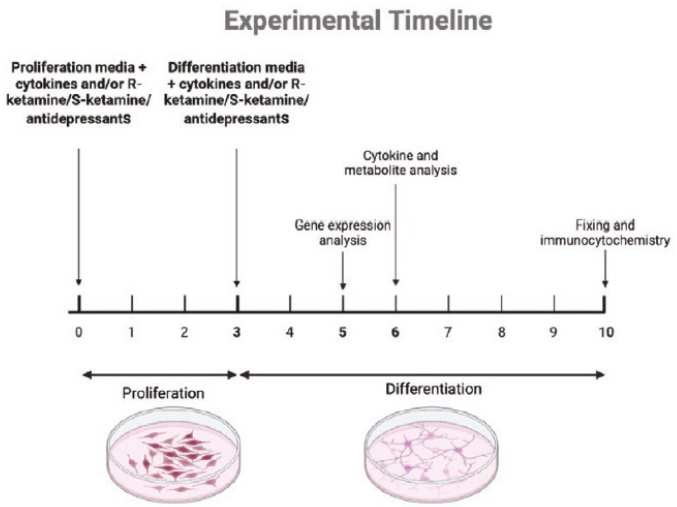



**MS:** sindrome metabolica **D:** sintomi depressivi

# Studio PNEI_MO



# KP e risposta al trattamento ADs




*International Journal of Neuropsychopharmacology*, 2024,pyae041
https://doi.org/10.1093/ijnp/pyae041
Advance access publication 19 September 2024
Regular Research Article

**Regular Research Article**

## Ketamine Prevents Inflammation-Induced Reduction of Human Hippocampal Neurogenesis via Inhibiting the Production of Neurotoxic Metabolites of the Kynurenine Pathway

Gargi Mandal,[#] Madeline Kirkpatrick,[#] Silvia Alboni, Nicole Mariani, Carmine M. Pariante, Alessandra Borsini

Stress, Psychiatry and Immunology Laboratory, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, King's College London, UK (Miss Mandal, Miss Kirkpatrick, Mrs Mariani, Dr Pariante, and Dr Borsini); Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy (Dr Alboni)

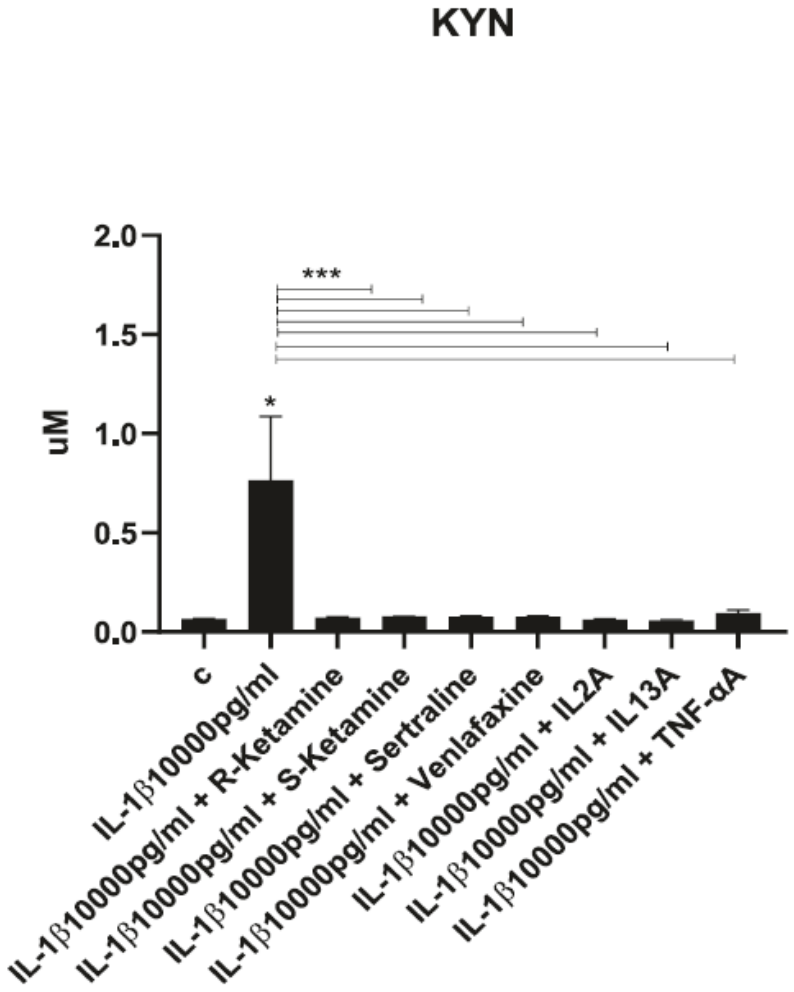


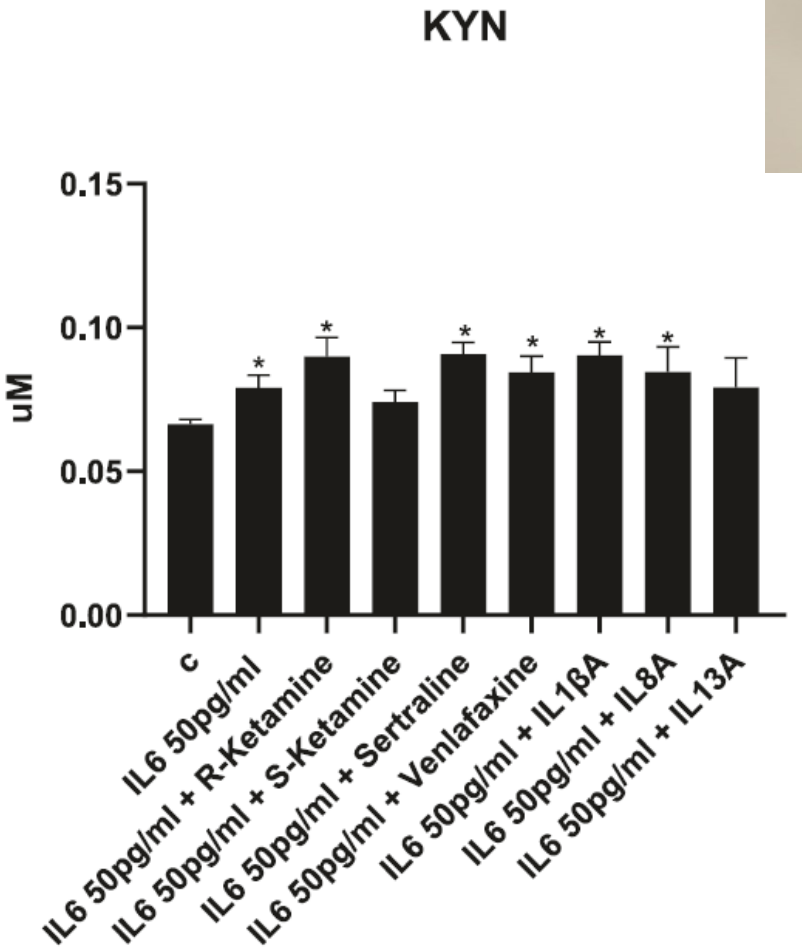
### Significance Statement

Several studies have shown that ketamine is a fast-acting, efficient antidepressant that alleviates symptoms even in those suffering with treatment-resistant depression. However, its mechanisms of action are unclear. In this study we demonstrate, for the first time (to our knowledge), that treatment in vitro of human hippocampal progenitor cells with R-ketamine or S-ketamine prevents the reduction in neurogenesis caused by IL-6 and IL-1b. Additionally, our results suggest that this is achieved via the ability of the ketamine enantiomers to counteract production of specific pro-inflammatory molecules, although with some enantiomer-specific effects. However, we observe that the neuroprotective effect of ketamine enantiomers only involves inhibition of the kynurenine pathway in the context of IL-1b, highlighting the importance of stratifying patients according to their unique inflammatory profile. Overall, our findings have important implications toward the search for new and more personalized antidepressant treatment,

**Key words:** cytokines, kynurenine pathway, hippocampal neurogenesis, apoptosis

# KP e risposta al trattamento ADs


*Mandal G. et al., 2024*

Inflammation
https://doi.org/10.1007/s10753-024-02135-x

REVIEW

# The Kynurenine Pathway in Gut Permeability and Inflammation

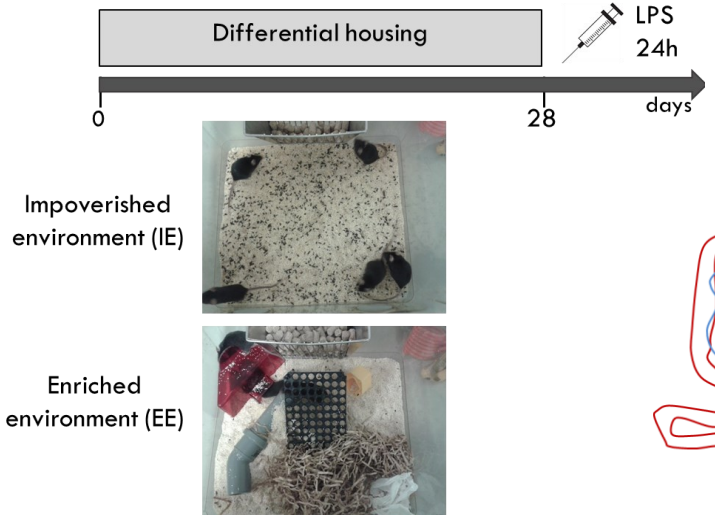
**Rowan Kearns**[1]

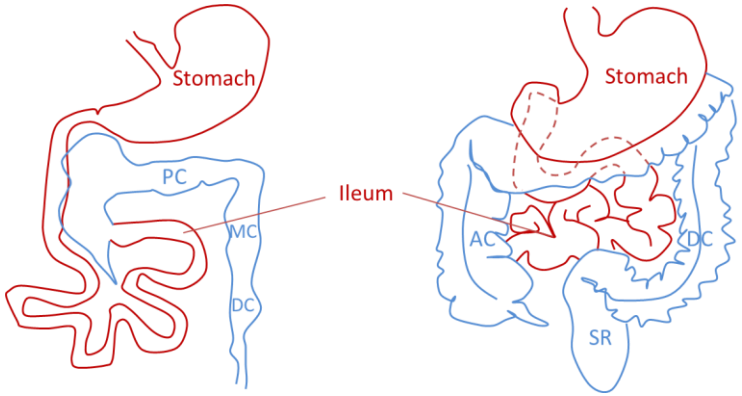
Received: 15 May 2024 / Revised: 9 July 2024 / Accepted: 21 August 2024

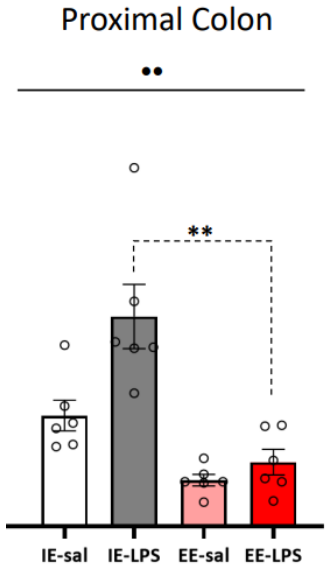

## Abstract

The gut-brain axis (GBA) is a crucial communication network linking the gastrointestinal (GI) tract and the central nervous system (CNS). The gut microbiota significantly influences metabolic, immune, and neural functions by generating a diverse array of bioactive compounds that modulate brain function and maintain homeostasis. A pivotal mechanism in this communication is the kynurenine pathway, which metabolises tryptophan into various derivatives, including neuroactive and neurotoxic compounds. Alterations in gut microbiota composition can increase gut permeability, triggering inflammation and neuroinflammation, and contributing to neuropsychiatric disorders. This review elucidates the mechanisms by which changes in gut permeability may lead to systemic inflammation and neuroinflammation, with a focus on the kynurenine pathway. We explore how probiotics can modulate the kynurenine pathway and reduce neuroinflammation, highlighting their potential as therapeutic interventions for neuropsychiatric disorders. The review integrates experimental data, discusses the balance between neurotoxic and neuroprotective kynurenine metabolites, and examines the role of probiotics in regulating inflammation, cognitive development, and gut-brain axis functions. The insights provided aim to guide future research and therapeutic strategies for mitigating GI complaints and their neurological consequences.

# Ricchi & Poveri



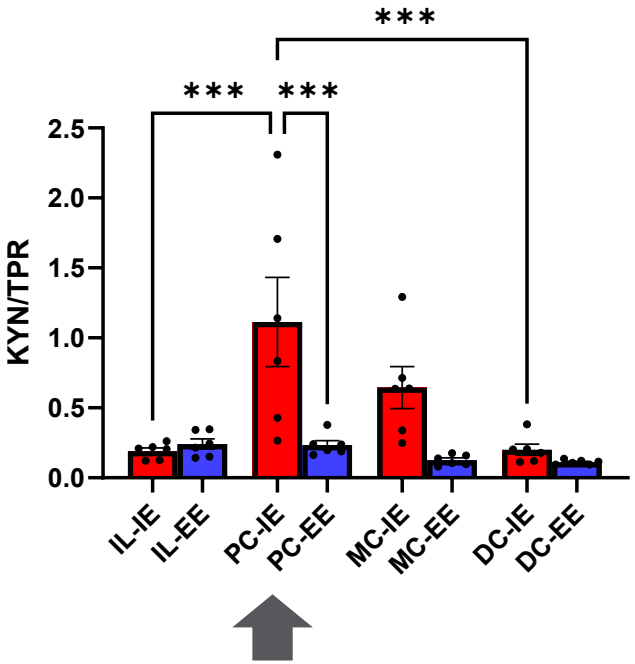

TNFα mRNA

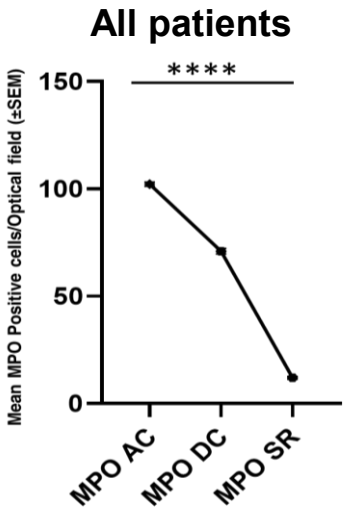
Citochine Pro-infiammatorie periferiche

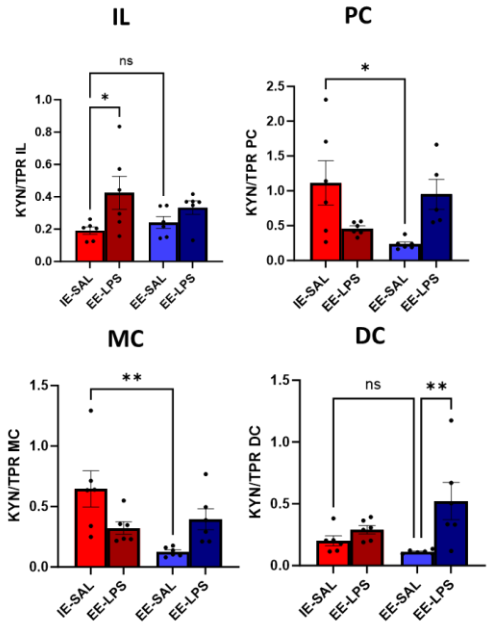
TNFα

IDO

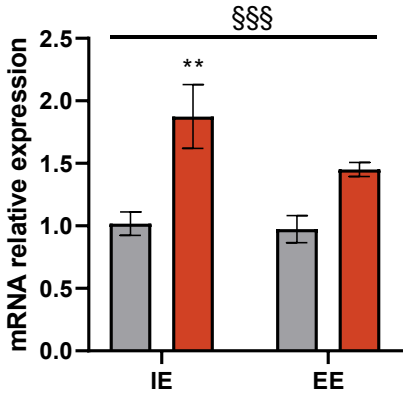
TRP Kyn

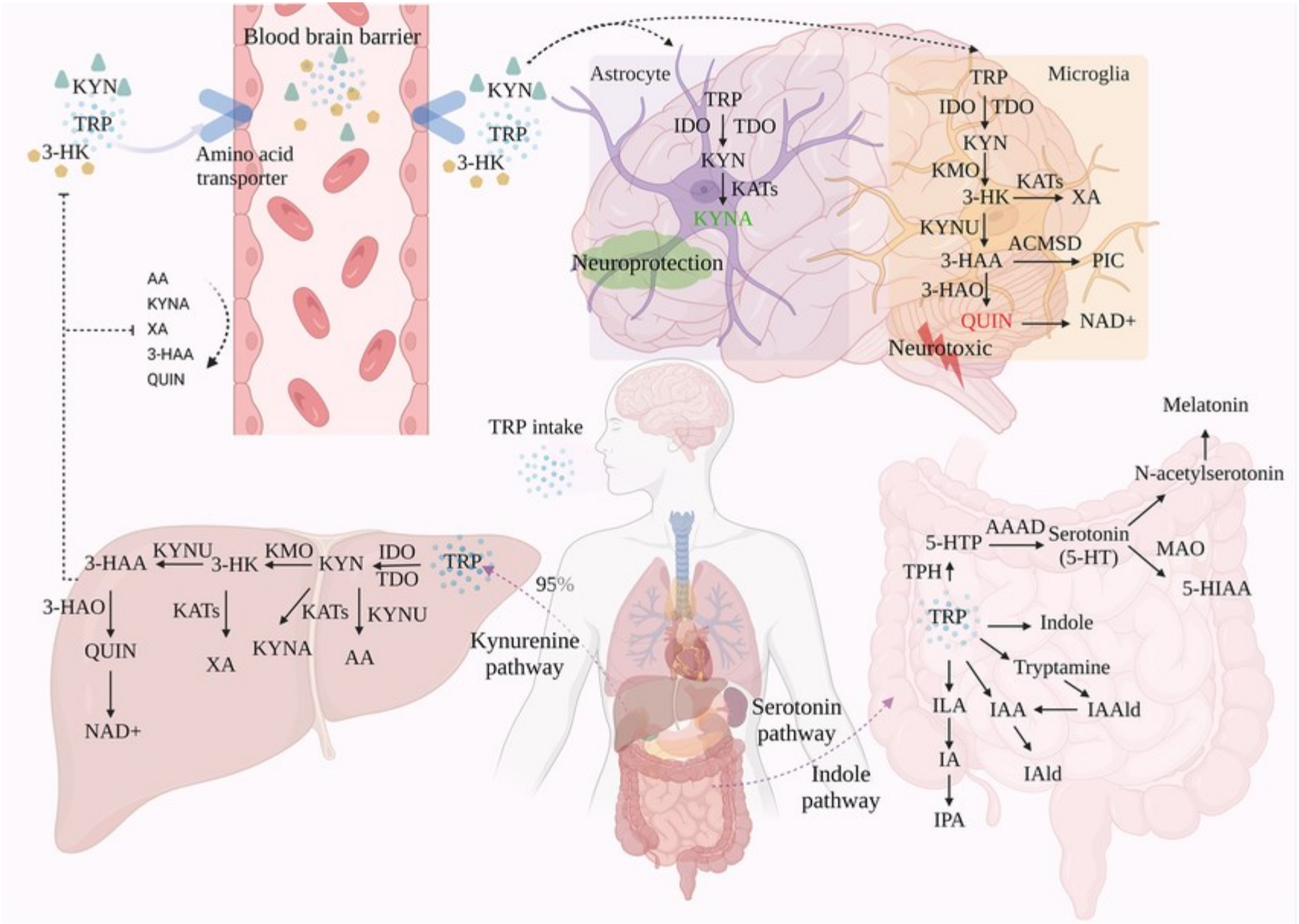



Nlrp3






*Li D. et al., 2022*

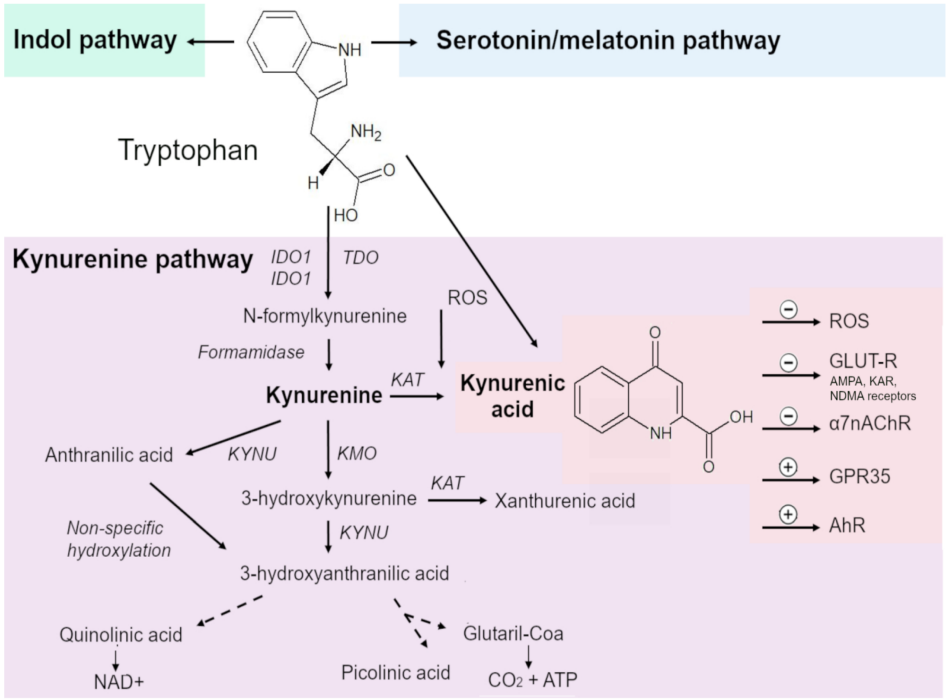
# HPLC/MS method

- TPR, KYN, KYNA, AA, XANA, 3HK, 3HANA, QUIN, PICA, NICA, NIC, NAM, NAD, CINA

- 5-HT, 5-HIAA, acetil-5-HT, DA, DOPAC, 3-MT, HVA, Ach, NE

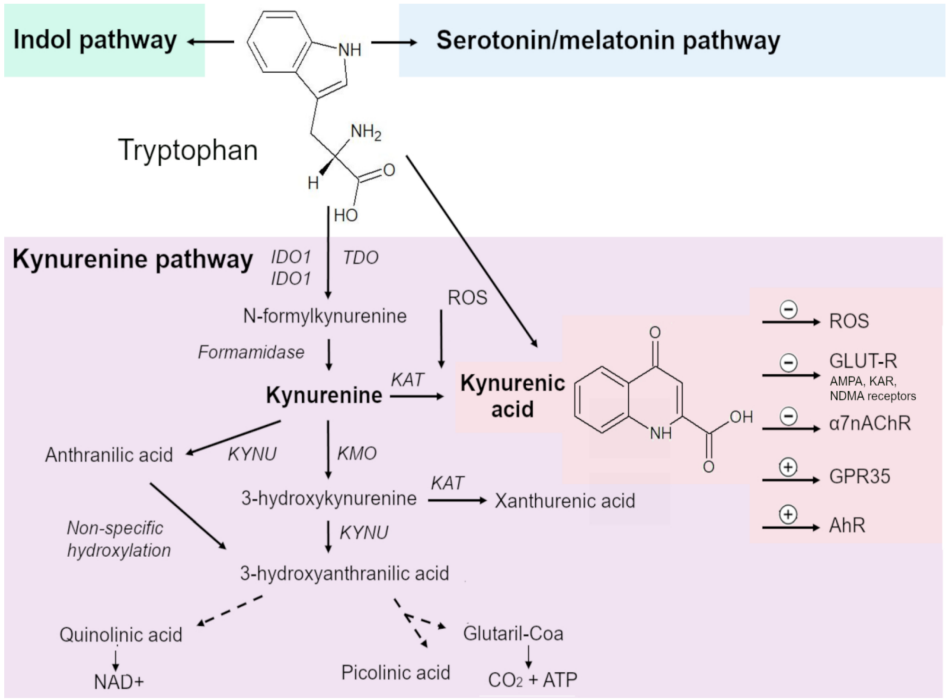
- Neopterine, MEL, Trimethylamine-N-oxide, carnosina

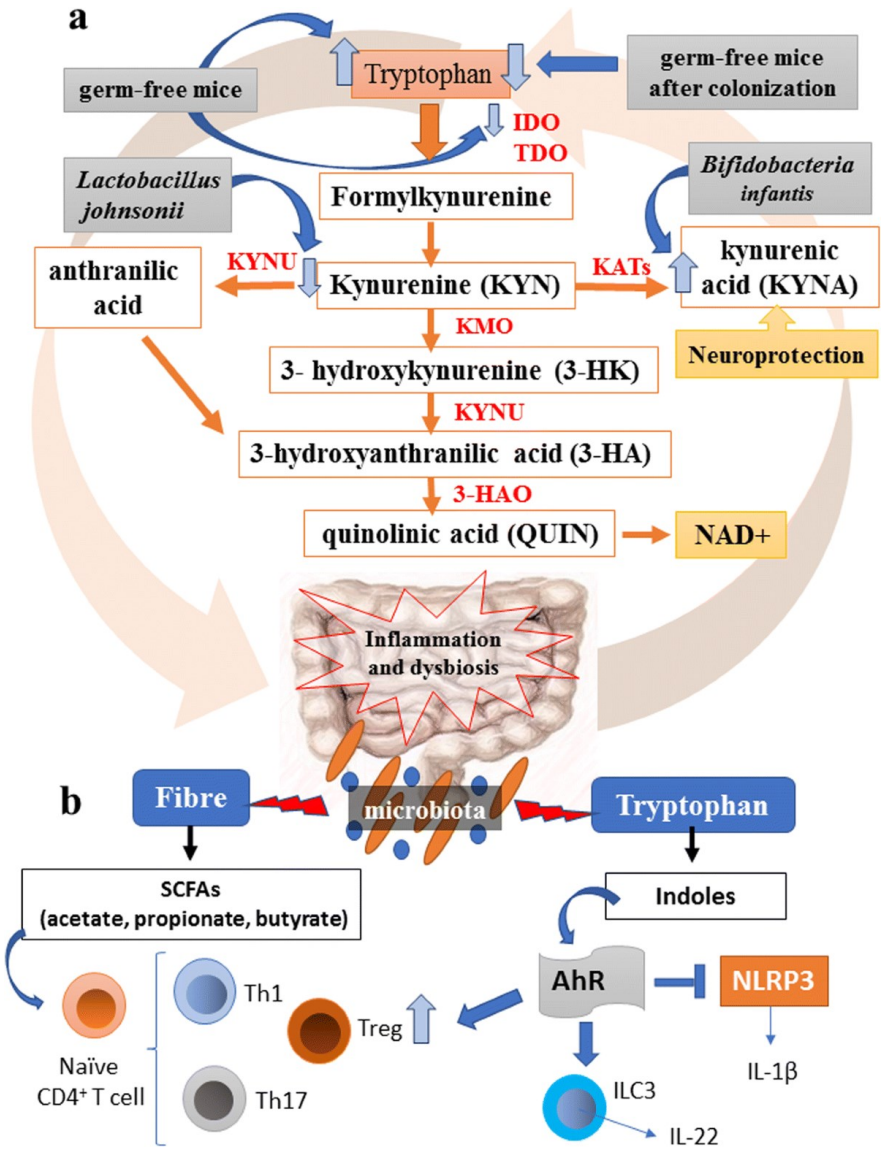
- PCS, PCG, Indole-3-pyruvic Acid, Indole-3-acetic-Acid, Indole-3-pyruvic Acid, Indole-3-proprionic, Indole-3-carboxaldehyde, Acid Indole-3-lactic Acid …



# HPLC/MS method

- TPR, KYN, KYNA, AA, XANA, 3HK, 3HANA, QUIN, PICA, NICA, NIC, NAM, NAD, CINA
- 5-HT, 5-HIAA, acetil-5-HT, DA, DOPAC, 3-MT, HVA, Ach, NE
- Neopterine, MEL, Trimethylamine-N-oxide, carnosina
- PCS, PCG, Indole-3-pyruvic Acid, Indole-3-acetic-Acid, Indole-3-pyruvic Acid, Indole-3-proprionic, Indole-3-carboxaldehyde, Acid Indole-3-lactic Acid …






Neurotoxicity Research (2019) 36:424–436
https://doi.org/10.1007/s12640-019-00057-3

REVIEW ARTICLE

# Microbiota Alterations in Alzheimer's Disease: Involvement of the Kynurenine Pathway and Inflammation

Michelle L. Garcez[1] · Kelly R. Jacobs[1] · Gilles J. Guillemin[1]

Received: 13 December 2018 / Revised: 30 April 2019 / Accepted: 2 May 2019 / Published online: 14 May 2019


**Abstract**
Alzheimer's disease (AD) is a neurodegenerative disease considered the major cause of dementia in the elderly. The main pathophysiological features of the disease are neuronal loss (mainly cholinergic neurons), glutamatergic excitotoxicity, extracellular accumulation of amyloid beta, and intracellular neurofibrillary tangles. However, other pathophysiological features of the disease have emerged including neuroinflammation and dysregulation of the kynurenine pathway (KP). The intestinal microbiota is a large and diverse collection of microorganisms that play a crucial role in regulating host health. Recently, studies have highlighted that changes in intestinal microbiota contribute to brain dysfunction in various neurological diseases including AD. Studies suggest that microbiota compositions are altered in AD patients and animal models and that these changes may increase intestinal permeability and induce inflammation. Considering that microbiota can modulate the kynurenine pathway and in turn neuroinflammation, the gut microbiome may be a valuable target for the development of new disease-modifying therapies. The present review aims to link the interactions between AD, microbiota, and the KP.

**Keywords** Alzheimer's disease · Microbiota · Probiotics · Inflammation · Kynurenine pathway

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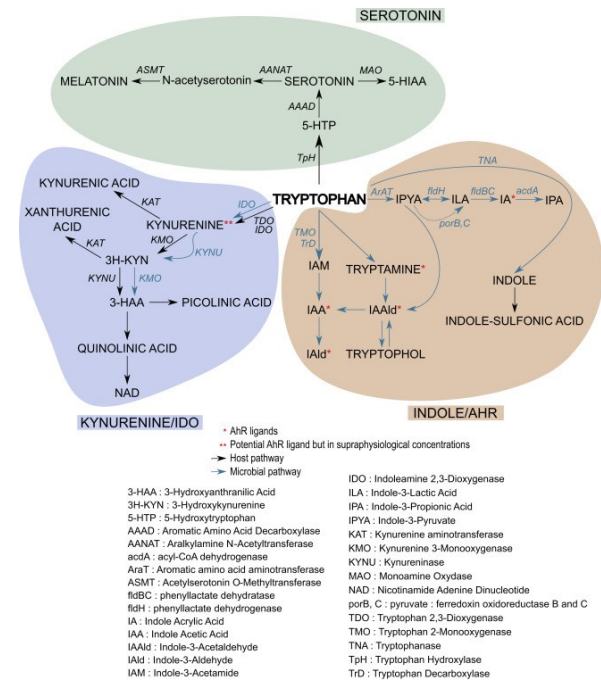
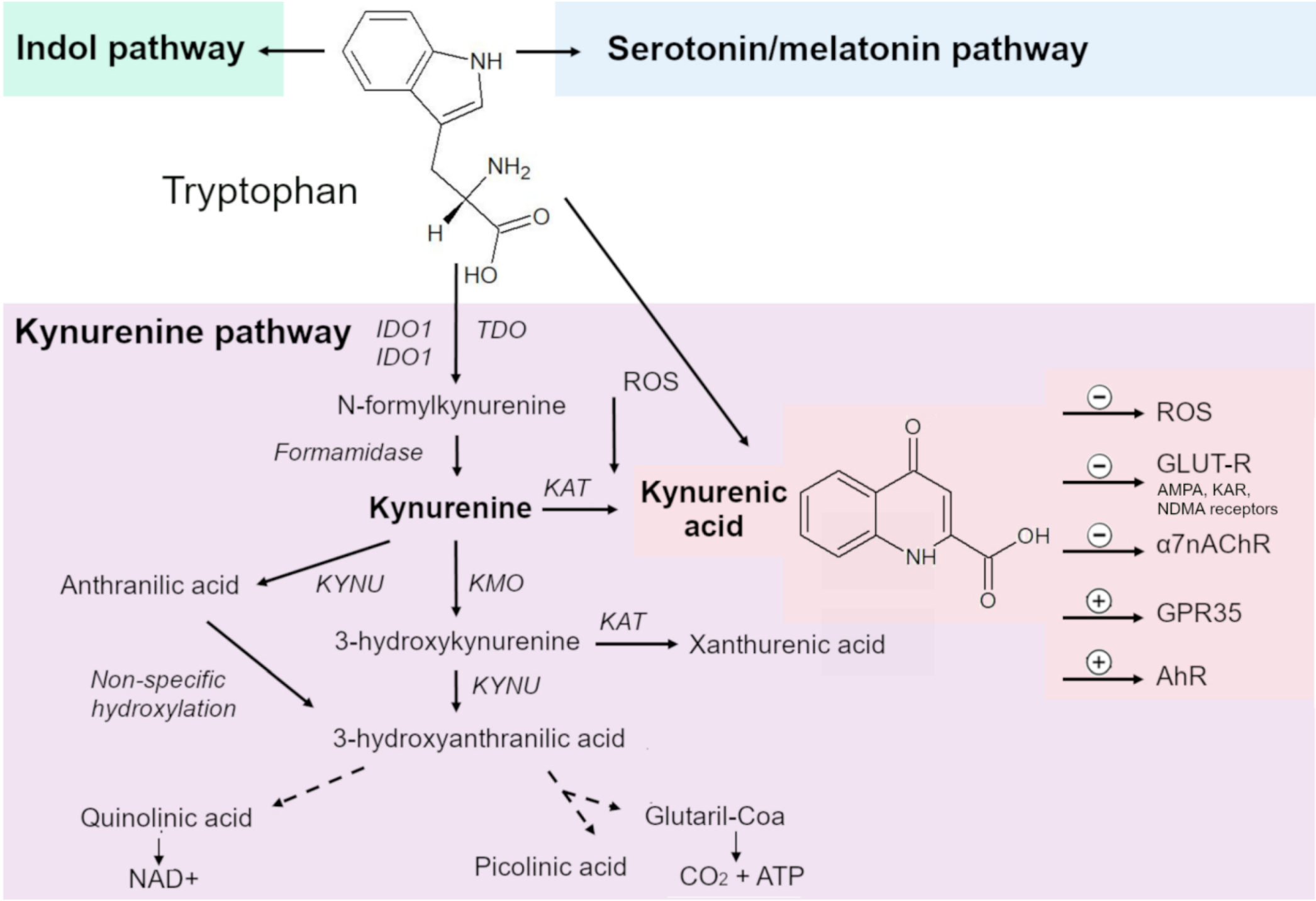
# Grazie per l'attenzione?


SEROTONIN
MELATONIN
ASMT
N-acetyserotonin
AANAT
SEROTONIN
MAO
5-HIAA
AAAD
5-HTP
TpH
TRYPTOPHAN
TNA
AraT
IPYA
fldH
ILA
fldBC
IA*
acdA
IPA
porB,C
KYNURENIC ACID
KAT
XANTHURENIC ACID
IDO
TDO
IDO
KYNURENINE**
KMO
KAT
KYNU
3H-KYN
KYNU
KMO
3-HAA
PICOLINIC ACID
QUINOLINIC ACID
NAD
TMO
TrD
IAM
TRYPTAMINE*
INDOLE
IAA*
IAAld*
INDOLE-SULFONIC ACID
IAld*
TRYPTOPHOL
KYNURENINE/IDO
INDOLE/AHR
* AhR ligands
** Potential AhR ligand but in supraphysiological concentrations
Host pathway
Microbial pathway
3-HAA : 3-Hydroxyanthranilic Acid
3H-KYN : 3-Hydroxykynurenine
5-HTP : 5-Hydroxytryptophan
AAAD : Aromatic Amino Acid Decarboxylase
AANAT : Aralkylamine N-Acetyltransferase
acdA : acyl-CoA dehydrogenase
AraT : Aromatic amino acid aminotransferase
ASMT : Acetylserotonin O-Methyltransferase
fldBC : phenyllactate dehydratase
fldH : phenyllactate dehydrogenase
IA : Indole Acrylic Acid
IAA : Indole Acetic Acid
IAAld : Indole-3-Acetaldehyde
IAld : Indole-3-Aldehyde
IAM : Indole-3-Acetamide
IDO : Indoleamine 2,3-Dioxygenase
ILA : Indole-3-Lactic Acid
IPA : Indole-3-Propionic Acid
IPYA : Indole-3-Pyruvate
KAT : Kynurenine aminotransferase
KMO : Kynurenine 3-Monooxygenase
KYNU : Kynureninase
MAO : Monoamine Oxydase
NAD : Nicotinamide Adenine Dinucleotide
porB, C : pyruvate : ferredoxin oxidoreductase B and C
TDO : Tryptophan 2,3-Dioxygenase
TMO : Tryptophan 2-Monooxygenase
TNA : Tryptophanase
TpH : Tryptophan Hydroxylase
TrD : Tryptophan Decarboxylase


Indol pathway
Serotonin/melatonin pathway
Tryptophan
Kynurenine pathway
IDO1
IDO1
TDO
N-formylkynurenine
Formamidase
Kynurenine
KAT
Kynurenic acid
ROS
Anthranilic acid
KYNU
KMO
3-hydroxykynurenine
KAT
Xanthurenic acid
Non-specific hydroxylation
KYNU
3-hydroxyanthranilic acid
Quinolinic acid
NAD+
Picolinic acid
Glutaril-Coa
CO2 + ATP
ROS
GLUT-R
AMPA, KAR, NDMA receptors
α7nAChR
GPR35
AhR