JANUARY 2024, ISSUE 5

ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

Dear ISTRY members, friends, colleagues, and the tryptophan research community,

Happy New Year and welcome to 2024! On behalf of the ISTRY executive committee, we want to thank you for another year of supporting the cause of ISTRY throughout 2023 and we look forward to another great year of exciting tryptophan research and new discoveries ahead.

2024 will be an exciting year for ISTRY as we prepare to welcome the international tryptophan research community to Jena, Germany. It's been a long 5 years wait and we are very much anticipating welcoming our fellow ISTRY 'family' at the upcoming meeting. ISTRY has announced travel awards to subsidize travel expenses for delegates, particularly targeting students and postdocs. Please click on this link to apply. The closing date is January 31, 2024.

The local ISTRY organizing committee is working hard to make sure that the program will be filled with interesting topics and talks that will intrigue and enhance your understanding of tryptophan research from researchers all over the world. Registration and abstract submission is currently underway. For more information, please visit our ISTRY meeting website here. To learn more about the meeting venue and hear from our ISTRY President, Prof. Florian Zepf, on what Jena has to offer in this video. We look forward to seeing you at the 16th ISTRY meeting in Jena on April 24-26, 2024.

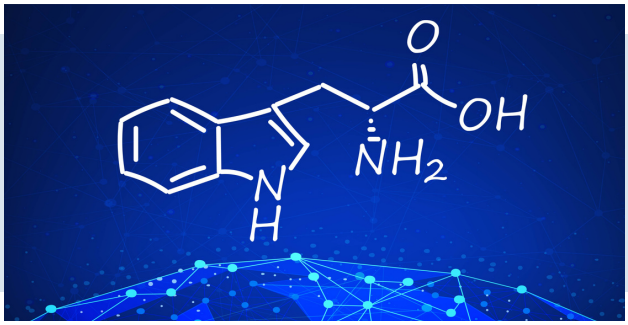
In this issue of the newsletter, the ISTRY media team has put together an 8-minute short-read article on the theme of kynurenic acid to start the year. I hope you learn some interesting facts and insights on the role of kynurenic acid in health and diseases.

Last but not least, ISTRY wishes you a prosperous, joyful, and Happy New Year!

Best wishes,
Dr. Edwin Lim (Secretary)
On behalf of the ISTRY Executive Committee

Jena image sources:
www.jenaparadies.de/:

WHAT'S INSIDE THIS ISSUE:



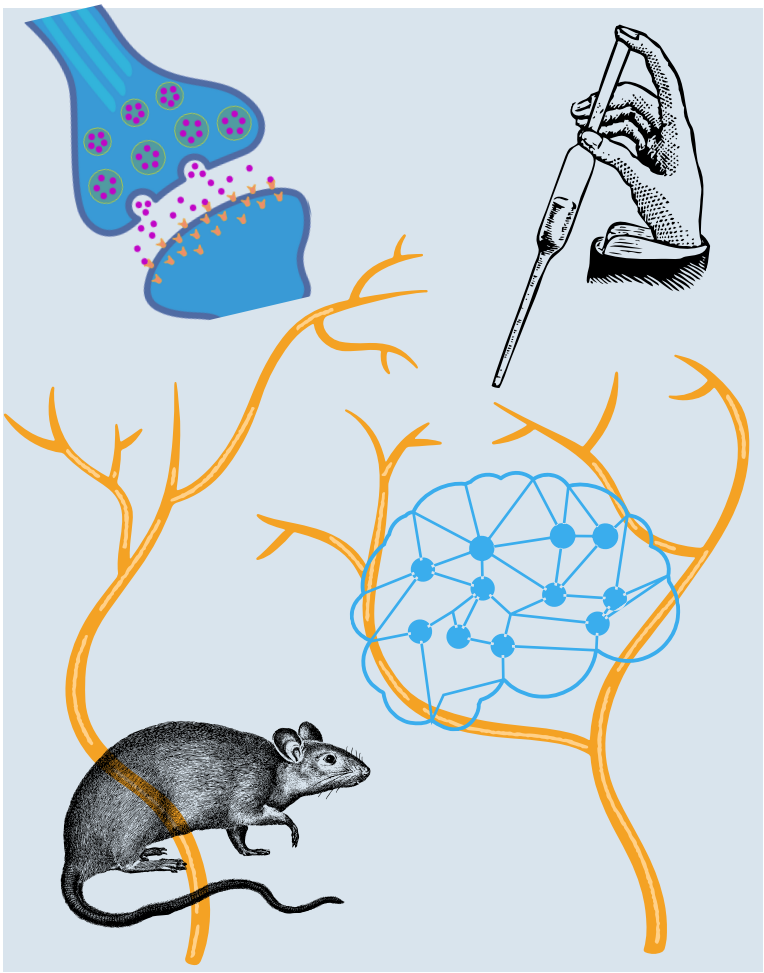
THE PAST, PRESENT, AND FUTURE OF CLINICAL RESEARCH ON KYNURENIC ACID

Written by the ISTRY Media Team

This year marked 170 years of research on kynurenic acid (KA) since its discovery by the German chemist Justus con Liebig in 1853. Kynurenic acid is a quinolinemonocarboxylic acid that is quinoline-2-carboxylic acid substituted by a hydroxy group at C-4. It is a conjugate acid of kynurenate and a downstream metabolite of the kynurenine pathway. It has been of interest due to its neuroactive function when first recognized in the early 1980s. Now, we know that it has a role as a G-protein-coupled receptor agonist, an NMDA and nicotinic receptors antagonist, and is more commonly known for its role against excitotoxicity.

Some of our ISTRY eminent scientists such as Professor Emeritus Robert Schwarcz, Trevor Stone, and Flavio Moroni (who are all Musajo Medalists) working in the tryptophan field have unlocked promising discoveries of targeting KA for therapeutic applications in health and diseases. The work of KA and neurodegeneration is no stranger to the TRP research community.

In this issue, the ISTRY media team have prepared a high-level overview and personal perspective of where we are in terms of the role of KA in health and diseases, beyond neurodegeneration.



Kynurenic acid and neurodegeneration

As an NMDA antagonist, the level of KA in neurodegenerative diseases is reduced in people with Huntington's, Parkinson's and Alzheimer's Diseases (HD, PD and AD) when compared to healthy control. Hence, KA is thought to play a neuroprotective role against excitotoxicity in neurodegeneration. On the contrary, recent studies have also reported higher levels of KA in neurodegenerative diseases, thought to be an adaptive, neuroprotective mechanism in response to pathological neurodegenerative sequelae (e.g. inflammation, astrogliosis, and reactive gliosis). This has been observed in patients with AD and during relapsing phases of multiple sclerosis, though not during remission. Furthermore, KA levels can vary when comparing levels in the central nervous system to the periphery within neurodegenerative diseases. This is not surprising considering KA has poor blood-brain barrier permeability. The disparity in KA level between cerebrospinal fluid (CSF) and blood is a topic of interest for its rationale in the progression of neurodegenerative diseases and remains to be elucidated.

Ongoing preclinical studies demonstrate that KA and its analogs can reduce tau phosphorylation, another feature of neurodegeneration. Targeting tau and excitotoxicity makes KA a potential therapeutic target in neurodegenerative diseases affected by kynurenine pathway alteration. Increasing endogenous KA level pharmacologically via KMO inhibition is a prime target for treating neurodegeneration as shown in several preclinical experimental models such as mice, drosophila, and primates with promising outcomes.

Further research is required to reduce any extraneous neurodegeneration that can be associated with KMO inhibition. A dose-dependent relationship between KA and neuroprotection has also yet to be established, as research also indicates that it can impair cognition at high concentrations (see below). Lastly, there is a need to improve blood-brain barrier penetration of KA analogs, though the current state of research is promising.

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Kynurenic acid and neuropsychiatry

Widespread interest in the role of KA in the pathophysiology of psychiatric disorders including, schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) has emerged primarily based on its antagonist ability of the glutamatergic NMDA receptor. Similar to observational studies in neurodegenerative diseases, KA exhibits diverse changes across different biological samples including peripheral blood, CSF, and postmortem brain tissue in these psychiatric disorders.

In peripheral blood samples, meta-analyses report KA to be reduced in mood disorders (i.e., MDD and BD), whereas KA is not altered in schizophrenia. However, individual studies in schizophrenia show that KA can be increased or decreased depending on the cohort.

In schizophrenia elevated concentrations of KA have recurrently surfaced in CSF samples, indicating a potential role in the neurobiology of these conditions. Notably, BD individuals with prior psychotic episodes exhibit selectively elevated CSF KA, whereas those with ongoing depressive symptoms display unchanged levels. Furthermore, MDD subjects show unchanged KA levels in CSF, suggesting a potential overlap in the depressive symptom domain across these disorders.
Postmortem brain analyses reveal conflicting results, likely influenced by factors such as sex-, cohort- and brain regional differences which makes identifying a clear role of KA difficult to ascertain.

The intricate variations in KA across biological substrates and psychiatric disorders (and neurodegenerative diseases) emphasize the multifaceted nature of its involvement. Further research particularly in CSF and postmortem brain samples are required to enhance our understanding of the neurobiological role of KA in these complex mental health conditions.

Kynurenic acid and immunology

The KP is well known for its immune suppression role via the IDO-Kynurenine-AhR axis. Recently, there has been evidence that downstream metabolites of the KP are also involved in immune suppression, especially KA. Other than kynurenine, KA is also an agonist of AhR leading to immunosuppression. Further, KA can exert immunosuppression via 2 other mechanisms including agonist of G-protein-coupled receptor (GPR)-35 and inducer of Tumor necrosis factor-(TNF) stimulated gene (TSG)-6. Hence, in the context of neuroinflammation and neurodegeneration, brain KA level will be important to counteract NMDA-induced excitotoxicity and chronic pro-inflammation conditions.

Kynurenic acid as oncometabolite in cancer

Since the discovery of the immunosuppressive role of KP metabolites, the cancer field has quickly adopted the idea of KP metabolites as endogenous immune modulators and targets of interest leading to many cancer clinical trials. There are suggestions that the KP metabolite(s) involved in cancer may fit the term as oncometabolite such as kynurenine. It is possible that KA may be an oncometabolite considering its role in immunomodulation. It has been shown that cancer cells can produce KA to exert an anti-tumor immune response, thereby high level of KA in the presence of a tumor may be detrimental. Interestingly, this high level of KA may provide a serendipitous chance to confer neuroprotection which may explain the inverse association between cancer and AD. Further studies are warranted to examine the role of KA in cancer and AD.

Impact of lifestyle factors on endogenous Kynurenic acid levels

Perhaps one of the underappreciated values of research is the effect of lifestyle factors on tryptophan metabolism. It is known that lifestyle factors such as sleep, physical activity, and diet can all impact the endogenous levels of KA.
For example, KA levels have been linked to sleep deprivation. Dr. Ana Pocivavsek's lab has been forefront in this area of research showing that increased KA can disrupt the sleep-wake cycle and sleep deprivation can increase KA levels in preclinical studies, leading to a vicious cycle of poor sleep quality and further deprivation. Inhibition of the KA-producing enzyme, KAT-II was able to reverse this effect.
Since the landmark paper from Prof Raus's lab identifying skeletal muscle as a potential endogenous source of KA, the role of physical activities on tryptophan metabolism has gained much-needed attention. This brings insight into understanding how exercise may provide beneficial effects on diseases via alteration of the tryptophan metabolism.

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For example, exercise intensity can affect KA levels; exercise-induced alteration in KA level can affect the immune landscape in diseases; exercise and neuroplasticity (BDNF) can affect KAT activities.

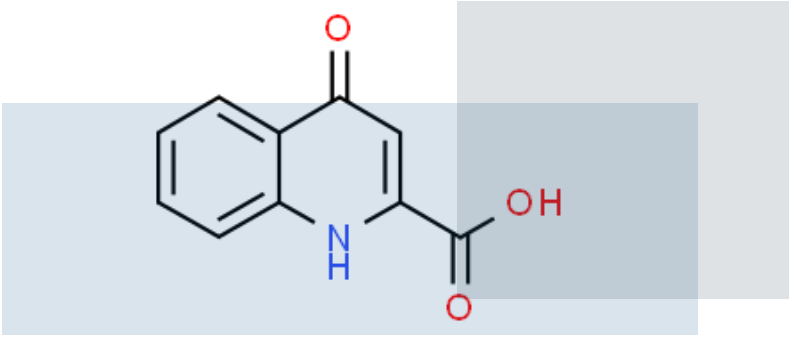
It is not surprising that diet can impact a host's tryptophan metabolism considering tryptophan is an essential amino acid that has to be acquired through our diet. However, the impact is not limited to the amount of dietary tryptophan on its downstream metabolite levels. It is increasingly clear that the type of diet can impact endogenous KP metabolite levels, especially KA. For example, several studies indicate that a diet high in carbohydrates (e.g. Western-style diet) has been associated with lower levels of KA. Higher intake of plant-based food (e.g., Mediterranean diet) was associated with higher KA levels. Although the mechanism is not yet fully understood, it is highly plausible that KA may be directly absorbed from the diet as previous studies reported some of the highest KA levels are found in honeybees, and some fresh vegetables such as broccoli and potato. Hence, diet may provide a non-pharmacological avenue to increase endogenous KA production apart from exercise.

Is Kynurenic acid a good or bad molecule?

It's interesting that after 170 years of research, we are still learning about the contribution of KA to health and diseases. A lot of current research focuses on its beneficial effects and ways to increase its level endogenously, at least from a neurodegenerative perspective. However, in the context of cancer, KA can potentially be an oncometabolite that in excess may not be a good thing. Perhaps after reading this point and further learning about KA in schizophrenia and sleep, you may wonder, can too much KA be bad? As I learned from experience, the world of biochemistry/metabolomics is not a binary fashion as what we see in genomic research. The key to homeostasis is understanding that too much of a good/bad thing can be bad and it's about striking the right balance.

Understanding how alteration to tryptophan metabolism and its metabolite, especially KA will potentially pave the way for a holistic precision medicine approach to treat various diseases. The therapeutic approach is currently targeted at increasing KA levels but should couple with reliable biomarkers to ensure the best clinical outcome in the best interest of the patients. There is an uptake on the innovation of biomarker space where measurement of KA levels extends beyond blood and CSF, especially non-invasive biofluids such as saliva, tears, urine, and sweat in recent years. This can be beneficial considering the ease of collection enabling more longitudinal studies to facilitate a better understanding of metabolic homeostasis in disease progression to pave for precision medicine.

As far as clinical research is concerned, there is still a slow uptake of this information on KP and lifestyle from a data analysis perspective. We have yet to see clinical studies adjusting KA levels as confounders from lifestyle factors in their data analysis. Indeed, this is an exciting and rapidly growing field of research that is intricate and complex. Our high-level personal perspective has touched on some of the key points of interest regarding KA and neurodegeneration, neuropsychiatry, immunology, cancer, and lifestyle. In such a short-read it is impossible to capture the complexities of the field, but we hope you have enjoyed our overview and we look forward to discussing further at our upcoming ISTRY meeting in Germany, where KA was first discovered.



CONTACT US

Webpage: istry.org
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