JUNE 2023, ISSUE 4

ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

Dear members of ISTRY and the Tryptophan Research community,
It's already mid-year, and as I work with my fantastic ISTRY media team crews, reviewing and choosing articles relating to tryptophan research for our monthly featured articles, it is always exciting and tough to decide on which one to feature – there are just so many to choose from every month! This means our field continues to progress and deepen our knowledge of tryptophan research in human health.

In this issue, we will be highlighting some of the recent advancements in tryptophan research, with a focus on depression. We will also be sharing updates on upcoming conferences and an interview with one of our longstanding tryptophan researchers – Prof. Emeritus Flavio Moroni.

I encourage all of you to stay engaged, share your work, and contribute to the continued growth and success of our society. Thank you for your commitment to advancing the field of tryptophan research, and I look forward to working with all of you in the year ahead.

Best wishes,
Dr. Edwin Lim
Secretary of ISTRY

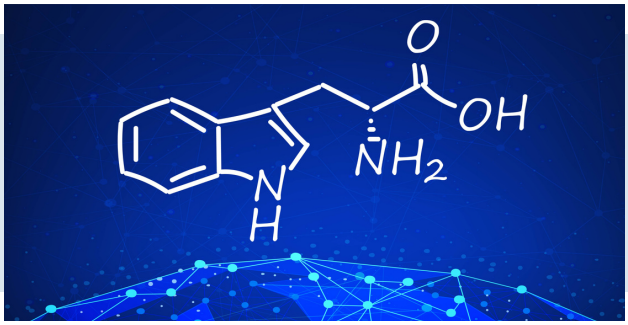
RECENT UPDATES OF ISTRY ACTIVITIES

It has been a while since the last issue, and the ISTRY media team has successfully organized two (3rd and 4th) webinars. Webinar 3 took place on October 4, 2022, with a theme focused on cancer, and more recently, Webinar 4 on April 18, 2023, with a theme on nutrition. In the cancer-themed webinar, we were honored to have the support of Prof. George Pendergast, who chaired the session with three prolific researchers discussing the roles of KP and cancer. Some key take-home messages included the identification of a new target, IL4-induced 1 interaction with KP in cancer immunotherapy (by Dr. Christiane Opitz), molecular insights into KP-AhR interaction in cancer (by Prof. Tracy McGaha), and the synergistic effect of IDO inhibition with genotoxic therapies in cancer (by Prof. Matthew Ciorba). In the nutrition-themed webinar, we learned about how nutritional factors modulate ACMSD activity to affect quinolinic acid and niacin production from Prof. Yukari Egashira and the role of tryptophan metabolism in host-microbe interaction, impacting the gut-brain axis, from Prof. Gerard Clarke. If you missed the webinars, the recordings can be found here.

Another exciting update is the decision from the executive committee confirming the in-person (16th) ISTRY conference meeting in Jena, Germany, scheduled to take place from April 24 to 26, 2024. Planning is currently underway, and abstract submissions are expected to open in late Q3 or early Q4. Please spread the word and save the date. We look forward to seeing you in person.

We also want to welcome our new executive committee member, Dr. Ana Pocivavsek from the University of South Carolina, USA, who will oversee the America region. She has been trained under the mentorship of Prof. Robert Schwarcz, a Musajo memorial medallist recognized for his outstanding lifetime professional contribution to the tryptophan field and the success of ISTRY. We believe that Dr. Pocivavsek will continue Prof. Schwarcz's legacy and bring new frontiers to the tryptophan field.

WHAT'S INSIDE THIS ISSUE:



TRYPTOPHAN METABOLISM AND DEPRESSION

This year, we commemorate 60 years since the idea of biochemical involvement, specifically serotonin, in affective disorder. Let's take some time to appreciate the important role of serotonin in depression, which can be traced back to Dr. Alec Coppen, who pioneered the serotonin depletion theory. What is underappreciated is that Dr. Coppen's theory about the involvement of biochemical compounds in affective disorders, was a very new concept to the research community at that time. The field has since evolved beyond serotonin to encompass tryptophan (TRP) metabolism entirely, including the kynurenines, and has started to appreciate the metabolic role of TRP in symbiosis between host and microbiota. In this issue, let's examine some key aspects of the role of tryptophan metabolism in depression (IP Lapin, 1969).

Over the past years, a considerable body of research has suggested a link between neuroinflammation and depression. While neuroinflammation plays a critical role in the protection and repair of the brain, chronic or excessive inflammation can have detrimental effects on brain function and contribute to the development of various neurological disorders.
Serotonin plays a role in modulating immune function, and dysregulation of the serotonergic system has been implicated in the pathogenesis of various neuropsychiatric disorders, including depression. Recent studies have found a relationship between neuroinflammation and serotonin. Pro-inflammatory cytokines generated during neuroinflammation have been shown to impair serotonin signaling by affecting the expression of serotonin receptors, transporters, and enzymes involved in serotonin synthesis and metabolism. This disturbance has been linked to the development of depression due to reduced serotonin availability in the brain.

By the late 1990s “cytokine sickness behavior theory” was proposed by Keith Kelly and Robert Dantzer. This theory involves the modulation of serotonin, specifically through the depletion of TRP. Pro-inflammatory cytokines have been shown to activate indoleamine 2,3-dioxygenase (IDO) diverting TRP away from serotonin production towards the KP, contributing to the depletion of TRP and leading to the production of neuroactive KP metabolites. While there is ample evidence that supports links between TRP metabolism and depression it is hard to separate the effects of KP activation from inflammation as these are integrated in so many studies. It is unclear whether KP activation precedes inflammation or if it can occur independently in depression.

Tryptophan metabolites as targets of depression

Like many other aspects of the CNS, the dogma of the KP in the brain is being challenged by newly published research. Previously, many of the studies focused primarily on glial cells, which is not surprising as these cell types have been shown to become activated in different disease states and are associated with inflammatory responses. Classically microglia have been

shown to express kynurenine 3-monooxygenase leading to the generation of quinolinic acid. Whereas astrocytes have been shown to express kynurenine aminotransferases leading to the production of the neuroprotective metabolite, kynurenic acid. However, it is becoming clear that other cell types within the CNS contribute to the levels of metabolites detected and may play an even bigger role than glial cells, such as neurons and dendritic cells (featured in our Feb/Mar & Oct 2022 Highlights).

Additionally, other peripheral cell types and systems can impact the level of central KP metabolites. This can be via peripheral KP metabolites crossing the blood brain barrier (BBB) directly, such as kynurenine and 3-hydroxykynurenine, as well as TRP itself. Or through the upregulation of peripheral immune modulators which can regulate the CNS immune response and alter KP activity. These factors are upregulated in different disease states and during chronic stress contributing to neuropsychiatric disorders. Alternatively, activated immune cells can cross the BBB and contribute to the central levels of KP metabolites directly.

Another key contributor to TRP metabolite levels are gut microbes. It is becoming increasingly clear that dysbiosis has detrimental effects and has been associated with depression (Reviewed here). Microbiota-derived TRP metabolites, such as indoles, are distinct yet have profound ramifications when it comes to human diseases. Not surprisingly, dysbiosis activates the mucosal innate immune response leading to IL-1β and TNF-α production thereby further affecting the KP. Regardless if KP metabolites are produced centrally or peripherally, or by microbiota these metabolites have been shown to play a role in neuropsychiatric diseases.

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TRYPTOPHAN METABOLISM AND DEPRESSION CONTINUED

Non-pharmacological interventions of depression by tryptophan metabolism

Among the many things that the COVID-19 pandemic has taught us is that lifestyle risk factors are linked to depression and the KP. Perhaps exploring how these factors influence the KP can shed some light on non-pharmacological means to improve our mental health. Several findings show that both exercise and diet can modulate the KP and potentially impact the development and progression of depression.

Exercise has been shown to have anti-inflammatory effects on the body, which can help regulate the KP. It has also been shown to increase the production of KYNA, which can help protect the brain from neuroinflammation and oxidative stress. In addition, it has been shown to increase the levels of serotonin in the brain, which can help alleviate symptoms of depression and anxiety.

The KP is regulated by enzymes that require specific nutrients, such as vitamin B6 and B3. Therefore, a diet deficient in these vitamins can lead to an imbalance in the KP and an increased risk of psychiatric disorders. In addition, certain dietary factors, such as inflammation-promoting foods like processed meats and sugar, can activate the KP and contribute to the development of depression. For example, Dr. Francis et al showed that those who consumed a western-style diet (high fat, high sugar) had lower levels of KYNA and were linked to more severe depressive symptoms despite the absence of inflammation.

In summary, both diet and physical activity can influence the KP and potentially impact the development and progression of depression and other affective disorders. This may offer non-pharmacological means to target depression by rebalancing the KP homeostasis. These findings have implications in future clinical studies examining KP profiling in diseases where dietary and physical activity information should be collected, checked, and adjusted for any potential confounding effects.

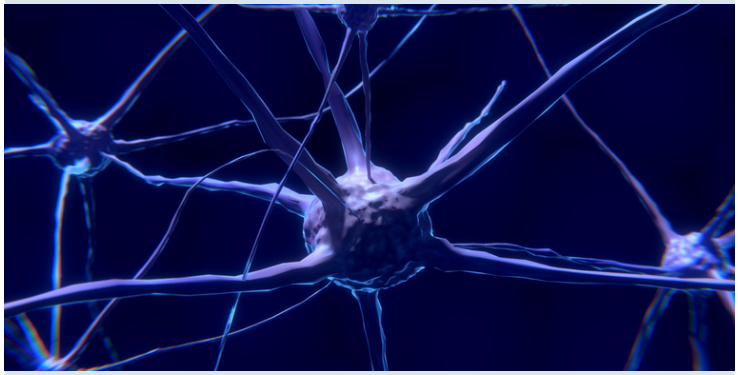
Consideration for outcome measures of depression in TRP/KP

As new research such as clinical trials, lifestyle interventions and KP modulators are being studied, the ability to capture multi-dimensional outcomes with functional implications becomes more important for translational research. In the context of depression, this means going beyond measuring mood or sickness behaviors to capture the full spectrum of symptoms including affective, somatic, behavioral and cognitive features.

Psychometric assessment of depression is typically conducted via self-reported questionnaires, with cut-off scores determining clinically significant groups and changes. However, the ability to draw more meaningful conclusions from results based on a cut-off score can limit our conceptualization of depression as a unitary construct. However, it has in fact been shown that kynurenine metabolites have been implicated in different types of symptoms in depression, specifically, anhedonia in depressed adolescents (Gabbay et al) as well as suicidality in both major depression (Sublette et al) and post-partum depression (Achtyes et al).

We need to be aware of the constructs and factor structure of the scales that we use to measure depressive symptomology and should consider using subscales when interpreting our results, rather than an overall score. Additionally, we should carefully consider using multiple adjunct scales to complement the typical mood measures. Further, changes in symptomology should also be measured alongside functional outcomes in participants, such as sedentary behaviors or independent activities of daily living.

Overall, psychometric scale choice and interpretation is imperative to better understand the relationship between different symptom clusters and sub-types in depression. This more nuanced approach is of pertinence in interventional studies, in order to measure specific and meaningful changes. In this way, the methods of measurement, interpretation and contextualization of depressive symptomology is directly related to the social and economic value of the results we aim to achieve.



RESEARCHER HIGHLIGHT: PROFESSOR FLAVIO MORONI

Written by: Miss Feride Eren

Professor Flavio Moroni, a distinguished figure in the field of tryptophan research, has had an illustrious career. As the President of ISTRY from 2012 to 2015 and a recipient of the Musajo Memorial Medal in 2022 during the ISTRY Webinar, his contributions have been widely recognized. Currently an Emeritus Professor at the University of Florence, he specializes in medical toxicology and anaesthesiology. Professor Moroni's research focuses on understanding excitatory transmission, excitotoxicity, and reducing neuronal death in relation to age and brain damage.

During a recent interview, Professor Moroni graciously shared insights into his early career, his interest in kynurenine research, and his advice for young researchers. Approximately 40 years ago, he delved into the mechanisms of tryptophan in the brain, particularly its role in excitation. Initially, his studies centered around acetylcholine and its functional participation in cholinergic neurons, exploring the effects of different drugs and behavioral activities. Later, he turned his attention to GABA and glutamate research to deepen his understanding of brain excitation.

In 1981, Professor Trevor Stone, a fellow Musajo Memorial Medal Winner, published a paper on the potential transmitter role of quinolinic acid (QUIN), a tryptophan metabolite. This, coupled with research from other scientists, including Robert Schwarcz, highlighting the neurotoxicity of quinolinic acid, prompted Professor Moroni to initiate experiments on QUIN and kynurenic acid. His early focus was on reducing neuronal death, and his studies led to the discovery of 3-indolpyruvic acid as a compound that increased KYNA levels but not KYN levels.
Professor Moroni emphasizes the importance of nurturing young scientists, each of whom has their own projects and responsibilities within his team. He encourages them to take initiative and be creative in their research. His advice to young researchers is to maintain passion, curiosity, and resilience as they pursue their scientific endeavors.

Now retired from the University of Florence, Professor Moroni finds solace in the tranquil surroundings of his family house in the beautiful southern region of Tuscany. With newfound free time, he enjoys tending to his garden and discovering ways to prepare olives, savoring the joys of a well-deserved retirement.

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