DECEMBER 2025, ISSUE 8

ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

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

As we approach the final weeks of 2025, there is a familiar sense of urgency alongside a welcome feeling of relief. Many of us are busy wrapping up projects, deadlines and commitments, while also looking forward to celebrating the end of the year with friends, family and loved ones. It is also a timely moment to reflect on some of the highlights and developments across our society over the past year.

One important update is that the ISTRY Media Team has undergone several changes, including the addition of new members. We are pleased to welcome a new Head of Media and Communications, Dr Samara Walpole, who has taken over leadership of the team last month. Prof Edwin Lim has transitioned back into an advisory role and will continue to support the team with strategic guidance.

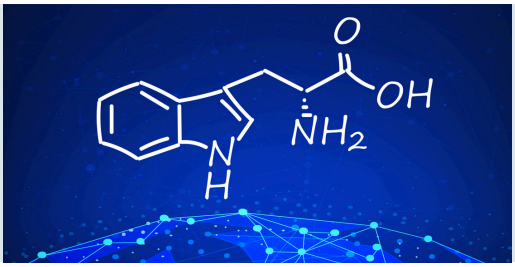
Planning for the ISTRY 2026 Meeting in Padova, Italy is also well underway. We are delighted to see strong engagement from the community, with several symposia already accepted and abstract submissions open until 6 January 2026. Further details and updates can be found on the conference website.

In this issue of the newsletter, you will also find an opinion piece on tryptophan metabolism and sleep regulation written by our President and Vice-President, Profs Stefano Comai and Ana Pocivavsek. In addition, with the generous support of Dr Johanna Gostner, our Media Team interviewed our most recent Musajo Medalist, Prof Emeritus Dietmar Fuchs, who shares reflections on his scientific journey, career highlights and sources of inspiration.

We hope you enjoy this issue and continue to find the ISTRY community a stimulating and supportive space for sharing ideas, research and collaboration. ISTRY would also like to wish you a joyful festive season and a Happy New Year!

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

WHAT'S INSIDE THIS ISSUE:



TRYPTOPHAN: ONE AMINO ACID, TWO BEDTIME STORIES

Written by Professor Stefano Comai and Professor Ana Pocivavsek

Tryptophan (Trp) is an essential amino acid that serves not only as a substrate for protein synthesis but also as a precursor for several biologically active compounds that profoundly influence brain function and behavior, including the sleep/wake cycle. Once absorbed from the diet, Trp can be metabolized through multiple pathways. The relative activity of these pathways is determined by a complex interplay of metabolic, hormonal, and immune factors; for instance, inflammatory cytokines induce indoleamine 2,3-dioxygenase, diverting Trp toward kynurenine production at the expense of serotonin synthesis, while conditions favoring serotonergic metabolism promote the generation of melatonin and the maintenance of normal sleep–wake rhythmicity.

In the brain, Trp availability is tightly regulated by transport across the blood–brain barrier through the large neutral amino acid (LNAA) carrier, which also transports leucine, isoleucine, valine, phenylalanine, and tyrosine. Consequently, the ratio of Trp to the sum of competing LNAAs determines the extent of its central uptake and subsequent conversion to serotonin. Serotonin acts as a key neuromodulator throughout the brain, influencing mood, appetite, thermoregulation, and cognition, as well as playing an essential role in the regulation of the sleep/wake cycle. Activity of serotonergic neurons is highest during wakefulness, decreases during non-rapid eye movement (NREM) sleep, and is minimal during rapid eye movement (REM) sleep, indicating that serotonin contributes to the initiation and maintenance of sleep primarily through the modulation of arousal networks. Experimental and clinical studies have shown that increasing Trp intake enhances serotonergic neurotransmission, shortens sleep latency, and improves sleep continuity, particularly in individuals with mild sleep disturbances. Dietary interventions that elevate the plasma Trp/LNAA ratio, such as administration of Trp, α-lactalbumin-enriched proteins, or carbohydrate-rich meals, consistently increase brain serotonin synthesis and are associated with improved subjective sleep quality. In addition, serotonin synthesized in the pineal gland provides the immediate substrate for melatonin production. This transformation occurs via the sequential actions of arylalkylamine N-acetyltransferase (AANAT), which converts serotonin into N-acetylserotonin, and acetylserotonin O-methyltransferase (ASMT), which methylates N-acetylserotonin to form melatonin (N-acetyl-5-methoxytryptamine). The activity of AANAT exhibits a strong circadian rhythm under the control of the suprachiasmatic nucleus (SCN), the master clock of the hypothalamus. During the dark phase, sympathetic activation of the pineal gland stimulates AANAT, resulting in a marked nocturnal rise in melatonin synthesis and secretion. Circulating melatonin reaches its peak during the middle of the night and declines toward morning, providing an endocrine signal of darkness that synchronizes circadian rhythms and facilitates the transition from wakefulness to sleep. Melatonin acts through two high-affinity G protein–coupled receptors, MT1 and MT2, distributed in several brain regions involved in sleep and circadian regulation. MT1 receptors are particularly abundant in the SCN, locus coeruleus, and dorsal raphe, where they contribute to the temporal organization of REM sleep and to the circadian control of the sleep–wake cycle, while MT2 receptors, more prominently expressed in the thalamus, hippocampus, and preoptic area, are implicated in NREM sleep regulation and sleep homeostasis. The distinct localization and signaling of these receptors account for the complementary roles of melatonin in modulating both the circadian and the homeostatic components of sleep. Acting through MT1 and MT2, melatonin not only facilitates sleep onset but also contributes to the architecture and restorative quality of sleep, linking the circadian timing system to the physiological need for sleep. Experimental studies in receptor knockout mice and pharmacological investigations with selective MT1 and MT2 ligands have confirmed that MT1 activation primarily influences REM sleep and circadian entrainment, whereas MT2 activation favors slow-wave sleep and enhances sleep consolidation. In humans, exogenous melatonin produces a mild hypnotic effect characterized by reduced sleep onset latency and improved sleep efficiency. However, due to its short half-life and low bioavailability, its ability to sustain sleep throughout the night is limited.

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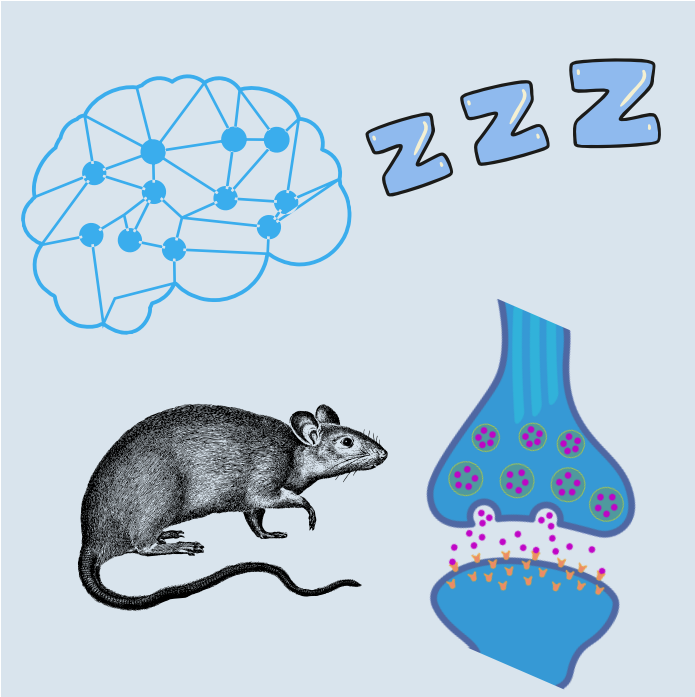
Controlled-release melatonin formulations and synthetic MT1/MT2 receptor agonists such as ramelteon and tasimelteon have been developed to mimic the physiological nocturnal profile of melatonin and have demonstrated efficacy in treating insomnia and circadian rhythm sleep–wake disorders. Clinical and meta-analytic data confirm that dietary or supplemental Trp enhances both serotonergic and melatonergic activity. A daily intake of at least one gram of Trp reduces wake after sleep onset and may improve sleep continuity and efficiency, while lower doses show more variable results. Such effects reflect the coupling between peripheral Trp availability, central serotonin synthesis, and nocturnal melatonin secretion, collectively constituting the biochemical substrate of physiological sleep regulation. This serotonergic–melatonergic branch of tryptophan metabolism thus represents a fundamental molecular axis linking nutritional, neurochemical, and circadian processes, and its integration with the kynurenine pathway provides a broader framework for understanding how tryptophan metabolism modulates sleep through both neurotransmitter and immune-mediated mechanisms.



While the serotonergic-melatonergic pathway has long been recognized as a key regulator of sleep, a parallel branch of tryptophan metabolism, the kynurenine pathway, is gaining increasing attention for its influence on arousal and sleep architecture. Traditionally studied in the context of immune activation, neurodegeneration, and psychiatric illness, this pathway is now appreciated as a dynamic interface between metabolism, inflammation, and neural function. Among the kynurenine metabolites, kynurenic acid (KYNA) has emerged as a particularly complleing modulator of sleep-wake behavior.

The pathway begins with the conversion of tryptophan to kynurenine through enzymes such as indoleamine 2,3-dioxygenase (IDO1), which is strongly upregulated by pro-inflammatory cytokines. As a result, inflammation not only diverts tryptophan away from serotonin synthesis but also increases kynurenine availability, effectively linking immune status to downstream kynurenine metabolism. Kynurenine readily enters the brain, where it is metabolized within astrocytes by kynurenine aminotransferase II (KAT II) into KYNA. Because KYNA itself crosses the blood-brain barrier poorly, its central actions depend largely on local production.

Once formed, KYNA acts as an enodgenous antagonist at α7 nicotinic acetylcholine receptors (α7nAChRs) and N-methyl-d-aspartate receptors (NMDARs) in the brain. Both receptors are critically to cognition, arousal and the coordination of sleep states. Elevated KYNA levels have been detected in the cerebrospinal fluid and postmortem brain tissue of individuals with neuropsychiatric disorders such as schizophrenia and bipolar disorder, conditions frequently accompanied by cognitive dysfunction and significant sleep disturbances. These findings, along with extensive preclinical evidence demonstrating reductions in extracellular glutamate and y-aminobutyric acid (GABA) following KYNA elevation, underscore how KYNA-mediated inhibition of excitatory and inhibitory neurotransmission can reshape the sleep-wake cycle.

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Extensive animal studies have illuminated KYNA's direct impact on sleep physiology. Experimental increases in brain KYNA, typically achieved through peripheral kynurenine administration, produce delayed onset of both REM and NREM sleep, reduced total sleep time, diminished REM-associated theta oscillations, and increased wakefulness, all in a dose-dependent manner. Since hippocampal theta rhythms during REM are thought to support memory processing, such alterations may have downstream cognitive implications. Conversely, targeted reduction of KYNA via selective, irreversible KAT II inhibition normalizes sleep onset and architecture even in the presence of excess kynurenine, strongly suggesting a causal role for KYNA in modulating sleep behavior.

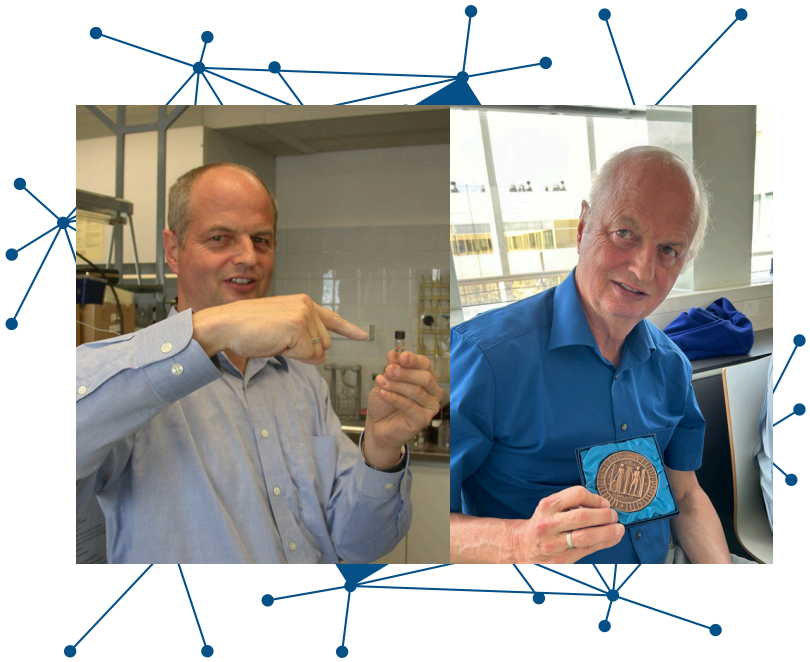
The influence of the kynurenine pathway begins early in life. Mice with partial deficiency of kynurenine monooxygenase (Kmo) exhibit chronically elevated KYNA levels and display decreased sleep, prolonged wakefulness, and altered spectral power during REM and NREM sleep. Similarly, adult offspring exposed to heightened kynurenine levels in utero, resulting in elevated fetal brain KYNA, show lasting deficits in REM duration and sleep initiation. Importantly, these abnormalities are reversible through KAT II inhibition, highlighting KYNA as a mechanistic driver.

Beyond its classical receptor targets in the central nervous system, KYNA also interacts with aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor increasingly recognized for its influence on circadian and metabolic regulation. Several kynurenine pathway metabolites, including kynurenine itself, are endogenous AhR agonists. Although the specific contributions of AhR signaling to sleep regulation remain under active investigation, its established roles in clock-gene expression and circadian entrainment make it an intriguing point of convergence between metabolism and the temporal organization of physiological processes. This growing area of research suggests that kynurenine metabolites may shape sleep not only through rapid neurotransmitter modulation but also through slower transcriptional and circadian mechanisms.

Although KYNA has been a focal point of sleep-related research, the broader kynurenine pathway likely contributes additional influences. Metabolites such as quinolinic acid and 3-hydroxykynurenine, known for their effects on excitability and oxidative stress, represent plausible but understudied modulators of sleep physiology. Together, the emerging evidence suggests that the kynurenine pathway is not simply a metabolic diversion from serotonin synthesis but a multifaceted regulator of sleep-wake behavior, integrating signals from immune activation, glial metabolism, and neurotransmitter systems. As the field continues to refine our understanding of these interactions, the kynurenine pathway may offer new perspectives, and potentially new targets, for improving sleep health.

In conclusion, while both the sertonergic-melatonergic pathway and the kynurenine pathway clearly shape sleep, it remains largely unknown whether these branches of tryptophan metabolism directly communicate with one another. Each pathway influences sleep through distinct neurochemical mechanisms, yet both are sensitive to shared regulatory signals such as inflammation, metabolic state, and glial activity. These common upstream pressures suggest that interactions between melatonin signaling and kynurenine-derived metabolites may exist, even if they have not yet been mapped. Clarifying whether, and how, these pathways intersect will be essential for understanding how the brain integrates metabolic and immune cues to orchestrate sleep-wake behavior.

RESEARCHER HIGHLIGHT
PROFESSOR DIETMAR FUCHS



At the 2024 International Society for Tryptophan Research (ISTRY) meeting in Jena, Professor Dietmar Fuchs was honored as the Musajo Medalist for 2025. This prestigious award, presented since 1995, recognizes his sustained research achievements in patient-related immunobiology and his outstanding contributions to the field of tryptophan metabolism. Over more than 35 years, Professor Fuchs has advanced our understanding of tryptophan's role in health and disease, uncovering critical links between immune activation, neurotransmitter synthesis, and inflammatory processes. His collaborative approach with clinicians worldwide and dedication to mentoring young scientists have left a lasting impact on the field. We had the privilege of speaking with Prof. Fuchs about his career journey, scientific insights, and reflections on supporting the next generation of researchers.

Early Beginnings

Professor Dietmar Fuchs began his scientific journey as an analytical chemist, earning his doctorate at the Leopold-Franzens University of Innsbruck, where he studied complex formation of cations with acid amides. His growing interest in clinical research led him to the Medical University of Innsbruck, joining Prof. Wachter's group to develop innovative HPLC methods with fluorescence detection for analyzing pteridines, particularly neopterin. This work revealed a critical link between neopterin formation and tryptophan degradation, as both immunobiochemical pathways are activated by similar processes. The cytokine interferon-gamma, produced during the immune reaction, is the most important activating signal.

While his career included visiting positions at several institutions, Innsbruck remained his primary base, where he analyzed samples from global collaborators and advanced research that bridged chemistry and clinical relevance.

"tryptophan metabolism was particularly interesting to me because breakdown to kynurenine correlates so well with neopterin formation in many diseases."

Career Highlights

When asked to reflect on his career highlights, Professor Fuchs highlighted that their research was able to demonstrate correlations between neopterin and tryptophan markers with the pathology of a wide variety of diseases ranging from infections, malignant and neurological disorders to allergies and asthma, in close cooperation with many clinical scientists worldwide. A pivotal contribution of his work was uncovering the link between inflammatory reactions and neuropsychiatric symptoms, showing how inflammation disrupts the synthesis of dopaminergic and noradrenergic neurotransmitters. Another significant finding was identifying that increased vitamin demand during inflammatory responses is responsible for moderate hyperhomocysteinemia.

As a "preclinical" researcher, Professor Fuchs emphasized maintaining strong connections with clinicians to ensure his immunobiology research translated to patient care. Reflecting on his career, he describes that it was a great pleasure to be honored with the Musajo Medal for this work.

Career Advice

One piece of advice from Professor Fuchs to our ECRs is to not draw conclusions solely from isolated datasets and to always view in-vitro results in relation to the in-vivo situation.

"My advice is to give space to the critical discussion of results."

Life after Research

Now in retirement, Prof. Fuschs is trying to devote more time to his surroundings and connecting his artistic eye with scientific thinking. He enjoys engaging in landscape photography and occasionally stopping by his former workplace.

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Webpage: istry.org
Email: media_team@istry.org
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