



# Histamine research advancements in the second year of the COVID-19 pandemic: report of the European Histamine Research Society (EHRS)

Ilona Obara<sup>1</sup> · João Paulo S. Fernandes<sup>2</sup> · Ekaterini Tiligada<sup>3</sup>

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## Abstract

In the light of cancellation of the 50th Annual Meeting of the European Histamine Research Society (EHRS) due to continuing challenges and restrictions imposed by the coronavirus disease 2019 (COVID-19) outbreak, the EHRS Council decided to organize a series of online events spread in 2021 to allow dissemination of histamine research progress and advancement among the Society members and beyond. This report summarizes the outcomes of the EHRS Council initiative that comprised the organization of four webinars, each focusing on a highly relevant histamine research scientific area. These included insights into novel therapeutic targets related to the histaminergic system in the eye, histamine intolerance, and the role of histamine and the histaminergic system in the regulation of the nervous system, as well as an update on studies leading to the development of novel methods for histamine detection. The outcome of this series of virtual events conformed that histamine research continued to develop despite the pandemic, and we witnessed stimulating advancements in 2021. Importantly, the EHRS Council brought histaminologists together in this unprecedented time.

## Introduction

As a result of the continuing challenges and restrictions imposed due to the coronavirus disease 2019 (COVID-19) outbreak, the face-to-face 50th Annual Meeting of the European Histamine Research Society (EHRS) due in 2021 [1, 2], has been postponed till autumn 2022. The Society has always been passionate about promoting knowledge and gathering new information within all aspects of histamine and related fields [3]. Hence, the EHRS Council decided to organize a series of online events spread in 2021 to allow dissemination of histamine research progress and advancement among the Society members and beyond. Notably,

this activity ended with an online webinar on the contribution of mast cells (MCs) and basophils in inflammatory and (auto)immune diseases, co-organized by the EHRS and the Japanese Histamine Research Society (JHRS) [4] in January 2022 [5].

This report summarizes the outcome of the EHRS Council initiative and demonstrates the successful efforts of the EHRS members to keep up the good spirit and research enthusiasm during the COVID-19 pandemic. In total, there were four webinars. Each webinar focused on a highly relevant scientific area, attracted over 40 attendees from academia, research institutions and industry, representing most European countries, the Americas, East Asia and the Middle East and sparked influential discussions among the global histamine audiences.

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✉ Ilona Obara  
ilona.obara@ncl.ac.uk

<sup>1</sup> School of Pharmacy and Translational and Clinical Research Institute, The Faculty of Medical Sciences, Newcastle University, King George VI Building, Newcastle upon Tyne NE1 7RU, UK

<sup>2</sup> Department of Pharmaceutical Sciences, Universidade Federal de São Paulo, Diadema, Brazil

<sup>3</sup> Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

## Role of histamine in the eye

Despite intense research efforts during the last three decades, the clarification of histamine pharmacology in the eye remains elusive. Many EHRS members have recognized for some time that the eye is clearly an exciting and promising target organ for research. Therefore, Professors Emanuela Masini (University of Florence, Italy), Holger Stark (Heinrich Heine University Düsseldorf, Germany) and Katerina

Tiligada (National and Kapodistrian University of Athens, Greece) organized a webinar entitled ‘*Gaining insight into novel roles of histamine in the eye*’ on June 17, 2021.

This session provided new knowledge on the role of histamine in the regulation of eye physiology and pharmacology and its importance in the search for novel strategies to treat eye pathologies. Compared to *per os* formulations, one of the main challenges in ocular drug design is the variation of pH values in the different eye compartments, the need to address topical, subconjunctival or intravitreal routes of drug administration, as well as the chemical aspects to avoid ocular irritation as pointed out by Professor Holger Stark. Professor Stark suggested that, while all histamine receptor subtypes are expressed in the eye, the most interesting avenue for the development of novel topical therapeutic strategies for glaucoma and conjunctivitis would be the exploration of histamine  $H_3$  and  $H_4$  receptor ligands. In fact, Drs Laura Lucarini and Silvia Sgambellone (University of Florence, Italy) demonstrated the potential value of the novel  $H_3$  receptor antagonist-nitric oxide (NO) donor hybrid compound ST-1989 in preclinical models of ocular hypertension and ischemia/reperfusion of the retinal artery in New Zealand white rabbits. The presented data suggested long-lasting and beneficial effects of this compound in regulating increased intraocular pressure and future application against glaucoma. In addition to  $H_3$  receptors, also  $H_4$  receptors seem to be involved in the regulation of the histamine-mediated ocular inflammatory conditions, particularly in conjunctival inflammation, as shown by Katerina Tiligada.

It was concluded that continuing research in the field will lead to a better understanding of the putative functions of the  $H_3$  and  $H_4$  receptors, thus adding to the clarification of histamine pharmacology in the eye beyond the classical use of  $H_1$  antagonists.

## Role of histamine in diet

Another area of growing interest in recent years is associated with the impact of low-histamine diet and its role in the regulation of histamine intolerance. Thus, Professors Madeleine Ennis (Queen’s University Belfast, UK), Mitsunobu Mio (Okayama University, Japan) and Katerina Tiligada organized a webinar entitled ‘*Low Histamine Diets: Facts and Controversies*’ that was held on November 18, 2021.

The webinar presented the current state of the art on the role of enzymes involved in the formation and metabolism of histamine and their contribution, together with histamine itself, to the function of the gastrointestinal system in health and in disease conditions. Professor Wiesława Agnieszka Fogel (Medical University of Łódź, Poland) discussed the challenges associated with changes on the activity of diamine oxidase (DAO) in several gastrointestinal conditions

and critically evaluated the available literature supporting the contribution of alterations in DAO activity regulation in improving these conditions. While Professor Fogel questioned the quality and design of the existing studies, Professor Madeleine Ennis also challenged the design of the studies, particularly with regards to the lack of healthy controls and measurements of histamine metabolizing enzymes in the intestinal mucosa before and after histamine exposure. She also emphasized that histamine levels in foods can vary significantly, even in the same food product, as this depends on maturity, storage time and particular treatment processes, and that there are very few foods that present high histamine content. These facts simply add to the controversies around food histamine content that can pose significant challenges or even hamper medical diagnosis and guidance. Notably, Dr Caterina Chliva (University General Hospital ‘Attikon’, Athens Greece) pointed out that ingested histamine is often regarded as the cause of health complaints even though scientific evidence supporting this clinical claim is rather limited and often contradictory. In fact, there are reports supporting the benefit of low histamine diet in conditions like urticaria with gastrointestinal involvement, although the robustness of the study design and the outputs can be easily disputed.

In conclusion, even though there is some clinical evidence on the association between histamine content/DAO activity and gastrointestinal disorders, scientifically robust evidence and reliable analytical methods are urgently required to help define the role and impact of ingested histamine in human health and disease. These approaches, together with randomized control trial strategies, will help to accurately diagnose and clinically manage histamine-sensitive conditions.

## Role of histamine in the nervous system

The role of histamine as an important regulator of the nervous system function, particularly at the brain level, has been explored for many years. The recent advancements of this research area have been presented and discussed in the ‘festive’ virtual poster event organized by Drs Paul Chazot (Durham University, UK) and Ilona Obara (Newcastle University, UK) on December 16, 2022. Whilst the presenters were mainly early career researchers and Ph.D. students, the discussion gathered both junior and senior members of the Society and beyond.

We learnt from Ricardo Marquez Gomez (University of Oxford, UK) that histamine-positive clusters of axonal projections were found in the bed nucleus of stria terminalis (BNSTov) located in the striatal vicinity at postnatal days 9–12 (P9–12), a crucial period for striatal development. Given the low striatal histaminergic innervation at this age range, he explored whether BNSTov could serve as an

extra-striatal source of histamine during P9-12 and showed results that suggest a novel role of histamine as a paracrine modulator of striatal synaptic transmission. We also learnt from Dr Ling Shan (Leiden University Medical Centre, Netherlands) that narcolepsy type 1 (with cataplexy) is associated with loss of hypocretin-1 expressing neurons and the increased numbers of histidine decarboxylase positive histaminergic neurons in the hypothalamus. He performed an immunohistochemical analysis by staining sleep–wake related neuronal populations and the presence of microglia reactions in the hypothalamus comparing narcolepsy type 1 with idiopathic hypersomnia and matched controls.

The event continued with short poster presentations, mostly from PhD students. Alessia Costa, (University of Florence, Italy), Lola Hardt (Bordeaux University, France), Alessandra Franceschini, (University of Florence, Italy) and Rocio Valle-Bautista (Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, México) presented their work on the role of histamine and the histaminergic system as an important modulator of memory. Histamine cross-talk with chronic stress and neuropathic pain was explored by Barbara Rani (University of Florence, Italy) and Katarzyna Szczepańska (Jagiellonian University, Poland), respectively, whereas histamine in neurodegenerative disorders such as Parkinson's disease or loss of muscles control were discussed by Agnieszka Olejarz-Maciej (Jagiellonian University, Poland) and Savina Apolloni (Fondazione Santa Lucia Istituto di Ricovero e Cura a Carattere Scientifico, Italy), respectively.

## Novel methods for histamine detection

Reliable quantification methods of the effective histamine concentration being released, for instance in the extracellular fluids are critical to the better understanding of the functional implications of histamine in the regulation of multiple biological processes. Unfortunately, data reporting in vivo histamine levels often remain controversial, pointing to continuing challenges regarding the reliability of the available quantification methods. Therefore, there is an urgent need to identify novel, more reliable quantification methods as well as to compare and critically evaluate the available methods to identify the gold standard to support scientific research, industry and other relevant stakeholders. Interestingly, in the webinar on ‘*Novel ways of detecting histamine*’ organized by Professor Detlef Neumann (Hannover Medical School, Germany), Dr Ilona Obara and Professor Pertti Panula (University of Helsinki, Finland) on September 23, 2021, Dr Parastoo (Parry) Hashemi (Imperial College London, UK) showed a novel voltametric method to measure the levels of evoked histamine release and uptake, potentially offering an in-depth view of in vivo histamine

brain chemistry in physiological and inflammation models. This novel approach, combined with mathematical and pharmacological tools, may provide insights into the interconnectivity between central histamine and serotonin circuits, in both normal, acute and chronic inflammation states and contribute to the elucidation of the putative H<sub>3</sub> receptor-mediated serotonin inhibition in the brain. Also, Dr Heike Bähre (Hannover Medical School, Germany) reported on the suitability of a highly sensitive liquid chromatography-mass spectrometry (LC-MS/MS) technique for the simultaneous detection and quantification of histamine and its metabolites in serum and tissues, including 1-methylhistamine, thus emphasizing its advantages when compared to other available analytical methods.

Certainly, progress in histamine research during the pandemic was not limited to the online webinars. The progressive return to lab activities enables experimental research in the field to restart. More than 1350 papers mentioning histamine and its involvement in various biological processes have been published during 2021 according to PubMed. Several of them involved both young and senior members of the Society. There were also special issues in peer-reviewed journals led by members of the Society that focused on histamine research. The issue on the “*Molecular Biology of Histamine Systems*” is edited for the International Journal of Molecular Sciences by Paul Chazot and Ilona Obara and that on “*The Challenge of New Therapeutic Approaches for Unmet Therapeutic Needs*” has been edited for Frontiers of Pharmacology by Arianna Carolina Rosa, Vadim Sumbayev, Ioanna Andreadou and Mitsunobu Mio.

It should be noted that due to the pressure of an urgent treatment for COVID-19, many papers reporting on histamine receptor antagonists repurposing studies against COVID-19 as well as on the role of histamine in the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection were published. Special mention should be given to the paper co-authored by Madeleine Ennis and Katerina Tiligada who focused mainly on histamine H<sub>2</sub> receptor antagonists to critically review the available literature on the role of histamine receptors and their ligands on SARS-CoV-2 infection and COVID-19 cases [6]. This paper stemmed from the discussion on clinical trials to combat COVID-19 and the plenary talk delivered by Professor Madeleine Ennis during the 49th annual online EHRS meeting [2].

In conclusion, despite the continuing challenges and restrictions imposed due to the COVID-19 pandemic histamine research has continued to develop and we witnessed interesting advancements in 2021. Importantly, the EHRS Council brought us together in this unprecedented time. The next meeting, which will mark the 50<sup>th</sup> Anniversary of the EHRS will be held in Hannover, Germany. It will be jointly organized by Professors Thomas Werfel and Holger Stark

and their colleagues. The proposed dates are set for 1–4 September 2022 with further information being shared via our website: <https://www.ehrs.org.uk/>.

**Author contributions** IO wrote the main report text. JPSF and ET reviewed and edited the report. All authors approved the final version.

## Declarations

**Conflict of interest** The authors declare no competing interests.

## References

1. European Histamine Research Society, <https://www.ehrs.org.uk/>. Accessed on 13 Apr. 2022.
2. Kay L, Obara I. Meeting report of the 49th annual meeting of the European Histamine Research Society (EHRS). *Inflamm Res*. 2020;69(10):1015–7. <https://doi.org/10.1007/s00011-020-01390-6>.
3. Tiligada E, Ennis M. Histamine pharmacology: from Sir Henry Dale to the 21st century. *Br J Pharmacol*. 2020;177(3):469–89. <https://doi.org/10.1111/bph.14524>.
4. Japanese Histamine Research Society, <http://www.jhrs.umin.jp/en/index-e.html>. Accessed on 13 Apr. 2022.
5. Tiligada E, Gibbs BF, Tanaka S. Novel insight into the role of mast cells and basophils: joint webinar of the Japanese and the European Histamine Research Societies (JHRS/EHRS). *Inflamm Res*. 2022. <https://doi.org/10.1007/s00011-022-01575-1>.
6. Ennis M, Tiligada K. Histamine receptors and COVID-19. *Inflamm Res*. 2021;70:67–75. <https://doi.org/10.1007/s00011-020-01422-1>.

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