

JOINT CONFERENCE

of the **Polish Society for Histamine Research**
and the **Histamine Research Society Europe**

22-24 October 2026
Lodz, Poland

Biogenic Amines and Related Biologically Active Compounds with **Histamine** as a **Key Amine**



55
Years

of the
European
Histamine Society

52nd

European
Histaminologists
Meeting

40
Years

of the Polish Society
for Histamine
Research

20th

Biennial
PTBH
Conference

Dear Friends,

Welcome to our jubilee meeting

In 1971, more than half a century ago, Czesław Maslinski organised the Satellite Symposium on Histamine at the XXV International Congress of Physiological Sciences in Łódź. Fascinated by this multifunctional biogenic amine, attendees decided to combine their efforts to gain deeper insight by forming the Histamine Club, which met annually to exchange new knowledge. This brilliant idea has endured, and today we meet again!

The Histamine Club's first meeting took place in Paris in 1972, and subsequent meetings have been held in different cities across Europe. Our anthem, with extra verses provided by Anita Sydbom, describes these meetings.

In 1981, the society was renamed as the European Histamine Research Society, and in 2024, the Histamine Research Society Europe.

In 1986, Polish members registered the Polish Society for Histamine Research and established biennial October conferences titled "Biogenic Amines and related biologically active compounds" to include other amines, as few scientists in Poland were exclusively involved in histamine research.

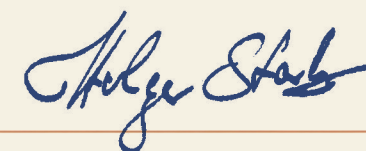
The lively exchange of information led to new discoveries about histamine metabolism, functions, receptors, and its interplay with other amines and systems. Each year, many papers were and are published.

Sadly, James Black, Bertil Diamant, Franc Erjavec, Robin Ganellin, Wilfried Lorenz, Pier Francesco Mannaioni, Czesław Maslinski, Bruno Mondovi, Rado Nosal, Jean Louis Parrot, Heinz Schild, Wolfgang Schmutzler, Walter Schunack, Borje Uvnas, Geoffrey West, and other great researchers in the field are no longer with us.

Let us continue their work to discover everything that histamine does both in health and disease.



President
Polish Society for Histamine Research



President
Histamine Research Society Europe

Scientific Programme

THURSDAY, 22 OCTOBER 2026	
12:00	WELCOME <i>Wiesława Agnieszka Fogel and Holger Stark</i>
12:15–13:15	SESSION IA. HISTAMINE SISTER – DOPAMINE
12:15 L1	DEVELOPMENTAL ROLES OF DOPAMINE IN EARLY BRAIN AND REGENERATION <u>Panula P.</u> ¹ ¹ Department of Anatomy, University of Helsinki, Haartmaninkatu 8, 00290 Helsinki, Finland
12:45 L2	DOPAMINE IN THE GUT <u>Magdalena Kurnik-Łucka</u> Department of Pathophysiology, Jagiellonian University Medical College, Krakow, Poland
13:15–14:15	LUNCHTIME (lunch served in hotel restaurant)
14:15–15:45	SESSION IB. HISTAMINE SISTER – SEROTONIN <i>Chairs: Jerzy Jochem & Barbara Radomańska</i>
14:15 L3	THE PSYCHEDELIC 5-METHOXY-DIMETHYLTRYPTAMINE (5-MEO-DMT) COUNTERACTS BEHAVIORAL CONSEQUENCES OF CHRONIC RESTRAINED STRESS WHILE INDUCING DISTINCT BRAIN ORGANIZATION OF NEUROTRANSMISSION SYSTEMS Chloé Aman ¹ , Julien Macé ¹ , Abdeslam Chagraoui ² , <u>Philippe De Deurwaerdère</u> ¹ ¹ Institute of Cognitive and Integrative Neuroscience of Aquitaine, CNRS UMR 5287, University of Bordeaux, France. ² INSERM 1239, University of Rouen, France.
14:45 O1	EFFECTS OF PSYCHEDELIC DRUGS SUCH AS PSILOCYBIN ARE ENHANCED BY mGlu_{2/3} GLUTAMATE RECEPTOR ANTAGONISTS, IMPROVING THERAPEUTIC EFFECTIVENESS AND REDUCING ADVERSE EFFECTS B. Chruścicka-Smaga ¹ , J. Turek ¹ , B. Pochwat ¹ , Z. Bedrood ² , Ł. Gąsior ¹ , M. Bijata ² , J. Włodarczyk ² , A. Szewczyk ¹ , <u>A. Pilc</u> ¹ . ¹ Maj Institute of Pharmacology, Polish Acad. Sci., Smętna 12, 31-343 Kraków, ² Nencki Institute of Experimental Biology, Polish Acad. Sci., Pasteura 3, 02-093 Warsaw, Poland.
15:05 O2	MULTITARGET ACTION OF 1,3,5-TRIAZINE 5-HT₆ RECEPTOR AGENTS IN SEARCH FOR NEW THERAPIES OF ALZHEIMER'S DISEASE <u>Handzlik, J.</u> Chair of Chemical Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland
15:30–16:10	POSTER SESSION – ORAL PART <i>Chairs: Bernhard Gibbs & Katarzyna Szczepańska</i>
15:30 OP1	THE SEARCH FOR MAO B INHIBITORS AMONG THIOHYDANTOIN DERIVATIVES <u>Dorota Łazewska</u> , Agata Doroz-Płonka, Maria Kaleta, Michalina Biela, Katarzyna Kieć-Kononowicz, Chair of Chemical Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College in Kraków, Medyczna 9, 30-688 Kraków, Poland
15:34 OP2	INTERACTIONS BETWEEN THE HISTAMINERGIC AND OREXINERGIC SYSTEMS IN THE CENTRAL CARDIOVASCULAR REGULATION IN HAEMORRHAGIC HYPOTENSION IN RATS Jasikowska K. ¹ , <u>Gadek A.</u> ¹ , Giuliani D. ² , Ottani A. ² , Guarini S. ² , <u>Jochem J.</u> ¹ ¹ Department of Physiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland; ² Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Sezione di Farmacologia e Medicina Molecolare, Università di Modena e Reggio Emilia, Modena, Italy

15:38 OP3	DUAL CHOLINESTERASE INHIBITION AND HISTAMINE H₃ RECEPTOR ANTAGONISM IMPROVE COGNITION AND REDUCE APOPTOSIS IN A MOUSE MODEL OF SCOPOLAMINE-INDUCED AMNESIA Wajd Ebdah ^{1,2} , Shilu DeepaThomas ^{1,2} , <u>Nermin Eissa</u> ³ , Petrilla Jayaprakash ^{1,2} , Dorota Łazewska ⁴ , KatarzynaKieć -Kononowicz ⁴ and BassemSadek ^{1,2*} ¹ Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates ² Zayed Center for Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates ³ Department of Biomedical Sciences, College of Health Sciences, Abu Dhabi University, Abu Dhabi, United Arab Emirates ⁴ Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University-Medical College, Kraków, Poland
15:42 OP4	SEX-DEPENDENT DIFFERENCES IN NEUROPATHIC PAIN: INSIGHTS FROM FUNCTIONAL METABOLIC PHENOTYPING AND IMMUNOLOGICAL ALTERATIONS <u>Magdalena Maciuszek</u> ¹ , Magdalena Białoń ¹ , Justyna Barut ² , Marta Kamińska ³ , Katarzyna Starowicz ¹ , Natalia Małek ⁴ , Katarzyna Popiolek-Barczyk ¹ ¹ Department of Neurochemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Smetna 12 street, 31-343 Cracow, Poland ² Department of Brain Biochemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Smetna 12 street, 31-343 Cracow, Poland ³ Department of Clinical Science Faculty of Medicine, University of Bergen, Haukelandsveien 28, 5009 Bergen, Norway ⁴ Department of Biological Chemistry and Bioimaging, Faculty of Chemistry, Wrocław University of Science and Technology, 27 Wybrzeże Stanisława Wyspiańskiego st., 50-370 Wrocław, Poland
15:46 OP5	COMBINING OF THE HISTAMINE H₃ RECEPTOR ANTAGONIST ADS1017 WITH ARYLPIPERAZINE FRAGMENTS, TYPICAL FOR 5-HT RECEPTOR LIGANDS. <u>M. Staszewski</u> ¹ , G. Satała ² , E. Böttger ³ , H. Stark ³ , K. Szczepańska ² , T. Karcz ⁴ , A. Bojarski ² , K. Walczyński ¹ ¹ Department of Synthesis and Technology of Drugs, Medical University of Lodz, ul. Muszyńskiego 1, 90-151 Łódź, Poland ² Department of Medicinal Chemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków, Poland ³ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstr. 1, Duesseldorf 40225, Germany ⁴ Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland.
15:50 OP6	RATIONAL DESIGN OF MULTITARGET-DIRECTED LIGANDS TARGETING THE HISTAMINE H₃ RECEPTOR AND FERROPTOSIS PATHWAYS <u>Živkovic, A.</u> ¹ , Gajić, M ¹ , Karacora, B ² , Böttger E ¹ , Janine Beccu ¹ , Carsten Berndt ² , Stark, H ¹ ¹ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstr. 1, Düsseldorf, Germany; ² Department of Neurology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine University, Moorenstr. 5, Düsseldorf 40225, Germany
15:54 OP7	METABOLIC EVALUATION OF HISTAMINE H₃ RECEPTOR ANTAGONISTS IN HUMAN LIVER MICROSOME INCUBATIONS <u>Böttger, E.</u> ¹ , Gajić, M ¹ , Schultes, M ¹ , Krolkowski, P ¹ , Živkovic, A ¹ , Stark, H ¹ ¹ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstr. 1, 40225 Duesseldorf, Germany
15:58 OP8	MECHANISTIC INSIGHTS INTO THE ACTION OF HISTAMINE-FUNCTIONALIZED PLA NANOPARTICLES LOADED WITH 5-FLUOROURACIL AGAINST GASTRIC CANCER CELLS IN VITRO. Patrycja Jaroniek ^{1,2} , Marek Brzeziński ³ , Zuzanna Świniarska ^{2,3} , Magdalena Chmiela ¹ <u>Veronika Gonciarz</u> ^{1,*} ¹ Department of Immunology and Infectious Biology, Institute of Microbiology, Biotechnology and Immunology, Faculty of Biology and Environmental Protection, University of Lodz, Banacha 12/16, 90-237 Lodz, Poland; ² Bio-Med-Chem Doctoral School of the University of Lodz and Lodz Institutes of the Polish Academy of Sciences, University of Lodz, Matejki 21/23, 90-237 Lodz, Poland; ³ Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland;
16:10–16:30	COFFEE BREAK
16:30–17:00	GB WEST LECTURE <i>Chair: Madeleine Ennis</i>
16:30 L4	THE DIVERSE ROLES OF HISTAMINE IN MODULATING COGNITIVE FUNCTIONS AND MAINTAINING INTERNAL BALANCE <u>M. Beatrice Passani</u> Dept. of Health Sciences, University of Florence Italy
17:00–18:50	SESSION II. HISTAMINE, A KEY AMINE <i>Chairs: Pertti Panula & W. Agnieszka Fogel</i>
17:00 L5	HOW THE BRAIN'S HISTAMINE SYSTEM INFLUENCES NEURODEVELOPMENTAL AND NEURODEGENERATIVE DISORDERS <u>Dariusz Szukiewicz</u> Department of Biophysics, Physiology & Pathophysiology, Faculty of Health Sciences, Medical University of Warsaw, 02-004 Warsaw, Poland;

17:30 03	PRENATAL HISTAMINE DEFICIENCY AND THE DEVELOPMENT OF NEURONAL CIRCUITS <u>Ellender, T</u> <i>University of Antwerp (Uantwerpen), Universiteitsplein 1, 2610, Wilrijk, Belgium</i>
17:50 04	THE OVBNST: A NOVEL HISTAMINERGIC SOURCE MODULATING CORTICOSTRIATAL SYNAPTIC TRANSMISSION DURING EARLY POSTNATAL DEVELOPMENT <u>Ricardo Márquez-Gómez</u> ^{1,2} , Yasmin Cras ⁴ , Brenna Parke ³ , Thomas De Backer ⁴ , L. Sophie Gullino ² , Parastoo Hashemi ³ , Tommas Ellender ^{2,4} ¹ Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK Affiliation; ² Department of Pharmacology, University of Oxford, Oxford, UK ³ Department of Bioengineering, Imperial College London, London, UK ⁴ Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium
18:10 05	HISTAMINERGIC ALTERATIONS IN PRECLINICAL MODELS OF ANOREXIA NERVOSA AND BINGE EATING DISORDER: TWO SIDES OF THE SAME COIN? Costa, A. ¹ , Micioni Di Bonaventura, E. ² , Titi, C. ³ , Mottarlini, F. ⁴ , Botticelli, L. ² , Einaudi, G. ² , Passani, M.B. ³ , Cifani, C. ² , Fumagalli, F. ⁴ , Caffino, L. ⁴ , Micioni Di Bonaventura, M.V. ² , <u>Provensi, G</u> ¹ . ¹ Dept. of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy; ² School of Pharmacy, University of Camerino, Camerino, Italy; ³ Dept. of Health Sciences, University of Florence, Florence, Italy. ⁴ Dept of Pharmacological and Biomolecular Sciences “Rodolfo Paoletti”, University of Milan, Italy
18:30 06	PARADOXICAL KINESIA, EMERGENCY STRENGTH, AND DRAMATIC CLINICAL BEHAVIORS, POTENTIAL ROLE OF BRAIN HISTAMINE FROM THE TUBEROMAMMILLARY NUCLEUS <u>David Roeltgen</u> ¹ , James Stellar ² ¹ Neurology, Cooper University Hospital; ² Psychology, University of Albany
20:00	DINNER at the venue restaurant
FRIDAY, 23 OCTOBER 2026	
09:00–11:30	SESSION III. HISTAMINE & IMMUNOLOGY <i>Chairs: Detlef Neumann & Jaroslaw Dastych</i>
09:00 L6	BP1.7881A, THE FIRST DUAL HISTAMINE H₁-H₄ RECEPTOR ANTAGONIST: FROM PRECLINIC TO CLINICAL PHASE 2 STUDIES <u>Ligneau X</u> ¹ , Bayol S ¹ , Calmels TPG ¹ , Rouanet S ¹ , Boudeau A ¹ , Berrebi-Bertrand I ¹ , Delallée N ¹ , Boschat AC ¹ , Robert P ¹ , Labeeuw O ¹ , Duvauchelle T ² , Le Gall M ² , Lecomte JM ² , Schwartz JC ^{1,2} and Finance O ¹ ¹ Bioprojet-Biotech, 4 rue du Chesnay-Beauregard, 35760 Saint-Grégoire, France ² Bioprojet-Pharma, 115 rue d’Aboukir, 75002 Paris, France
09:30 L7	ENLIGHTNING H₁R PHARMACOLOGY USING A FLUORESCENCE-BASED CONFORMATIONAL BIOSENSOR <u>Vischer, H.F.</u> ¹ , Chen, Y. ¹ , Josimovic, I. ¹ , Buzink, M. ¹ , Leurs, R. ¹ ¹ Amsterdam Institute of Molecular and Life Sciences, Division of Medicinal Chemistry, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.
10:00 07	IGE-DEPENDENT HISTAMINE RELEASE FROM HUMAN BASOPHILS IS INVERSELY ASSOCIATED WITH PRODUCTION OF THE ANTI-INFLAMMATORY LIPID MEDIATOR RESOLVIN-D1 Priscilla S. Yowa ¹ , Catarina Rosado ² , Francesca Levi-Schaffer ³ , <u>Bernhard F. Gibbs</u> ² . ¹ Kent and Medway Medical School, Canterbury, UK; ² Life Sciences, Canterbury Christ Church University, Canterbury, UK; ³ School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel.
10:20 L8	FUNCTIONAL ROLES OF MAS-RELATED G PROTEIN-COUPLED RECEPTOR FAMILY IN SCRATCHING <u>Satoshi Tanaka</u> ¹ ¹ Laboratory of Pharmacology, Division of Pathological Sciences, Kyoto Pharmaceutical University
10:50 08	DISCOVERY OF CLOCINIZINE AND ANALOGUES AS POTENT ANTHELMINTIC AGENTS IN VITRO AND IN VIVO Siegl-Breno MA ¹ , Lemes BA ² , Oltramari GP ¹ , Lopes FB ¹ , de Moraes J ² , <u>Fernandes JPS</u> ¹ ¹ Department of Pharmaceutical Sciences, Federal University of São Paulo, Diadema, Brazil; ² Guarulhos University, Guarulhos, Brazil.
11:10 09	STAPHYLOCOCCUS AUREUS A-HEMOLYSIN REPROGRAMS DNA METHYLATION IN HUMAN TH₁ CELLS <u>Marcin Ratajewski</u> <i>Laboratory of Epigenetics, Institute of Medical Biology, Lodz, Poland.</i>

11:30–11:50	COFFEE BREAK
11:50–13:00	SESSION IV. HISTAMINE H₃R ANTAGONISTS <i>Chairs: Holger Stark & Jadwiga Handzlik</i>
11:50 L9	HISTAMINE H₃ ANTAGONISTS – PAST AND FUTURE <u>Carruthers, N.I</u> <i>NDC Medchem Consulting LLC, California, U.S.A.</i>
12:20 010	COMBINED G9A INHIBITION AND HISTAMINE H₃ RECEPTOR ANTAGONISM ENHANCES MEMORY AND ATTENUATES HIPPOCAMPAL OXIDATIVE STRESS IN BTBR MICE <u>Hajar, M</u> ^{1,2} , Jayaprakash, P ^{1,2} , Stark, H ³ , <u>Sadek, B</u> ^{1,2} ¹ Pharmacology and Therapeutics, College of Medicine and Health Sciences, Al Ain, United Arab Emirates; ² Zayed Center for Health Sciences, United Arab Emirates University, AlAin, United Arab Emirates; ³ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
12:40 011	PITOLISANT, A HISTAMINE H₃ RECEPTOR ANTAGONIST/INVERSE AGONIST, REDUCES PAIN HYPERSENSITIVITY AND ALTERS MORPHINE ANALGESIA, ANXIETY-LIKE BEHAVIOUR AND METABOLISM IN A SEX-DEPENDENT MANNER IN A MURINE MODEL OF NEUROPATHIC PAIN. Magdalena Maciuszek ¹ , Magdalena Białoń ¹ , Tomasz Lenda ² , Patrycja Mieszczak ³ , Justyna Barut ³ , Katarzyna Starowicz ¹ , <u>Katarzyna Popiolek-Barczyk</u> ^{1,2} ¹ Department of Neurochemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna 12 Str., 31-343 Krakow, Poland ² CEPHARES, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna 12 Str, 31-343 Krakow, Poland ³ Department of Brain Biochemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna 12 Str, 31-343 Krakow, Poland
13:00 012	EFFECT OF HISTAMINE H₃ RECEPTOR ANTAGONIST/INVERSE AGONIST DL76 ON HISTOPATHOLOGICAL AND MATRIX METALLOPROTEINASE-2 AND -9 EXPRESSION CHANGES IN EXPERIMENTAL PERIODONTITIS IN RATS <u>Geremek, M</u> ¹ , Kruszniewska-Rajs, C ² , Drozdowska, B ³ , Gola, J ² , Łażewska, D ⁴ , Jochem J ⁵ ¹ Public Health Department, Faculty of Public Health in Bytom, Medical University of Silesia in Katowice, 40-055 Katowice, Poland ² Department of Molecular Biology, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia in Katowice, 40-055 Katowice, Poland ³ Department of Pathomorphology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, 40-055 Katowice, Poland ⁴ Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna St, 30-688 Kraków, Poland ⁵ Department of Physiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, 40-055 Katowice, Poland
LUNCHTIME (lunch served in hotel restaurant)	
15:00–16:40	SESSION V. FUTURE DRUGS <i>Chairs: Rob Leurs & Dariusz Matosiuk</i>
15:00 L10	NOVEL MODAFINIL DERIVATIVES TO FIGHT NARCOLEPSY Werner, T ¹ , Krolikowski, P ¹ , Živkovic, A ¹ , <u>Stark, H</u> ¹ ¹ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstr. 1, 40225 Duesseldorf, Germany
15:30 013	RATIONAL DESIGN OF DUAL H₃R/G9A LIGANDS FOR PRADER-WILLI SYNDROME RESEARCH <u>Gajić, M</u> ¹ , Werner, T ¹ , Böttger E ¹ , Cebzan A ² , Djokovic, N ² , Nikolic, K ² , Živkovic, A ¹ , Stark, H ¹ ¹ Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstr. 1, Düsseldorf, Germany; ² Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia
15:50 L11	TOWARDS MULTI-TARGET LIGANDS FOR PAIN THERAPY: DESIGN AND BIOLOGICAL EVALUATION OF COMPOUNDS DIRECTED AT SIGMA-1, HISTAMINE H₃, AND M-OPIOID RECEPTORS <u>Katarzyna Szczepańska</u> ¹ , Tadeusz Karcz ² , Szczepan Mogilski ³ , Wojciech Pietruś ¹ , Maria Dichiarà ⁴ , M. Carmen Ruiz-Cantero ⁵ , Ilona Obara ⁶ , Emanuele Amata ⁴ , Enrique J. Cobos ⁵ , Andrzej J. Bojarski ¹ ¹ Department of Medicinal Chemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland ² Department of Chemical Technology and Biotechnology of Drugs, Jagiellonian University Medical College, Kraków, Poland ³ Department of Pharmacodynamics, Jagiellonian University Medical College, Kraków, Poland, ⁴ Department of Drug and Health Sciences, University of Catania, Catania, Italy, ⁵ Department of Pharmacology and Neurosciences, University of Granada, Granada, Spain, ⁶ School of Pharmacy, Faculty of Medical Sciences, Newcastle University, Newcastle-Upon-Tyne, United Kingdom
16:30	VISITING LODZ
19:00 or 20:00	Gala dinner at the venue restaurant

SATURDAY, 24 OCTOBER 2026

09:00–10:30	HRSE GENERAL ASSEMBLY
10:00–11:00	PTBH GENERAL ASSEMBLY
11:00–11:15	COFFEE BREAK
11:15–13:05	SESSION VI. NEW METHODOLOGIES IN HISTAMINE RESEARCH <i>Chairs: Joao Fernandes & Aleksandra Zivkovic</i>
11:15	NEW METHODS OF LABELING BIOLOGICALLY ACTIVE COMPOUNDS WITH FLUORESCENT AND METALLOCARBONYL TAGS 014 K. Koprowska ^{1,2} , S. Michlewska ³ , M. Gapińska ³ , A. Wrona-Piotrowicz ⁴ , B. Rudolf ⁴ ¹ BioMedChem Doctoral School of University of Lodz and Institutes of Polish Academy of Science, Matejki 21/23, 90-237 Lodz, Poland, ² Medical University of Lodz, Faculty of Pharmacy, Department of Synthesis and Technology of Medicinal Substances, Muszyńskiego 1, 90-151 Lodz, Poland, ³ University of Lodz, Faculty of Biology and Environmental Protection, Banacha 12/16, 90-237 Lodz, Poland ⁴ University of Lodz, Faculty of Chemistry, Department of Organic Chemistry, Tamka 12, 91-403 Lodz, Poland
11:35	PHOTOPHARMACOLOGY OF G PROTEIN-COUPLED RECEPTORS: PROSPECTS AND PITFALLS WITHIN THE HISTAMINE RECEPTOR FAMILY L12 Rob Leurs, AIMMS Drug Discovery Center, Medicinal Chemistry, Vrije Universiteit Amsterdam. r.leurs@vu.nl
12:05	CONCENTRATION- AND ENDPOINT-DEPENDENT RESPONSES OF PRIMARY HUMAN OSTEOBLASTS TO ROSAVIN, A CHARACTERISTIC CONSTITUENT OF RHODIOLA ROSEA 015 Wojdasiewicz, P. ¹ , Wróbel, E. ¹ , Stolarczyk, E.U. ² , Stolarczyk, K. ³ , Mikulska, A. ¹ , Maślińska, M. ⁴ , Turczyn, P. ⁵ , Szukiewicz, D. ¹ ¹ Department of Biophysics, Physiology and Pathophysiology, Faculty of Health Sciences, Medical University of Warsaw, Poland; ² Spectrometric Methods Department, National Medicines Institute, Warsaw, Poland; ³ Faculty of Chemistry, University of Warsaw, Poland; ⁴ Department of Rheumatology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland; ⁵ Department of Early Arthritis, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland
12:25	FROM ONCOGENIC SIGNALING TO CELLULAR CHEMISTRY: RAMAN READOUTS OF FLT3 INHIBITION IN ACUTE MYELOID LEUKEMIA 016 Paulina Laskowska ^{8,1,2} , Sylwia Orzechowska ^{8,3} , Aleksandra Borek-Doroszc ³ , Anna M. Nowakowska ³ , Maciej Szydlowski ¹ , Przemysław Juszczyński ¹ , Małgorzata Barańska ^{3,4} , Piotr Mrówka ^{1,2,5} , Katarzyna Majzner ^{3,4} ¹Department of Experimental Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland ²Biobank, Institute of Hematology and Transfusion Medicine, Warsaw, Poland ³Faculty of Chemistry, Jagiellonian University, Krakow, Poland ⁴Jagiellonian Centre for Experimental Therapeutics (JCET), Jagiellonian University, Krakow, Poland ⁵Department of Biophysics, Physiology and Pathophysiology, Medical University of Warsaw, Warsaw, Poland
	CLOSING REMARKS <i>Presentation of winners of competition for the best presentation & bursaries</i>
14:00	LUNCH
	Cultural EVENT for attendees leaving on Sunday & Monday
	Dinner at the venue restaurant

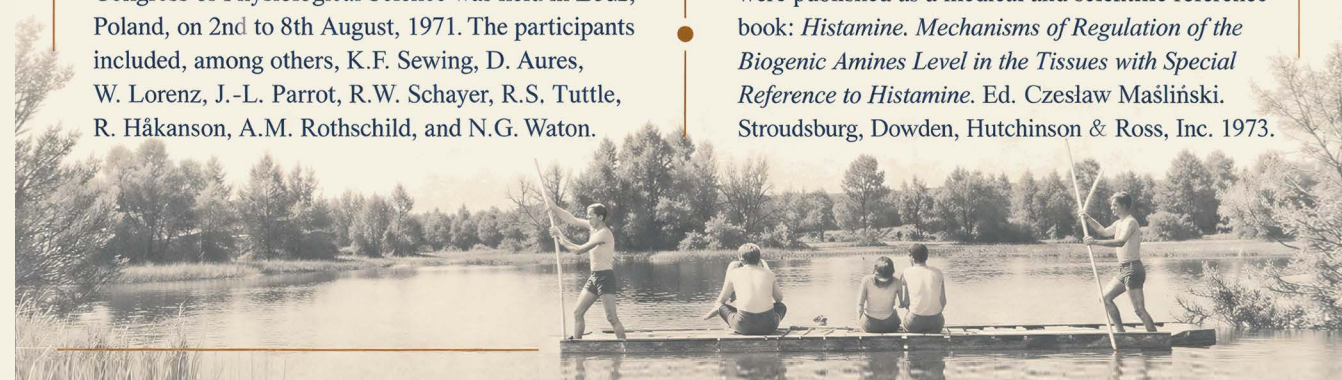


Czesław Maśliński
Founder of the Histamine Club - 1971



Satellite symposium of the XXVth International Congress of Physiological Science was held in Łódź, Poland, on 2nd to 8th August, 1971. The participants included, among others, K.F. Sewing, D. Aures, W. Lorenz, J.-L. Parrot, R.W. Schayer, R.S. Tuttle, R. Håkanson, A.M. Rothschild, and N.G. Waton.

The proceedings for the 1971 Łódź symposium were published as a medical and scientific reference book: *Histamine. Mechanisms of Regulation of the Biogenic Amines Level in the Tissues with Special Reference to Histamine*. Ed. Czesław Maśliński. Stroudsburg, Dowden, Hutchinson & Ross, Inc. 1973.



Lodz hosted European Histaminologists also in the following years



ABSTRACTS

Developmental roles of dopamine in early brain and regeneration

Pertti Panula

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Dopamine plays well known roles in mammalian motor system by modulating the striato-pallido-thalamo-cortical system by nigrostriatal inputs, and in reward system through the ventral tegmental inputs to nucleus accumbens.

Much less understood are the effects dopamine has on neural stem cells, neuronal migration, synaptogenesis and regeneration.

In a series of studies, we have used zebrafish to establish the roles of dopamine in differentiation of transmitter specific populations using translation inhibition, CRISPR/Cas methodology to produce mutant fish lines, in situ hybridization, immunocytochemistry and high-resolution microscopy.

Zebrafish possess two tyrosine hydroxylase genes, th1 and th2, both of which produce dopamine in distinct complementary cell groups. Translation inhibition of th2, but not th1, increased the number of histaminergic and hypocretin neurons in developing zebrafish.

Application of L-DOPA or dopamine receptor agonists increased the number of histamine neurons in developing brain. These results suggest that dopamine restricts the number of histamine and hypocretin neurons during development.

In developing zebrafish brain, dopaminergic axons expressing th1 extend to the spinal cord at the same time as the primary motor neurons

develop in the anterior horn. Translation inhibition of th1 mRNA reduced the number of motor neurons, and dopamine promoted generation of spinal motor neurons in the lesioned spinal cord of adult zebrafish.

Factors affecting development of dopaminergic neurons are of high interest, because these neurons degenerate in Parkinson's disease.

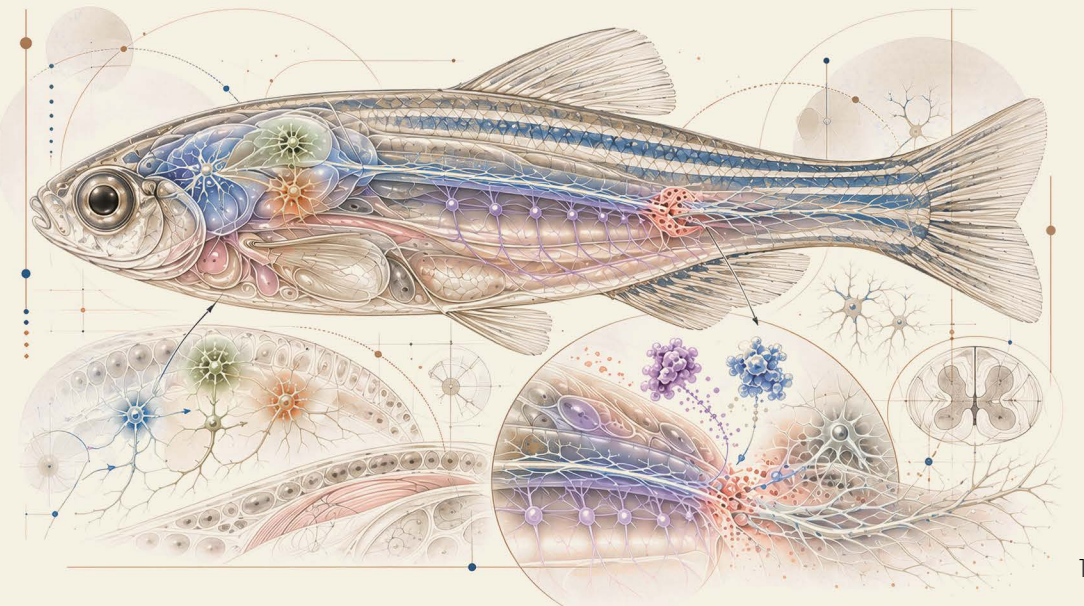
Mesencephalic astrocyte derived neurotrophic factor (MANF) is recognized as a dopaminergic neurotrophic factor, which can protect dopaminergic neurons from neurotoxic damage.

We showed that in zebrafish brain, translation inhibition of MANF decreased expression of both th1 and th2 mRNA, and numbers of neurons in distinct cell populations in developing brain. These effects were compensated by coinjection of MANF mRNA.

In contrast, a mutant zebrafish lacking cerebral dopamine neurotrophic factor (CDNF) showed no decline in th1 or th2 expression, although numbers of dopaminergic neurons in some nuclei were abnormal.

The numbers of histamine and hypocretin neurons in the brains of *cdnf*^{-/-} zebrafish were abnormally low.

The results show that dopamine has distinct roles in brain development and damage repair, and known trophic factors which rescue dopamine neurons from toxin effects also regulate development of dopamine neurons.

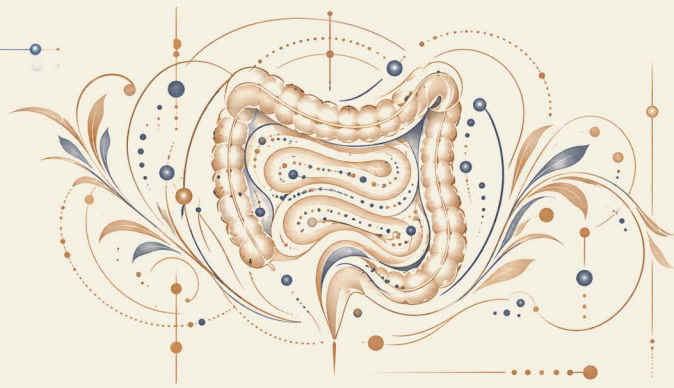


Dopamine in the gut

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For more than half a century, dopamine has been regarded primarily as a neurotransmitter of the central nervous system, shaping movement, motivation, reward, and cognition. Within the gastrointestinal tract, its role has traditionally been viewed through a similarly narrow lens—as a local regulator of motility and secretion.

Recent advances reveal that dopaminergic system in the gut extends far beyond the enteric nervous system.

Dopamine is produced locally by multiple cellular sources and acts on an unexpectedly broad repertoire of target cells, including epithelial cells, intestinal stem cells, immune cells, endothelial cells, and neurons.

This evolving concept positions dopamine as a key regulator of gut homeostasis. It contributes to epithelial barrier maintenance, regulates mucosal immunity, shapes inflammatory responses, influences tissue regeneration and wound healing, modulates vascular function, and participates in bidirectional communication with inte-

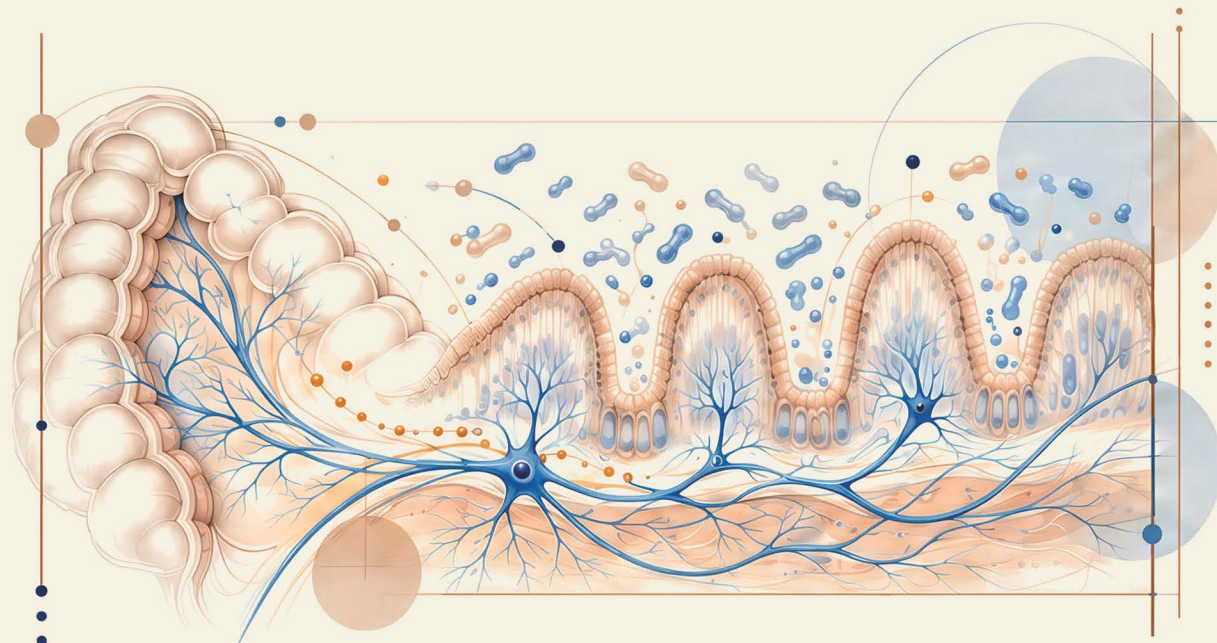
stinal microbiota.

Through these diverse actions, dopamine links neural, immune, epithelial, microbial, and metabolic pathways into a dynamic regulatory network that maintains intestinal homeostasis and adapts to physiological stress and metabolic state of the host.

This emerging biology of dopamine raises new fundamental questions, and these questions signal more than incremental progress—they represent a conceptual shift.

Understanding this expanded biology of gut dopamine may in the future redefine therapeutic strategies for inflammatory bowel disease, functional gastrointestinal disorders, colorectal cancer, metabolic diseases, and even disorders involving the gut-brain axis.

The future of gut dopamine research is therefore not simply about understanding another neurotransmitter; it is about uncovering a previously underappreciated dopaminergic homeostatic network.



The psychedelic 5-methoxy dimethyltryptamine (5-MeO-DMT) counteracts behavioral consequences of chronic restrained stress while inducing distinct brain organization of neurotransmission systems

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Aims: 5-Methoxydimethyltryptamine (5-MeO-DMT) is a psychedelic that acts on serotonergic receptors. Like other psychedelics, it induces rapid and long-lasting antidepressant/anxiolytic effects after acute administration, and it has the advantage of producing short-lived hallucinogenic effects.

The neurobiological mechanisms underlying these effects are still poorly understood but are thought to involve monoaminergic systems. We hypothesized that 5-MeO-DMT attenuates persistent behavioral deficits following chronic stress by reorganizing monoaminergic (dopamine, norepinephrine, serotonin) and amino acid (GABA, glutamate, aspartate) systems in the brain.

Materials and Methods: Half of a cohort of male C57BL/6J mice was subjected to a chronic restraint stress protocol (2-h during 3 weeks). One week later, the animals received 5-MeO-DMT (5 mg/kg intraperitoneally) or its vehicle (3% DMSO in saline).

Thereafter, the animals were evaluated in behavioral tests (one/day) during 4 days: forced swim test, tail suspension test, sucrose preference test, elevated O-maze. One day after the last behavioral assessment, animals were sacrificed by cervical dislocation.

Their brain was collected to performed neurochemical measurements in 18 brain regions using high pressure liquid chromatography coupled with electrochemical detection.

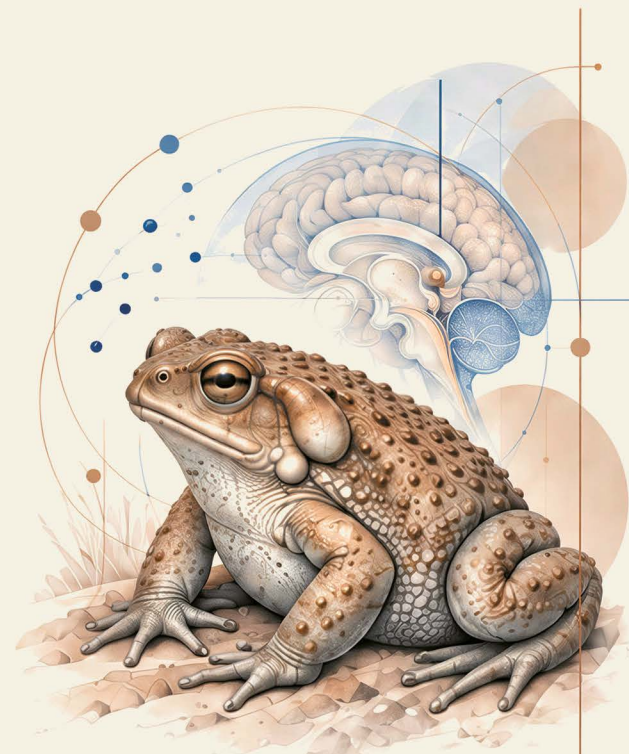
Results: Male C57BL/6J mice subjected to chronic restraint stress showed behavioral deficits in all tests. 5-MeO-DMT, with no effect on its own, reduced stress-induced behavioral deficits, except for anxiety-like behavior.

Stress increases tissue levels of several neurotransmitters (or metabolites) in the prelimbic cortex and, to a lesser degree, in some regions, including the dorsolateral striatum. 5-MeO-DMT,

which reduces neurotransmitters in the ventral tegmental area, mitigates some, but not all the neurochemical effects induced by stress, and promotes new ones like in the orbitofrontal cortex.

A novel neurochemical organization arising from the combination of stress and 5-MeO-DMT is also supported by the analysis of interregional correlations of compounds across the brain. This analysis shows that the correlation profiles for a given compound differ across the four groups.

Conclusion: Chronic stress induces persistent behavioral alterations and regional remodelling of neurotransmission systems, while 5-MeO-DMT would correct these deficits by modifying the organization of neurotransmission systems.



Effects of psychedelic drugs such as psilocybin are enhanced by mGlu_{2/3} glutamate receptor antagonists, improving therapeutic effectiveness and reducing adverse effects.

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Background: Hallucinogenic compounds from various pharmacological classes, such as ketamine or scopolamine, demonstrate rapid and long-lasting antidepressant effects, often after a single dose, in both preclinical and clinical studies.

Although these compounds differ in their primary mechanisms of action (glutamatergic or cholinergic system), they appear to share secondary mechanisms, including modulation of glutamatergic transmission.

Our own studies have shown that group 2 metabotropic receptor antagonists (the mGlu_{2/3} receptor antagonist LY341495 and the mGlu₂ receptor negative modulator VU6001966) potentiate the antidepressant effects of both ketamine and scopolamine [1,2]. Importantly, combined administration of mGlu_{2/3} receptor modulators with hallucinogens allows for significantly lower doses and reduces adverse effects.

Aims: Our studies aimed to investigate whether similar interactions occur between psilocybin and mGlu₂ receptor antagonists.

Materials and Methods: The antidepressant-like effects were evaluated in mice using the tail suspension test. The head twitch response was used as a measure of hallucinogenic-like behavior.

Changes in phosphorylation of AMPA receptors (GluA1 subunit at serine 831) and ERK1/2 protein in the prefrontal cortex of naive mice and in the morphology of dendritic spines were also evaluated.

Results: Our results demonstrate that a single, subeffective dose of LY341495 significantly enhances the antidepressant-like effects of psilocybin in the tail suspension test in naive mice.

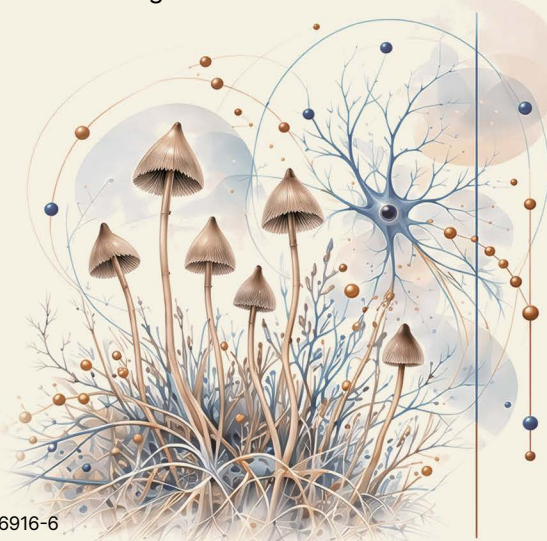
The effect is rapid (1 h) and long-lasting (3 and

7 days). Co-administration of LY341495 also affects the psilocybin-induced head twitch response, suggesting a potential reduction of side effects.

These behavioral outcomes are further correlated with time-dependent (at 10 min, 1 h, 24 h, and 3 days) changes in phosphorylation of AMPA receptors (GluA1 subunit at serine 831) and ERK1/2 protein in the prefrontal cortex of naive mice. A significant increase in the activity of both signaling molecules coincides with changes in dendritic spine morphology 3 days after co-administration of psilocybin and LY341495.

Conclusion: Targeting two distinct neurotransmission systems with two substances administered at lower doses may reduce the likelihood of adverse effects while enhancing therapeutic efficacy, thereby achieving a more optimal balance between safety and effectiveness.

This co-administration approach seems to better address the multifaceted nature of depression, potentially improving treatment outcomes while minimizing undesired effects.



References:

1. Podkowa, K, et al., Psychopharmacology, 2016, 233/15-16, 2901-14
2. Babii Y et al., Psychopharmacology, 2025, DOI: 10.1007/s00213-025-06916-6

Acknowledgements:

This research was funded by the National Science Center, Poland, under grant number 2023/49/B/NZ7/02978, awarded to Andrzej Pilc.

Multitarget action of 1,3,5-triazine 5-HT₆ receptor agents in search for new therapies of Alzheimer's disease.

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Background: Current Alzheimer's disease (AD) pharmacotherapy improves memory and cognitive functions of patients but cannot inhibit progressive neurodegeneration, requiring multitarget approaches.

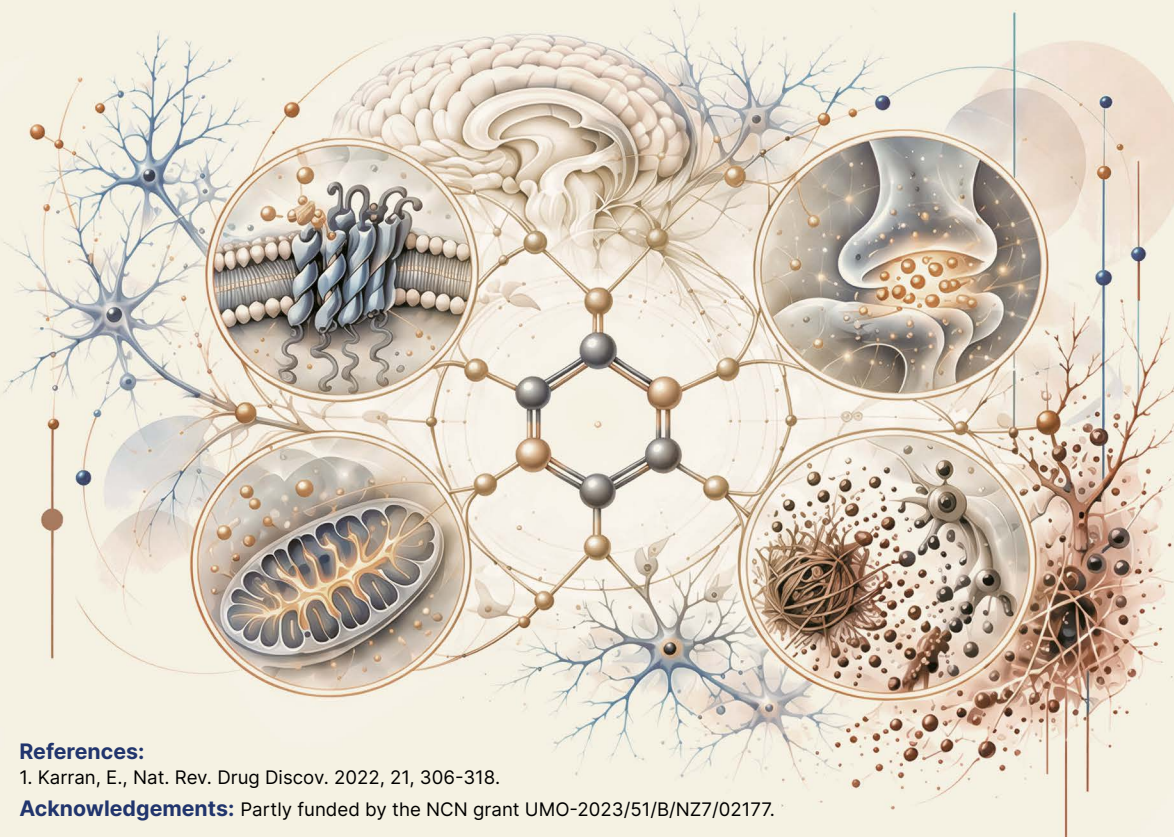
The 5-HT₆ receptor modulation can simultaneously cover several hypotheses postulated for successful AD therapy [1], but none of 5-HT₆R antagonists has passed Phase III of clinical trials, indicating too narrow, indole and sulfone-containing structural variety, responsible for the defeat.

Aims: Based on the scaffold developed for H₄-histamine receptor antagonists, an identification of original, non-indole and non-sulfo-

ne,1,2,3-triazine 5-HT₆R ligands, followed by rational pharmacomodulation to extend 5-HT₆R selective- to multitarget action, was the aim of this study.

Materials and Methods: Rational design, chemical synthesis and pharmacological screening were used.

Results and Conclusions: New 1,3,5-triazine 5-HT₆R agents, also inhibiting necroptosis kinase or regulating neuroprotection transcription factors, have been found. Favorable pharmacodynamic and pharmacokinetic profile of the "hits" found offers prospects for improving AD therapy.



References:

1. Karran, E., Nat. Rev. Drug Discov. 2022, 21, 306-318.

Acknowledgements: Partly funded by the NCN grant UMO-2023/51/B/NZ7/02177.

The search for MAO B INHIBITORS among thiohydantoin derivatives

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Background: Monoamine oxidase B (MAO B) is the predominant isoform in the human brain. MAO B catalyses the oxidative deamination of β -phenylethylamine, which stimulates the release of dopamine and inhibits its reuptake by neurons. In the human brain, MAO B activity increases with age and is elevated in certain neurodegenerative diseases, such as Parkinson's disease (PD) [1].

Currently, three MAO B inhibitors, i.e. selegiline, rasagiline and safinamide, are used for the symptomatic treatment of PD. As part of the screening of thiohydantoin derivatives synthesised at Chair of Chemical Technology and Biotechnology of Drugs UJCM, compound ChM6 (2-((Z)-3-chlorobenzylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one) showed promising ability to inhibit human MAO B (hMAO B) with an IC₅₀ of 50 nM.

Aim: A search for new hMAO B inhibitors among imidazothiazines. Compound ChM6 was chosen as the lead structure. Plans have been made to replace the chlorine with other substituents (F, Br, CH₃, OCH₃), to introduce a second substituent, and to change the position of the substituent(s) on the phenyl ring.

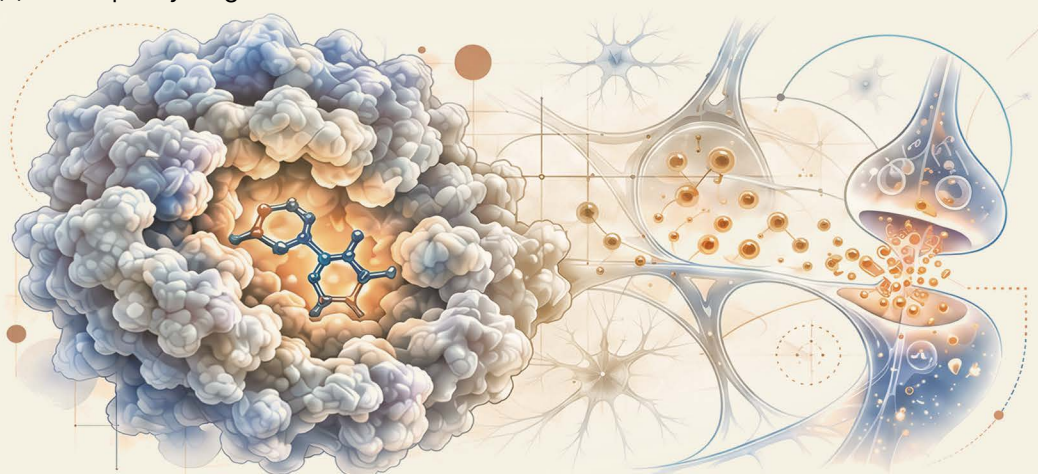
Materials and Methods: The target compounds were obtained by Knoevenagel condensation of the corresponding aldehydes with 2-thiohydantoin, followed by cyclisation with dibromopropane.

The ability to inhibit hMAO B was determined using a spectrometric assay with Amplex Red as the indicator. First, all compounds were tested at a concentration of 1 μ M to assess their ability to inhibit MAO B activity. Compounds that demonstrated more than 50% inhibition in two independent assays were subjected to further testing (at various concentrations) to calculate the IC₅₀ values.

Results: The results showed that the compounds exhibited variable ability to inhibit hMAO B activity.

Many compounds demonstrated good hMAO B inhibitory activity with IC₅₀ values below 450 nM. SAR analysis revealed that the activity depended on the type of substituent(s) introduced and its/their position on the phenyl ring.

Conclusion: Imidazothiazines are promising hMAO B inhibitors, but further experimental studies are necessary to assess their full therapeutic potential in PD.



References: [1] Tan, Y.Y.; Jenner, P.; Chen, S.D. Monoamine Oxidase-B Inhibitors for the Treatment of Parkinson's Disease: Past, Present, and Future. *J. Parkinsons Dis.* 2022, 12, 477–493.

Acknowledgements: This research was supported by Jagiellonian University Medical College in Kraków grant no N42/DBS/.....

INTERACTIONS BETWEEN THE histaminergic AND orexinergic systems in the CENTRAL CARDIOVASCULAR REGULATION in haemorrhagic hypotension in rats

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Background: The histaminergic and orexinergic neuronal systems are able to influence the central cardiovascular regulation, and both histamine and orexin A (OXA) administered intracerebroventricularly (icv) evoke a long-lasting pressor effect in rats subjected to haemorrhagic hypotension (1-2).

Aim: The study was undertaken to examine possible functional interactions between the central histaminergic and orexinergic systems in cardiovascular regulation in haemorrhagic hypotension.

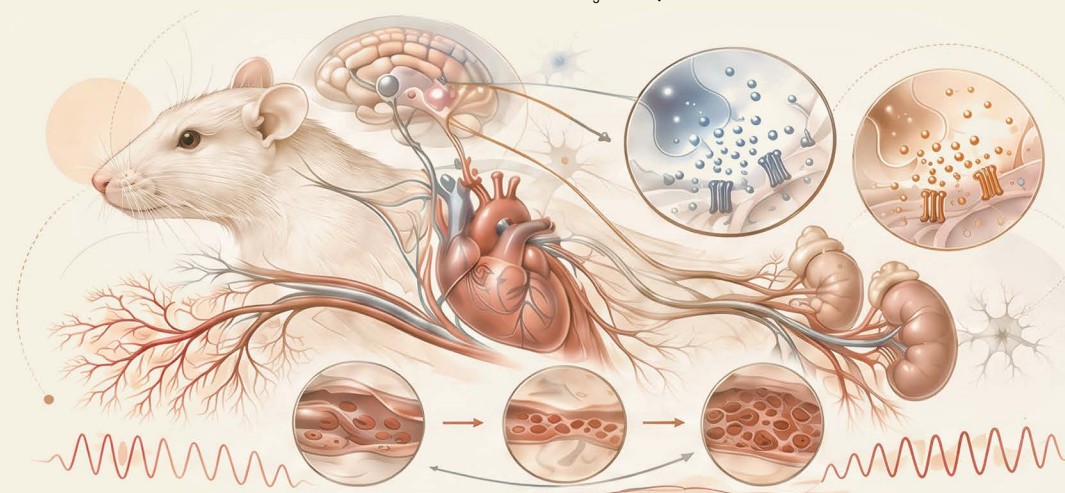
Materials and Methods: Studies were carried out in anaesthetized with ketamine/xylazine (100 mg/kg + 10 mg/kg, intraperitoneally) male Wistar rats subjected to a reversible haemorrhagic hypotension with mean arterial pressure (MAP) 30-35 mmHg.

Immediately after bleeding termination, the animals were pre-treated icv with histamine receptor antagonists or saline, and 5 min later – treated icv with OXA (1.5 nmol) or saline.

Results: Haemorrhagic hypotension was accompanied by decreases in pulse pressure (PP), heart rate (HR) and mesenteric blood flow (MBF). OXA induced increases in MAP and MBF, with no significant influence on PP and HR, as compared to the control saline-treated group. Pre-treatment with both H₁ receptor antagonist chlorpheniramine (50 nmol) and H₃ receptor blocker VUF 5681 (25 nmol) reduced OXA-induced increases in MAP and MBF, as measured 20 min after treatment and did not influence PP and HR.

There were no effects of H₂ and H₄ receptor antagonists ranitidine (50 nmol) and JNJ 10191584 (25 nmol), respectively, on OXA-mediated cardiovascular changes. Histamine receptor antagonists given alone did not influence measured haemodynamic parameters.

Conclusion: There are functional interactions between the histaminergic and orexinergic neuronal systems in the central cardiovascular regulation in haemorrhagic hypotension, and H₁ and H₃ receptors are involved.



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[1] Jochem J. *Naunyn-Schmiedeberg's Arch Pharmacol* 2004, 369(4), 418–27.

[1] Jochem J, Zwirska-Korczala K, Zabielski R, Kato I, Kuwahara A. *J Physiol Pharmacol* 2006, 57(Suppl 11),115–24.

Dual cholinesterase inhibition and histamine H₃ receptor antagonism improve cognition and reduce apoptosis in a mouse model of scopolamine-induced amnesia

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Background: Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with cholinergic dysfunction, neuroinflammation, oxidative stress, and neuronal loss.

Histamine H₃ receptor (H₃R) antagonists enhance the release of several neurotransmitters, including acetylcholine, making dual modulation of H₃R and cholinesterase an attractive multitarget therapeutic strategy.

Aims: To investigate the cognitive-enhancing and neuroprotective effects of E100, a dual-active histamine H₃ receptor antagonist and cholinesterase inhibitor, in a mouse model of scopolamine-induced amnesia.

Materials and Methods: Male C57BL/6 mice received scopolamine (2 mg/kg, i.p.) to induce cognitive impairment. E100 (5, 10, or 15 mg/kg, i.p.) was evaluated against donepezil and pitolisant.

Cognitive performance was assessed using the Novel Object Recognition, Y-Maze, Three-Chamber, Fear Conditioning, and Elevated Plus Maze tests.

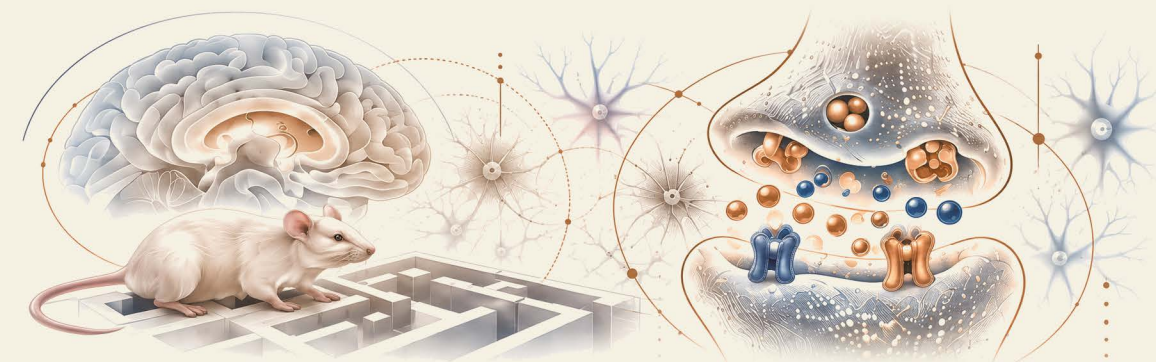
Hippocampal and cerebellar tissues were analyzed for acetylcholinesterase activity, oxidative stress markers (GSH, SOD, MDA), pro-inflammatory cytokines (TNF- α and IL-1 β), and

caspase-1 activity. Histaminergic involvement was confirmed using the selective H₃R agonist (R)- α -methylhistamine (RAMH).

Results: E100 produced dose-dependent improvements in recognition, spatial, associative, and social memory, with the 10 mg/kg dose showing optimal efficacy comparable to donepezil and pitolisant. E100 also alleviated anxiety-like behavior in scopolamine-treated mice.

Biochemically, E100 significantly reduced acetylcholinesterase activity, suppressed TNF- α and IL-1 β production, restored antioxidant defenses by increasing GSH and SOD while reducing MDA, and decreased caspase-1 activity, indicating reduced apoptosis. Co-administration of RAMH attenuated the cognitive benefits of E100, confirming the critical contribution of H₃ receptor antagonism to its mechanism of action.

Conclusion: Dual targeting of histamine H₃ receptors and cholinesterase effectively improves cognitive function while attenuating neuroinflammation, oxidative stress, and apoptosis in experimental amnesia. These findings support H₃ receptor antagonism combined with cholinesterase inhibition as a promising multitarget therapeutic strategy for Alzheimer's disease and other neurodegenerative disorders.



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[3] Sharma, K., Eur. J. Med. Chem. 2019, 180, 238–261.

Sex-dependent differences in neuropathic pain: insights from functional metabolic phenotyping and immunological alterations

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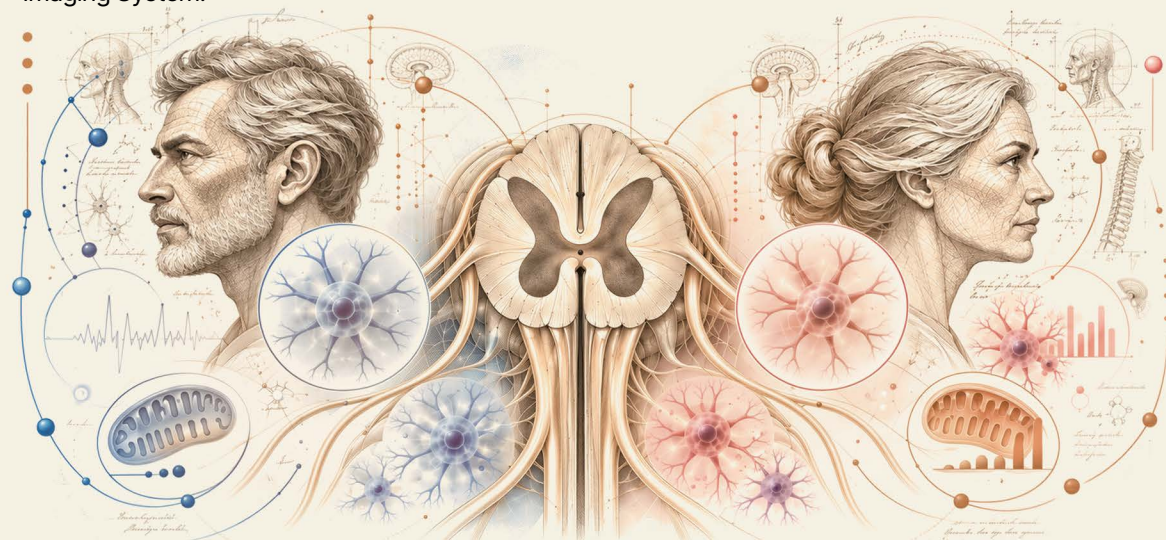
Background: Sex is recognized as a significant biological variable in chronic neuropathic pain. Emerging evidence suggests that neuroimmune interactions contribute substantially to sex-related differences in pain mechanisms.

Aims: The aim of this study was to identify sex-dependent differences in metabolic and immunological responses in the spinal cord of neuropathic mice.

Materials and Methods: Neuropathic pain was induced via chronic constriction injury (CCI) of the sciatic nerve in male and female mice. Fourteen days post-surgery, animals were monitored in Promethion metabolic cages for 24 hours. Parameters assessed included oxygen consumption (VO₂), carbon dioxide production (VCO₂), respiratory exchange ratio (RER), energy expenditure (EE), and locomotor activity. Spinal cord immunoprofiles were evaluated using the Hyperion Imaging System.

Results: Neuropathic males exhibited a reduced RER compared to naive controls, while no change was observed in females. Females showed lower EE in both naive and CCI groups. Furthermore, CCI females displayed decreased sleep time compared to naive. Locomotor activity remained unchanged across all groups. Preliminary immunological analyses indicated reduced GFAP (astrocyte marker) expression in CCI females, whereas CCI males exhibited increased GFAP levels. IBA1 (microglial marker) levels were elevated in both sexes following CCI. Furthermore, we demonstrated that naive males exhibit increased expression of the histamine H₃ receptor. In addition, CCI induces an increase CCI females compared to naive females, while a decrease is observed in CCI males.

Conclusion: These data reveal sex-dependent differences in metabolic and immunological responses in neuropathic mice, emphasizing the necessity for sex-specific approaches in the development of pain therapies.



Acknowledgements: Work was financed by a grant from the National Science Centre, Poland, SONATA 2019/35/D N27/01042, OPUS 2023/49/B/N27/02172.

Combining of the histamine H₃ receptor antagonist ADS1017 with arylpiperazine fragments, typical for 5-HT receptor ligands.

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Aim: The histamine H₃ receptor (H₃R), mainly localized in the CNS, constitutes a useful drug target for multiple central nervous system disorders, with exhibiting anxiolytic-like or antidepressant effects. As a heteroreceptor, H₃R controls the release of various neurotransmitters, including serotonin. There are a few articles describing H₃R ligands simultaneously targeting 5-HT_{1A} or 5-HT_{2A} receptors as an innovative option for treating depressive and psychotic disorders.

The multipotent profile might constitute a therapeutic approach for various neurodegenerative diseases.

The ADS1017 has been previously described as the H₃R antagonist/inverse agonist. In this study, we have combined the ADS1017 core with some arylpiperazine fragments to evaluate their influence on the selected 5-HT receptor subtypes.

Materials and Methods: All newly synthesized compounds were evaluated ex vivo as H₃R antagonists/inverse agonists on the guinea pig ileum (gpH₃R). To determine their inhibition constants (K_i), the compounds were also tested in competition binding experiments using membranes from HEK293 cells stably expressing the human 5-HT_{1A} receptor and CHO-K1 cells expressing

the human 5-HT_{2A} receptor. Derivatives with the highest potency were subjected to the human H₃R radioligand displacement assay.

Results and Conclusions: All tested compounds showed low to moderate affinity at gpH₃R. Then, all compounds were tested for their affinity at 5-HT_{1A} and 5-HT_{2A} receptors. The substitution of the phenyl ring in the direction from position 2 to 4 increased the affinity at H₃R as expected, while such substitution decreased the affinity at serotonin receptors. This is consistent with knowledge regarding the design of H₃R and 5-HT receptor ligands.

This did not allow us to find an optimal solution and a derivative with promising activities for both receptors.

The pA₂=7.46 at the gpH₃R of UM-MSt337 designed by a combination of the guanidine-containing part of ADS1017, with the benzylpiperazine fragment, constitutes the compound with the highest affinity in this series. K_i=62.19 nM at the hH₃R of UM-MSt316 designed by a combination of phenoxyheptylpiperazine fragment of ADS1017 showed the highest affinity at hH₃R. Unfortunately, both compounds showed low activity towards serotonin receptors.



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Acknowledgements: This work was founded by the Medical University of Lodz, grant number 503/3-016-01/503-31-001.

Rational design of multitarget-directed ligands targeting the histamine H₃ receptor and ferroptosis pathways.

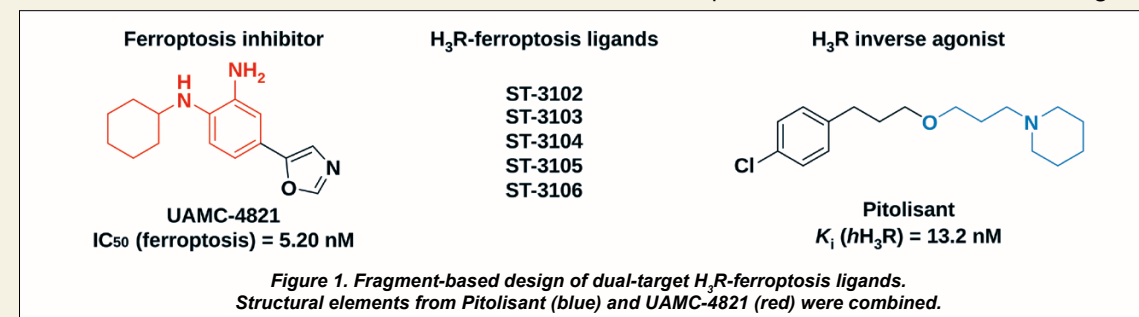
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Background: Ferroptosis, an iron-dependent form of regulated cell death, has been increasingly detected to be implicated in neurodegenerative disorders.

of Pitolisant, the clinically approved H₃R inverse agonist[2], with fragments derived from the potent ferroptosis inhibitor UAMC-4821[1] (Fig. 1).



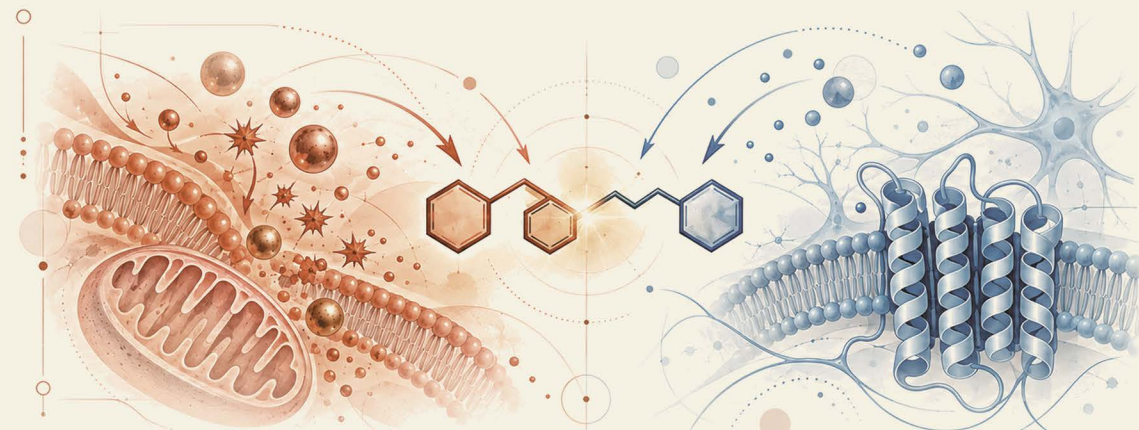
tive disorders.[1] The histamine H₃ receptor (H₃R) modulates the release of multiple neurotransmitters and plays an important role in wakefulness, cognition, and neuroprotection.[2] Despite the therapeutic significance of both targets, the potential synergistic relationship between H₃R modulation and ferroptosis regulation remains largely unexplored.

Aims: Design, synthesis, and evaluation of a small focused library derivatives based on structural motifs of H₃R ligands and ferroptosis inhibitors.

Materials and Methods: A knowledge-based hybrid design approach combined structural motifs

Results: Among the newly synthesized compounds, ST-3104 and ST-3106 demonstrated high H₃R affinity, with K_i values of 266 nM and 85 nM, respectively, and showed minor inhibitory effects on ferroptosis in mouse embryonic fibroblasts.

Conclusion: This work establishes proof-of-concept for the rational design of hybrid molecules targeting H₃R and ferroptosis-related pathways. The obtained compounds demonstrated high H₃R affinities, whereas further optimization is needed to improve ferroptosis inhibition and achieve balanced dual-target activities.



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[2] Panula, P et al., *Pharmacol Rev* 2015, 67(3), 601-655.

Metabolic evaluation of histamine H₃ receptor antagonists in human liver microsome incubations.

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Background: Early H₃R ligands were structurally derived from histamine and retained its imidazole ring; however, this moiety was later found to inhibit cytochrome P450 enzymes through complexation of the imidazole nitrogen with the heme-iron in the enzyme active site, thereby creating a substantial drug-drug interaction liability.

This finding is part of a shift toward non-imidazole scaffolds, which offered improved binding affinity, enhanced CNS penetration, and reduced potential for CYP450 inhibition.

The phenoxypropylpiperidine motif emerged from this effort as an advantaged non-imidazole core, demonstrating potent, selective H₃R antagonism and in vivo efficacy at low doses.

Sex is a further variable relevant to metabolic screening: in humans, sex differences in drug metabolism reflect the female-predominant expression of CYP3A4, the most important P450 catalyst of drug metabolism in human liver, whereas CYP1A2 shows higher protein abundance and activity in male-derived liver microsomes.[1–4]

Aims: The evaluation of a broad library of H₃R ligands in terms of pharmacokinetics and CYP-enzyme inhibition.

Materials and Methods: A broad library of phenoxypropylpiperidine derivatives was synthesized with modifications in the arbitrary region. The compounds were evaluated for H₃R binding affinity.

Highly affine H₃R antagonists were subsequently subjected to a microsomal stability assay using male and female human liver microsomes (HLMs) and NADPH as a cofactor.

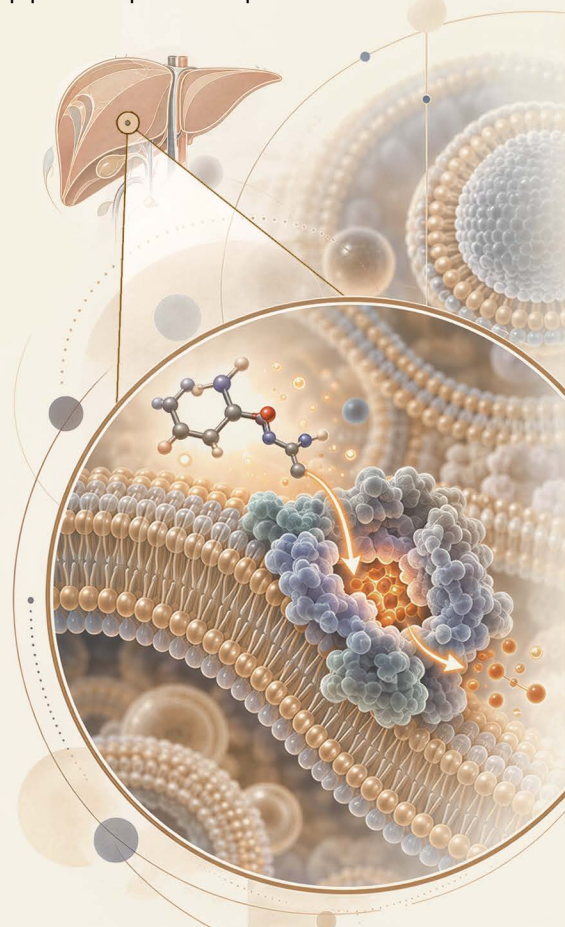
Quantification was performed via LC-MS. For selected candidates the identification of the responsible CYP-enzyme for metabolization and potential CYP-inhibition was examined.

References:

- [1] Ghamari, N et al., Pharmacol Ther 2019, 200, 69–84.
- [2] Yang, R et al., Pharmacol 2002, 66 (3), 128–135.
- [3] Fuscoe, J C et al., Drug Metab Dispos 2020, 48 (6), 447–458.
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Results: Among the compounds, modest difference in stability towards HLMs was displayed. Microsomal stability studies confirmed metabolic stability in human liver microsomes with negligible sex-dependent differences and predominant CYP3A4-mediated metabolism.

Conclusion: Human liver microsome incubations are a suitable tool for metabolic stability screening of H₃R antagonists. Stability of various ligands is in a comparable range proving the pharmacokinetic benefit of the phenoxypropylpiperidine pharmacophore.



Mechanistic insights into the action of histamine-functionalized PLA nanoparticles loaded with 5-fluorouracil against gastric cancer cells *in vitro*.

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Background: Gastric cancer is among the leading causes of cancer-related deaths worldwide.

Modern treatment approaches include nanoparticles (NPs) designed to target cancer cells, release a therapeutic cargo facilitating inhibition of their expansion, thereby improving anti-tumor therapies.

The success of NPs, created to deliver anti-cancer agents and biologically active compounds, may depend on selecting the way to target cancer cells.

Aims: This study focused on examining the effects of NPs made of polylactic acid (PLA) with histamine (His) end groups and loaded with 5-fluorouracil (5-FU), a known anti-cancer drug (PLA-His-5-FU), towards human gastric cancer AGS cells *in vitro*.

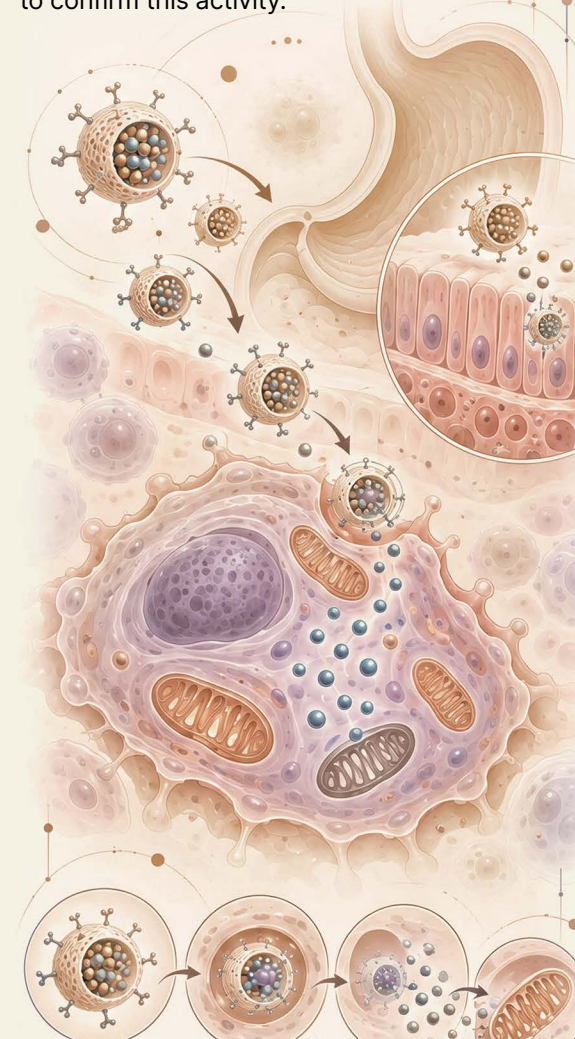
Materials and Methods: AGS gastric cancer cells were stimulated for 24h or 72h in a medium containing *Helicobacter pylori* antigen alone, NPs alone or in combination: *H. pylori* antigen and NPs.

Results: Incubation of AGS cells with NPs PLA-His-5-FU resulted in diminished membrane mitochondrial potential and induction of cell apoptosis, along with cell cycle arrest and reduction of cell proliferation.

Furthermore, NPs tested provoked secretion of pro-inflammatory cytokines: tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β by AGS cells and induced activation of nuclear factor alpha B (NF-κB) signaling pathway in THP-1 blue monocytes, indicating the ability to promote the development of a milieu for infiltration and activation of immunocompetent cells.

NPs did not increase intracellular adhesion molecules (ICAM-1) deposition on AGS cells, thus potentially preventing the distribution of cancer cells.

Conclusion: The PLA-His-5-FU NPs show a promising anti-cancer activity towards gastric cancer cells AGS *in vitro*, better than PLA-OH-5-FU and can be used for further *in vivo* studies to confirm this activity.



The **diverse roles** of **histamine** in modulating **cognitive functions** and maintaining **internal balance**.

M. Beatrice Passani

Dept. of Health Sciences, University of Florence Italy

Nature has evolved physiological mechanisms that optimise homeostatic regulation and behavioural responses, enabling organisms to survive in constantly changing environmental conditions.

For example, mammals possess multiple lipid-sensing systems distributed throughout the body that communicate information about energy status and the palatability of food to the central nervous system.

In turn, neural circuits centred in the hypothalamus and modulated by several neurotransmitters coordinate the behavioural and physiological responses required to maintain energy balance during both food abundance and scarcity.

This intricate bidirectional communication between peripheral organs and the central nervous system forms the gut-brain axis, which integrates peripheral metabolic signals with emotional and cognitive brain centres.

Within this framework, histamine, a phylogenetically ancient biogenic amine found in invertebrates, reptiles, and mammals, plays a central role in the regulation of metabolic homeostasis, energy metabolism, and food intake. In peripheral tissues, histamine released by mast cells, other immune cells, and microorganisms residing in the gastrointestinal tract influences metabolic processes involved in energy balance as well as nutrient absorption.

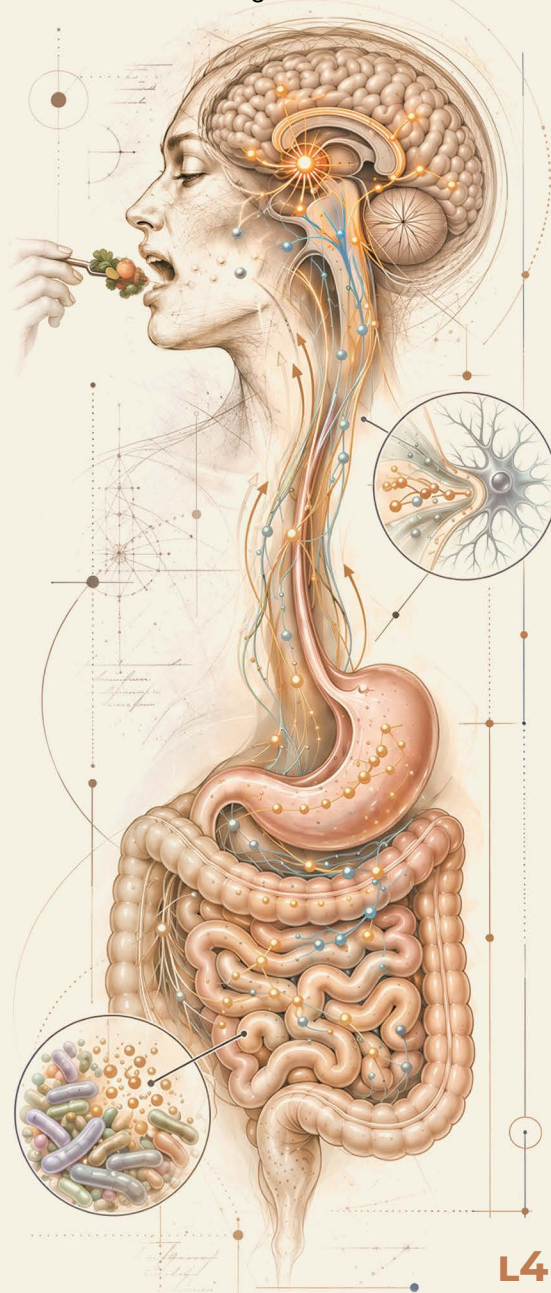
In the central nervous system, hypothalamic histaminergic neurons exert a broad range of effects.

Histaminergic signalling is essential for motivated behaviours by regulating arousal during goal-directed activities, supports learning and memory, and modulates behavioural responses to stress.

The diversity of these functions is likely achieved through the selective activation of distinct neuronal circuits. Consequently, histamine is uniquely positioned to influence multiple components of the energy-regulatory network, ultimately shaping foraging strategies and feeding behaviour.

In this review, I examine the role of histamine as a neurotransmitter, a peripheral modulator, and a metabolite produced by intestinal microorganisms in the regulation of energy intake, energy

expenditure, and eating behaviour. I also discuss the contribution of histamine to gut-brain axis signalling and explore its implications for physiological regulation, as well as its involvement in metabolic and neurological disorders.



L4

How the **brain's histamine system** influences **neurodevelopmental** and **neurodegenerative disorders**.

Dariusz Szukiewicz

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Histamine (HA) is a natural compound that performs many different functions in the body.

It works by binding to four specific receptors H1R through H4R, all of which are present in the brain.

Together, histamine and the nerve fibers projecting from the tuberomammillary nucleus (TMN)—which reach almost all brain areas—make up the histaminergic system.

Thus, while remaining a mediator of the inflammatory reaction and immune system function, HA also acts as a neurotransmitter and a modulator of other neurotransmitter systems in the central nervous system (CNS).

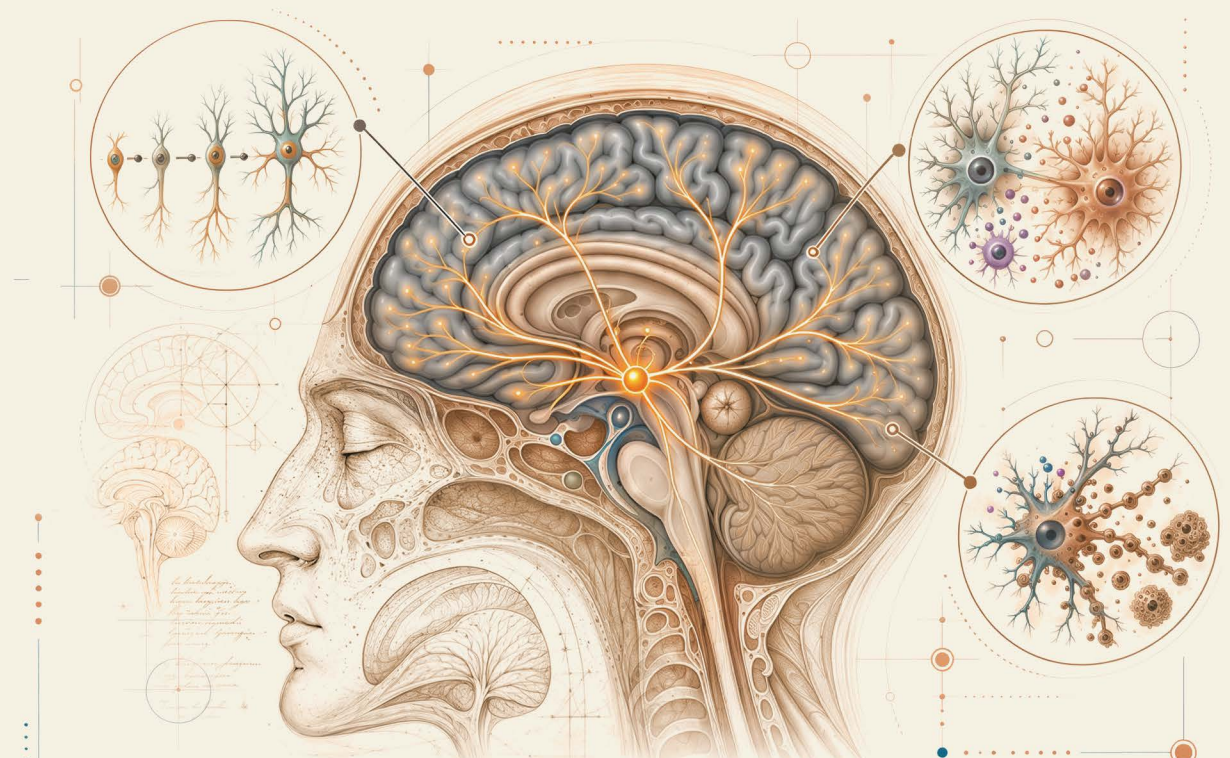
While the exact mechanisms remain somewhat mysterious, neuroinflammation appears to be a major driving factor in both developmental and degenerative brain conditions (neuropsychia-

tric), including conditions like autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), Alzheimer's disease (AD), and Parkinson's disease (PD).

Due to the rising incidence of these conditions and their significant socioeconomic burden, the urgent need for effective therapies has directed scientific focus toward the brain's histaminergic activity and associated signaling networks.

The current stage of knowledge regarding the involvement of HA and the histaminergic system within the CNS in the pathomechanisms of neurodevelopmental and neurodegenerative disorders will be presented.

To that end, the functions of HA in neurodevelopment, neuroinflammation, and neurotransmission are also addressed.



Reference: Szukiewicz D, International Journal of Molecular Sciences 2024, 25(18), 9859.

L5

Funding: JPI-Flag-Era HA-Ction; Progetti di Interesse Nazionale (PRIN), Bhistrot n. 2022YZRF4E; Banca d'Italia.

Prenatal histamine deficiency and the development of neuronal circuits.

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Background: Tourette's syndrome (TS), frequently comorbid with obsessive-compulsive disorder (OCD), is a neurodevelopmental disorder affecting approximately 1 in 160 individuals.

Although its aetiology remains incompletely understood, severe TS cases have been associated with mutations in the histidine decarboxylase (HDC) gene, which encodes the rate-limiting enzyme for histamine synthesis; affected patients show reduced histamine levels.

While TS and OCD are commonly conceptualised as basal-ganglia disorders, stress and anxiety can markedly exacerbate tic expression.

The bed nucleus of the stria terminalis (BNST) is a key regulator of stress- and anxiety-related responses, interacts functionally with basal-ganglia circuitry, and contains dense histaminergic innervation during early postnatal development.

Recent evidence further identifies the oval BNST as an extrastriatal source of histamine capable of modulating developing cortico-striatal synaptic transmission [1].

Aims: We hypothesised that BNST development is important for the emergence of TS- and OCD-relevant phenotypes and that reduced histamine availability alters the development and circuit integration of BNST neurons.

Specifically, we aimed to characterise a glutamatergic BNST neuronal subpopulation expressing Ca²⁺-calmodulin-dependent protein kinase II (CaMKII) and determine how altered histamine levels affect its intrinsic electrophysiological

properties, development, and synaptic connectivity.

Materials and Methods: CaMKII-expressing BNST neurons were investigated using a multi-modal approach combining electrophysiological recordings to define their intrinsic membrane and firing properties, immunohistochemistry to identify and characterise CaMKII-positive neurons within the BNST, and synaptic-tracing approaches to examine their circuit connectivity.

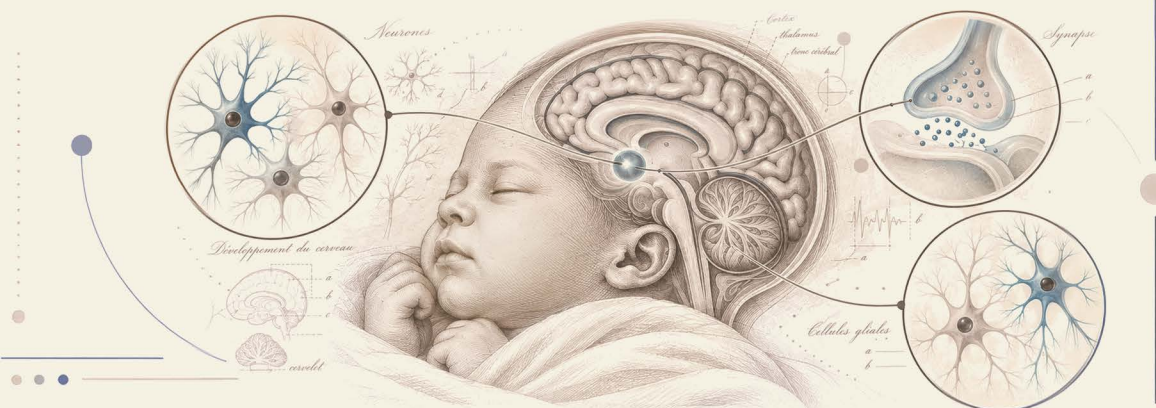
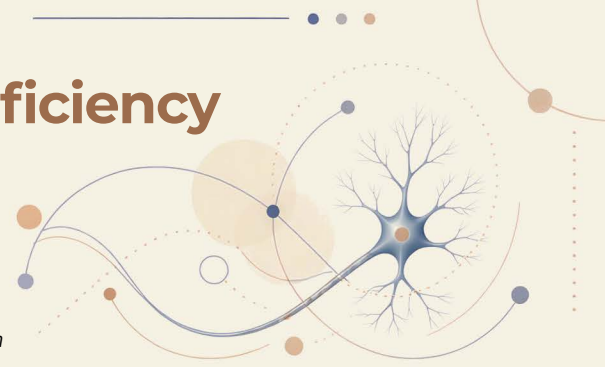
Experimental manipulation of histamine levels was used to assess the consequences of histamine dysregulation for neuronal development and synaptic integration.

Results: CaMKII-expressing neurons constituted an electrophysiologically distinct neuronal population within the BNST compared with non-CaMKII neurons.

Altered histamine levels affected the developmental profile of these neurons and modified their synaptic connectivity.

These findings indicate that histamine availability during early development contributes to the maturation and circuit integration of a defined glutamatergic BNST neuronal population.

Conclusion: Perinatal histamine dysregulation alters BNST neuronal development and synaptic connectivity. These developmental changes may contribute to abnormal stress- and anxiety-related circuit function and, consequently, to stress-induced exacerbation of tic expression in TS, particularly in individuals with OCD comorbidity.



References: [1] Marquez-Gómez, R., Parke, B., Cras, Y., Gullino, S. L., Hashemi, P., Ellender, T., Journal of Neuroscience 2026, 46, e1230252026.

The ovBNST: a novel histaminergic source modulating corticostriatal synaptic transmission during early postnatal development.

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⁴Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

Aims: Histamine modulates the intrinsic electrical properties of Striatal Projection Neurons (SPNs) during development^{1,2}.

Paradoxically, histamine innervation to the striatum is sparse during early life and adulthood, questioning the physiological source of striatal histamine.

We addressed this question by looking at a histamine fibres plexus located in the Bed Nucleus of Stria Terminalis (BNST) as potential source of striatal histamine.

Materials and Methods: P9–15 mice were used for experiments. Cortico-striatal inputs were optically activated with ChR2-EYFP and washed-in histamine and thiopermide were used to dissect H₃R modulation of cortico-striatal EPSPs.

Histamine-containing fibres were mapped using immunohistochemistry for histamine, CTIP2 and PKC-δ. Fast-scan cyclic voltammetry (FSCV), hGRAB-HA1 sensors, and in vivo fibre photometry were used to detect striatal histamine following electrical stimulation of the oval nucleus of the BNST (ovBNST).

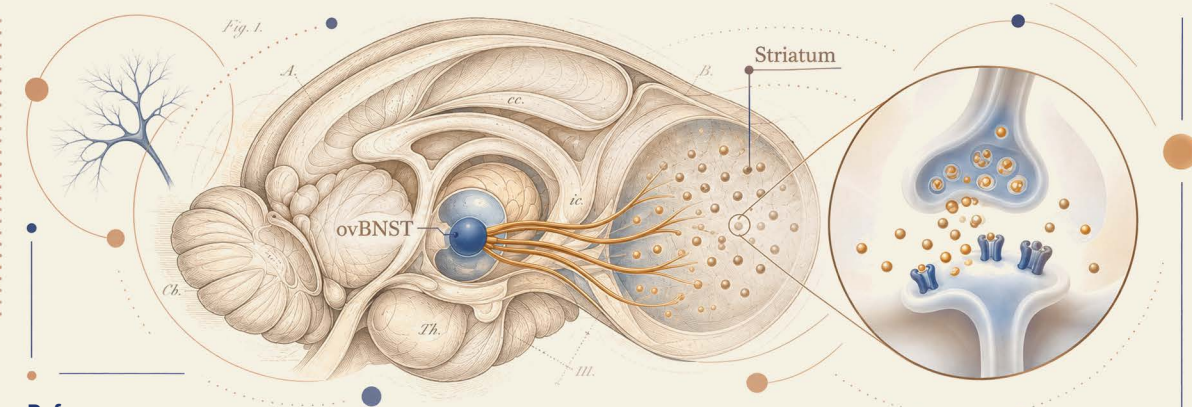
Results: Histamine can modulate the intrinsic properties of SPNs and reduce the cortico-striatal EPSPs amplitude as early as P9.

A plexus of histamine-positive fibres was localized into the ovBNST. FSCV and GRAB-HA1 imaging in brain slices showed that histamine released from ovBNST can persist longer than dopamine and be detected in the striatum.

In vivo fibre photometry confirmed that histamine released from ovBNST can reach the striatum.

Finally, histamine release evoked by ovBNST stimulation was sufficient to suppress mPFC-striatal synaptic transmission through H₃ receptors.

Conclusion: Histamine released from ovBNST crosses systems and anatomical boundaries (limbic > basal ganglia) acting as a paracrine neuromodulator of the cortico-striatal transmission during development.



References:

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- [2] Marquez-Gomez R., Han, S. Woodman, M., Ellender, T. Histaminergic Control of Corticostriatal Synaptic Plasticity during Early Postnatal Development. Journal of Neuroscience, 2020. 40(34):6557–6571

Histaminergic alterations in preclinical models of anorexia nervosa and binge eating disorder: two sides of the same coin?

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¹Dept. of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy;

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Aims: Binge eating disorder (BED) and anorexia nervosa (AN) are complex and partially opposite eating disorders characterized by dysregulated food intake, altered reward processing, and maladaptive stress-related responses.

Current pharmacological options remain limited, highlighting the need for novel therapeutic targets.

Neuronal histamine (HA) is a key modulator of feeding, arousal, reward, and stress responses. This study aimed to investigate whether remodeling of the central histaminergic system contributes to pathological eating behaviors and whether modulation of HA neurotransmission may represent a therapeutic strategy.

Materials and Methods: To induce binge-like eating, female rats were exposed to repeated cycles of intermittent food restriction/refeeding and access to palatable food, resulting in binge episode following a 15-min "frustration stress" exposure to the sight and smell of the same food without access to it. The expression of HA-related genes, namely Hdc, Hnmt, Hrh1, Hrh2, Hrh3, and Hrh4, was determined by RT-PCR in the hypothalamus, frontal cortex, hippocampus, nucleus accumbens, and striatum.

The efficacy of a pharmacological treatment modulating HA neurotransmission was tested in rats displaying binge-like eating. To induce AN, the ac-

tivity-based anorexia (ABA) rat model was used.

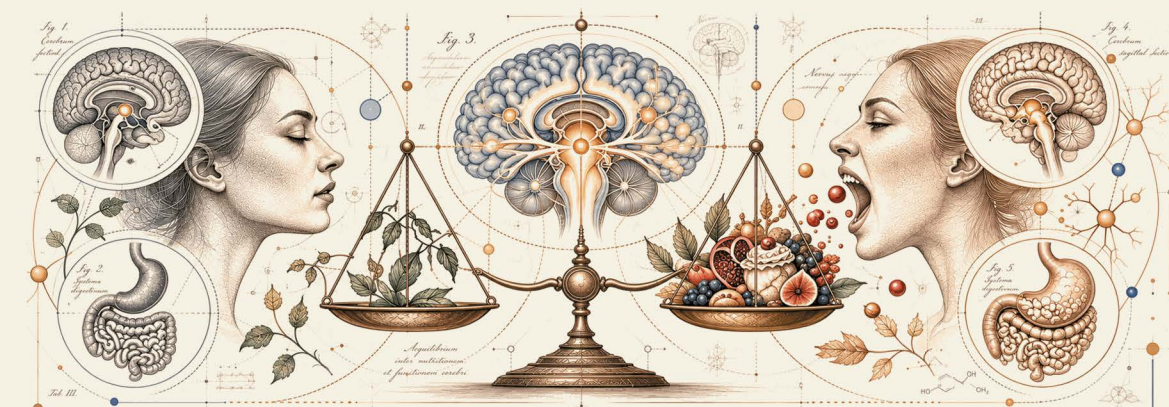
Female rats were sacrificed during the acute anorectic and recovery phases, and the expression of the same HA-related genes was assessed in the hypothalamus and frontal cortex.

Results: Binge-eating animals showed significant region-specific alterations in the expression of HA biosynthetic and catabolic enzymes, as well as HA receptors, compared with control animals, suggesting reduced HA neurotransmission.

Consistently, acute, repeated, and chronic pharmacologically induced enhancement of HA neurotransmission prevented binge-like eating. Preliminary data from the ABA model revealed dynamic remodeling of histaminergic markers in the hypothalamus and frontal cortex during the acute phase, with reduced Hnmt and altered receptor expression, suggesting increased HA availability and compensatory receptor adaptation.

Most alterations were normalized during the recovery phase.

Conclusion: These findings support an important and distinct role for histaminergic neurotransmission in maladaptive eating behaviors. Modulation of HA neurotransmission may therefore represent an innovative therapeutic approach for eating disorders.



Paradoxical kinesia, emergency strength, and dramatic clinical behaviors, potential role of brain histamine from the tuberomammillary nucleus.

David Roeltgen¹, James Stellar²

¹Neurology, Cooper University Hospital; ²Psychology, University of Albany

Background: Paradoxical Kinesia (PK) is a sudden brief period of markedly improved goal-directed movement that occurs in patients with severe Parkinson's Disease (PD) who are confronted by life-threatening situations. It has been reproduced in animals with dopamine depletion induced by 6-hydroxydopamine and MPTP.

Marked increases in movement in non-PD humans and animals occur in other life-threatening situations, including pre-death energy surges, "trance-induced" strength (e.g., lifting a car off someone), and "going berserk" in the setting of war, drug intoxication, or psychiatric disease. The neurobiology of this behavior, which might be labeled "fight or flight," is unknown.

Aims: To review available literature to support the hypothesis that histamine from the tuberomammillary nucleus (TMN) is a likely candidate for activation of this paradoxical increased motor activity (PIMA).

Materials and Methods: The authors examined medical and non-medical literature and reviewed personal experiences associated with PIMA and its neurobiology.

Results: The TMN receives its major input from the prefrontal and infralimbic cortex and limited input from the amygdala. The latter has a major output to the limbic cortex. These regions are significantly involved in response to threats. The

TMN has major outputs to multiple motor systems, including the basal ganglia, the anterior thalamus, motor nuclei in the cerebellum, and the peduncular tegmental nuclei.

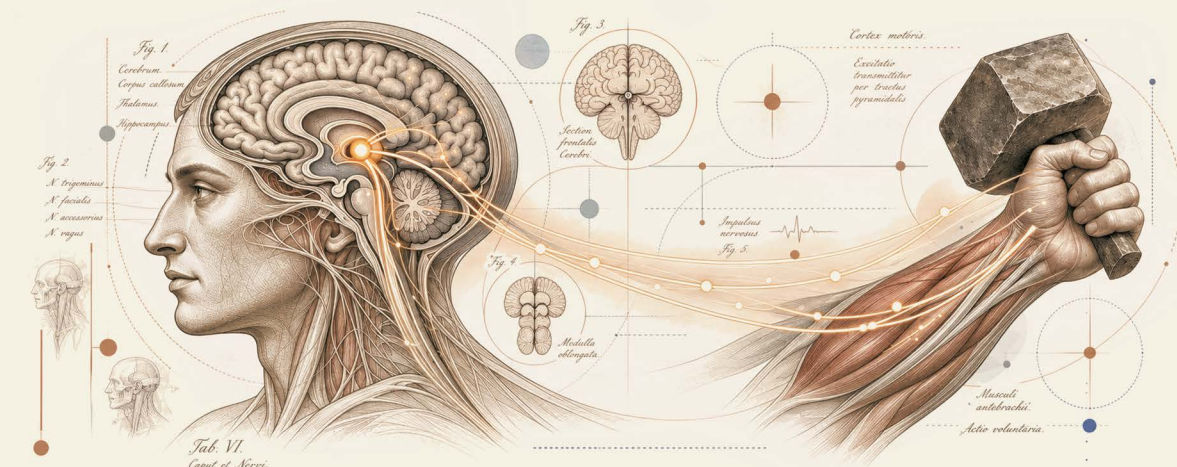
Another major innervation of the TMN is the locus coeruleus (LC). These innervations help explain histamine's role in motivated arousal. The absence of histamine reuptake mechanisms in the basal ganglia and the neurotoxicity of sustained histamine increases may help account for the brief time frame of the behaviors involved.

Experimental support for this model comes from animals made severely parkinsonian from dopamine depletion. Evidence shows that PK, when produced by threat stimuli (e.g. putting a rat in ice water), is not due to residual dopamine and that histamine H₂ in the entopeduncular nucleus and H₃ in the anterior thalamus contribute to the behavior.

Noradrenergic output from the LC likely accounts for much of the autonomic arousal associated with these behaviors, and there is some evidence that it may also directly influence motor systems.

Therefore, it is unlikely that the behaviors are due solely to histamine, and that they have, to some degree, multiple interactive mechanisms.

sions: It is likely that histamine produced by the TMN plays a major role in PIMA associated with life-threatening stimuli in humans and in animals.



BP1.7881A, the first dual histamine H₁-H₄ receptor antagonist: from predinic to clinical phase 2 studies

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H₄ receptors were shown to modulate functions of immune cells such as eosinophils, basophils, while H₁ receptors participate to the histamine-mediated responses in allergy diseases.

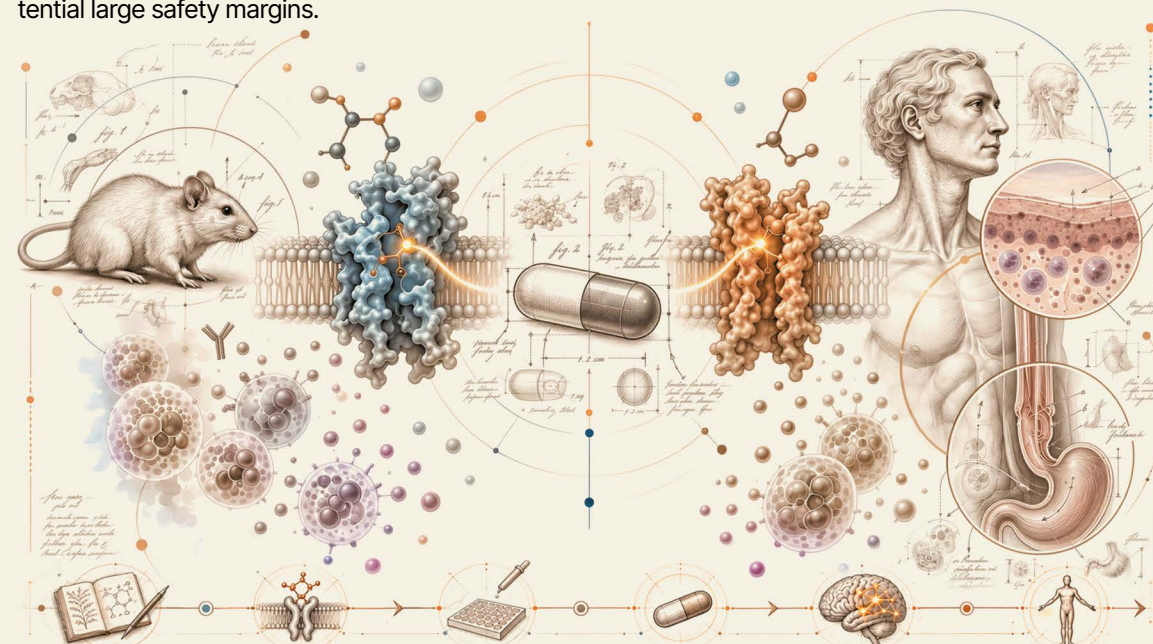
Thus, our strategy was to design a dual H₁-H₄ receptor antagonist to address causes and symptoms of immune disorders and BP1.7881A was identified as a highly selective and potent H₁-H₄ antagonist with K_i values of 1.3 and 5.6 nM at histamine H₁ and H₄ receptors, respectively.

This compound was found to be orally available with a low brain penetration in rodents avoiding H₁ receptor-related CNS side effects, such as drowsiness. Furthermore, BP1.7881A demonstrated activities in multiple allergy/inflammation H₁- and H₄-related *in vivo* and *ex vivo* models.

IND-enabling studies were then performed and allowed us to enter into clinical development. Specifically, 13-week toxicity studies in rats and monkeys evidenced a good safety profile with potential large safety margins.

Clinical phase 1 study in healthy volunteers showed a very good pharmacokinetic profile (T_{max} of 0.5-1 h, a half-life of 7-12 h, and a clearance of 62-105 L/h with a dose-dependent exposure). In addition, the H₁ antagonism was evidenced from the dose of 10 mg in the histamine prick test and the H₄ antagonism from the dose of 30 mg in one *ex vivo* test based on the imetit-induced change in eosinophil shape. These latter studies confirmed the activity of BP1.7881A on both targets in humans following oral administration (target engagement).

Then, BP1.7881A was moved in patients (phase 2/ PoC studies) in order to assess the efficacy as well as the safety of this new product in both atopic dermatitis (AD) and in eosinophilic oesophagitis (EO). The AD study was completed and confirmed the good tolerability without getting positive outcomes on primary endpoints (EASI score) and the EO study is still on going.



L6

Enlightning H₄R pharmacology using a fluorescence-based conformational biosensor.

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¹ Amsterdam Institute of Molecular and Life Sciences, Division of Medicinal Chemistry, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

Agonist-induced G protein-coupled receptor (GPCR) signaling involves an outward movement of the intracellular end of transmembrane (TM) helix 6 to open the heterotrimeric G protein coupling interface.

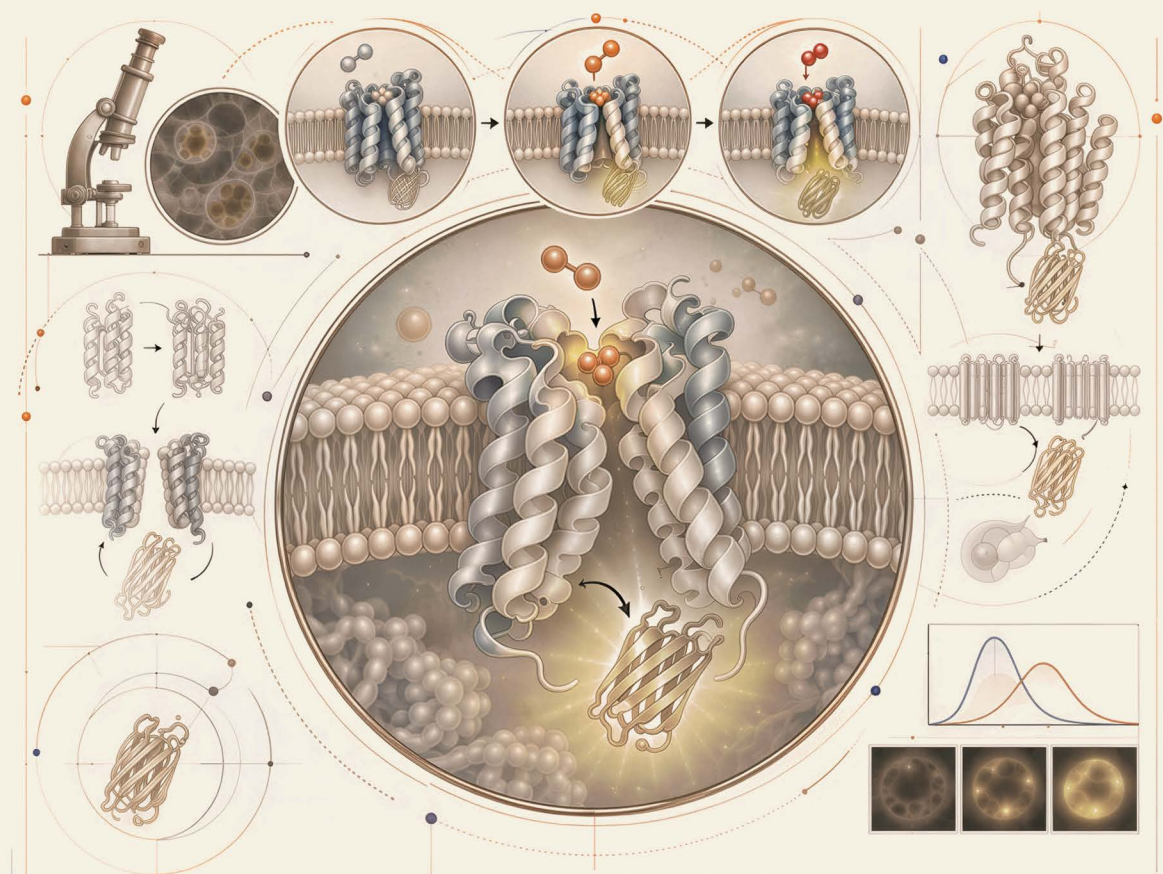
This conformational change can be measured by replacing the intracellular loop between TM5 and TM6 with an environmentally sensitive, circularly permuted enhanced green-fluorescent protein (cpEGFP).

The genetically-encoded GPCR activation-based histamine biosensor GRAB-HA was developed based on the human histamine H₄ receptor (H₄R) and optimized to monitor endogenous histamine levels in mouse brain *ex vivo* and *in vivo*.

However, efficacy of synthetic and (pre)clinical H₄R ligands has not been evaluated on this biosensor.

Tested H₄R compounds elicited the expected biosensor activation profiles, reflecting their, antagonistic, partial or full agonistic properties, and confirming the utility of the sensor in differentiating pharmacological signatures of clinically relevant ligands.

Moreover, the real-time detection also allowed assessment of ligand binding kinetics. In summary, GRAB-HA represents a powerful live-cell assay for quantitative and dynamic assessment of H₄R ligands, also providing a translational tool for preclinical discovery and functional profiling.



L7

IgE-dependent histamine release from human basophils is inversely associated with production of the anti-inflammatory lipid mediator resolvin-D1.

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¹Kent and Medway Medical School, Canterbury, UK;

²Life Sciences, Canterbury Christ Church University, Canterbury, UK;

³School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel.

Introduction: Basophils are thought to contribute to the pathogenesis of allergic inflammation by releasing histamine, leukotriene C4, and platelet activating factor as well as immunomodulatory cytokines (e.g. IL-4 and IL-13) following IgE-mediated activation.

However, recent studies have demonstrated that other allergic effector cells, such as mast cells, may also actively promote the resolution of inflammation by producing the anti-inflammatory lipid mediators such as resolvin D1 (RvD1) [1].

Aims: To determine whether basophils produce RvD1 in a range of donors with varying IgE-mediated histamine releasability. We also wished to address whether basophils express the RvD1 receptor, GPR32, and thus potentially respond to this anti-inflammatory lipid.

Materials and Methods: Human basophils were isolated from buffy coat blood by Ficoll-Paque density centrifugation and purified to over 90% purity by immunomagnetic cell sorting.

Constitutive expressions of the key enzyme responsible for RvD1 synthesis, ALOX15, as well as the RVD1 receptor, GPR32, were determined by Western blotting and immunofluorescence microscopy.

A portion of basophils were also stimulated for 30 min with and without anti-IgE for RvD1 production (measured by ELISA) and histamine release (determined spectrofluorometrically).

Histamine release was also determined after

30 min preincubation of basophils with 10 nM RvD1 to assess whether this lipid mediator impacted on degranulation following further stimulation with anti-IgE (in addition to controls).

Results: We observed that both ALOX15 and GPR32 were detectable in human basophils using both Western blotting and immunofluorescence microscopy, albeit with marked inter-donor variability. However, densitometric analysis revealed that constitutive ALOX15 expressions were inversely associated with the ability of basophils from different donors to release histamine following IgE-mediated stimulation.

Moreover, basophils from non-IgE-releasing donors released significantly more RvD1 to anti-IgE, as determined by ELISA, than IgE releasers (603 213 pg/million basophils versus 128 68 pg/million basophils net release, respectively; $p < 0.04$ for $n = 4$ in each group). In contrast, expression of the RvD1 receptor, GPR32, on basophils from these donors was only slightly reduced in IgE-responders. Furthermore, RvD1 did not reduce basophil IgE-dependent degranulation.

Conclusion: These findings demonstrate that basophils in certain donors are a source of RvD1 and may therefore contribute to the pro-resolving effects of this lipid in allergic inflammation.

However, this potential anti-inflammatory function is inversely related to histamine releasability and may be less pronounced in basophils from allergic donors with highly reactive phenotypes.

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Functional roles of Mas-related G protein-coupled receptor family in scratching.

Satoshi Tanaka¹

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Background: Activation of mast cells occur in IgE-dependent and IgE-independent manner. Most of the latter responses are induced by cationic secretagogues, including compound 48/80 and neuropeptides. In 2006, Tatemoto et al. demonstrated that Mas-related G protein-coupled receptor X2 (MRGPRX2) should mediate secretagogues-induced degranulation of mast cells [1].

McNeil et al. demonstrated that pseudo allergy responses are abolished in Mrgprb2 deficient mice and Mrgprb2 should be a primary murine orthologue of MRGPRX2 [2].

We observed mRNA expression of the other Mrgpr subtypes, such as Mrgpra4, b1, b2, b10, c11, and e, in murine cultured mast cells [3], raising the possibility that the functions of MRGPRX2 are mediated by the other Mrgpr subtypes.

Aims: The purpose of this study is to investigate the effects of MRGPRX2 antagonists on scratching behaviours induced by intradermal injections of various MRGPRX2 agonists.

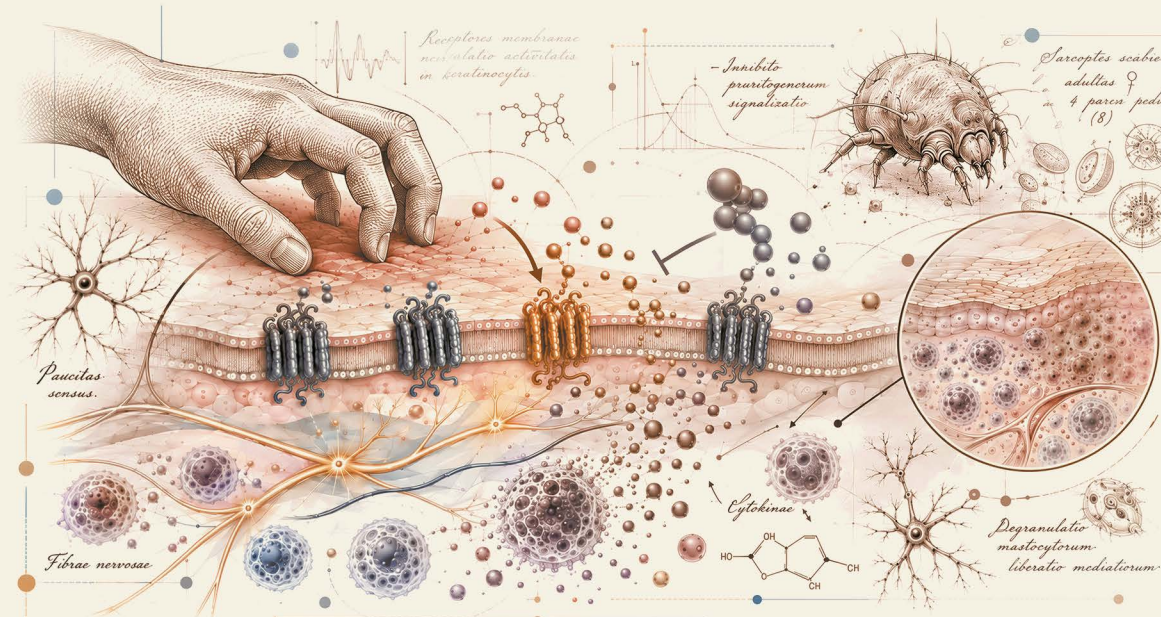
ching behaviours induced by intradermal injections of various MRGPRX2 agonists.

Materials and Methods: Scratching behaviours induced by intradermal injections of MRGPRX2 agonists were video-recorded and manually counted.

Results: A previously reported MRGPRX2 antagonist suppressed scratching induced by substance P and compound 48/80.

Chloroquine-induced scratching remained unchanged in the presence of the antagonist. Interestingly, the antagonist strongly suppressed scratching observed in house dust mite allergen-induced murine atopic dermatitis model, which was insensitive to fexofenadine.

Conclusion: An MRGPRX2 antagonist may have a potential to suppress a broad range of scratching. Identification of its murine targets will lead to deeper understanding of cutaneous itch.



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Discovery of **clocinizine** and **analogues** as potent **anthelmintic agents** *in vitro* and *in vivo*.

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Background: Helminthic infections are among the most neglected diseases worldwide. It is estimated that 1 billion people are infected with helminths, but no important anthelmintic agent has been introduced in therapy since albendazole, underscoring the need for novel anthelmintics.

Recently, our group demonstrated the anthelmintic efficacy of some antihistamines against *Angiostrongylus cantonensis* (causative agent of neuroangiostrongyliasis) and *Schistosoma mansoni* (schistosomiasis), with a focus on cinnarizine.

Aim: Considering the presence of a putative histamine receptor in the nematodes, in this work, novel analogues of cinnarizine were designed, synthesised, and assessed for their anthelmintic potential and to unveil the relationship between antihistamine and anthelmintic activities.

Materials and Methods: A set of cinnarizine analogues containing modifications in the benzhydryl and cinnamyl moieties was synthesised with high yields.

These compounds were tested against L1 and L3 larvae of *A. cantonensis* *in vitro* as well as adult worms of *S. mansoni*. The most promising compound, clocinizine, was selected for further assessment of its *in vivo* efficacy using an *S. man-*

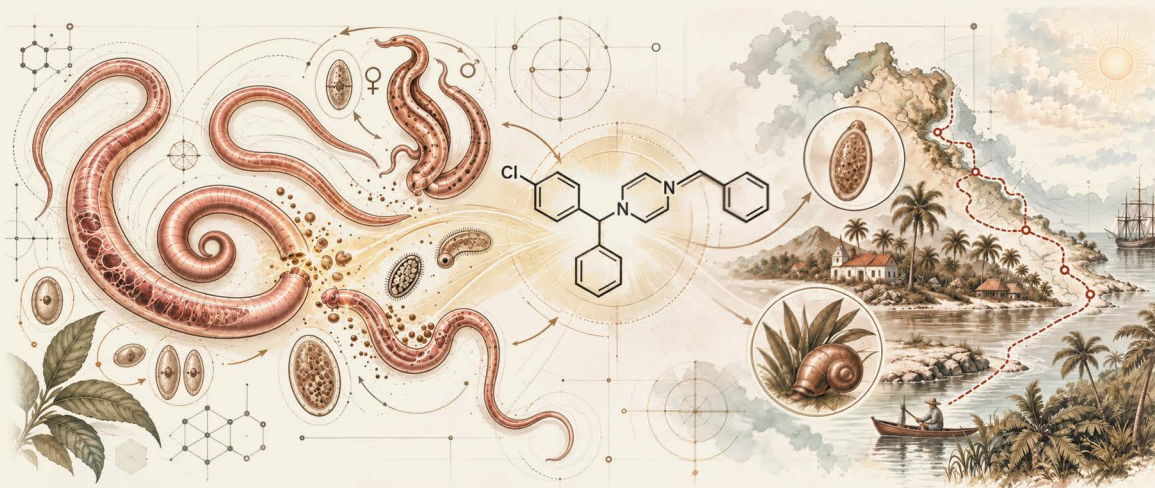
soni infection model previously described by us.

Results: 4 compounds were identified to have potent anthelmintic activity against both larval stages of *A. cantonensis*, while only clocinizine demonstrated activity against both male and female adult worms of *S. mansoni*. none of the compounds showed activity against *Caenorhabditis elegans*, suggesting that the anthelmintic activity of such compounds may rely on targets related to parasite-host interaction mechanisms rather than on histamine modulation.

Initial SAR findings indicated that modifications to the aromatic moieties provided a substantial increase in activity, and the basic amino group of piperazine is essential to activity.

Clocinizine was selected for *in vivo* studies in an *S. mansoni* infection model (400 mg/kg p.o., single dose), showing comparable efficacy to praziquantel in eliminating the infection by *S. mansoni*, with no significant toxicity in mice or rats.

Conclusion: Clocinizine represents a candidate for further studies as an antischistosomal agent. Other identified compounds can also serve as prototypes for designing novel agents with improved anthelmintic activity.



References: Roquini D et al., ACS Omega 2024, 9, 31159-65.
Lemes BL et al., ACS Infect. Dis. 2025, 11, 2871-81.
Castro T et al., Sci. Rep. 2025, 15, 30816.

Staphylococcus aureus α -hemolysin reprograms DNA methylation in human **Th1 cells**.

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Aim: *Staphylococcus aureus* α -hemolysin is a major pore-forming virulence factor that modulates immune-cell function at sublytic concentrations.

Since we previously showed that α -hemolysin alters the epigenetic landscape of human Th17 cells, the aim of this study was to determine whether this toxin also affects DNA methylation and related regulatory mechanisms in differentiating human Th1 lymphocytes.

Materials and Methods: Naive human CD4⁺ T cells isolated from buffy coats of healthy anonymous donors were differentiated into Th1 cells for 5 days in the presence of 75 ng/mL α -hemolysin.

Transcriptomic changes were analyzed by RNA-seq and validated by quantitative PCR. Protein levels of selected DNA methylation regulators were assessed by western blotting.

Genome-wide DNA methylation was examined by whole-genome bisulfite sequencing (WGBS) using samples from five donors. H3K36me3 occupancy at selected differentially methylated regions (DMRs) was evaluated by chromatin immunoprecipitation.

Results: α -Hemolysin altered the expression of more than 2,300 genes in differentiating Th1 cells, including multiple immune-related transcripts.



Quantitative PCR confirmed the upregulation of IFNG, IL2, IL6, IL13, GZMB, and HELLS.

At the protein level, α -hemolysin increased HELLS, DNMT3A, and H3K36me3, while reducing DNMT3L expression.

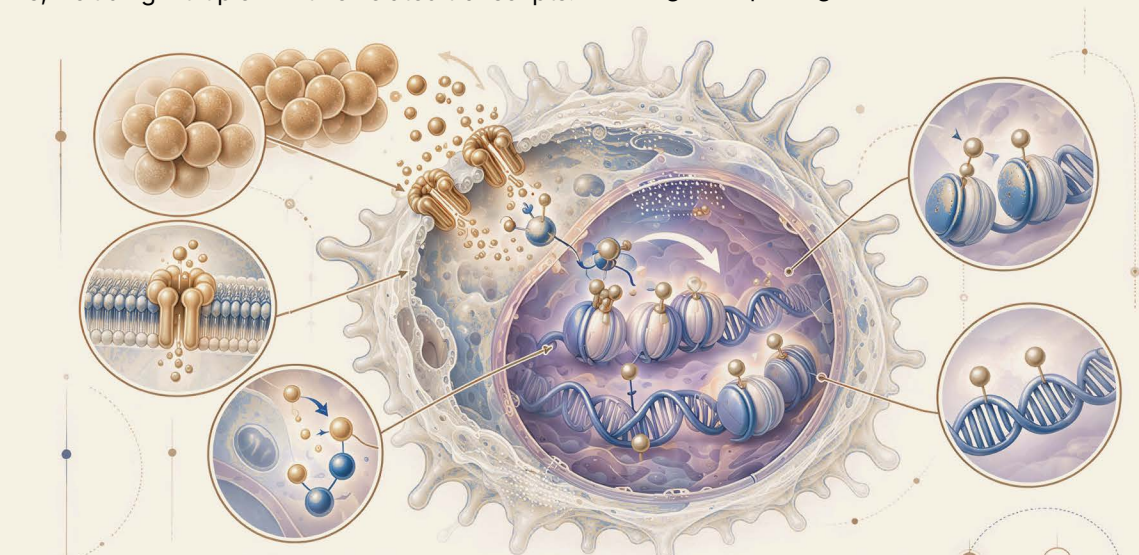
WGBS revealed relatively modest changes in CpG methylation but a more pronounced increase in non-CpG methylation (CHG and CHH) across multiple genomic regions. In total, 6,182 CG-type, 1,147 CHG-type, and 12,391 CHH-type DMRs were identified in gene regions.

ChIP analysis demonstrated increased H3K36me3 enrichment at DMRs within the LAMC1, ZC3H12C, and LTBP3 loci.

Conclusion: These findings show that *S. aureus* α -hemolysin acts as a potent epigenetic modulator in human Th1 cells.

The toxin induces broad transcriptomic remodeling accompanied by altered expression of DNA methylation machinery and widespread changes in genomic methylation, particularly in non-CpG contexts.

This mechanism may contribute to the plasticity and functional reprogramming of T cells during host-pathogen interactions.



Histamine H₃ antagonists – past and future.

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The histamine H₃ receptor was initially characterized by Jean-Charles Schwartz in rat brain tissue in 1983 via classical pharmacological methods as a presynaptic autoreceptor. Subsequently, it was shown, again by Schwartz, to be a presynaptic heteroreceptor on non-histaminergic neurons.

This research afforded key compounds, agonists and antagonists, including the prototypical H₃ antagonist thioperamide in 1983.

This period of research may be considered the “imidazole era” with ligands retaining the imidazole nucleus present in the cognate ligand.

The field changed rapidly in 1999 following the cloning of the human histamine H₃ receptor by Lovenberg which was followed by the cloning of the rat histamine H₃ receptor in 2000 and the human H₄ receptor in 2001.

These events prompted intense interest in histamine H₃ as a target, with several major pharmaceutical companies employing high-throughput

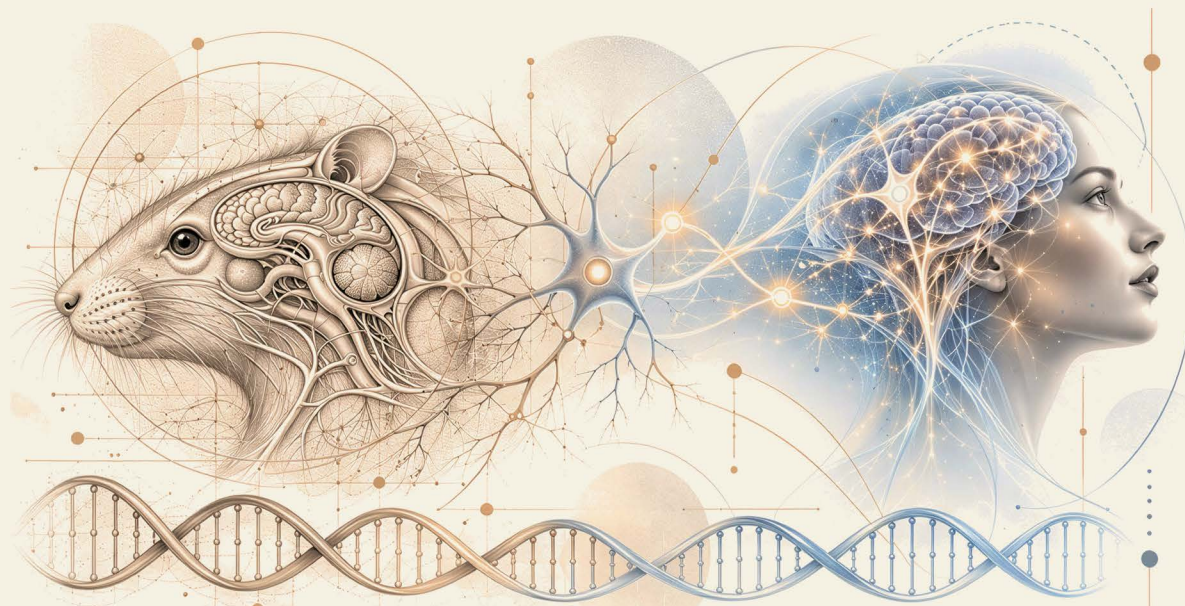
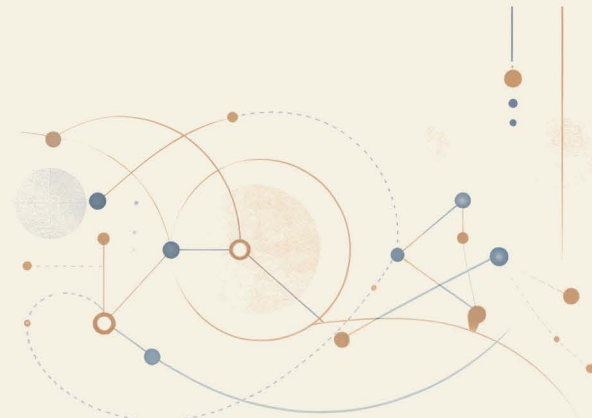
screening methods, leading to the discovery of numerous small-molecule non-imidazole structures. At the same time the regional expression pattern of the receptor was now known and shown to be predominantly in the CNS.

A better understanding of the role of the H₃ receptor was also gained by evaluating the phenotype of knock out animals.

Consequently, many potential therapeutic applications for H₃ antagonists were envisioned and over the following decade considerable preclinical and clinical data was generated that supported possible indications.

However, despite this activity, only one compound, pitolisant (Wakix®) has been added to the clinician's armamentarium.

This talk will review the history of H₃ antagonist research and reflect on what may be missed opportunities and what opportunities remain for new therapies.



Combined G9a inhibition and histamine H₃ receptor antagonism enhances memory and attenuates hippocampal oxidative stress in BTBR mice.

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Background: Cognitive deficits are a key challenge in neurodevelopmental disorders, and dual targeting of epigenetic and histaminergic pathways may offer therapeutic benefit [1].

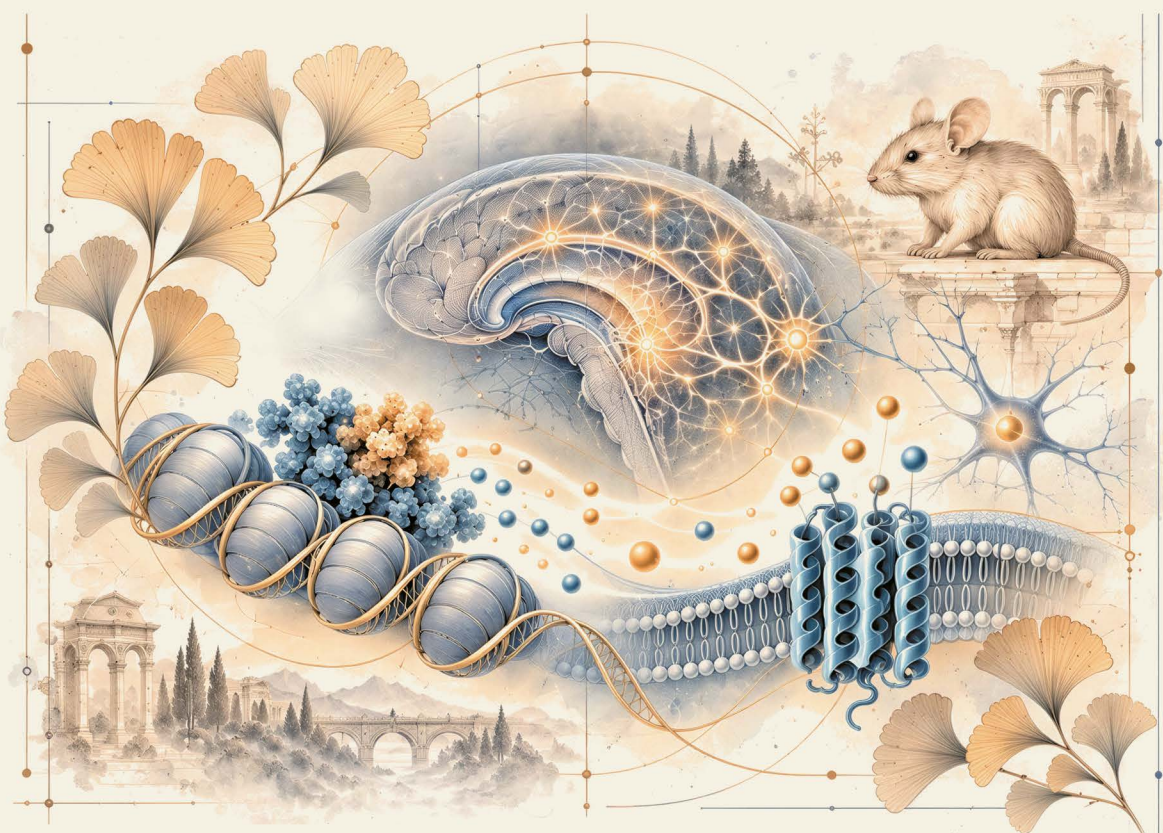
Aims: To assess the effects of A-366, a dual G9a inhibitor and histamine H₃ receptor antagonist, on cognition and oxidative stress in BTBR mice.

Materials and Methods: Male BTBR T+tf/J mice received A-366 for 21 days at 0.5–2 mg/kg i.p. Cognitive behavior was evaluated using fear conditioning, novel object recognition, and open field tests. Hippocampal SOD activity

and MDA levels were measured as oxidative stress markers.

Results: A-366 improved contextual and cued memory, enhanced object recognition, and maintained exploratory activity. It also increased hippocampal SOD activity and reduced MDA levels.

Conclusion: Chronic A-366 treatment improved cognitive performance and reduced oxidative stress, supporting dual G9a/H₃ receptor targeting as a promising strategy for cognitive dysfunction in neurodevelopmental disorders.



References:

[1] Hajar, M; Werner, T; Gajic, M; Stark, H; Sadek, B. Med Res Rev. 2025, 1-17.

Pitolisant, a histamine H₃ receptor antagonist/inverse agonist, reduces pain hypersensitivity and alters morphine analgesia, anxiety-like behaviour and metabolism in a sex-dependent manner in a murine model of neuropathic pain.

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Background: Multimodal pain therapy is a growing trend in chronic pain management, with the histamine 3 receptor (H₃R) being a promising target for new analgesics research.

We introduce an innovative therapeutic approach utilizing the clinically approved H₃R antagonist/inverse agonist, pitolisant (PIT), combined with morphine (M).

Aims: This strategy aims to synergistically reduce pain while enabling significant opioid dose reduction and decreased side effects.

Materials and Methods: We used chronic constriction injury to the sciatic nerve in male and female mice to model neuropathic pain.

Mechanical and thermal thresholds were assessed in von Frey and cold plate tests after PIT administration (1, 5, 10, and/or 20 mg/kg, i.p.), and the possible participation of spinal H₁R and H₂R in these antinociceptive effects was determined.

The neurochemical assessment of monoamines after PIT treatment (10 mg/kg) was also performed (HPLC). The effects of PIT (10 mg/kg) and M (20 mg/kg) co-administration on metabolic and behavioural parameters were evaluated using

Promethion Metabolic Cages System and Open-Field test. In addition, we examined whether co-administration of sub-effective doses of PIT (1 mg/kg) and M (5 mg/kg) produces analgesia.

Results: PIT reduced hypersensitivity more effectively in males, which correlated with elevated spinal levels of monoamines. Spinal H₁R/H₂R blockade diminished PIT-induced analgesia. Co-administration of PIT and M at ineffective doses produced significant analgesia in both sexes.

PIT alone did not impair locomotor activity, anxiety-like behaviour, and metabolism, while increasing food/water consumption in males. PIT reversed M-induced locomotor impairment in males, but did not mitigate sleep-like behaviour disturbances, anxiety in both sexes; or female-restricted metabolic reductions.

Conclusion: Our study identifies PIT as a potent antinociceptive and co-analgesic, and propose an innovative pharmacological approach that pairs pitolisant with morphine to harness the potent analgesia of opioids and mitigate their side effects, addressing critical gaps in current chronic pain treatment paradigms.

Acknowledgements: We are pleased to acknowledge the generous support of the National Science Centre, Poland, granted based on decisions 2019/35/D/NZ7/01042, and 2024/55/B/NZ7/02610. The research was carried out with the use of the CEPHARES infrastructure at the Maj Institute of Pharmacology, co-financed by the European Regional Development Fund, Measure 4.2 of the Smart Growth Operational Programme 2014-2020.

Effect of histamine H₃ receptor antagonist/inverse agonist DL76 on histopathological and matrix metalloproteinase-2 and -9 expression changes in experimental periodontitis in rats.

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Background: Periodontitis, a worldwide public health problem, is characterized by bacterial host-mediated inflammation affecting general health and quality of life. Its progression is modulated by selected matrix metalloproteinases (MMPs).

Aims: The aim of this study was to evaluate the effect of DL76, histamine H₃ receptor antagonist/inverse agonist, on anatomical, histological as well as MMP-2 and MMP-9 expression changes in a rat model of ligature-induced periodontitis.

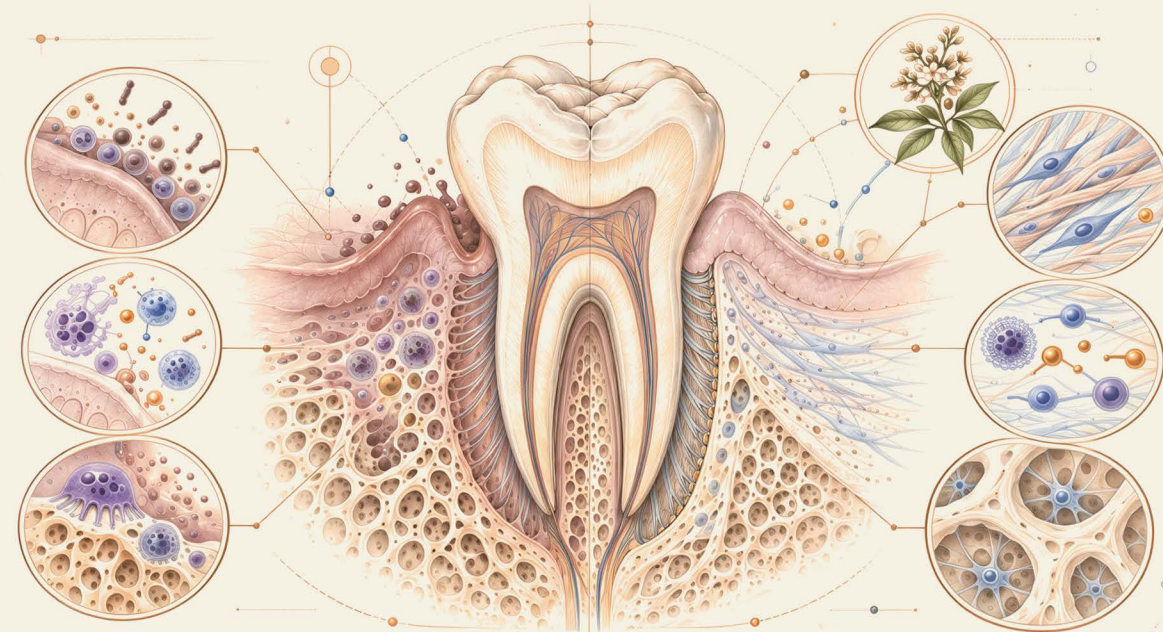
Materials and Methods: The study was conducted on adult male Wistar rats. Under general anesthesia, experimental periodontitis was induced by ligating the right maxillary second molar (R), while the contralateral left molar (L) served as the control.

The animals were divided into two groups, the

saline-treated control group (S), in which 0.9% NaCl was administered subcutaneously once daily for 28 consecutive days and the experimental group (DL), in which DL76 was administered.

Results: Higher level of mucosal inflammation with lymphocytic infiltration and alveolar bone loss, accompanied by overexpression of the MMP-9 gene, was found in the SR than in the SL samples. The treatment with DL76 led to decreases in mucosal inflammation, alveolar bone loss, as well as lower expressions of MMP-2 and MMP-9 genes in periodontitis-induced molars, compared to saline-treated control.

Conclusion: DL76 can affect the development of experimental periodontitis in rats by reducing the histopathological changes and expressions of MMP-2 and MMP-9.



Novel modafinil derivatives to fight narcolepsy.

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Background: Modafinil (Vigil®) and pitolisant (Wakix®) are clinically approved drugs for the treatment of narcolepsy with different modes of action on neurotransmitters. Whereas modafinil is modulating dopamine transporters (DAT), pitolisant is modulating the histamine H₃ auto- and hetero-receptors. Both served as the starting point for the development of a novel series of multitarget-directed ligands [1] for the central nervous system (CNS) targeting both the histamine H₃ receptor (H₃R) and monoamine transporters (MATs).

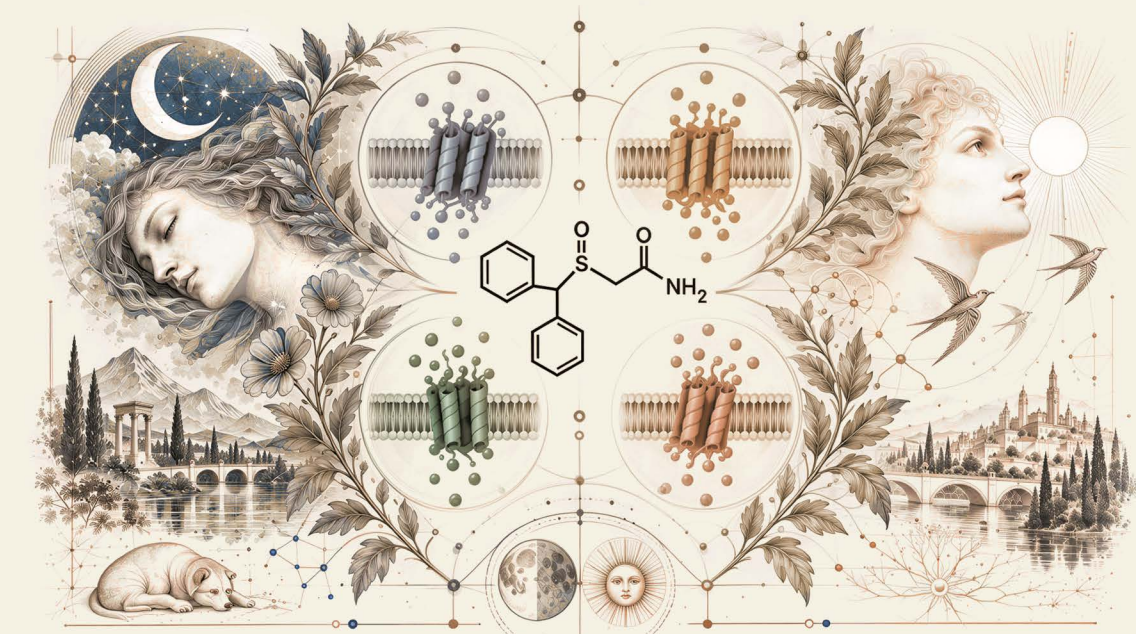
Aims: By incorporation of the H₃R pharmacophore of pitolisant [2] into the modafinil scaffold, we designed and synthesized a compound library simultaneously exhibiting H₃R and multiple MAT affinities.

Materials and Methods: In vitro radioligand binding studies of the newly synthesized compounds revealed H₃R affinities in the low nanomolar concentration range and variable degrees of DAT, serotonin transporter (SERT), and norepi-

nephrine transporter (NET) interaction.

Results: These ligands show two distinct pharmacological profiles: dual-target H₃R/DAT ligands combining the actions of pitolisant and modafinil, and quadruple-target ligands with balanced nanomolar affinities for H₃R, DAT, SERT, and NET. Structure activity relationships highlighted the preference of amide-containing compounds for DAT binding and balanced MAT affinity of respective amine analogues. Selected compounds exhibited CNS drug-likeness and target selectivity over other G protein-coupled receptors.

Conclusion: These results establish a rational design strategy for a novel multitargeting ligand class with distinct MAT affinities in combination to H₃R affinity for further pharmacological development and provide chemical tools to explore different monoaminergic and histaminergic modulation in sleep-wake regulation and numerous other CNS related disorders.



References: [1] M. A. Khanfar et al. Front. Neurosci.. 2016, 10, 201.

[2] C. R. Ganellin et al., in Successful Drug Discovery Vol. 3, Ed. J. Fischer, C. Klein, and W. E. Childers), Wiley-VCH Verl., Weinheim/Germany, 2018, pp. 359-381.

Rational design of dual H₃R/G9a ligands for Prader-Willi syndrome research.

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² Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia

Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder characterized by hyperphagia, cognitive impairment, and behavioural disturbances, with limited therapeutic options. Histamine H₃ receptor (H₃R) antagonism and G9a histone methyltransferase inhibition represent complementary therapeutic strategies that may address both symptomatic manifestations and underlying molecular mechanisms of PWS.[1]

Aims: The design, synthesis, and evaluation of a focused library of sixteen 6-methylpyrimidine derivatives based on structural motifs of known G9a inhibitors and H₃R ligands.

Materials and Methods: A focused library of sixteen 6-methylpyrimidine derivatives was synthesized with systematic modifications at the C-2 and C-4 positions of the pyrimidine core. The compounds were evaluated for H₃R binding affinity and G9a inhibitory activity.

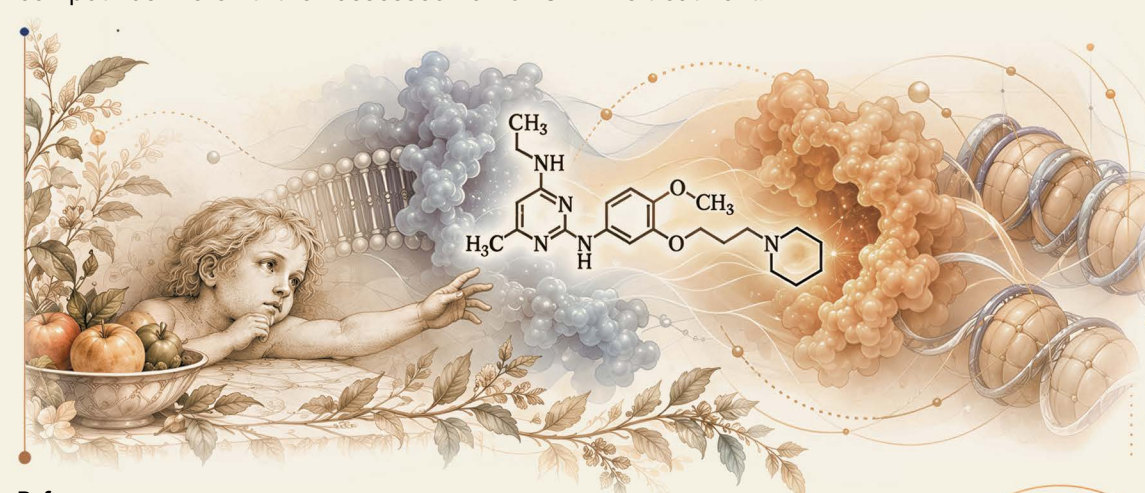
Structure-activity relationships were established, while molecular docking studies were performed to rationalize ligand-target interactions. Selected compounds were further assessed for CNS-

-relevant lipophilicity, cytotoxicity and metabolic stability in human liver microsomes.

Results: Among the synthesized compounds, compound ST-2657 showed the most balanced pharmacological profile, exhibiting high H₃R affinity (K_i = 25 nM), potent G9a inhibition (IC₅₀ = 64 nM), alongside minimal cytotoxicity and physiologically relevant lipophilicity (logD = 2.06), suggesting potential for CNS exposure.

Microsomal stability studies confirmed that compound ST-2657 is metabolically stable in human liver microsomes with negligible sex-dependent differences and predominantly CYP3A4-mediated metabolism, supporting its suitability for further pharmacokinetic evaluation.

Conclusion: This study demonstrates the feasibility of developing dual H₃R/G9a ligands using a 6-methylpyrimidine scaffold. Compound ST-2657 emerged as a promising lead candidate with a balanced pharmacological profile, supporting further optimization toward potential therapeutic applications for Prader-Willi syndrome treatment.



References:

[1] Hajar, M et al. Med Res Rev 2025, 45(6), 1547-1563.

Towards multi-target ligands for pain therapy:

design and biological evaluation of compounds directed at **sigma-1**, **histamine H₃**, and **μ-opioid receptors**.

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Background: Chronic pain, including neuropathic pain as one of its major forms, remains a significant clinical challenge due to the limited efficacy and adverse effects of current pharmacotherapies.

Multi-target-directed ligands (MTDLs) offer a promising strategy to improve analgesic efficacy by simultaneously modulating complementary pain-related targets.^{1,2}

Aims: The aim of this study was to identify novel multi-target ligands combining histamine H₃ receptor (H₃R) antagonism, sigma-1 receptor (σ1R) antagonism, and μ-opioid receptor (MOR) agonism as potential candidates for chronic pain treatment.

Materials and Methods: An integrated computational workflow combining similarity analysis, machine learning models, and structure-based virtual screening was employed to identify candidate compounds.

Selected molecules were subsequently evaluated in radioligand binding assays to determine their affinity for H₃R, σ1R, and MOR.

Results: The applied workflow enabled efficient

prioritization of compounds with a high probability of engaging multiple targets while maintaining favorable drug-like properties. A leading structure was identified as the first-in-class ligand capable of simultaneously interacting with H₃R, σ1R, and MOR.

This compound exhibited the highest affinity toward σ1R, whereas its affinity for H₃R and MOR remained moderate, indicating the need for further optimization to achieve a balanced multi-target profile.

In addition, several dual-target ligands were identified, supporting the validity of the applied design strategy. Notably, one compound displayed one of the highest affinities for σ1R and demonstrated antagonist activity at this receptor in vivo, confirming its functional relevance.

Conclusion: These findings demonstrate the feasibility of a multi-target approach for chronic pain drug discovery and identify promising lead compounds for further optimization and evaluation in animal models of chronic pain.

References: [1] Szczepańska, K.; Karcz, T.; Dichiaro, M.; et al. *J. Med. Chem.* 2023, 66 (14), 9658–9683. [2] García, M.; Virgili, M.; Alonso, M.; et al. *J. Med. Chem.* 2020, 63 (24), 15508–15526.

Funding: This research was funded by the National Science Centre, Poland (2022/45/B/NZ7/03101).

New methods of labeling biologically active compounds with **fluorescent** and **metallocarbonyl** tags.

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Background: As the incidence of cancer and other civilization-related diseases continues to rise, there is an increasing need for fast, affordable, and non-invasive methods to monitor biological processes and support medical diagnostics. [1, 2]

Aims: This research focused on the development of novel markers with potential applications in biomolecule and drug labeling, as well as in medical diagnostics and bioimaging.

Materials and Methods: The first part of research focused on the development of metal carbonyl markers detectable by infrared (IR) spectroscopy for biomolecule labeling.

These compounds enable protein modification through thiol-reactive maleimide chemistry, undergo visible light-induced conversion into fluorescent derivatives, and exhibit selective cytotoxicity toward cancer cells while showing enhanced cellular uptake. [3]

The work also led to the synthesis of fluorescent pyrene-based markers containing cyclooctyne groups for bioorthogonal “click” reactions, allowing efficient and selective biomolecule labeling.

Their excellent photophysical properties and lack of toxicity toward normal and cancer cells make them promising candidates for safe bioimaging and diagnostic applications.

Results: In this communication, we want to present biological properties of new metallocarbonyl and fluorescent markers. The results we have obtained are interesting both from the scientific and application perspective.

Conclusions: We would like to present a strategy for introducing these markers into biomolecules as obtained compounds can be used in imaging biochemical processes occurring in living organism with high probability.

References: [1] C. G. Parker, M. R. Pratt, *Cell* 2020, 180(4), 605–632.

[2] J. L. Lau, M. K. Dunn, *Bioorganic & Medicinal Chemistry* 2018, 26, 2700–2707.

[3] K. Koprowska et al., *Dalton Transactions* 2025, 54, 16864–16875.

Funding: This work was funded by University of Lodz, IDUB Doctoral Research Grants 4/DGB/2022.

Photopharmacology

of G protein-coupled receptors: prospects and pitfalls within the histamine receptor family.

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Family A GPCRs represent the largest class of cell surface receptors, playing crucial roles in various physiological processes and serving as attractive targets for drug development.

Optical, non-invasive modulation of GPCR activity holds great promise for spatial-temporal control of cell signaling and ultimately precision medicine.

In Amsterdam we have been generating novel photoswitchable ligands capable of reversibly controlling GPCR activity in a light-dependent manner for a number of aminergic and peptide receptors.

Through computational modeling and structural analyses, we have elucidated the critical interactions between the ligands and receptor binding sites that govern the reversible photoisomerization process for a number of GPCRs.

This knowledge paves the way for rational de-

sign strategies in developing next-generation photoswitchable GPCR modulators with improved affinity and selectivity.

The current designs have enabled precise spatiotemporal manipulation of receptor signaling both in vitro and in vivo.

Animal studies utilizing photopharmacological agents exhibited remarkable control over receptor activation in a number of in vivo applications showcasing the technique's promise for future therapeutic use.

Yet, during our journey, we have also encountered a fair number of pitfalls that hinder the design of ultimate phototools.

Especially, species differences in GPCRs, chemical stability of GPCR phototools and finding the right balance between photochemistry and pharmacology are important factors to consider in the development of a proper photo-ligand.



Concentration- and endpoint-dependent responses

of primary human osteoblasts to rosavin, a characteristic constituent of *Rhodiola rosea*.

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Background: Rosavin is the species-specific phenylpropanoid of *Rhodiola rosea* and, together with salidroside, one of the two compounds to which standardized preparations are titrated. Both are widely consumed without prescription.

Evidence that rosavin affects bone metabolism has come almost exclusively from rodent models and immortalized osteoblast-like lines, and no data existed for primary human bone-forming cells [1].

Aims: To determine whether rosavin modifies the response of primary human osteoblasts under mineralizing conditions, and whether the effect is uniform across endpoints, concentrations and combination with salidroside.

Materials and Methods: Primary human osteoblasts (PromoCell C-12720) were cultured for 21 days in growth medium, mineralization medium, or mineralization medium containing rosavin at 50 or 100 μ M.

Rosavin identity was confirmed by ESI-QTOF-MS. BMP-2 and CX3CL1 in conditioned media and total β -catenin in lysates were quantified by ELISA.

Culture organization was assessed by phase-contrast microscopy with Fiji/ImageJ area-fraction analysis. In a separate series, rosavin 50 μ M, salidroside 50 μ M and their equimolar combination were compared.

Non-parametric testing and, for the combination series, pre-specified Welch ANOVA with Games-Howell post-hoc correction were applied.

Results: The responses were not uniform. BMP-2 secretion increased significantly only at 100 μ M, on days 14 and 21, whereas confluence and cuboidal morphology were most pronounced at 50 μ M [2].

CX3CL1 showed the opposite dependence, rising

References: [1] Wojdasiewicz, P., Int J Mol Sci 2024, 25, 2117.

[2] Wojdasiewicz, P., Int J Mol Sci 2025, 26, 6075.

[3] Wojdasiewicz, P., Mol Biol Rep 2026, 53, 796.

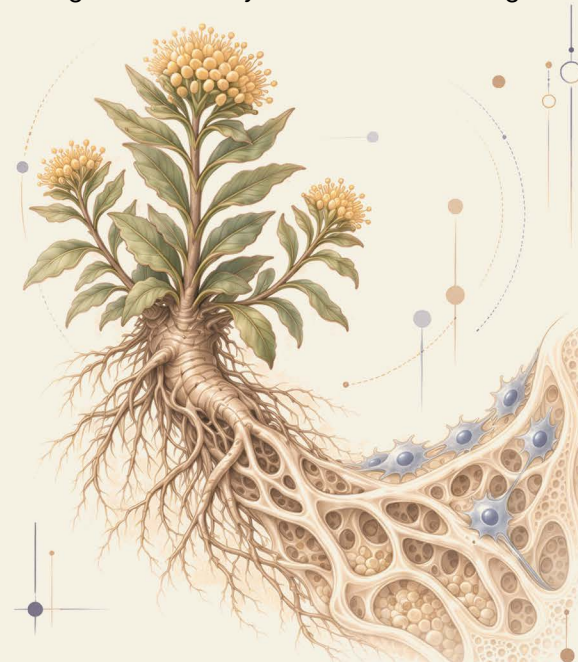
at 50 μ M versus mineralization control (+8% at day 14, +22% at day 21) and falling at 100 μ M by day 21 [3].

Total β -catenin at day 14 was lowest under rosavin 50 μ M (8.9 ± 3.8 ng/mL), 62% below the mineralization control and 2.6- to 3.2-fold below every other condition (Welch ANOVA $p = 0.003$; rosavin versus salidroside $p = 0.002$).

The equimolar combination did not reproduce this reduction (26.5 ± 16.9 ng/mL) and showed the lowest, most variable cell coverage of any condition.

Conclusion: Within one experimental platform, three readouts of the same cell peaked at different concentrations, and the combination did not reproduce the effect of either constituent alone.

A standardized plant preparation cannot be characterized by its marker compound, and single-endpoint, single-concentration designs risk being simultaneously correct and misleading.



From **oncogenic signaling** to **cellular chemistry**: **Raman readouts** of **FLT3 inhibition** in acute myeloid leukemia.

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Background: FLT3 internal tandem duplications (FLT3-ITD) generate persistent kinase signaling and define a therapeutically actionable subtype of acute myeloid leukemia (AML).

Genotyping identifies the lesion but does not reveal how a living leukemic cell changes biochemically when the pathway is blocked.

Raman microspectroscopy records an intrinsic molecular fingerprint without dyes or antibodies and has proven useful for resolving hematologic phenotypes and immune-cell activation states [1-3].

Aims: To test whether Raman profiles discriminate FLT3-ITD from FLT3-wild-type (FLT3-WT) AML cells and provide an early, mutation-dependent readout of response to gilteritinib.

Materials and Methods: A paired THP-1 model comprising engineered FLT3-ITD cells and FLT3-WT controls was examined by confocal Raman microspectroscopy before and after exposure to 1.5 nM gilteritinib.

Hyperspectral maps were interrogated using k-means clustering, principal component analysis and partial least-squares discriminant analysis.

The treatment-associated pattern was subsequently evaluated in primary AML cells grouped by FLT3 status.

Results: FLT3-ITD cells exhibited a reproducible fingerprint distinct from FLT3-WT controls, with major contrasts in lipid- and hemoprotein-associated signals.

After gilteritinib exposure, the FLT3-ITD spectra shifted toward the untreated FLT3-WT state, whereas FLT3-WT controls showed no comparable displacement.

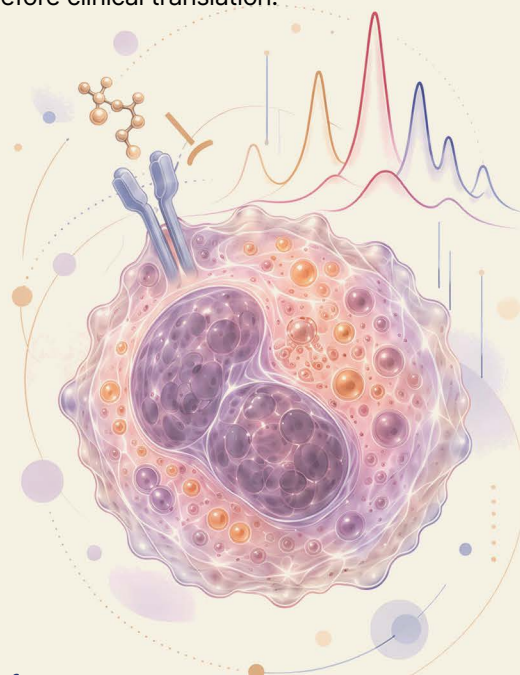
This biochemical response preceded overt loss of viability. Primary FLT3-ITD AML cells reproduced the direction of the treatment-induced shift, while FLT3-WT samples did not. Responsive

bands reflected lipids, protein secondary structure and aromatic amino-acid residues.

Conclusion: Oncogenic FLT3 signaling and its pharmacological inhibition leave measurable, mutation-dependent biochemical fingerprints in AML cells.

Raman microscopy could therefore complement genotyping with a rapid, label-free functional readout of target engagement and early drug response.

Validation in larger patient cohorts and standardization of acquisition and analysis are required before clinical translation.



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