第 22 回日本ヒスタミン学会

The 22nd Annual Meeting of Japanese Histamine Research Society

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ABSTRACT BOOK

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Preface

The 22nd Annual Meeting of Japanese Histamine Research Society

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It is my great honor to report that the 22th annual meeting of the Japanese Histamine Research Society (JHRS) was held in Hiroshima from 1 to 2 February 2020 in the first season of plum blossom of Reiwa era in Japan. It was not only the first meeting of JHRS in Hiroshima, but also the very last opportunity of live assembly of the members before COVID-19 pandemic.

Recent development of gene engineering and analysis has been accelerating the progress of life and medical sciences. Whole exome or even genome analysis became daily research practice. Consequentially, main targets of gene analysis are shifting from bodies and tissues to individual cells which constitute tissues and lesions. Because of such progress, interdisciplinary activities became even more important than before.

When I ask medical students on clinical practice about possible targets for antibody medications, many of students raise histamine. I then ask molecular weight of histamine to choose from a) 100, b) 1,000, c) 10,000, d) 100,000, e) 1,000,000. As you might predict, only few students choose 100. The knowledge of precise molecular weight of histamine, 111 may not be necessary for the treatment of allergic disease with antihistamines. However, it is important to know in clinical practice that histamine is produced from a single amino acid, histidine from one step chemical reaction, and that a large amount of histamine may be produced from fish meet by an enzyme of bacteria on the fish. It is also important to know how quickly histamine is degraded outside cells to think about roles of histamine in the body, and treatments for histamine-mediated diseases.

Histamine is quite versatile in function and interacts with a variety of molecules in the body. In the skin, histamine plays an important role in urticaria and atopic dermatitis for which H1-antihistamines are commonly used in the treatment. However, skin reactions evoked by a simple injection of histamine into the skin are largely different from those observed in real patients, indicating that our understanding of histamine in the pathogenesis of these diseases is still incomplete.

This meeting has been organized by two scientists with the research background of mast

cells and intracellular signal transductions. It was a fortunate to have invited Dr. Yoshimichi Okayama, in the Immune-Allergy Project team, Nihon University, and Dr. Zhong Chen, the President of Zhejiang University for Special Lectures about mast cells and central nerve system, respectively. I deeply appreciate all contributors, participants and sponsors, providing seminars, beverages, etc. It was fantastic to have even more papers presented than before under the pressure of COVID-19 spreading.

I wish everybody who have a look at this proceeding enjoy a progress of histamine research and know how the meeting was fruitful.

ABSTRACTS

Special Lectures

S-1 Novel therapeutic targets for cerebral disorders: cell-type specific histamine H2 receptor

Zhong Chen

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The neurotransmitter histamine receives less attention compared with other biogenic amines, because of its moderate and complicated actions in the brain. Our previous study discovered that histamine H2/H3 receptors in neurons and H1/H2 receptors in astrocytes are implicated in the process of excitotoxicity, neuronal autophagy, glutamate metabolism and glial scar formation following cerebral ischemia (1-4). It suggests that histamine receptors in different cells may have distinctive actions in the brain, which may be the reason for the less understanding of the role of histamine receptors in brain disorders. So, we generated mice with selective deletion of histamine receptors in different types of neuron or glia by Cre-loxp system to dissect their actions in cerebral disorders. We found that deletion of H1 receptors in cholinergic neurons (*Hrh1*$^{fl/fl}$*;ChAT*^{Cre}), but not the glutamatergic (*Hrh1*$^{fl/fl}$*;CaMKII*α^{Cre}) or dopaminergic neurons (*Hrh1*$^{fl/fl}$*;DAT*^{Cre}), selectively leads to schizophrenia-like negative symptoms, suggesting H1 receptors in cholinergic neurons could serve as a therapeutic target for the negative symptoms in schizophrenia. Interestingly, our study revealed that deletion of H2 receptor in glutamatergic neurons (*Hrh2*$^{fl/fl}$*;CaMKII*α^{Cre}) induced sensorimotor gating deficit, hyperlocomotion, social impairment and anhedonia, which are linked to the schizophrenia. Over-expression of H2 receptor in mPFC glutamatergic neurons rescued MK-801 induced schizophrenia-like phenotypes. So, H2 receptor in glutamatergic neuron may be critical for the pathogenesis for schizophrenia. We also investigated the role of H2 receptor in oligodendrocyte in white matter damage. We found that H2 receptor negatively regulates differentiation in oligodendrocytes following neonatal hypoxia-ischemia through binding with Axin2 and subsequently acting on Wnt/β-catenin signaling pathway. Our results suggest that the H2 receptor in oligodendrocytes (*Hrh2*$^{fl/fl}$*;CNPase-Cre*) could serve as an effective and secure therapeutic target for the retard of oligodendrocyte differentiation and remyelination in the pathological progress of neonatal hypoxic-ischemic encephalopathy. The in-depth understanding of the potential actions of cell type specific histamine receptors is the necessary stepping stone to unlock the wide-ranging applications of histamine related agents in the clinical arena.

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S-2 Expression and function of Mas-related G protein-coupled receptor X2 in mast cells

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Human skin mast cells (MCs), but not lung MCs, are activated by neuropeptides such as substance P (SP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide and somatostatin, but not neurokinin (NK) A or NK B, resulting in degranulation.(1, 2) Although the NK-1 receptor (NK-1R) is a receptor for SP, SP-induced histamine release from human skin MCs is not blocked by an NK-1R-specific antagonist.(3) Mas-related G protein-coupled receptor X2 (MRGPRX2) is a member of the Mas-related gene family and is primarily expressed in human dorsal root ganglia, and a subgroup of these receptors (MRGPRX1-X4, MRGPRD, MRGPRE, MRGPRF, MRGPRG, Mas1L) are expressed in human neurons.(4, 5) MRGPRX2 was found to be a receptor for basic peptides including SP, VIP, cortistatin, somatostatin and compound 48/80 in human cord blood (CB)-derived cultured MCs.(6) We have reported that human skin MCs and synovial MCs, but not lung MCs and peripheral blood-derived cultured MCs, express functional MRGPRX2 on their cell surfaces.(7)

Patients with chronic urticaria (CU) reportedly exhibit enhanced wheal reactions, compared with healthy control subjects, when some neuropeptides such as SP and VIP are intradermally injected.(8, 9) We, thus, hypothesized that the number of MRGPRX2-positive (+) MCs or the frequency of MRGPRX2 expression in skin MCs from patients with CU is likely to be elevated. We found that the number of $MRGPRX2^+$ skin MCs and the percentage of $MRGPRX2^+$ MCs in all the MCs from severe CU patients were significantly higher than those from normal control subjects.(7) In CU patients, eosinophil infiltration is commonly observed.(10, 11) Studies showing the marked deposition of major basic protein (MBP) and eosinophil cationic protein in CU lesions (12-14) have provided evidence that eosinophil granule proteins are released and could contribute to local inflammatory processes in patients with chronic idiopathic urticaria either directly or indirectly via other inflammatory cells. We found that MBP and eosinophil peroxidase (EPO), but not eosinophil derived neurotoxin, induced histamine release from human skin MCs through MRGPRX2.(7)

Mrgprb2, the orthologue of the MRGPRX2. However, ~53% overall sequence similarity between these two receptors. Sequence similarities at the N-terminal 60 amino acids and the C-terminal 80 amino acids are ~34% and ~47%, respectively.(15) While SP activates MRGPRX2 with EC_{50} of 152 nM, it activates Mrgprb2 with an EC_{50} value of 54 μM.(15) McNeil et al.(16) reported that Mrgprb2 is a target of small-molecule drugs such as atracurium,

succinylcholine and ciprofloxacin, associated with systemic pseudo-allergic, or anaphylactoid, reactions using Mrgprb2 knockout mice. Meixiong et al.(17) reported that mast cell activation via Mrgprb2 evoked non-histaminergic itch in mice independently of the FcεRI-histamine axis. Compared with IgE-FcεRI stimulation, Mrgprb2 activation of MCs was distinct in both released substances (histamine, serotonin, and tryptase) and the pattern of activated itch-sensory neurons.(17) Green et al.(18) reported that the mast-cell-specific receptor Mrgprb2 mediates inflammatory mechanical and thermal hyperalgesia and is required for recruitment of innate immune cells at the injury site. They also found that SP facilitates migration of immune cells via Mrgprb2.(18) These findings identify MRGPRX2/Mrgprb2 as an important neuroimmune modulator and a potential target for treating CSU, pseudo-allergic, or anaphylactoid, reactions, itch and pain.

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ABSTRACTS

Morning Seminars

M-1 The utility of antihistamines in atopic dermatitis

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Atopic dermatitis results from skin barrier dysfunction and exposure to allergens, and is primarily characterized by repeated cycles of exacerbation and recovery from pruritic and eczematous lesions. Numerous inflammatory mediators are involved in the pathogenesis of atopic dermatitis. Histamine is a pruritogen, and is known to induce allergic reactions and reduce the function of the skin barrier.

The majority of patients with atopic dermatitis often scratch their eyelids as they develop allergic conjunctival disease such as atopic keratoconjunctivitis. Several studies also reported that atopic dermatitis is more common among patients with chronic urticaria than among healthy individuals.[1] Thus, oral antihistamines may be effective at reducing scratching behaviors associated with conjunctivitis and urticaria in patients with atopic dermatitis.

Rupatadine is a second-generation antihistamine and platelet-activating factor (PAF) receptor antagonist. PAF is a lipid mediator produced by eosinophils and mast cells, and is involved in the processes of platelet activation, and eosinophil migration and activation.

Recent evidence suggests that platelets are involved in the inflammatory response, in addition to hemostasis. We have previously found that patients with atopic dermatitis have higher levels of platelet activation markers in the plasma than healthy individuals, and that the level of these markers is associated with the severity of atopic dermatitis.[2,3] We also demonstrated in a murine model of atopic dermatitis that leukocyte infiltration into the site of dermatitis can be attenuated by reducing platelet counts in the blood.[4] Taken together, these findings suggest that platelets play an important role in allergic inflammation of the skin.

Patients with atopic dermatitis are often characterized by having a high eosinophil count in the peripheral blood and subsequent infiltration of eosinophils in the lesions. Eosinophils are activated by cytokines, chemokines, and lipid mediators, and migrate to the site of dermatitis. Thus, eosinophils play an important role in allergic inflammation.

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M-2　Advances in management and elucidation of pathophysiology in patients with urticaria and angioedema

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【Abstract】Urticaria and angioedema are common diseases, but approaches to treatment vary greatly depending on each case and type. Japanese guideline for diagnosis and treatment of urticaria 2018 has been revised with the primary focus on consistency with the Global Guidelines and to serve as a guideline for physicians and patients. The action guidance for the treatment of urticaria, the items of treatment evidence by disease type based on the verification of the evidence, and the methods for assessing the disease status of urticaria such as UAS7 and UCT was added as new items in the new guideline. In addition, there is an impression that the lineup of therapeutic agents and evaluation tools for managing patients with urticaria was gradually established, following the emergence of omalizumab as a new treatment for chronic spontaneous urticaria (CSU). Moreover, the importance of classifying angioedema, which is classified as one of the major categories of urticaria in the guidelines, has been advocated by focusing on two main mediators, histamine and bradykinin. This lecture focuses that we will reconsider the action guidelines in daily practice to manage urticaria and angioedema along with Japanese guideline for diagnosis and treatment of urticaria 2018. I also introduce some ideas for daily practice of urticaria and angioedema at Division of Dermatology of Kobe University.

In the dermatological field, the pathophysiology of other inflammatory skin diseases such as psoriasis and atopic dermatitis is rapidly elucidating. In contrast, the pathophysiological condition of urticaria was not discussed in detail in the Japanese and Global guidelines. However, elucidation of the pathophysiology of urticaria is gradually progressing following the discovery that omalizumab, an anti-IgE antibody, was found to be effective for CSU and other forms of urticaria. In this lecture, I introduce recent progress in elucidating the pathogenesis of urticaria, focusing on CSU and prospects for future treatment progress. Furthermore, I will introduce recent urticaria research conducted at Division of Dermatology of Kobe University, and reconsider initiatives for medical examination cooperation for patients with urticaria and angioedema.

ABSTRACTS

Luncheon Seminar

L-1 The ideal antihistamine treatment for allergic diseases from the viewpoint of pharmacological actions.

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Since Sir Henry Dale, a Nobel laureate in Physiology or Medicine, discovered the activities of histamine in 1910, a large number of studies have been conducted on histamine's physiological and pathological actions. While histamine was considered an allergy-causing "bad guy," recent studies have indicated that histamine also has beneficial physiological activities. Antihistamines have a long history in their development. Antihistamines released earlier in the market are called first-generation antihistamines. Second-generation antihistamines were introduced around 1980 and later. First-generation antihistamines inevitably exhibited central depressant/sedative activities. Moreover, they showed low specificity and adverse reactions (thirst, urinary retention, tachycardia, etc.) due to effects such as anticholinergic effects. Therefore, to overcome these drawbacks, various types of pharmacological improvements were performed during development of second-generation antihistamines.

The guideline for allergic diseases, such as pollenosis and atopic dermatitis, recommends non-sedating antihistamines with low central nervous system (CNS) penetration to avoid suppressing histamine's CNS actions. Positron emission tomography (PET) is often used to evaluate the efficacy of CNS drugs by determining the drugs' neuronal receptor occupancy rate. While the blood concentration levels of a drug are frequently determined clinically, i.e., via therapeutic drug monitoring, CNS drugs do not necessarily show a correlation between their blood concentration levels and the effects. We reported the brain H1 receptor occupancy measurements of antihistamines, antidepressants, and antipsychotics in humans. In the present review, the results of our previous studies on the significance of brain histamine H1 receptor occupancy of histamine H1 blockers are summarized from the perspective of histamine function in the CNS.

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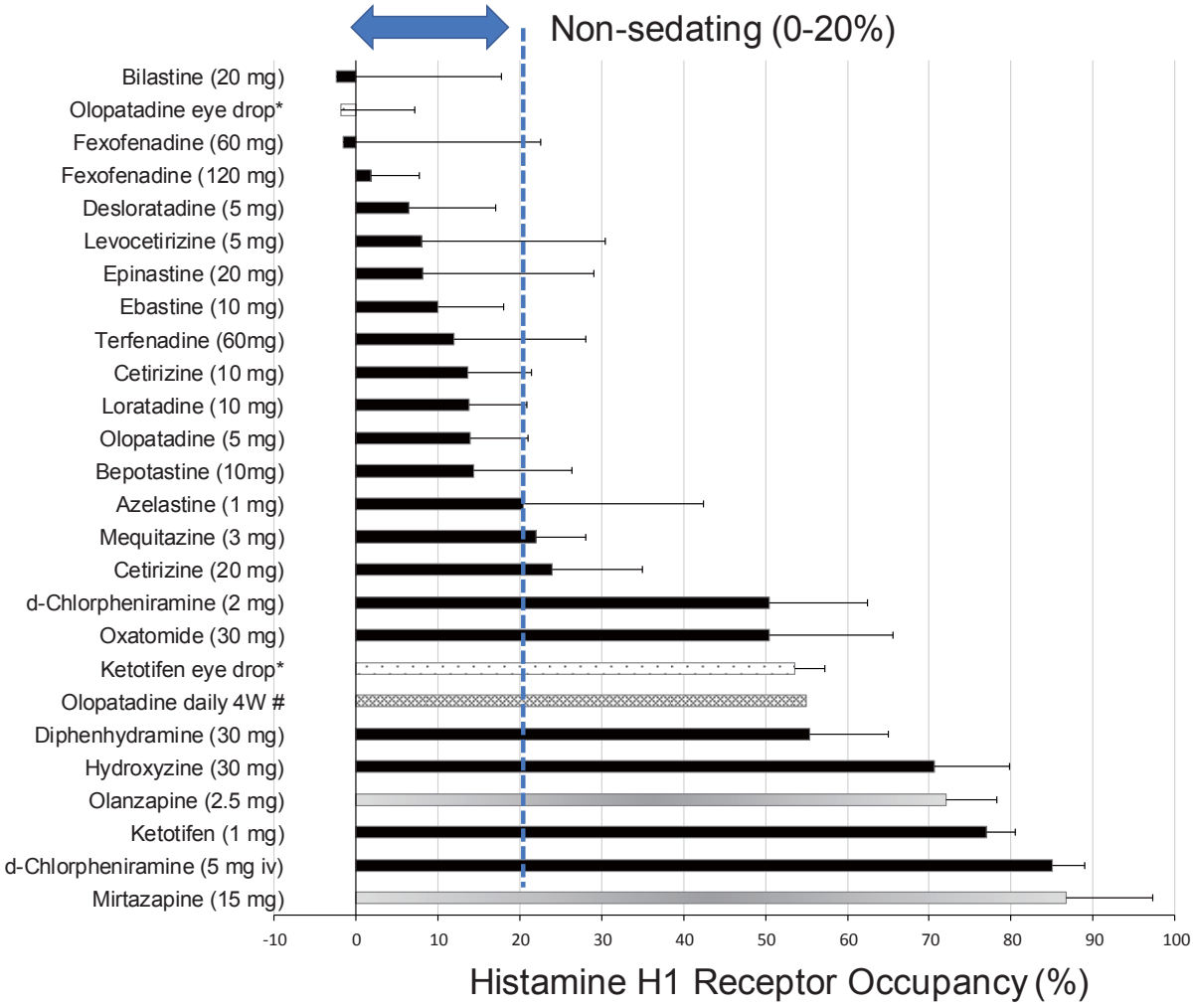

Figure. Evaluation of sedative properties of H1 antagonists based on histamine H1 receptor occupancy. H1 receptor was measured by positron emission tomography (PET) using [^{11}C] doxepin after single oral administration of H1 antagonists to normal healthy male volunteers. The occupancy data are the average ± SD. The antidepressant mirtazapine and the antipsychotic olanzapine are highly sedative and occupy most H1 receptors at the lowest dose (shown in light gray columns). Olanzapine (5 mg), which occupies a large amount of H1 receptors in the brain, is also approved for the use of chemotherapy-induced nausea and vomiting. It is classified as "non-sedating" when the H1 receptor occupancy rate is 20% or less. *: Eye drops, iv: Intravenous injection. #: When 5 mg of olopatadine is administered twice a day for 4 weeks, the H1 receptor occupancy rate increases from 15% to 55%. Otherwise, the data were obtained at the Tmax of single oral administration. Modified based on 1) and 2).

ABSTRACTS

Young Investigator Session

Y-1 Histamine induced high mobility group box-1 release from vascular endothelial cells

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【Abstract】

High mobility group box-1 (HMGB1), a nonhistone chromatin-binding nuclear protein, can be actively secreted into the extravascular space by endothelial cells. HMGB1 was reported to have pro-inflammatory effects on endothelial cells and increase the vascular endothelial permeability. Histamine is a major preformed mediator released by mast cells and it strongly increases vascular permeability through H1 receptor on endothelial cell. However, the relationship between histamine and HMGB1 mediated-signaling in vascular endothelial cells has never been studied before. In our study, the results show that histamine can induce HMGB1 translocation from the nucleus to cytoplasma in EA.hy 926 endothelial cells in a dose- and time-dependent manner. Moreover, these effects could be prevented by antagonist of H1 receptor, but not by H2 and H3/4 receptor antagonists. Our study suggests that the action of histamine on the activation of vascular endothelial cells may be associated with HMGB1 mobilization and subsequent signaling.

Y-2 Effects of antihistamines on brain energy consumption during cognitive tasks (positron emission tomography study)

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【Abstract】

We previously demonstrated, using positron emission tomography (PET), that antihistamine treatment was associated with increased brain glucose (energy) consumption during cognitive tasks in healthy young adults after treatment with antihistamines. Healthy young men were recruited for cognitive study (n=18) and for resting study (n=6), in a double-blind, placebo-controlled, three-way crossover study. Following a baseline scan using PET and [18F]fluorodeoxyglucose (FDG-PET), the subjects received single doses of non-sedative antihistamine (levocetirizine 5 mg) or sedative antihistamine (diphenhydramine 50 mg), and were scanned again 3 hours later. Brain energy consumption changes were calculated based on the 2 PET scans. The present results demonstrated that the brain glucose consumption is stable in resting condition both after treatment with placebo and antihistamines while the brain energy consumption increased during tasks after treatment with antihistamines more than after placebo treatment. The present findings suggested that the increased energy consumption was more associated with higher energy demands during cognitive tasks.

Y-3 Analysis of astrocyte-specific histamine N-methyltransferase knockout mice

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【Abstract】

Brain histamine acts as a neurotransmitter to control various physiological processes. We have revealed the importance of histamine N-methyltransferase (HNMT), an enzyme for histamine inactivation, for brain histamine system. Although previous studies reported the neuronal and astrocytic expression of Hnmt, it is still unknown the contribution of each cell type to histamine inactivation. In the present study, we created astrocyte-specific Hnmt knockout mice (cKO mice) and analyzed their phenotype. Brain histamine concentration of cKO mice was not significantly different from that of control mice. Behavioral test battery showed the lower locomotor activity of cKO mice, although anxiety-like behaviors and depression-like behaviors were not altered by astrocytic Hnmt deletion. These results demonstrated that Hnmt in astrocytes was involved in locomotor activity in spite of the small contribution of astrocytic Hnmt to brain histamine concentration.

Y-4 Chronic histamine decrease in adult mice brain induced increased depression-like behavior and decreased locomotor activity

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【Abstract】
Histamine acts as a neurotransmitter and regulates several physiological functions in the central nervous system. Recent studies reported that the decrease of histamine system was observed in neuropsychiatric disorders such and Alzheimer's disease and narcolepsy. However, it is not elucidated whether the decreased brain histamine plays a causative role in those disorders. In this study, we used histidine decarboxylase (Hdc) flox mice and adeno-associated virus (AAV) to induce chronic depletion of histamine in the brain. Hdc conditional knockout (cKO) mice was generated by injecting AAV expressing Cre recombinase into the tuberomammillary nucleus. We confirmed decreased expression level of Hdc mRNA, and protein level of Hdc and brain histamine contents. In behavioral experiments, cKO mice showed increased depression-like behavior and decreased locomotor activity. In the sleep analysis, cKO mice showed decreased wakefulness and increased non-REM sleep. Our data suggested chronic histaminergic dysfunction plays a causative role in neuropsychiatric disorders.

Y-5 Histamine Excites Rat Intracardiac Ganglion Neurons Via Activation of TRPC Channels

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【Abstract】
Although anaphylaxis associated acute coronary syndrome is reported to be mediated by histamine, its underlying mechanism is still poorly understood. Given that cardiac functions are greatly regulated by the autonomic nervous system and that intracardiac ganglia act as relay stations for all parasympathetic input to the heart, we clarified the intracellular mechanisms of histamine-evoked depolarization on rat intracardiac ganglion neurons in vitro with perforated patch clamp recording. First, this depolarization was induced via histamine receptor 1 (H1 receptor). Second, histamine evoked current via phosphoinositide-specific phospholipase C (PLC). Third, histamine-activated PLC increased intracellular Ca2+ concentration. Finally, an increase of intracellular Ca2+ concentration led to activate TRPC channel. Taken together, these results indicate that histamine facilitates the excitation of intracardiac ganglion neurons via distinct H1 receptor dependent signaling pathways that ultimately activate TRPC channels.

Y-6 Possible involvement of endoplasmic reticulum stress response on allergic degranulation

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【Abstract】
When stress was exposed to cells, a problem occurs to the protein folding mechanism in the endoplasmic reticulum, which abnormal proteins accumulates. Such a condition is termed endoplasmic reticulum stress, and cells activates various stress response mechanisms to try to avoid against the stress. On the other hand, it has been suggested that activation of the endoplasmic reticulum stress response may be caused not only due to the accumulation of abnormal proteins in the endoplasmic reticulum but also by a physiological reaction. In this study, we focused on the IRE1-XBP1 pathway, one of the major pathways of the endoplasmic reticulum stress response mechanism, and examined the possibility that the endoplasmic reticulum stress response is activated in the degranulation reaction caused by antigen-antibody reaction in mast cells. In the present study, it was suggested that type I allergy, which is thought to be caused by degranulation through antigen-antibody reaction, may activate the IRE1-XBP1 pathway.

Y-7 The degranulation mechanism of RBL-2H3 cells with a calcium ionophore A23187

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【Abstract】
A23187 is one of antibiotics and used widely as a calcium ionophore. The effect of A23187 has been thought as a carrier ionophore that binds with Ca^{2+} and then transports Ca^{2+} across plasma membrane. But we found A23187 could not induce degranulation and continuous $[Ca^{2+}]_{in}$ increase of RBL-2H3 cells treated with YM58483, a store operated calcium (SOC) channel inhibitor under extracellular Ca^{2+} existence. And low concentration of A23187 could induce Ca^{2+} release from ER without IP_3R and RyR. 5 min stimulation of RBL-2H3 cells by 500 μM A23187 could aggregate STIM1, ER membrane protein, but 15min stimulation could not. And 15min stimulation lead to increased permeability of RBL-2H3 cells. Degranulation of RBL-2H3 cells by A23187 showed byphargic alteration at about 15min. These results show the different mechanism for A23187 that works first ER membrane, maybe as an ionophore, induces SOCE, neutralizes calcium ATPase (SERCA, PMCA) in consort with Ca^{2+}, and finally changes the permeability of plasma membrane.

Y-8 Influence of cyclophosphamide on L-Asparaginase-induced allergy in animal model

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【Abstract】

We examined the effect of cyclophosphamide (CY) on L-Asparaginase (L-ASP) allergy. Male BALB/c mice were sensitized by L-ASP with Al(OH)3 gel on days 1 and 15. Then, the right ears of the mice were i.d. sensitized by L-ASP. CY was i.p. injected on days –1 and 13. The serum were collected on day 27. Total IgE level in the serum were measured by ELISA. RBL-2H3 cells were sensitized by the serum and stimulated by L-ASP to determine β-hexosaminidase (β-Hex) release in vitro. L-ASP sensitization increased serum IgE level, which was enhanced by CY at 150 mg/kg. When RBL-2H3 was sensitized L-ASP-allergic mice serum in vitro, L-ASP stimulated β-Hex release from the cells. The serum of CY-treated mice induced higher β-Hex release than normal. Anti-IgE Ab inhibited allergic β-Hex release both in vitro and ex vivo. From these results, it was concluded that (1) Anti-IgE Ab can be a candidate for the treatment of L-ASP allergy, (2) CY suppressed Treg function, which may enhance Th2 response so as to augment L-ASP allergy.

Y-9 Effects of histamine and cytokines on TF-expression and inter-cellular gap formation of HUVECs

Akiko Kamegashira, Yuhki Yanase, Shunsuke Takahagi, Kazue Uchida, Tomoko Kawaguchi, Michihiro Hide

Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University

【Abstract】

The coagulation cascade has been suggested to be involved in the pathogenesis of chronic spontaneous urticaria (CSU). However, the trigger of the coagulation pathway in patients with CSU remains unclear. Previously we reported that histamine and lipopolysaccharide (LPS) synergistically induced the expression of tissue factor (TF) on human umbilical vein endothelial cells (HUVECs) which then induced inter-cellular gap formation via the extrinsic coagulation cascade. On the other hand, the elevations of TNF-α, IL-1β, IL-33 and VEGF have been reported in serum of a certain population of patients with CSU. In this study, we examined the effects of TNF-α, IL-1β, IL-33, VEGF, LPS and histamine on TF expression and intercellular gap formation of HUVECs. The expression of TF mRNA and surface protein of TF on HUVECs in response to histamine or VEGF were synergistically enhanced by the treatment with TNF-α, LPS, IL-1β or IL-33. Moreover, TF activity and inter-cellular gap formation of HUVECs in response to histamine or VEGF were also synergistically increased in the presence of TNF-α, LPS, IL-1β or IL-33.

Y-10　Increase of tissue factor expression on the surface of peripheral monocytes of patients with chronic spontaneous urticaria

Ryo Saito, Yuhki Yanase, Kazue Uchida, Tomoko Kawaguchi, Michihiro Hide
Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University

【Abstract】
We investigated the role of tissue factor (TF), which is expressed on peripheral monocytes and may activate the blood coagulation pathway in association with chronic spontaneous urticaria (CSU). TF expression levels on monocytes detected by RT-PCR and flow cytometry were significantly higher in patients with CSU than those in healthy donors. Moreover, the expression of mRNA, surface protein and biological activity of TF, which evaluated by the ACTICHROME® TF assay, on monocytes were all enhanced by the treatment with LPS, but not with histamine. Furthermore, inter-cellular gap formation of endothelial cells was monitored by impedance analysis and it was induced in the presence of plasma and monocytes treated with LPS. TF expression on monocytes is enhanced in patients with CSU in a histamine-independent manner and drives vascular endothelial cell inter-cellular gap formation via the extrinsic coagulation cascade. This cascade may contribute to the pathogenesis of CSU, especially that refractory to antihistamines.

ABSTRACTS

Oral Presentations

O-1 Potential role of G protein-coupled receptor 3 in the brain mast cells following brain ischemia

Shigeru Tanaka[1], Yuhki Hamakawa[1], Yuhki Yanase[2], Hiroko Shiraki[1], Masahiro Yamamoto[1], Kana Harada[1], Izumi Hide[1], and Norio Sakai[1]

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【Abstract】

G protein-coupled receptor (GPR) 3 belongs to a member of constitutively active Gs-coupled receptors, and have known to enhance neurite outgrowth and modulate neuronal survival. Here, we investigated whether GPR3 expression is modulated following brain ischemia. We found that GPR3 mRNA expression transiently increased in the ischemic hemisphere as early as 4 h after transient middle cerebral artery occlusion in Wistar rats and C57BL/6 mice. Analyses of Percoll density gradient fractions from an ischemic brain homogenate indicated that mast cells are the source of GPR3 in the ischemic brain. We further addressed GPR3 expression in the bone marrow-derived mast cells (BMMCs). GPR3 mRNA was highly upregulated as early as 1–2 h and declined when BMMCs were stimulated by IgE-mediated dinitrophenyl conjugated human serum albumin or adenosine triphosphate. Compared with BMMCs from wild-type mice, BMMCs from GPR3 knockout mice showed significantly increased degranulation in response to various degranulation stimuli. These results suggest that GPR3 may play a role in inhibiting the degranulation of the mast cells and modulates inflammatory responses triggered by brain ischemia.

O-2 The effects of Simvastatin and PCSK9 inhibitor on degranulation of RBL-2H3 cells by antigen-antibody reaction.

Michiko Yoshii[1], Ai Kitazaki[2], and Koichiro Ozawa[1]

[1] Department of Pharmacotherapy, Graduate School of Biomedical and Health Sciences, Hiroshima University, [2] School of Pharmaceutical Sciences, Hiroshima University

【Abstract】

Hypercholesterolemia is a major problem for arteriosclerosis. Mast cells in arteriosclerosis plaque induce inflammatory reaction, increase vesicular permeability, and facilitate arterial sclerosis. In this study, we evaluated the pharmacological effect of simvastatin (SV), HMG-CoA reductase inhibitor and SBC115076 (SBC), PCSK9 inhibitor, on degranulation in RBL-2H3 cells. SV decreased significantly degranulation induced by DNP-BSA, A23187 and thapsigargin (Tg). SBC had no effect. Mevalonate or geranylgeraniol cotreatment prevented the inhibition of degranulation by SV. SV had no effect on increase of $[Ca^{2+}]_{in}$ by any stimulation. Immunostaining results of RBL-2H3 cells indicated SV did not change IgE and Orai1 visually. MTT assay of RBL-2H3 cells treated with SV or SBC showed no significant change. In conclusion, SV has inhibitory effect of degranulation of RBL-2H3 cells, and probably this effect is induced by altered localization of small GTPase involved with vesicle transport not by reduced cholesterol.

O-3 AMP-activated kinase-mediated suppression of degranulation of murine mast cells

Satoshi Tanaka

Department of Pharmacology, Kyoto Pharmaceutical University

【Abstract】

Accumulating evidence suggests that low grade chronic inflammation, which affects the profiles of adipocytokine production, should occur in adipose tissues under obese conditions. The number of infiltrated mast cells was found to be increased in the interstitium of the adipose tissues of obese patients. Recently, an activator of AMP-activated kinase (AMPK), AICAR, was found to suppress degranulation of murine mast cells, indicating that some modulators of energy metabolism, such as adiponectin and AMPK, should regulate mast cell functions. Here we investigated the mechanism of AICAR-mediated suppression of murine mast cell activation. Pretreatment with adiponectin or AICAR significantly suppressed the production of inflammatory cytokines in murine bone marrow-derived cultured mast cells (BMMCs) in the presence of various stimulus, such as the antigen, Toll-like receptor agonists, and thapsigargin. AICAR suppressed the elevation of cytosolic Ca^{2+} concentrations, aggregation of STIM1, and decreased actin polymerization induced by the antigen or thapsigargin. These findings suggest that AMPK suppressed Ca^{2+} mobilization induced in activated murine mast cells.

O-4 The role of histamine in the progression of oral squamous epithelial cancer

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1: Div. of Bioregulatory Pharmacology, Dept. of Pharmacology, Iwate Med. Univ.
2: Div. of Oral and Maxillofacial Surgery, Dept. of Oral and Maxillofacial Reconstructive Surgery, Sch. of Dent., Iwate Med. Univ.
3. Div. of Anatomical and Cellular Pathology, Dept. of Pathology, Iwate Med. Univ.

【Abstract】
Malignant tumor cells produce histamine and express histamine receptors. Tumor microenvironments turning into acidic condition contribute to proliferation, migration, and metastasis. Our hypothesis is that histamine can modulate the proton excretion and pH sensing in the extracellular space. The current studies focus on the effects of histamine and antihistamine agents for regulation of proton excretion molecules and proton sensing.
Human oral cancer cell line (HSC4) were cultured with exposure of histamine or antihistamine drugs. Gene expressions on histamine receptors, proton excretion molecules, and proton sensing GPCR were evaluated with qPCR. Histamine exposure for 24 hours significantly increased gene expression of H2R, H3R, ATP6V1G1, SLC4A1, SLC4A9, while Carbonic anhydrase (CA)-9 and-12 revealed the significant decrease. H2R antagonist inhibited gene expression of ATP6V1G1, SLC4A1, SLC4A9. H2R antagonists showed probable effectiveness in regulation of microenvironment of tumors.

O-5 Histaminergic pathway in the brain and vigilance status

Tadaho Nakamura[1], Fumito Naganuma[1], Hiroshi Kuroyanagi[1], Masato Tanaka[1], Takeo Yoshikawa[2], Kazuhiko Yanai[2], Nobuyuki Okamura[1]
[1]Division of Pharmacology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University
[2]Department of Pharmacology, Tohoku University Graduate School of Medicine

【Abstract】
The histaminergic neurons in the tuberomammillary nucleus play an important role in the regulation of vigilance status in rodents. The precise neural circuit of histaminergic neurons, however, which related to the regulation of vigilance status still remains to be elucidated. We used the chemogenetic approach in a Hdc-Cre mouse line and examined whether the specific activation of histaminergic neurons altered vigilance status. We also determined the projection from histaminergic neurons which related to the vigilance regulation. We found that the acute specific activation of histaminergic neurons increased arousal status for a short period. Histaminergic neurons projected to the various brain region including cortex, anterior hypothalamus, amygdala, and midbrain which related to the regulation of vigilance status in rodents. These results indicated that the specific histaminergic projection might be important for the regulation of vigilance status.

O-6 The involvement of histamine on nociceptive behaviors induced by intrathecally administered cholecystokinin-8

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【Abstract】

The sulfated octapeptide cholecystokinin (CCK-8) is present in the dorsal horn of the spinal cord. Intrathecal (i.t.) injection of CCK-8 elicited a behavioral response consisting of scratching, biting and licking in mice. CCK-8-induced behavioral response was dose-dependency showed a bell-shaped pattern, and the maximum effect was observed at 10 amol and 10 pmol. The nociceptive behaviors induced CCK-8 were inhibited by i.t. administration of CCK-B (CCK2) receptor antagonist and were abolished in histidine decarboxylase-deficient mice. The tachykinin neurokinin-1 (NK1) receptor antagonists inhibited CCK-8 (10 pmol, not 10 amol)-induced behavioral response. The behavioral responses elicited by CCK-8 were inhibited by the antagonist for the polyamine-binding site of the N-methyl-D-aspartate (NMDA) receptor. The present result suggested that nociceptive behaviors induced by i.t. administration of CCK-8 are mediated through the spinal release of histamine and are elicited via activation of NK1 and NMDA receptors.

O-7 Analyses of histamine in the hypertension-induced cardiorenal syndrome model mice (ANS mice)

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【Abstract】

The number of patients with cardiovascular and chronic kidney diseases has been recently increasing, and both are known to be complicated and are risk factors for each other. By using LC-MS/MS, we searched for relating amines for these diseases in hypertension induced cardiorenal syndrome model mice (ANS: Angiotensin II, Nephrectomy, Salt mice) as a clue to elucidating its mechanism, and observed that histamine from ANS mice blood was increased approximately twice as compared with the control group.

We found that cardiorenal functions were significantly reduced in HDC-KO ANS-treated mice compared to wild-type ANS mice. The H3 blocker reduced cardiorenal function in wild-type ANS mice, whereas cardiorenal dysfunctions of them were reduced by administration of H3-specific agonist, imesulidine. The transcriptome analyses revealed that inflammatory statuses of tissues in the ANS model mouse administered with imesridine were improved as compared with the non-administered ANS model mice.

O-8 Mechanism of NFAT-signaling suppression by pyrogallol

Mizuguchi H[1], Nakano T[2], Nishida K[2], Ito T[2], Wakugawa T[2], Kaminuma O[3], Kitamura N[4], Ishida T[5], Yabumoto M[6], Kitamura Y[7], Takeda N[7], Fukui H[6, 7]

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【Abstract】

Pollinosis is a seasonal allergic rhinitis suffered from 30% of Japanese population. We have demonstrated that histamine H_1 receptor (H1R) and IL-9 gene are the pollinosis-sensitive genes and PKCδ signaling and NFAT signaling are involved in their expressions. Pyrogallol is the anti-allergic compound found in Awa-tea. Pyrogallol inhibited ionomycin (IO)-induced dephosphorylation and nuclear translocation of NFAT. Pull-down assay revealed that pyrogallol strengthened interaction between NFATc1 and calcineurin (CN). Further studies demonstrated that CN binding site 2 in NFATc1 was involved in pyrogallol's effect. Poly(U)-binding-splicing factor 60 (PUF60) was identified as NFATc2 binding protein using pyrogallol-immobilized affinity chromatography. Pyrogallol suppressed IO-induced interaction of PUF60 with NFATc2. Knockout of PUF60 gene suppressed IO-induced IL-9 gene upregulation. Data suggest that pyrogallol suppressed NFAT signaling through the inhibition of NFAT dephosphorylation by the isoform-dependent manner.

O-9 Analysis of histamine concentration in sweat obtained from patients with cholinergic urticaria.

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Department of Dermatology, Institute of Biomedical & Health Sciences, Hiroshima University

【Abstract】

Introduction: Histamine in sweat were measured and compared with basophil reactivity to purified sweat antigen in patients with CholU. Methods: Nine patients with CholU were recruited along with enrollment of patients with atopic dermatitis (AD), patients with chronic spontaneous urticaria (CSU) and healthy controls. Histamine in sweat was measured by high performance liquid chromatography. Results: Histamine concentrations in sweat of patients with CholU were higher than those in plasma of healthy subjects. Increased concentrations of sweat histamine were also observed in several sweat samples obtained from patients with AD or CSU, and healthy controls. In several subjects, histamine concentrations in sweat were higher than those to induce skin reactions upon intradermal injection. There was positive correlation between histamine release from the subjects' basophils against the sweat antigen, and sweat histamine concentrations. Discussion: Considering leakage of sweat into the dermis reported in patients with CholU, the leakage of sweat with high concentrations of histamine through sweat gland may induce the wheal formation in association with sweat allergy in CholU.

NEWSLETTER

Mini Review
submitted by Wada Prize Winner

Special Remark
by the President of JHRS

Next Meeting
announced by the next chairperson

Report on World Histamine Symposium

Report on EHRS Meeting

Mechanisms Underlying the Excitatory Effect of Histamine on Intrinsic Neurons of Rat Heart

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2 Department of Physiology, School of Allied Health Sciences, Kitasato University;

3 Division of Homeostatic Development, National Institute for Physiological Sciences;

The intrinsic cardiac nervous system plays an important role in regulating cardiac function and contains parasympathetic ganglia. Signaling by these ganglia is postulated to contribute to the pathogenesis of coronary artery vasospasm given that this can be induced by locally administering the parasympathetic neurotransmitter acetylcholine (1) (Fig. 1). More specifically, this implicates hyperactivity in intracardiac ganglion neurons as these are the postganglionic neurons of the parasympathetic nervous system. Interestingly, histamine is known to increase the excitability of intracardiac ganglion neurons (2-3) although the mechanism is unclear, and severe allergic reaction episodes can sometimes induce coronary artery vasospasm. Thus, we briefly summarize novel findings regarding the mechanisms underlying histamine-induced excitation of rat intracardiac ganglion neurons in this review (Fig. 2).

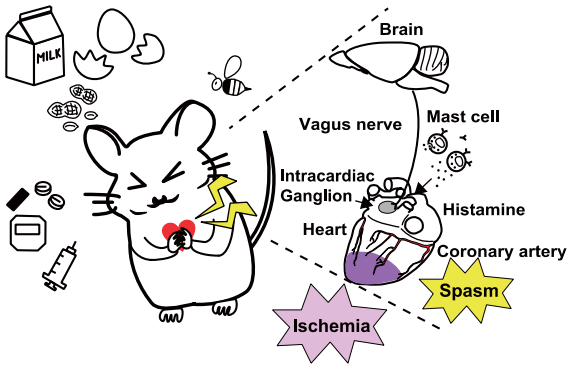

Figure 1. Possible mechanisms underlying histamine-induced spasms of the coronary artery via activation of the parasympathetic nervous system during acute allergic reaction.

Histamine activates intracardiac neurons via H_1 receptors and TRPC channels

In our recent electrophysiological study, histamine-induced depolarization of rat intracardiac ganglion neurons was inhibited by the H_1 receptor antagonist triprolidine and mimicked by the H_1 receptor agonist 2-pyridylethylamine. This suggests that histamine activates rat intracardiac neurons via H_1 receptors. It is well established that H_1 receptors activate phospholipase C (PLC) via $G_{q/11}$ signaling, resulting in the breakdown of phosphoinositide and the production of inositol trisphosphate (IP_3). A major downstream effect of this PLC-signaling pathway is the activation of TRPC channels, which are non-selective cation channels with high Ca^{2+} permeability. In our study, inhibiting TRPC activity with relevant channel blockers diminished histamine-induced depolarization thus confirming the involvement of TRPC channels.

Histamine inhibits the M current

Low-threshold KCNQ K^+ channels, also known as M-type K^+ channels, are negative regulator of excitability in a variety of neurons (4). Stimulation of receptors that are upstream of $G_{q/11}$ signaling produces M-current depression, primarily through phosphatidylinositol 4,5-bisphosphate (PIP_2) depletion by PLC-mediated hydrolysis (5). In our study, histamine application suppressed the M-current presumably through H_1 receptor activation.

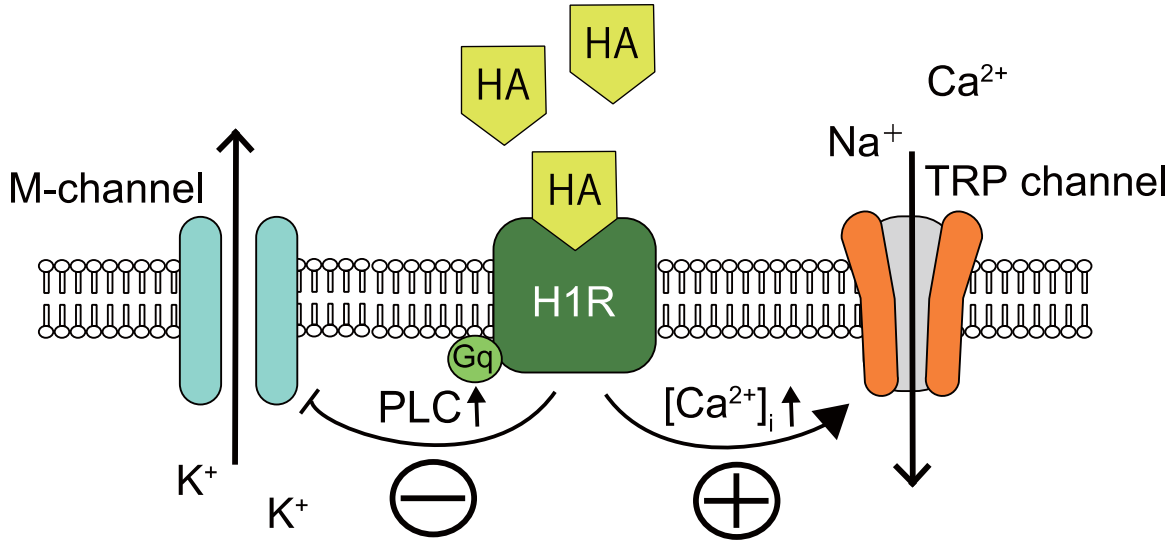

Figure 2. Schematic representation of the mechanisms underlying histamine-induced excitability in rat intracardiac ganglion neurons

Conclusion

Histamine increases intracardiac ganglion neuron excitability via a two-pronged, H_1 receptor dependent mechanism – activating TRPC channels and suppressing M-current. This provides a mechanistic framework for understanding how severe allergic reaction episodes can provoke coronary artery vasospasm. More broadly, it suggests an under-explored modulatory mechanism for neuronal activity in the intrinsic cardiac nervous system which, given the presence of histamine in the heart, might even be applicable to the other cardiac disease such as arrhythmias or heart failures.

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これからのヒスタミン研究に関する私の所感

福井裕行
日本ヒスタミン学会　会長
医療法人錦秀会　顧問
徳島大学　名誉教授

新型コロナウイルス感染症のパンデミックな流行中ですが、皆さまにおかれましては、不自由な中、研究、教育、医療、及び、その他の社会活動を日々工夫しながらやり遂げる努力を続けられていることと思います。致死的な怖さを持つ新型ウイルスに対して有効な治療手段がなかったことから、また、私事として教授職を終え、特任教授、医療法人顧問と社会的活動が少なくなってきたことから、この一年間の私の活動は最低レベルになってしまいました。現在は、新しいワクチンの成功による感染症の抑え込みを強く期待し、更に、新規治療薬の開発による本感染症の克服を心待ちにしております。このような不幸な非常時に生きている訳ですが、歴史的に考えた時、本当に生き延びることのできるものが篩にかけられる時代を過ごしているのではないかと思っております。

そこで、ヒスタミン研究について論じたいと思います。ヒスタミンの立ち位置は何かと言いますと、アセチルコリン、及び、カテコラミン、セロトニンなどの生体アミンと同じレベルの生理的、病理的に重要な活性物質であると思います。これらの生理活性物質の受容体、情報伝達機構解明の研究から多くの治療薬が開発され、薬理学はもとより、医学の中心的存在であったことは疑いもありません。今後も、研究の進展と医学への還元が続くものと考えられます。ヒスタミンに関しては、H_3受容体、H_4受容体サブタイプの機能解明と治療薬開発が強く期待されます。既に、H_3受容体拮抗薬のピトリサントがナルコレプシー治療薬として開発され、更に、H_3受容体拮抗薬による神経疾患治療薬、H_3受容体作動薬による肥満、糖尿病、腎疾患治療薬、H_4受容体拮抗薬による免疫疾患、炎症性疾患治療薬の開発が期待されます。H_1受容体、H_2受容体の場合、それぞれがアレルギー疾患、消化性潰瘍に対して支配的に関与していることから、治療薬開発に成功しました。H_3受容体、H_4受容体標的薬が治療薬として確立できるか否かは、それぞれの受容体により支配的関与を受けているかどうかが重要だと思われます。

時代が移り、サイトカインなどのペプチド系活性物質を始めとして、多くの活性物質が同定されました。複雑な生体機構解明のためには、これらの活性物質の関

与を考慮した研究を進める必要があります。また、細胞内情報伝達機構解明も目覚しく発展しました。一方、多くの疾患は多因子疾患として複数の病理機構が絡み合って関与していることが明らかにされつつあります。このような状況から、難治性疾患、即ち、多因子疾患の治療法解明には、それに関与する複数の機構解明による支配的関与の証明が必要であると考えられます。
再度、ヒスタミンの関与する多因子疾患の治療法確立の課題に戻りますと、ヒスタミンが支配的に関与する疾患の同定とその病理機構解明を進める必要があります。多因子疾患の機構解明と治療法確立には、ヒスタミンが関与する病理機構解明に並行して、ヒスタミン以外の病理機構の解明も必須であります。そして、それぞれの機構を標的とする治療薬による積極的併用療法による治療法を確立する必要があります。振り返りますと、ヒスタミンという生理活性物質を取り巻く研究テーマが、生理・病理機構の解明、更に、疾患の克服に向かって大膨張していると思います。このような状況において、ヒスタミン研究を進めることが私の考える方向性です。私の所感が皆さまの研究の参考になれば幸いです。研究とは独創性が生命です。インパクトの強い研究成果を期待します。

第 23 回日本ヒスタミン学会のご案内

当番幹事（実行委員長）　田中智之
京都薬科大学　病態薬科学系　薬理学分野　教授

ヒスタミン研究は長い歴史を持ちますが、今なお年間 1,000 報以上の研究論文が発表されています。みなさまもご存知の通り、その機能は多岐にわたっており、汲めども尽きぬ関心をよぶ興味深い生理活性物質です。私自身、この学会に参加することを通じて、ライフサイエンスに幅広い関心をもって取り組むことができたことは大変な幸運でした。この度、第 23 回大会を開催する機会を賜り、誠に光栄に感じております。

今回は、炎症と神経伝達というヒスタミンの代名詞ともいうべきトピックスに着目いたしました。慢性蕁麻疹をトピックとして、ドイツのシャリテ–ベルリン医科大学の Marcus Maurer 博士、京都大学医学研究科皮膚科学の神戸直智博士を特別講師として招聘いたします。また、本学会をリードするトップ研究者である東北大学医学研究科機能薬理学の谷内一彦先生をお招きし、ヒスタミンの中枢機能に関する特別講演を予定しております。

昨年は COVID-19 のパンデミックにより、日本ヒスタミン学会の集会は中止を余儀なくされましたが、今回は例年通り、様々な領域のヒスタミン機能を追求し、自由に議論する会となることを期待しております。ご協力のほど、宜しくお願い申し上げます。

会期：2022 年 1 月 7 日（金）午後、8 日（土）午前を予定しております。
会場：京都大学医学部　芝蘭会館稲盛ホール

ホームページ：近日中に日本ヒスタミン学会 web サイト(http://www.jhrs.umin.jp)で告知いたします。

Announcement of the 23rd Annual Meeting of Japanese Histamine Research Society

Histamine research has a long history and nowadays more than 1,000 research articles per year have been published in this field. Histamine is an active mediator, which is involved in diverse physiological functions, and is an inexhaustible source of excellent studies. Participation in the annual meeting of Japanese Histamine Research Society has provided me with a good opportunity to broaden my perspective on life sciences. It is my great honor to organize the annual meeting.

This meeting will focus on two traditional histamine topics, inflammation and neurotransmission. Two distinguished researchers in the field of urticaria research, Dr. Marcus Maurer, who is a professor at Charité-Berlin University of Medicine, and Dr. Naotomo Kambe, who is an associate professor at Kyoto University, will provide us with the special lectures. We will also welcome a special speaker in the field of neuroscience, Dr. Kazuhiko Yanai, who is a professor at Tohoku University and one of the leading scientists in the field of histamine research.

Unfortunately, pandemic of COVID-19 prevented us to get together last year, but I sincerely hope that we will share the information and discuss the diverse functions of histamine. I am looking forward to seeing all of you in Kyoto.

Sincerely yours,

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Web: To be announced in http://www.jhrs.umin.jp

Looking back World Histamine Symposium 2018, WHS2018

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World Histamine Symposium 2018 (WHS2018) was held at Shinsho Hall, The Kobe Chamber of Commerce and Industry from July 7 to 9, 2018 under the theme, 'Expanding Histamine Research'. WHS2018 was a satellite symposium of the 18th World Congress of Basic and Clinical Pharmacology (WCP2018) from July 1 to 5, 2018 at Kyoto International Conference Center. The first international histamine meeting, International Histamine Symposium, organized by Professor Kenji Tasaka, Okayama University, was held from July 25 and 26, 1981 in Okayama. The second meeting, International Sendai Histamine Symposium, from November 22-25, 2000, in Sendai was organized by Professor Takehiko Watanabe under the theme, 'Histamine Research in the New Millennium'. Then WHS2018 was the third one.

WHS2018 started in heavy rain days often seen at late rainy season in Japan. Truly, we had record heavy rain. It seemed to be affected by global warming. Many places were damaged by flood disasters. Some participants in neighboring area to Kobe had no choice but to be absent from the meeting because of traffic-stopping. Fortunately, participants from abroad and remote areas in Japan safely arrived in Kobe, and the symposium started as scheduled. The welcome eve was intimately held on July 6 at Kobe-kitano Hotel by Professor Takehiko Watanabe's support, and participants enjoyed meeting again.

The plenary session was held for three days with 26 symposiums and 21 poster presentations. Participants were gathered from the United Kingdom of Great Britain and Northern Ireland, China, Italy, Finland, Germany, The Netherlands and The United States of America with 13 lectures. Lectures were truly world-leading. Excursion to Himeji Castle, a National treasure of Japan, was taking place by bus on an unexpectedly sunny day between meetings. Participants tried climbing the large wooden castle with flowing sweat. Flower arrangement and tea party were scheduled. The flower arrangement was enjoyed. Unfortunately, the tea party had to be canceled due to the bad weather. The farewell party was enjoyed on the top floor of Ariston Hotel Kobe surrounded by the night view. Fortunately, my son's piano performance added a kind of grace.

Histamine receptor ligands have brilliant histories, because antihistamines, histamine H_1 and H_2 receptor antagonists contributed to the therapy of allergic diseases and peptic ulcers, respectively. Currently, pathological mechanisms of histamine H_3 and H_4 receptor-related diseases are extensively investigated, and the development of novel therapeutics is highly expected. On the other hand, most diseases are multifactorial. For example, the pathological mechanism of allergic rhinitis was proven to consist of histamine H_1 receptor-related and -unrelated ones, and combination therapy with an antihistamine and another drug is thought promising for excellent alleviation. 'Expanding Histamine Research' was the theme of WHS2018. I would like to propose that we need the diversity of histamine research.

In conclusion, I wish to express my deepest thanks to all the committee members, all the people participated and all other people involved. WHS2018 could not succeeded at all without strong support of Professor Mitsunobu Mio, Shujitsu University. I express the special appreciation to Professor Mio for his excellent secretary work and strong support. Creation of abstract was achieved by strong help of Professors Hiroyuki Mizuguchi, Osaka Ohtani University, and progress of the symposium was smoothly guided by Professor Satoshi Tanaka, Kyoto Pharmaceutical University. I express the sincere appreciation to their thoughtful supports.

World Histamine Symposium 2018, WHS2018 を振り返って

World Histamine Symposium 2018 (WHS2018) が、'Expanding Histamine Research' というテーマの下に、2018 年（平成 30 年）7 月 7 日-9 日に神戸市中央区港島の Shinsho Hall, The Kobe Chamber of Commerce and Industry（神戸商工会議所会館 神商ホール）において開催された。また、本シンポジウムは、2018 年 7 月 1-5 日に京都市で開催された 18th World Congress of Basic and Clinical Pharmacology (WCP2018) のサテライトシンポジウムとして開催された。我が国においてヒスタミン研究者が集う最初の国際学会として、International Histamine Symposium が、1981 年（昭和 56 年）7 月 25, 26 日に田坂賢二教授（岡山大学）により岡山市で開催された。２回目の学会は、International Sendai Histamine Symposium が渡邉建彦教授（東北大学）により、'Histamine Research in the New Millennium'というテーマの下に，2000 年（平成 12 年）11 月 22-25 日に仙台市で開催された。本シンポジウムはヒスタミン研究者が集う 3 回目の国際学会となった。

本シンポジウムの梅雨明けによく見られる集中豪雨に見舞われながらの開会となった。豪雨は地球レベルの温暖化の影響を受けているようで、記録的な豪雨

であった。各地で大災害が引き起こされた。陸上交通が止まったことから、兵庫県神戸市に隣接する地域である、岡山県、広島県、高知県、徳島県から出席予定の先生方が欠席せざるを得なかった。幸いなことに、外国からの先生方を含め、遠路から参加の先生方は大きな問題なく到着し、学会は予定どおり開始できることとなった。前夜には、渡邉建彦教授の支援で、神戸北野ホテルにてウェルカムパーティーが開催され、学会開催のムードは盛り上がることとなった。

翌日より 3 日間に亘って学会が開催され、26 題のシンポジウム講演、及び、21 題のポスター発表が行われた。外国からは、英国、中国、イタリア、フィンランド、ドイツ、オランダ、及び、米国の学者の参加により、13 の講演が行われた。ヒスタミン研究の世界最先端の成果が発表された。学問の合間に、姫路城へのエクスカーション、及び、生花により日本を楽しんでもらった。お茶の計画もあったが、悪天候によりお茶の先生が神戸市に到着できず、非常に残念であった。日本の最高の城郭である姫路城は、大阪からやゝ距離があるが神戸市からは近いことから、良い訪問機会であった。また、最終日のフェアウェルパーティーでは神戸の夜景を楽しんでいただいた。愚息のピアノ演奏も先生方に楽しんでいただいた。

ヒスタミン研究は、抗ヒスタミン薬（ヒスタミン H_1 受容体拮抗薬）によるアレルギー疾患治療薬開発、及び、ヒスタミン H_2 受容体拮抗薬による消化性潰瘍治療薬開発により、輝かしい医学研究の歴史を刻んできた。現在、ヒスタミン受容体の新しいサブタイプの関与する疾患の解明による新たな治療薬開発が待望されている。一方、多くの疾患は多因子疾患であることが明らかにされている。ヒスタミンの関与する疾患が、ヒスタミン以外の機構の関与を受ける場合、ヒスタミンの機構に対する薬物とそれ以外の機構に対する薬物による積極的併用療法の対象になる。現在は、本シンポジウムのテーマ、'Expanding Histamine Research'の時代として、ヒスタミン研究の多様性が必要な時代ではないかと言うことを提案したい。

本シンポジウムの開催に当たって、見尾光庸教授（就実大学）の協力がなければ到底為し得ませんでした。それに加え、水口博之教授（大阪大谷大学）、田中智之教授（京都薬科大学）、更に、多くの先生方の協力によりヒスタミン研究に関する 3 回目の国際大会の開催に成功することができました。ここに謹んで深い感謝を申し上げたいと思います。

ヨーロッパヒスタミン学会報告 2019, 2020

【1】48th Annual Meeting of European Histamine Research Society

第 48 回 EHRS 年会は、2019 年 5 月 15 日～18 日の 4 日間、ポーランドの古都クラクフで、街の中央にある中央市場広場に面した International Cultural Centre を会場として Jagiellonian University（右上）の Katarzyna Kieć-Kononowicz 教授の主催で開催されました。この大学は 1364 年創建のポーランド最古の大学で、地動説を唱えたコペルニクス、ベンゾジアゼピンを開発したレオ・スターンバック、第 264 代ローマ教皇ヨハネ・パウロ 2 世などを輩出しています。JHRS からは Scientific Committee に福井裕行先生が関わられ、私は Abstract Evaluation & Student Bursary Award Committee で開催前から若手研究者の抄録審査を担当しました。

5 月 15 日は Registration、ポスター貼付、Opening lecture（Prof. S. Chlopicki）、招待講演（Prof. H. Timmerman）、Welcome reception がありました。翌 16 日から 18 日までは白熱したセッションが続きました。16 日最初の Scientific session は、2018 年 10 月 7 日にご逝去された岡山大学名誉教授で JHRS 名誉会員でもあった田坂賢二先生を偲んで、Histamine and allergy―Session dedicated to the memory of Prof. Kenji Tasaka として行われました。このセッションでは、私から Kenji Tasaka, a pioneer of histamine research in Japan というタイトルで、田坂先生の業績、EHRS との関わりや EHRS での受賞歴、ポーランドヒスタミン学会の名誉会員でありポーランド科学アカデミーからコペルニクスメダルを送られるなど、ポーランドとの関わりも深かったことなどを紹介させていただきました。続いて福井裕行先生が、Combination therapy of allergic rhinitis to a high-degree by suppressing histamine H1 receptor-PKC delta NFAT signaling というタイトルで招待講演をなさいました。午後からの中枢神経系のセッションでは、谷内一彦先生が Histamine N-methyltransferase in the brain というタイトルで招待講演をなさいました。東北大学や岡山大学に留学しておられた中国の陳忠先生の研究室からは、陳先生をはじめ 4 名が参加され、神経細胞に発現するヒスタミン受容体の役割や調節機構について、エネルギッシュに進めておられる最新の研究を報告されました。夕方からはこの大学の最も古い建物で現在は大学の歴史を物語る博物館になっている Jagiellonian University Collegium Maius と、薬学の歴史を展示した Pharmacy museum（これもこの大学の付属施設；右下）を参加者全員で見学しました。

17 日には、ポスターのショートプレゼンテーションに続いて、2017 年に亡くなられたドイツの Armin Buschauer 先生を

偲んで、Biologically active compounds－Session dedicated to the memory of Prof. Armin Buschauer というセッションがありました。Buschauer 先生はヒスタミン受容体をはじめ種々な G タンパク質共役型受容体に対する低分子リガンドを合成され、GPCR の情報伝達機構の解析に貢献されました。この日は、プラダー・ウィリ症候群に対する pitolisant の効果（Holger Stark）、蛍光リガンド等を用いたヒスタミン受容体情報伝達の時空間的解析（Rob Leurs）、めまいに対する seliforant の作用（J. Dyhrfjeld-Johnsen）をはじめ、ヒスタミン受容体リガンドの最近の進歩を知ることができました。

最終日の 18 日は Young Investigator Awards Session が行われ、事前審査で選ばれたオランダ、UAE、アメリカ、イタリア、ポーランドの若手研究者たちが、有機合成から中枢神経系、免疫系などの様々な分野の研究を発表しました。その後 Allergy and Inflammation のセッションが行われました。今年の GB West Lecture は Prof. Francesca Levi-Schaffer で、肥満細胞並びに好酸球の活性抑制に関する講演を行いました。このほか、H3 あるいは H4 受容体が、喘息（J.P.S. Fernandes）、肺線維症（S. Sgambellone）、各種サイトカイン産生（R. Khanferyan）などに関与する報告や、粘膜の炎症における微生物由来ヒスタミンの役割に関する講演（L. O'Mahony）などを興味深く聴くことができました。

全プログラム終了後に総会があり、2020 年の主催をする Heinrich Heine University Dusseldorf の Prof. Holger Stark から翌年のスケジュールが示されました。しかし、その計画が COVID-19 の拡大のために中止になろうとは思ってもみませんでした。その後、恒例の Gala Dinner が、市内のポーランド料理店で開催され、Histamine Anthem の大合唱で会を終えました。

【2】49th Annual Meeting of European Histamine Research Society - Online Symposium

本来なら 2020 年 5 月に Prof. Holger Stark の主催で開催する予定であった第 49 回 EHRS 年会ですが、COVID-19 の拡大で WHO が 2020 年 3 月にパンデミックを宣言したことを受け、EHRS Council は Holger Stark と協議の上で対面開催を中止し、オンラインシンポジウムを開催することを決定しました。私も Council member の一人としてこの決定の過程に関わりました。

オンラインシンポジウムは 7 月 1 日、2 日の二日間で開催し、開催時間帯は、参加者がヨーロッパのみならず南北アメリカ大陸からアジア圏まで広がっていることから、ブラジル 8 時、英国 12 時、日本時間で 20 時に開始し、2 時間で終了と決められました。オンライン会議システムは、Blackboard Collaborate を使用し、Newcastle University の Dr. Ilona Obara と Trinity College Dublin の Prof. Astrid Sasse が共同で主催することになりました。

オンライン開催がうまくいくのかは心配でしたが、世界各国から参加があり、初日は 102 名、2 日目は 78 名が参加しました。EHRS の President である Prof Katerina Tiligada のオープニングリマークに続いて、初日は Plenary Lecture として、Prof. Madeleine Ennis から"Histamine H2 receptor and COVID-19"という up-to-date な講演がありました。その後、Netherlands Institute for Neuroscience の Dr. Ling Shan が、microglia における H4 拮抗薬の抗炎症作用に関する口演がありました。続いて Young Investigator Session が行われ、Ibrahim Alrashdi（Newcastle University）、Xiaoyuan Ma（Vriije Universiteit Amsterdam）、Maria Kakolyri（National and Kapodistrian University of Athens）がオンラインで発表を行いました。2 日目の Plenary Lecture

は Dr. Yves Auberson（Novartis Institutes for BioMedical Research）で、ナルコレプシーにおける H3 受容体の役割について講演されました。その後、2 日目の Young Investigator Session に移り、Cecilia M.S.Q. Aranha（Universidade Federal de São Paulo）、David Reiner（Heinrich Heine University Düsseldorf）、Mohamed Alawad（United Arab Emirates University）がそれぞれ発表を行いました。私は、Bursary Award Committee の Chair として、他の 2 名の先生方とオンライン学会とは別に Zoom で接続しながら 6 名の発表者の採点・集計を行い、最後の Katerina Tiligada の挨拶の中で発表するという当初の予定に間に合わせることができました。YIA の第一位は David Reiner （Germany）で、2021 年の年会参加費を無料とすることになっていましたが、残念なことに 2021 年の年会も COVID-19 のために対面開催が中止となってしまいました。

【3】2021 年の European Histamine Research Society - Online Meeting

2021 年の対面開催が困難になったことを受けて、EHRS Council メール会議やオンライン会議を行いました。その結果、6 月 17 日の日本時間 20 時より、2021 年第 1 回の Web 講演会を実施することになりました。詳細は EHRS や JHRS の facebook ページでお知らせいたします。今後も夏から秋にかけて、分野を決めて、その分野の専門家による Web 講演会を実施することを予定しており、引き続き、facebook やメールでお知らせする予定です。また、Young Investigator Session を秋に開催することも提案されています。本来ですと、2021 年は President や Council など役員の改選期にあたるのですが、対面の総会ができないため、 1 年間は現行の役員の任期を延ばすことも Web 会議、メールによる総会で決定されました。

COVID-19 の影響は多方面に及び、それを克服するためのオンライン学会やオンライン授業なども一般的になってきました。しかし国際学会をオンラインで開催するにあっては、時差の問題があるため、対面開催が可能な時間は 1 日に 1〜2 時間程度に限定されてしまいます。アットホームな雰囲気の中で、研究の話から文化の話まで、さまざまに語り合いながら友情を深め、その中からまた新たな研究のヒントを得るという、EHRS の良さがスポイルされてしまっているように思えてなりません。ワクチンが普及して、元のように対面の学会が行える日が一日も早く来ることを願ってやみません。

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