ABSTRACT

Symposia

S1D-1-1 Genetically engineered mice used as tools in the pathophysiological clarification of the role of histamine in allergic reactions

Hiroshi Ohtsu[1], Noriyasu Hirasawa[2]

[1]Grad. Sch. Engineering., Tohoku Univ., [2]Grad. Sch. Pharmaceu. Sci., Tohoku Univ.

Allergic reactions to metals are characterized by itching sensation, redness, swelling, and blistering in the affected skin region. The metal is ionized by the body fluids, penetrates the skin, or is absorbed from the digestive tract. Once incorporated into the system, it sensitizes the body. Ionized metals act as haptens by binding to Langerhans or dendritic cells, which enter the lymph nodes. Histamine is an important mediator of allergy to metals. However, its precise source and role in allergic response is yet to be determined. Using histidine-decarboxylase gene knockout mice, we demonstrated histamine-induced skin thickening during metal-induced inflammation. We have also generated reporter mice for this gene, in which the histamine-producing cells were expected to produce fluorescence. The green fluorescent protein gene was inserted at the transcription start site of the *HDC* gene in a bacterial artificial chromosome vector. The gene expression was confirmed in the tuberomammillary nucleus and in enterochromaffin-like cells, both of which are well-known histamine producers. Through nickel-induced inflammation in these mice, we aim to further elucidate the roles of histamine and histamine producing cells, which is important for skin pathology.

S1D-1-2 The histamine H4 receptor: Translation of preclinical pharmacology to clinical efficacy

Robin L. Thurmond

Janssen Pharmaceutical Research & Development, LLC

The histamine H4 receptor (H_4R) is a high affinity receptor for histamine and ligands that target the receptor have been reported to have effects in a variety of inflammatory and pruritic models. These data have generated interest in the therapeutic potential of these ligands for the treatment of asthma, atopic dermatitis, rheumatoid arthritis and many other diseases. The H_4R responses in eosinophils have been well characterized. In these cells the receptor mediates calcium responses and chemotaxis. The chemotactic effect of histamine (and other chemoattractants) can be detected by changes in cell shape related to actin reorganization. This has now been used in a clinical setting to test the target engagement of the H_4R antagonist JNJ-39758979 and the data show good correlation to the preclinical pharmacology data. JNJ-39758979 has also shown efficacy in preclinical pruritus and atopic dermatitis models. Preclinically it reduces histamine-induced scratching in mice and it reduces inflammation in a FITC-induced dermatitis model. These findings have been validated in the clinic with JNJ-39758979 being shown to reduce histamine-induce itch in humans and have effects in patients with atopic dermatitis. These recent clinical data support the translation of the preclinical findings with the H_4R in the areas of pruritus and atopic dermatitis.

S1D-1-3 Protective effect of histamine H3 receptor antagonist on cerebral ischemic injury

Wei-wei Hu[1,2], Xiang-nan Zhang[1], Hai-jing Yan[1], Hiroshi Ohtsu[2], Feng Han[1], Zhong Chen[1]

[1]Dept. Pharmacol., Key Lab. of Med. Neurobiol. of the Ministry of Health of China, Coll. Pharmaceu. Sci., Zhejiang Univ., [2]Dept. Engineering, Sch. Med., Tohoku Univ.

In the present study, we found that H3 receptor expression was upregulated after ischemia/reperfusion (I/R) both in transient middle cerebral artery occlusion and oxygen-glucose-deprivation/reperfusion models. Moreover, overexpression of H3R in HEK293 cells led to more cell death after serum deprivation. Either H3R antagonists (thioperamide, clobenpropit and A331440) or H3R knockout attenuated I/R-induced neuronal injury and apoptosis, which was reversed by its agonist immepip. Interestingly, H1 and H2 receptor-antagonists, alpha-FMH, a selective histidine decarboxylase (HDC) inhibitor, and HDC knockout all failed to compromise the protection by thioperamide. In addition, neuroprotection by thiopermide against I/R was reversed by 3-methyladenine and siRNA for Atg7. In Atg5-/- mouse embryonic fibroblasts, the protection was also diminished. Furthermore, either the peptide Tat-H3RCT414-436, which blocks chloride intracellular channel 4 (CLIC4) binding with the H3R, or siRNA for CLIC4 further increased I/R-induced autophagy and consequently protected against I/R injury. Therefore, we here provided direct evidence that H3R promotes I/R injury, its inhibition is protective, and this is independent of histamine, but attributable to suppressed H3R/CLIC4 binding-induced autophagy. Our results strongly suggest that H3R inhibition may be attractive as a potential clinical therapeutic target for cerebral ischemia.

Acknowledgement: This work was funded by the National Basic Research of China 973 Program (2011CB504403) the National Natural Science Foundation of China (81030061,81273506).

S1E-2-1 Introduction: New frontier in vascular biology

Hideyuki Yamawaki

Lab. Vet. Pharmacol., Sch. Vet. Med., Kitasato Univ.

Ischemic cardiovascular disease that is related to metabolic disorders including obesity, type II diabetes, atherosclerosis and hypertension is one of the leading causes for mortality in Japan. While a number of good drugs including inhibitors of renin-angiotensin system, Ca^{2+} antagonists, and statins have contributed to the treatment of those diseases, novel pharmaco-therapeutic targets are needed. Adipocytokine is an adipose-tissue derived cytokine and related to the pathogenesis of obesity-related cardiovascular disorders. Imbalanced secretion (good vs. bad adipocytokine) due to abnormal adipose hypertrophy may be related to the initiation and progression of the obesity-related cardiovascular diseases by directly acting on cardiovascular systems. Similarly, EDCF (endothelium-derived contracting factor) counteracts the vascular protective effects of EDRF (endothelium-derived relaxing factor) such as NO. Thus the imbalance of EDRF and EDCF may also underlie the pathogenesis of cardiovascular diseases related to metabolic disorders. In this symposium, we focus on adipocytokine and EDCF as well as their receptors including protease-activated receptor (PAR), discuss on the recently discovered mechanisms of their actions, and explore the novel pharmaco-therapeutic targets.