Mast Cell Mediators in Immediate Allergic Wheal Reaction

Jari Saarinen
Department of Dermatology, University of Kuopio, FIN-70210 Kuopio, Finland. E-mail: Jari.Saarinen@kuh.fi.

Jari Saarinen (*right*), Department of Dermatology, Kuopio University Hospital defended his thesis on Saturday 20th October 2001 in the Town Hall of Kuopio. Faculty Opponent was Professor Matti Hannuksela (*left*), Department of Dermatology Lappeenranta Central Hospital, and Chairman was Professor Maija Horsmanheimo (*middle*), Department of Dermatology, University of Kuopio.

Mast cells are resident effector cells, which are essential for the elicitation of the allergic response of immediate type. However, the release and significance of different mast cell mediators in the allergic wheal reaction are poorly understood, except for histamine. Therefore, in this study the involvement of mast cell mediators in the allergic prick test wheal induced by cow and bee allergen was investigated, with special attention being paid to histamine, leukotriene C_4 (LTC_4), prostaglandin D_2 (PGD_2), tryptase, chymase and interleukin-4 (IL-4).

Skin microdialysis was performed on a total of 31 cow-sensitive subjects to monitor the release of histamine, LTC_4 and PGD_2 during the wheal formation, but none of these mediators correlated with the prick test wheal size. The extent of histamine release correlated significantly with the number of tryptase-positive mast cells ($p=0.027$) and cow-specific IgE levels in serum ($p=0.009$), but LTC_4 and PGD_2 showed no relation. In addition, an inverse association between histamine and LTC_4 was apparent. None of the mediators alone can explain the extent of the wheal reaction. As the control for cow allergen, 6 beekeeper subjects sensitive to bee venom were microdialyzed and both histamine and LTC_4 were monitored during the challenge with bee venom. Again, an inverse relationship between histamine and LTC_4 was found, i.e., those 3 subjects with a high release of histamine liberated low levels of LTC_4 and vice versa.

In 10 cow-sensitive subjects, the changes in the number of mast cells with tryptase and chymase and their association with histamine release by microdialysis during the prick-test wheal were studied. The number of mast cells with tryptase and chymase activity decreased significantly at 30 min by 37% and 61%, respectively, when enzyme-histochemical methods were used for staining. Concomitantly, the sequential double-staining method revealed the more frequent appearance of mast cells with chymase immunoreactivity but not chymase activity indicating that chymase inactivation occurred during the wheal reaction. This inactivation may be due to chymase inhibitors, a1-proteinase inhibitor (α1-PI) and α1-antichymotrypsin (α1-AC), which showed high levels of their immunoreactivity in mast cells of already unchallenged skin. The extent of chymase inactivation determined histochemically correlated significantly ($p<0.05$) with the extent of histamine release. However, the alterations in tryptase- and chymase-positive mast cells during the wheal were not related to wheal size in the prick test. The extent of the prick test wheal induced by the cow allergen was also correlated with the number of mast cells showing tryptase activity, chymase activity, IL-4, α1-PI and α1-AC immunoreactivity in the healthy-looking skin of 50 cow-sensitive subjects. Tryptase-, chymase-, α1-PI- and a1-AC-positive mast cells revealed no association with the wheal size. In-

stead, a novel finding was that IL-4-positive mast cells were highly correlated with the wheal size ($p<0.003$). Furthermore, tryptase-, chymase- and IL-4-positive mast cells correlated significantly ($p<0.05$) with the levels of total IgE in serum but not with cow-specific IgE. These findings point to the clinical relevance of cutaneous mast cells and the significance of IL-4 though further studies are needed to elucidate its functions.

Prick tests were performed on the forearm skin of 51 atopic subjects sensitive to cows with a crude cow dander extract to investigate the effect of intracutaneously injected mepyramine, nordihydroguaiaretic acid (NDGA) and indomethacin (each at 10 and 100 μg/ml) on the subsequent wheal size. Mepyramine decreased the wheal by 33% ($p<0.001$) whereas NDGA showed no effect and indomethacin increased it by 27% ($p<0.02$). Fourteen subjects of 51 did not respond to mepyramine pretreatment with a diminished wheal size. Similarly, the leukotriene antagonist, zafirlukast (40 mg), was inefficient and indomethacin (100 mg) increased the wheal by 16.6% ($p=0.035$) when administered perorally to 5 other randomly chosen atopic subjects before prick-testing.

It is unhelpful to argue that one particular mast cell mediator is important in the allergic wheal reaction as histamine, LTC_4, PGD_2, chymase, tryptase and IL-4 are probably all important and present study give a little new information of them.

List of original publications

1. Saarinen JV, Harvima RJ, Naukkarinen A, Horsmanheimo M and Harvima IT. Release of histamine, leukotriene C_4 in immediate allergic wheal reaction as measured with the microdialysis technique. Arch Dermatol Res 2000; 292: 333–340.
2. Annila I, Saarinen JV, Nieminen MM, Moilanen E, Hahtola P, Harvima IT. Bee venom induces high histamine or high leukotriene C_4 release in skin of sensitized beekeepers. J Invest Allergol Clin Immunol 2000; 10: 23–228.
3. Saarinen JV, Harvima RJ, Naukkarinen A, Horsmanheimo M, Harvima IT. The release of histamine is associated with the inactivation of mast cell chymase during immediate allergic wheal reaction in the skin. Clin Exp Allergy 2001; 31: 593–601.
4. Saarinen JV, Harvima RJ, Naukkarinen A, Horsmanheimo M, Harvima IT. Interleukin-4 positive mast cells are highly associated with the extent of immediate allergic wheal reaction in the skin. Allergy 2001; 56: 58–64.
5. Saarinen JV, Harvima RJ, Horsmanheimo M, Harvima IT. Modulation of the immediate allergic wheal reaction in the skin by drugs inhibiting the effects of leukotriene C_4 and prostaglandin D_2. Eur J Clin Pharmacol 2001; 57: 1–4.

Long-wave Ultraviolet Radiation (UVA1) and Visible Light. Therapeutic and Adverse Effects on Human Skin

Desiree Wiegleb Edström
Department of Dermatology, Karolinska Hospital, Karolinska Intitutet, Stockholm, SE-171 76 Karolinska Hospital, Sweden.
E-mail: desiree.edstrom@ks.se

The effects on human skin of repeated UVA1 irradiation and visible light

Sun exposure is widely accepted as the major risk factor for developing skin cancer. Ultraviolet B radiation (290-320 nm) is considered the causative agent. However, it has been shown that long-wave ultraviolet A (UVA1: 340-400 nm) also induces non-melanoma skin cancer development in hairless mice.

The *p53* is a tumour suppressor gene, a gene that contributes to the development of cancer when it is inactivated. *P53* gene mutations are induced by ultraviolet radiation and found in squamous cell carcinoma, basal cell carcinoma and in actinic keratosis. We studied the effects of repetitive suberythemal fluences of long-wave ultraviolet UVA1 radiation and visible light in normal sun-shielded skin, using immunohistochemical staining for p53 and the downstream mediator p21WAF-1, a cycline-kinase inhibitor, bcl-2 an apoptosis inhibitor, Ki67 and cyclin A, proliferation markers. An increased expression of Ki67 after UVA1 and visible light were observed as a sign of increased proliferation. By comparison to untreated skin, increased expression of p53 protein, but not