Synopsis of Original Research Paper

Role of neuropeptides in neurogenic inflammation and its regulation

Itsuo Iwamoto

School of Medicine, Chiba University

Substance P (SP), a potent proinflammatory peptide which is present in sensory neurons, causes granulocyte (neutrophil and eosinophil) infiltration in mouse skin by inducing mast cell degranulation. Therefore, we determined which mediator from cutaneous mast cells mediates SP-induced granulocyte infiltration in the skin by the use of mediator antagonists. Subcutaneous injection of SP (10^{-7}–10^{-5}M) caused granulocyte infiltration in the skin of BALB/c mice in a time -and concentration- dependent fashion.

Pretreatment with the LTB_4 antagonist decreased SP-induced neutrophil and eosinophil infiltration in mouse skin at 6 h to the same extent that an inhibitor of mast cell degranulation disodium cromoglycate decrease those responses. However, pretreatment with the PAF antagonist affected neither SP-induced neutrophil nor eosinophil infiltration at 6 h. A LTC_4 / D_4 antagonist and a histamine H1 antagonist chlorpheniramine had no effect on the granulocyte infiltration, either. The LTB_4 antagonist also decreased SP-induced neutrophil, but not eosinophil, infiltration in mouse skin at 24 h. Second, we determined whether SP increases the expression of an adhesion molecule ICAM-1 on human vascular endothelial cells. The amount of ICAM-1 on human umbilical vein-derived endothelial cells (HUVEC) was measured by a cell ELISA assay using an anti-ICAM-1 monoclonal antibody. SP (10^{-3} M) increased ICAM-1 expression on HUVEC in a time-dependent fashion, reaching a maximum at 16 h. The amount of ICAM-1 on HUVEC was increased by 2.2-fold in the presence of SP (10^{-8} M), the potency of which was the same as that of IL-1 β (10 ng/ml). The C-terminal peptide SP_{6-11} also increased ICAM-1 expression on HUVEC, whereas the N-terminal peptide SP_{1-9} was inactive. Cycloheximide (0.5 mM) inhibited the increase in SP-induced ICAM-1 expression, indicating that SP induces the synthesis of ICAM-1 molecule. In addition, HUVEC were found to have high affinity SP binding sites (Kd = 0.69 nM, Bmax=l.6 x 10^4 sites/cell). We conclude that LTB_4 is a major mast cell-derived chemotactic mediator for initiating SP-induced neutrophil and eosinophil infiltration in mouse skin and that SP increases the expression of ICAM-1 on human vascular endothelial cells.