Bradykinin B2 receptor and dopamine D2 receptor cooperatively contribute to the regulation of neutrophil adhesion to endothelial cells*

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Leukocyte adhesion to the vascular endothelium contributes to many immunological and inflammatory disorders. These processes have been shown to be mediated by bradykinin receptor type 2 (B2R) and dopamine receptor type 2 (D2R). In a previous study, we reported the formation of a B2R-D2R heterodimer, possibly altering cellular functions. Hence, in the present study, we examined the effect of co-activation of endothelial cells with B2R and D2R agonists on the interaction of these cells with neutrophils. Bradykinin, the main B2R agonist, significantly increased cell adhesion, and this effect was reversed when the endothelial cells were additionally co-treated with a selective D2R agonist, sumanirole. These results were dependent on the incubation time, showing an opposite tendency after prolonged stimulation. Significant changes in the expression of adhesion proteins, such as E-selectin and intercellular adhesion molecule 1 in endothelial cells were observed. Additionally, the cells preincubated with tumor necrosis factor-α showed decreased cell adhesion and IL-8 release after long incubation with both agonists. The modulation of cell adhesion by D2R and B2R seem to be mediated via STAT3 phosphorylation. In summary, this study demonstrated a protective role of D2R in neutrophil-endothelial cell adhesion induced by bradykinin, especially in cytokine-stimulated endothelial cells.

Key words: bradykinin, bradykinin receptor, dopamine receptor, endothelial cells, neutrophil adhesion

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Abbreviations: BK, bradykinin; B1R, bradykinin receptor type 1; B2R, bradykinin receptor type 2; D2R, dopamine receptor type 2; GPCRs, G protein-coupled receptors; HOE 140, icatibant; ICAM-1, intercellular adhesion molecule 1; IL-8, interleukin-8; PMN, polymorphonuclear cells; STAT3, signal transducer and activator of transcription 3; SUM, sumanirole; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1
Figure S1. Neutrophil adhesion to endothelial cells after stimulation with B2R and D2R agonists at different concentrations. Labeled PMN were placed on confluent endothelial cells stimulated for 12 and 24 hours with BK (A), SUM (B), or with BK after preincubation with TNF-α (C). The bars represent the mean values ± S.D. calculated as the percentage of PMN adhesion to endothelial cells in relation to cells that were not treated with the agonists, assumed to be 100%. At least three experiments in duplicate were performed.