The multiligand cell surface receptor RAGE (Receptor for Advanced Glycation Endproducts) is involved in various pathophysiological processes, including late diabetic complications and Alzheimer's disease. RAGE is normally expressed at low levels on epithelial, neuronal and vascular cells but in pathological states the expression of RAGE is upregulated. In diabetes, elevated blood glucose promotes formation of advanced glycation end products (AGEs). AGEs as well as Aβ peptides are ligands for RAGE. The transmembrane protein RAGE is able to import Aβ from the blood into the brain. All deleterious effects mediated by membrane-bound RAGE are impaired by regulated ectodomain shedding of RAGE. After stimulation of RAGE ectodomain shedding, the ratio between membrane-bound RAGE and its soluble counterpart declines. This might result in a reduced uptake of Aβ into the brain and diminished RAGE-mediated neurotoxicity via cell membrane-bound RAGE.

We investigated how activation of various G protein-coupled receptors (GPCRs) modulates the RAGE shedding process. We also asked which signal transduction pathways regulate metalloproteinase-induced RAGE shedding. Application of protein kinase A (PKA) inhibitors did not prevent GPCR agonist-induced RAGE shedding. Furthermore, neither direct activation of adenylate cyclase by forskolin nor activation of PKA by 8-Bromoadenosine- 3’, 5’- cyclic monophosphate (8-Br-cAMP) had an enhancing effect on the shedding of RAGE. Thus, signaling pathways different from adenylate cyclase/PKA signaling must contribute in the regulation of RAGE shedding.