

STIMULATION OF PROTEINASE-ACTIVATED RECEPTORS 1 AND 2 INDUCES NEURODEGENERATION IN THE RAT OLFACTORY SYSTEM

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Alterations in the olfactory system and impairment of olfactory function have been reported in several neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases (1,2). The participation of proteinase activated receptors (PARs) in these neuropathological conditions has been postulated (3,4), but little is known on the expression and functional activity of PARs in the olfactory system. By using pharmacological, immunological and immunofluorescence techniques, we studied the presence, the signalling properties and cellular actions of PAR₁ and PAR₂ in the rat main olfactory bulb and in primary cultures of olfactory bulb and olfactory sensory neurons. PAR₁ and PAR₂ receptor activity was predominantly expressed in the olfactory nerve-glomerular cell layer (ON-GL), where selective peptide agonists inhibited cyclic AMP formation and stimulated [³⁵S]GTPγS binding, phosphoinositide hydrolysis, CaMKII phosphorylation and Rho activation. Nanomolar concentrations of thrombin and trypsin mimicked the actions of the peptide agonists. Olfactory bulb deafferentation by lesion of the olfactory mucosa caused a reduction of PAR₁ and PAR₂ receptor activity in ON-GL associated with a loss of olfactory marker protein and type III adenylyl cyclase immunoreactivities, suggesting the possible localization of a receptor population on olfactory nerve terminals. In primary cultures of olfactory bulb cells and olfactory neuroepithelial cells, exposure to either serine proteinases or selective peptide agonists caused a rapid neurite retraction and a long-term decrease of cell viability. Immunofluorescence analysis showed the presence of PAR₁ and PAR₂ in neurons and glial cells of olfactory bulb and in olfactory sensory neurons. These data provide the first evidence that PAR₁ and PAR₂ are expressed and functional in different structures of the olfactory system and suggest the possible involvement of the receptor in neurodegenerative processes affecting the olfactory function.

References

1. Talamo B.R., Rudel R., Kosik K.S., Lee V.M.-Y., Neff S., Adelman L. and Kauer J.S. (1989) *Nature* 337: 736-739.
2. Hawkes C.H., Shephard B.C. and Daniel S.E. (1997) *J. Neurol. Neurosurg Psychiatry* 62: 436-446.
3. Noorbakhsh F., Vergnolle N., Hollemberg M.D. and Power C. (2003) *Nat. Rev. Neurosci.* 4: 981-990.
4. Rohatgi T., Sedehizade F., Reymann K.G. and Reiser G. (2004) *Neuroscientist* 10: 501-512.