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Homologous desensitization of the human guanylate cyclase C receptor

Cell-specific regulation of catalytic activity

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Guanylate Cyclase C (GCC) serves as a receptor for the endogenous ligands, guanylin and uroguanylin, as well as the family of bacterial heat-stable enterotoxins (ST), which are one of the major causes of diarrhoea the world over. We had earlier provided evidence that GCC, present in the human colonic T84 cell line, is desensitized on prolonged exposure to ST, and this desensitization was reflected in a reduced ST-stimulated guanylate cyclase activity of GCC [Bakre, M.M. & Visweswariah, S.S. (1997) *FEBS Lett.***408**, 345−349]. In this study, we have investigated the mechanisms that underlie this cellular desensitization process. Desensitization of T84 cells was not a result of reduction in GCC present in membranes prepared from desensitized T84 cells, nor due to increased cGMP-phosphodiesterase activity associated with the membrane fraction. The decrease in ST-stimulatable guanylate cyclase activity of GCC was due to a dramatic reduction in the V_{max} of the cyclase, which was also seen when MnGTP was used as the substrate. GCC undergoes ligand-induced inactivation *in vitro*, which is alleviated in the presence of ATP. *In vivo* desensitized GCC could be further inactivated *in vitro* when preincubated with ST, indicating that the two mechanisms of GCC inactivation are distinct. Cellular refractoriness as reflected by a reduced responsiveness to further ST-stimulation following prior exposure to IST, coupled with GCC desensitization was also observed in another colonic cell line, Caco2. However, HEK293 cells, stably transfected with GCC cDNA, when exposed to ST for prolonged periods, did not result in GCC desensitization, indicating that desensitization of GCC appeared to be a cell specific phenomenon. GCC expressed in HEK293-GCC cells, however, showed *in vitro* ligand induced inactivation, suggesting that there are two independent means of ligand-induced desensitization of GCC, perhaps distinct from the mechanisms that have been described earlier for other members of the guanylate cyclase receptor family.