

INVOLVEMENT OF PKC IN THE ADAPTIVE CHANGES OF OPIOID RECEPTORS IN THE MYENTERIC PLEXUS AFTER CHRONIC SYMPATHETIC DENERVATION

¹Zanetti Elena, ¹Oldrini Rita, ²Pascale Alessia, ¹Canciani Luca, ¹Giuliani Daniela, ²Amadio Marialaura, ³Chiaravalli Annamaria, ¹Giaroni Cristina, ¹Lecchini Sergio, ¹Friego Gianmario.

¹Clinical and Applied Pharmacology Interuniversity Centre, University of Insubria and University of Pavia; ²Experimental and Applied Pharmacology Dept, University of Pavia; ³Dept. of Surgical Pathology Ospedale di Circolo of Varese

In the guinea pig colon, chronic ablation of the inhibitory sympathetic input to the cholinergic function entails supersensitivity to inhibitory κ - and μ -opioid agents on ACh release, suggesting the occurrence of adaptive changes to maintain homeostasis (1). The mechanisms underlying this adaptive change have not yet been completely unravelled. With this regard, PKC seems to have a prominent role. Functional evidences have demonstrated that the enzyme is positively regulated by κ - and μ -opioid receptors in the myenteric plexus. Such coupling may represent a negative feedback on opioid-mediated inhibition of ACh release, since PKC, per se, exerts a facilitatory effect on this parameter. After chronic sympathetic denervation, such restraint may abate owing to a reduced efficiency of the enzyme (2). The present study was undertaken to further investigate the involvement of PKC in the development of supersensitivity to κ - and μ -opioid agents in the guinea pig colon after chronic sympathetic denervation. In myenteric plexus synaptosomes obtained from sympathetically-denervated animals Ca^{++} -dependent PKC activity was significantly reduced ($-28.23 \pm 6.40\%$, $n=6$, vs normal preparations). In normal preparations this parameter significantly increased both in the presence of U69593 (κ -agonist) and of DAMGO (μ agonist); whereas, after chronic sympathetic denervation both agonists did not influence PKC activity. In myenteric plexus synaptosomes obtained from sympathetically-denervated animals, immunoreactivity levels to Ca^{++} -dependent PKC isoforms displayed different patterns of variability: PKC βI and γ levels decreased, PKC βII and α levels moderately increased. In longitudinal muscle-myenteric plexus preparations, immunofluorescent staining of κ - and μ -opioid receptors and of PKC βI , βII and γ was present in some neuronal populations. PKC α was localized prevalently on enteric glial cells. The present data provide direct evidence that in the guinea pig colon, chronic sympathetic denervation entails a reduction of Ca^{++} -dependent PKC activity in myenteric neurons, which may prevalently involve neuronally located βI and γ isoforms. Furthermore, the ability of κ - and μ -opioid receptors to activate PKC, in normal, but not in sympathetically-denervated preparations further strengthen the concept that the enzyme participates to development of supersensitivity to opioid agents in the guinea pig colon in these experimental conditions.

References: 1) Giaroni C. et al., Gastroenterology (1999) 117:1438-58; 2) Zanetti et al., (2003) Life Sci. 73:2641-54.