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# Morphological study of de novo endomorphin-2 biosynthesis

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Endomorphin 2 (E2) is an endogenous ligand of the mu opioid receptor that has spinal analgesic effect in different nociceptive modalities. E2-like immunoreactivity is present mainly in primary afferents in the spinal dorsal horn, but its biosynthetic pathway(s) is still unknown. We have pharmacological evidence for that membrane-bound dipeptidyl peptidase IV (DPP4) enzyme may be switched into “synthase” functional mode by the DPP4 inhibitor Ile-Pro-Ile (IPI) in depolarization sensitive manner and generates E2 extracellularly. In this study we looked for morphological evidence for the extracellular generation of E2 using high resolution immunogold detection method at electronmicroscopic level. I.t. administration of IPI (3-30 nmol/rat) was antihyperalgesic in carrageenan-induced hindpaw inflammation, as shown by the Randall-Selitto test. IPI-induced antihyperalgesia could be antagonized by the opioid receptor antagonist naloxone or by a specific antiserum to E2. Therefore, this action was likely to be mediated by E2 generation. Gold particles representing immunoreactive E2 were found mainly in the axoplasm but some were attached to the membrane of axon terminals in control animals. In IPI injected rats more particles were located in the membrane or in the extracellular space.These data suggest that de novo E2 biosynthesis may take place within the membranes or in the exracellular space in the spinal dorsal horn in persistent inflammatory conditions.