IN VITRO AND *IN VIVO* ANTI-INFLAMMATORY ACTIVITIES OF PSEUDOMORELIN, A GHRELIN-MIMETIC PSEUDOTETRAPEPTIDE

Ghè Corrado, Baragli Alessandra, Arnoletti Elisa, Deghenghi Romano, Muccioli Giampiero

Division of Pharmacology, Department of Anatomy, Pharmacology and Forensic Medicine, University of Turin, Turin, Italy

We have previously shown that the pseudotetrapeptide ghrelin analog pseudomorelin (Aib-w-w-φ[CH_2-NH-O]Gly-NH_2, PSM) stimulated GH secretion and inhibited isoproterenol-induced lipolysis similarly to ghrelin and its peptdyl (hexarelin) and non peptydil (MK0667) sinthetic analogs. Recent evidence suggests that ghrelin analogs may also possess anti-inflammatory properties acting on immune cells. In the present study we examined the effects of systemic (os, s.c.) and local administration of PSM on acute (carrageenan-paw edema) and subacute (cotton pellet-induced granuloma) inflammation in rats and mice and evaluated its modulatory activity on pro-inflammatory responses of the murine J774.A1 macrophagic cells. PSM administered 30 min before carrageenan injection produced a dose-related inhibition of paw edema. Such inhibition was evident in the late inflammatory phase, where prostaglandines biosynthesis and leukocytes infiltration occur, though not in the initial phase, which depends on histamine, serotonin and bradikinin release. Surprisingly, PSM anti-inflammatory efficacy was comparable with that of the non steroidal anti-inflammatory drug indometacin and occurred at doses lower than those found to stimulate GH secretion. In rats, the effect of PSM was reversed by co-treatment with the GHS-R1a antagonist D-Lys3-GHRP6 and was not influenced by adrenolectomy. Similarly, PSM inhibited cotton pellet-induced granuloma with an efficacy comparable to that of indometacin. Additionally, PMS displayed anti-inflammatory activities upon local administration on the inflamed paw, suggesting a direct effect on the inflammatory cells or their close targets. In fact, in J774.A1 macrophages, PSM as well ghrelin, prevented the increase of pro-inflammatory mediators (PGE_2, TNFα, IL6) production induced by bacterial lipopolysaccharides. Likely, such effect is mediated by a common high affinity binding site for ghrelin, PSM and other ghrelin analogs on these cells. Our data demonstrate for the first time that PSM admistered locally or systemically possesses *in vitro* and *in vivo* anti-inflammatory properties which are mediated by receptors on immune/macrophagic cells.