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Neuroimmune mechanisms of opioid antinociception in early inflammation – involvement of adhesion molecules

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Für meine Eltern

Abbreviations

(m)Abs	=	monoclonal antibodies
α-helical CRF	=	corticotropin releasing factor antagonist [9 – 41]
anti-α4	=	mouse anti-rat-α4 (CD49d) $IgG_{1κ,}$ (anti- α4)
anti-β2	=	mouse anti-rat-β2 chain (CD 18) $IgG_{1κ,}$ (anti-β2)
anti-DYN	=	rabbit anti-porcine cross reacting with Dynorphin-A (1 – 17) IgG
anti-β-END	=	rabbit anti-rat β-Endorphin IgG
anti-Met-ENK	=	rabbit anti-rat-methionine-Enkephalin IgG
anti-ICAM-1	=	mouse anti-rat-intercellular adhesion molecule-1 (CD54) $IgG_{1κ}$
anti-PECAM-1	=	mouse anti-rat-platelet endothelial cell adhesion molecule-1(CD31)
BL	=	baseline
CNS	=	central nervous system
CRF	=	corticotropin releasing factor
CTOP	=	D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2
CWS	=	cold water swim
DRG	=	dorsal root ganglia
DYN	=	dynorphin 1 - 17
β-END	=	β-endorphin
Met-ENK	=	met-enkephalin
FCA	=	modified Freund's complete adjuvant
Ig	=	immunoglobulin
i.pl.	=	intraplantar
IgSF	=	immunoglobulin superfamily
i.v.	=	intraveneous
NLX	=	naloxone hydrochloride
nor-BNI	=	nor-Binaltorphimine dihydrochloride

NTI	=	naltrindole hydrochloride
PENK	=	proenkephalin
POMC	=	proopiomelanocortin
PPT	=	paw pressure threshold
PT	=	paw temperature
PV	=	paw volume
s.c.	=	subcutaneous
SEM	=	standard error of means

Abstract

Pain can be effectively controlled by endogenous mechanisms based on neuroimmune interactions. In inflamed tissue immune cell-derived opioid peptides activate opioid receptors on peripheral sensory nerves leading to potent antinociception. This is brought about by a release of opioids from inflammatory cells after stimulation by stress (e.g. experimental CWS or surgery) or corticotropin-releasing factor (CRF). Immunocytes migrate from the circulation to inflamed tissue in multiple steps, including their rolling, adhesion, and transmigration through the vessel wall. This is orchestrated by adhesion molecules on leukocytes and vascular endothelium. Here I (**1**) evaluated mechanisms of intrinsic pain inhibition at different stages of Freund's adjuvant-induced inflammation of the rat's paw, and (**2**) examined the relative contribution of selectins, integrins α4 and β2, and IgSF members ICAM-1 and PECAM-1 to the opioid-mediated inhibition of inflammatory pain. I used paw pressure testing to asses nociceptive thresholds. I found that : (**1**) In early (6 h) inflammation leukocyte-derived β-END, Met-ENK, and DYN activate peripheral μ-, δ-, and κ-receptors to inhibit nociception. In addition, central opioid mechanisms seem to contribute significantly to this effect. At later stages (4 days), antinociception is exclusively produced by leukocyte-derived β-END acting at peripheral μ- and δ-receptors. CRF is an endogenous trigger of these effects at both stages. (**2**) Peripheral opioid antinociception elicited either by CWS or intraplantar administration of CRF was dramatically reduced by blockade of L- and P-selectins by fucoidin, and monoclonal antibody against ICAM-1. Although separate blockade of α4 and β2 integrins was not sufficient (present study), their simultaneous blockade extinguished CWS-induced antinociception [100]. CWS-induced antinociception was unaffected by blockade of PECAM-1. Together, these findings indicate that peripheral opioid mechanisms of pain inhibition gain functional relevance with the chronicity of inflammation. They establish selectins, integrins, and ICAM-1, but not PECAM-1 as major regulators, in the local opioid mediated control of inflammatory pain. Thus, pain is exacerbated by measures inhibiting the

immigration of opioid-producing cells or, conversely, antinociception might be conveyed by adhesive interactions that recruit those cells to injured tissue.

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