5. Conclusions and perspectives

Inflammation is an integral part of many acute and chronic painful conditions. Prominent examples include postoperative pain and chronic arthritis. This study shows that when facing a stressful situation, the organism mounts its own counter-regulatory response to cope with inflammatory pain. Evidently, this response consists of central and peripheral components, depending on the duration of inflammation. Tissue injury results in cell recruitment to fight pathogens and to provide endogenous pain inhibition. In later stages immune-derived β-END, acting exclusively at peripheral μ and δ receptors, dominates. In early inflammation central opioid receptors as well as immune-derived β-END, Met-ENK, and DYN, acting at peripheral μ, δ, and κ receptors, are involved. At both early and later stages CRF acts as an endogenous trigger to release opioids from immunocytes. My studies suggest that the contribution of the immune system to intrinsic pain inhibition becomes more important with the severity and chronicity of inflammation and that in acute painful states central mechanisms still hold an integral part in intrinsic antinociception. Clinical studies will have to determine whether spinal anesthesia-analgesia influences the potency of endogenous peripheral mechanisms of pain control, e.g. in the acute, postoperative setting [71, 116] and, therefore, whether their combination may influence sufficient pain control and decreased need for analgesics. The functional contribution of immune cells to the intrinsic peripheral pain control is supported by the engagement of the adhesion molecules. Importantly, blockade of adhesion molecules abolishes only the peripheral component of intrinsic opioid antinociception and is consistent with the notion that centrally mediated CWS-induced antinociception is independent of leukocyte extravasation. Notwithstanding, peripheral mechanisms of intrinsic pain control are potent and of clinical relevance because in patients undergoing surgery for knee injuries, opioid-containing immune cells are detectable in the inflamed synovium and the blockade of intraarticular opioid receptors by naloxone results in significantly increased postoperative pain for up to 4 h [71]. These findings provide insights into the organism's intrinsic mechanisms of pain control and open innovative strategies to develop drugs and alternative approaches to pain treatment. Immunocompromised patients (e.g. in AIDS, cancer, diabetes)

frequently suffer from painful neuropathies which can be associated with intra- and perineural inflammation with low $CD4^+$ lymphocyte counts [117-119.] Thus, it may be interesting to investigate the opioid production/release and the migration of opioid containing immune cells in these patients. It would be desirable to identify adhesion molecules, chemokines or other stimulating factors that selectively attract opioid producing cells to damaged tissue. It has been already shown that augmenting the synthesis and/or secretion of opioid peptides from peripheral sensory neurons by growth factors, stem cell- or gene-therapy decreased chronic inflammatory pain [120]. At present, the data point to a cautious use of treatments that interfere with the migration of opioid-containing leukocytes because they can lead to severly impaired endogenous pain inhibition. In the future, uncovering mechanisms that can selectively enhance the availability of immune-derived opioids will open exciting possibilities for pain research and therapy.