EVIDENCE FOR THE EFFECT OF PAIN ON IMMUNE FUNCTION AND INVOLVEMENT OF IMMUNE ACTIVATION IN NOCICEPTIVE TRANSMISSION

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Classically the CNS and the immune system (IS) were thought to operate independently of each other. This view has recently changed, first with the recognition that the brain modulates the IS, and later with the reverse: the IS modulates the CNS as well. A condition where this bidirectional link is particularly evident is pain.
Pain is an exquisite stressor, because it has both psychological and physiological components. The response of the CNS and of the HPA to perceived stress involves a network of signals including catecholamines and corticosteroids, that can deeply affect the IS. It has been suggested that the stimulation of nociceptive pathways in surgical intervention, as well as postoperative pain play an important role in surgery-induced immunosuppression, that has been associated to a higher risk of infection and metastatic diffusion. Therefore good postoperative pain control, achieved with not intrinsically immunosuppressive drugs, can help to attenuate immunosuppression and consequent augmentation of metastatic spreading. We have characterized several analgesic strategies that can be useful to prevent surgery-induced immunosuppression in an experimental model of peri-operative pain. On the other hand it is emerging that immune activation plays a significant role in both inflammatory and neuropathic pain. Both resident immune cells such as schwann cells and microglia and infiltrating immune cells release proinflammatory cytokines that induce hyperexcitable sensory states. We show, in a peripheral model of inflammation in the rat, a significant activation of spinal cord glial and microglia cells that release significant amount of the cytokine TNF in the spinal fluid. We also tested several analgesic drugs, both opioids and COX inhibitors, in order to identify a treatment able to counteract the TNF increase. Finally the involvement of immune system seems to be particularly relevant in neuropathic pain due to nerve injury. In a mouse model of peripheral nerve injury, we have analyzed the temporal expression of the proinflammatory cytokines IL-1β, IL-6 and TNF along the pain pathways in the peripheral (sciatic nerve, DRG) and the central (spinal cord) NS. Cytokines appear to be activated in the nervous tissue in parallel with the occurrence of painful behaviours such as allodynia and hyperalgesia. The chronic administration of a purinergic antagonist that prevents ATP-induced stimulation of IL-1 is able to reduce all the painful symptoms associated with neuropathy. In conclusion, the knowledge of the interplay between the NS and the IS in pain, can be relevant for the better use of old drugs and for the identification of new treatments.