Neuroinflammation as a cause of chronic pain

Citation for published version (APA):

Document status and date:
Published: 01/01/2012

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:
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Chapter 9

Summary and conclusion

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Chapter 9

Summary and conclusion

In the present thesis, we have studied the correlation between TNF-α and its receptors and the severity of postoperative radicular leg pain in LDH patients after discectomy. In addition, we examined the opposite clinical effects between TNFR1 and TNFR2 in the modulation of postoperative pain, the former being related to elevated pain and the latter to a lower intensity or absence of pain. Following this, we have investigated if the expression of these markers was associated with an unsuccessful long-term outcome in terms of pain sensation and the necessity of performing multiple surgeries in LDH patients. Finally, animal experiments were performed to gain insights into the mechanisms of the analgesic effects produced by TNF-α inhibition. Furthermore, we have investigated if peripheral blockage of TNF-α could hinder the expression of TNFR in the central nervous system of rats and therefore the development of pain behavior. The summarized results reported in this thesis are presented as follows;

In chapter 2 of this thesis we have summarized the current available knowledge from lesional, transgenic and pharmacological preclinical models that evidences the role of TNF-α as a key modulator in pain. This is done from a behavioral standpoint, where the pain behavior is observed as a direct result from TNF-α stimulation. This literature analysis showed that early and late changes of TNF-α levels in nervous and non-nervous tissue have a temporal and simultaneous effect on pain behavior. In addition, in this overview we delineate one of our research questions in relation to the relevance of the TNFR1 / TNFR2 expression ratio as an important factor in the generation of pain.

In chapter 3, we provided an extensive overview of the correlation between inflammation and chronic pain in humans. Here, we summarized the current state of knowledge regarding cytokine expression in human samples in direct association with clinical pain assessment. From this revision we can conclude that inflammation is a constant factor present in a wide range of chronic disorders related to pain. There is enough scientific evidence to suggest that an unbalance favoring proinflammatory cytokines is related to pain. In contrast, a decreased anti-inflammatory cytokines expression may reduce pain.

In our initial human studies, as described in chapter 4, we therefore analyzed TNF-α and TNFR levels in annulus fibrosus (AF), nucleus pulposus (NP), ligamentum flavum (LF) and paravertebral muscle biopsies that were collected
Summary and conclusion

in the course of a discectomy in LDH patients. The expression of these molecules in the NP correlate to the severity of postoperative radicular leg pain, indicating that these biomarkers may be employed to predict the clinical outcome of a discectomy. These observations furthermore suggest that in LDH patients with high TNF-α levels, anti-TNF-α therapy may be more effective to relief pain than a discectomy. In this respect it is interesting to note that increased TNFR1 levels correlated to increased pain, whereas TNFR2 was decreasedly expressed in patients with more pain. This differential TNFR expression may proof useful for future rationale drug design that is directed towards specific TNFR subtypes in order to reduce side effects.

Additional experiments described in chapter 5 show that the LDH biopsies also contain IL-1β and IL-6, indicating that these tissues are characterized by a general proinflammatory state. The cytokine levels, however, did not correlate with pre- or postoperative leg pain, suggesting that anti-TNF-α therapies may be more successful in pain management than anti-inflammatory ones. These observations reinforce the idea that once an inflammatory process is established, TNF-α may be one of the central players in the chronification of pain.

To further investigate their role in chronic pain, we analyzed TNF-α and TNFR expression in spinal biopsies from patients with recurrent LDH as described chapter 6. In line with our previous findings, patients that had undergone multiple spinal surgeries reported higher pain scores and expressed higher TNF-α and TNFR1 levels then patients that had undergone one LDH surgery. Together, these findings provide more evidence that local disc inflammation in LDH patients is closely involved in persistent postoperative leg pain and may be linked to failed surgery cases.

The observations in human samples prompted us to gain insight into the potential of TNF-α inhibitors to induce analgesic effects, and the mechanisms of action leading to these effects. To this end, we administered several drugs to the sciatic nerve CCI rat model and analyzed their effects on pain behavior, and TNF-α and TNFR expression in dorsal horn (DH) and dorsal root ganglion (DRG) samples. Chapter 7 describes a positive correlation between hypersensitivity behavior and TNF-α expression in the DH of CCI rats. A poor behavioral recovery also coincided with an increased TNFR1/TNFR2 expression ratio. Thalidomide treated CCI animals showed a significantly faster recovery from pain behavior and an attenuated TNF-α level and TNFR1/TNFR2 ratio. Because these effects were unmet by treatments with NO-711, IGF-1 or
ZVAD, we performed a follow-up study with TNF-α inhibitors that had different affinities for its membranous and soluble form. In chapter 8 we describe results obtained from CCI animals that had been treated with etanercept or infliximab. Though both drugs were able to diminished pain behavior and to reduce TNFR expression in DH and DRG, these effects were strongest in infliximab treated animals. This suggests that pain management can be achieved most effectively by inhibition of membranous TNF-α. Altogether, these findings provide new insights into the physiopathological mechanisms of inflammation in chronic neuropathic pain. We suggest that an unbalance between TNFR1 and TNFR2 is associated with the degree of pain experienced by patients. These findings stress the potential of anti-TNF-α treatment in a subset of LDH patients. In addition, they hint towards the possibility to use TNF-α or its receptors to predict the outcome of LDH surgery. They therefore suggest that the selection criteria for discectomy may be improved. Future studies are required to further identify if these inflammatory profiles are expressed individually in patients, and to unravel the factors that generate these differences.