

# Effect of housing in an enriched environment on the recovery from experimental inflammatory pain

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## SUMMARY

In this thesis, it was our aim to study the effect of an enriched environment (EE) on inflammatory pain, using a rat model of knee inflammation. This investigation mainly focused on behavioral outcomes.

In **chapter 1**, we introduced the field of postoperative inflammatory pain in the clinic as well as in experimental pain research with a special emphasis on the impact of the environment on it.

In chapters 2 to 4, we first addressed a methodological question about pain measurement: is the CatWalk, a gait computerized analysis technique, an appropriate tool to assess pain-induced gait changes in a rat model of carrageenan-induced inflammatory pain? In **chapter 2**, we demonstrated that, in the first 48 hours following the carrageenan injection, indeed the CatWalk technique allows objective analysis of gait changes, which at the same time parallel the development of mechanical hyperalgesia as assessed by the von Frey test. In **chapter 4**, we confirmed the causality of pain in the observed CatWalk-based gait changes by studying the effect of Fentanyl, an opioid analgesic, on the carrageenan-induced gait changes. In **chapter 3**, the use of the CatWalk technique was studied in the chronic phase of the knee inflammation. Our results indicated that, as of one week after the carrageenan injection, the CatWalk parameters affected by the carrageenan knee injection do no longer differ from pre-operative values whereas at the same time the von Frey withdrawal threshold indicates a mechanical hyperalgesia which lasts up to 4 weeks post-injection. These data suggest that, as of one week after the carrageenan injection, the animals do no longer adapt their gait to pain and the phenomenon of habituation is suspected to take place. In conclusion, our data indicate that the CatWalk is a potent and objective technique to assess pain-induced gait changes in correlation with mechanical allodynia in the carrageenan-induced inflammatory pain model. Nevertheless, its use is restricted to the acute phase of this model. Second, our results also indicate that a simultaneous use of both von Frey and CatWalk tests to assess pain in experimental pain research will result in a better and more reliable picture of the whole pain experience in the rat.

The following chapters focused on the influence of housing in an EE on behavioral pain recovery in the model of carrageenan-induced chronic knee inflammation. The EE consists of ten rats housed in a large cage ( $L \times W \times H = 2.0 \times 1.0 \times 0.8$  m) including extra nesting materials, tunnels and running wheels, as compared with standard housing (S-) where animals are singly housed in standard cage ( $L \times W \times H = 0.5 \times 0.2 \times 0.2$  m). Hence, the EE provides both greater physical and social stimulations. In **chapter 5**, EE-housing following the carrageenan knee injection led to a duration of mechanical hyperalgesia of 3 weeks in the ipsilateral paw, as compared with 4 weeks when rats are S-housed. Histological studies of the rat spinal dorsal horn indicated the astrocytes to be involved in this environmentally-driven reduction of inflammatory pain duration.

**Chapter 6** aimed at studying the effect of a pre-inflammation EE-housing on inflammatory pain duration. Comparison with post-inflammation EE-housing was studied as well as comparison with the combination of both a pre- and post-inflammation EE-housing. Our data demonstrated that a pre-inflammation EE-housing leads to a similar reduction of one week of the inflammatory pain duration than a post-inflammation EE-housing does. Besides, we also demonstrated that a combination of housing in an EE prior to and after the carrageenan injection leads to a duration of the mechanical allodynia of 2 weeks, as compared with 4 weeks in S-housed rats.

In **chapter 7**, we investigated to what extent each aspect of the EE differentially affects the development of inflammatory pain. In this study, four housing conditions were studied: a physically enriched environment (PE), a socially enriched environment (SE), a physically and socially enriched environment (EE) and a restricted standard environment (S-housing). Our results confirmed that the duration of carrageenan-induced mechanical allodynia if rats are kept in a S-housing is of 4 weeks and is of 3 weeks if rats are housed in an EE. Similarly, housing in a physically enriched environment (PE) also resulted in a reduction of the duration of mechanical allodynia of one week. And if housed in a socially enriched environment (SE), the carrageenan-induced mechanical allodynia lasted for 3 weeks and an half. Based on these results, we first concluded that both physical and social aspects of EE are involved in the reduction of inflammatory pain duration. In this experimental setting, the physical component has a major effect over the social aspect of the EE. Second, our data demonstrate that the beneficial effects on inflammatory pain duration of both components are inter-dependent, i.e. the effect of the social enrichment depends on the physical aspects of the environment (enriched or not) and reversely.

In **chapter 8**, we first discussed the use of the CatWalk technique in the field of experimental pain. Second, we discussed the behavioral outcomes from the different studies investigating the effect of an enriched environment on inflammatory pain. A general underlying biological mechanism was suggested.

In conclusion, the current work indicates a major effect of the environment on the development of carrageenan-induced inflammatory pain, prior to as well as after the induction of inflammation. Besides, our results emphasize the importance of both the physical and social enrichment of housing conditions. Human studies are needed to confirm the clinical implications of this work. Nevertheless, these findings urge the future development of a clinical healing environment including both physical and social enrichment, prior to and after the operation for post-operative inflammatory pain patients.