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Preclinical Assessment of Emotional Comorbidities of Neuropathic Pain using Behavioral Tests in Animal Models

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Neuropathic pain is a common form of chronic pain affecting 5% of the population. Patients suffering from neuropathic pain often experience psychopathological side-effects as anxiety and depression. Neuropathic pain is widely researched in preclinical animal studies investigating the effects of drugs on enhanced stimulus-evoked pain resulting from neuropathic pain. However, the main part of preclinical studies does not include emotional comorbidities of neuropathic pain. Given the importance on the quality of life of mood disturbances, it is crucial to perform pharmacological preclinical studies that consider the effect of drugs on the sensitivity to noxious stimuli as well as on the emotional state of the animals.

In Part I of this thesis, we showed that two animal models of traumatic neuropathic pain, tibial nerve transection (TNT) and chronic constriction injury (CCI), led to stable mechanical hypersensitivity for at least 4 weeks after surgery. Furthermore, we established two behavioral tests in our laboratory: to assess anxiety-like behaviors we used the elevated plus maze (EPM); to demonstrate depression-related behaviors we used the forced swimming test (FST). We successfully used automatic analysis for the EPM. However, automatic analysis of the FST led to dissatisfying results using different approaches.

Manual analysis of the FST showed a high intra-rater-reliability when the recorded experiments were analyzed again after 4 weeks and 2 years. There were no significant differences between original, second or third scoring. Correlation analyses showed a high correlation for immobile behavior ($r=0.89$) and swimming behavior ($r=0.8$) comparing the first and the second scoring and a medium correlation for climbing behavior ($r=0.64$). The later, third scoring led to lower correlation coefficients ($r=0.74$, $r=0.72$ and $r=0.3$, respectively). Furthermore, the inter-rater-reliability of manual analysis showed a high correlation for immobile ($r=0.71$) and climbing behavior ($r=0.8$), but only a medium correlation for swimming behavior ($r=0.31$).

In Part II, we compared two animal models of neuropathic pain regarding mechanical hypersensitivity and changes in behavior related to emotional comorbidities: CCI and (TNT). CCI-injured animals exhibited a significantly increased sensitivity to mechanical stimuli assessed with the electronic von Frey test ($p<0.001$) as well as significantly more anxiety-like ($p=0.003$) and depression-related behaviors ($p=0.006$). On the other hand, TNT induced mechanical hypersensitivity ($p<0.001$) but did not significantly influence anxiety-like ($p=0.075$) or depression-related behaviors ($p=0.11$). We could not confirm the correlation between degree of hypersensitivity and the development of psychopathological comorbidities which has been suggested in the literature. Therefore, we conducted the pharmacological experiments using the CCI model.

In Part III, we tested the effect of tramadol on nociceptive as well as emotional changes under neuropathic pain conditions. Tramadol, a weak μ-opioid receptor agonist which also induces serotonin release and inhibits the re-uptake of norepinephrine, is often used in the treatment of neuropathic pain. Again, CCI-injured animals exhibited mechanical hypersensitivity ($p<0.001$), which was reversed by tramadol ($p<0.05$). Anxiety-like behavior could be reversed by treatment with tramadol ($p<0.05$), the same could be demonstrated for the immobility time in the FST as a surrogate parameter for depression-related behavior ($p=0.004$). In the FST, tramadol increased swimming, a behavior which has been shown to be serotonin-mediated, in sham rats and, to a larger degree, in CCI rats.

The analysis of the effect size of tramadol confirmed that the activity of tramadol under neuropathic pain conditions was larger than under non-neuropathic conditions regarding all three entities: mechanical hypersensitivity (CCI 2.13, sham 0.39), anxiety-like behavior (CCI 0.85, sham 0.45) and depression-related behavior (CCI 1.24, sham 0.32). This suggests that tramadol may have acted specifically on the ongoing neuropathic pain state.

The results of Part III have been published in Caspani, Reitz et al. (2014) in Pharmacology Biochemistry and Behavior.

In summary, psychopathological comorbidities of neuropathic pain greatly influence the quality of life of patients. This study developed and validated a test battery for profiling the effects of established or novel

medications on neuropathic pain and its emotional comorbidities. Hopefully, this will add insight on more effective treatment options for neuropathic pain. In addition to the information on different analysis methods, different animal models of neuropathic pain and the effect of tramadol on reflex measures of stimulus-evoked pain as well as on anxiety-like and depression-related behaviors, this study strives to be a model for pharmacological studies investigating the effect of drugs on the major disabling symptoms of neuropathic pain.