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**Opioid-induced alterations in neurotransmitter concentration
measured by in vivo microdialysis in rats: a meta-analysis**

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The measurement of neurotransmitter baseline concentrations and their dynamical changes within different brain regions following the application of an opioid is a research area of high interest, e.g. for the understanding of opioid or any other substance use disorder as well as understanding basic principles of the reward system. For measuring these neurotransmitter dynamics in the rat model organism, an invasive method developed about 40 years ago is nowadays widely used: microdialysis. This technique, the design and implementation of a microdialysis experiment is beside all improvements over the decades still very challenging. In this study I conducted comprehensive meta-analysis to assess the influence of opioid administration on neurotransmitter concentrations measured by microdialysis across all previously examined rat brain regions. As there was a limited number of animals per experimental setup another aim of this study was to find effects that were not found yet due to the limitation in the single experimental setup. Moreover, the aim was to create a reference work for further studies in this field. This study tries to summarize single reported effects in a reasonable and comprehensive way to give an overview of the opioid effects on neurotransmitter concentrations within different brain areas and gives an overview over the existing studies. Therefore, in this meta-analysis after conducting a literature review, I included into the meta-analysis a total of 382 articles reporting about a total of 12300 rats using 38 different opioids in all brain regions. The extracted data were organized in a way that allowed us to conduct analysis for each drug, dose of drug, neurotransmitter, and brain region. For statistical analysis I used ANOVA with when necessary Bonferroni method to prevent false positive or negative results. The detailed results sorted by brain region are given in the tables in the attachments for future research groups as a help in planning their own experimental setup. For every found combination of brain area, opioid and measured NT the weighted average baseline is given.

The study shows the huge range of study designs as well as the problem of comparability. As the comparison of studies is important, future research groups could use it as data basis for their study design to enhance the comparability.

Beside providing this overview the analysis looked for significant differences in the variables strain, age, gender, route of administration and consciousness of the animals which were not found yet due to the limitation of the single experimental setup. Some significances according the variables were found in the concentration of dopamine in the nucleus accumbens after administration of 5mg/kg morphine. These give a clear hint toward the conclusion that the strain of the rat may play an important role in interpreting and comparing data. The Wistar strain constantly shows lower peaks for dopamine than the Sprague-Dawley strain. The results concerning the consciousness of the animals during the experimental phase showed also significant differences. The route of administration seems also to play a role in the study design as well. The peak maxima of the transmitter concentrations reached different highs at different peak times according to the route of administration. The sex and age of the rats showed no significant influence in this analysis.

These results should be taken as a starting point for further detailed research into the question if and how the influence of these variables on the neurotransmitter changes is to be concerned in future study designs.