Effects of phosphodiesterase 4 inhibition after a short memory retrieval of contextual fear conditioning in rats

9 IMPACTS OF THE STUDY

This study holds paramount significance in advancing our comprehension of the neurobiological processes underlying fear and traumatic memories, thereby bearing potential implications for understanding the mechanisms central to Post-Traumatic Stress Disorder (PTSD). Notably, the focus lies on elucidating the role of PDE4 in the regulation of contextual fear memory, particularly in the immediate aftermath of retrieval. Consequently, the outcomes of this study offer valuable insights poised to contribute to the development of more efficacious therapeutic approaches for PTSD and other disorders associated with fear memory.

The investigation centers on the impact of PDE4 on fear memory after a brief retrieval. While the effects of PDE4 inhibition on spatial and recognition memories are well-documented and have shown potential to enhance cognition in both animal and human studies, the present investigation specifically examines its impact on fear memory. Furthermore, since ROF is already an approved medication for Chronic Obstructive Pulmonary Disease (COPD) and psoriasis treatment in humans, its potential repurposing for other therapeutic regimens is promising. However, there are dose-limiting effects for roflumilast due to its emetic side-effects in human translation. Gebr32a and A33 do not exhibit this emetic profile in a surrogate test in rodents (Schepers et al., 2023). Therefore, it is intriguing for future evaluations to better understand the effects induced by A33 and Gebr-32A, particularly because similar effects were observed here for the effects induced by PDE4D or PDE4B inhibition and non-selective PDE4 inhibition in the DH. Although not fully explored here, the use of inhibitors of these subtypes may favor clinical application, albeit requiring further evaluation. Consequently, these points open new avenues for scientific projects that may include new researchers and contribute to understanding. In this regard, the study contributes to an improvement in future interventions in fear memory processing through PDE4 inhibition mechanisms, where the mechanisms involving PDE4B and PDE4D

inhibition remain undiscovered, but this study highlights the potential for a deeper evaluation of these mechanisms.

In a previous study, we found that inhibiting PDE4 maintains the extinction of fear responses (Sohn et al., 2020). This current study underscores the potential of using PDE4 inhibition as a strategic approach to promote extinction and reduce fear responses in PTSD patients, without compromising other forms of memory. This outcome it is important once the amnesic drugs, such as the pan-inhibitors of protein synthesis present risk for clinical use and not selectively impair the fear memory but neuronal functions as a whole. In this way, this study point benefits for fear reduction, through an extinction facilitation but also improveing a non-emotional memory.

Since fear memories are often resistant to treatment in PTSD patients, strategies aiming to attenuate fear memories can be limited in their effectiveness (Kindt, 2018). Therefore, targeting PDE4 could be a promising avenue for developing new and innovative treatments for PTSD.

In the PTSD scenario, the results obtained here propose new possibilities to explore refined protocols for treating PTSD patients. The resistance of fear memory is one of the most significant challenges in PTSD treatment, especially for extinction-based therapy such as prolonged exposure therapy, where patients may express a recovery of fear responses. Here, PDE4 inhibition after a short retrieval facilitated extinction the following day, potentially representing a better response of patients exposed to extinction-based treatments. The FDA-approved status of ROF favors its clinical use, and its effects observed here require only a single administration, suggesting a lower impact of adverse medication responses induced by ROF.

Moreover, this study engenders new ideas about fear memory manipulation for PTSD. PDE4 inhibition appears to alter the fate of memory retrieval, and a better understanding of the molecular mechanisms involved in this process may enhance comprehension of the intracellular pathways involved, potentially opening new avenues for intervening in memory processes. For instance, the PDE4 after a short retrieval may improve the

therapeutic time window for amnesic drugs that have been studied for impairing the fear memory sustaining, such as endocannabinoids. Although these interferences also require further evaluation points a great opportunity for interfering directly with the fear memories.

The development of this study resulted in a published paper entitled “Phosphodiesterase 4 inhibition after retrieval switches the memory fate favoring extinction instead of reconsolidation” in Scientific Reports (Appendix 2), with more papers in preparation. Therefore, the project which includes this study and the previous one performed during my master degree permitted the contribution for the science in an international scale. The both experiments showed a potential participation of the PDE4 inhibition in the extinction facilitation. Together, these publications, as well as the others in preparation, contributes for a better understanding about the PDE4 regulation effect in the fear memory regulation.

In a personal aspect, the study allowed a professional experience in an international university, because a part of the Ph.D. thesis was conducted at Neuroscience and Psychiatry department of School for Mental Health and Neuroscience, Maastricht University the Netherlands. The supervision proceeded by professors Dr. Jos Prickaers, Dr. Tim Vanmierlo and Dr. Daniel van the Hove permitted a revision of the study in different points of view, as a consequence, this professional experience improved data interpretation and promoted international cooperation between Maastricht University and Universidade Federal do Paraná. Additionally, the collaboration with Maastricht University during all the period of project allowed the double doctorate diploma. This international diploma represents an opportunity to reach good future positions in international companies.