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MEETING ABSTRACT

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Histone deacetylase inhibitors rescue impaired fear extinction in a persistent and context-independent manner

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Background: A novel strategy in the treatment of anxiety and fear-related disorders is to augment extinction-based therapy by boosting gene transcription via administration of histone deacetylase inhibitors (HDACi) during extinction consolidation (a time point where new gene synthesis is required to initiate the formation of fear-inhibitory memories). However, information regarding the persistency and context-independency of this approach in pathological models of impaired fear extinction remains largely unknown. We have previously shown that MS-275 (HDAC1-, HDAC2- and HDAC3-isoform inhibitor) applied during the critical extinction consolidation period can rescue impaired extinction consolidation/retrieval in 'weak' conditioned 129S1/SvImJ mice. Here, we assessed whether MS-275 can promote persistent and context-independent fear inhibition and also to identify potential extinction-relevant molecular mechanisms invoked.

Methods: S1 mice were subjected to multi-trial cued fear conditioning/extinction paradigms to assess the ability of pharmaceutical ligands, including the HDACi MS-275 and the dopamine precursor L-DOPA, to promote long-term and context-independent protection against the return of fear (spontaneous recovery/fear renewal). Histone acetylation changes following fear extinction were measured using fluorescent immunohistochemistry and extinction-induced increases in histone acetylation in the promoter regions of dopaminergic receptor genes were quantified using chromatin immunoprecipitation.

Results: Here, we replicated the finding that MS-275 can rescue impaired fear extinction in S1 mice, and now show that MS-275 can promote a persistent (reduced fear during a long-term memory test) and context-independent (reduced fear in a novel context) fear-inhibitory memory. Rescue of impaired fear extinction was associated with higher histone acetylation in MS-275 treated mice in the infralimbic cortex, a brain region where long-term memories are primarily stored. Moreover, enhanced histone acetylation was observed in the promoter region of the dopamine D_1 receptor. The finding that increasing dopaminergic signalling, via L-DOPA, rescued impaired fear extinction consolidation in S1 mice provided functional proof-of-principal that dopaminergic signalling is an important signalling pathway promoted by enhanced histone acetylation.

Discussion: These data reveal that HDACi rescued impaired fear extinction in extinction-impaired S1 mice in a persistent and context-independent manner, which is of high clinical relevance. Moreover, these data reveal that this rescue of impaired fear extinction was associated with enhanced expression of a neuroplasticity-related gene within a key fear-extinction-relevant brain region, revealing a potential molecular mechanism via which HDACi may rescue aberrant fear. This was further underscored by the finding that pharmaceutical enhancement of dopaminergic signalling was able to rescue extinction deficits in S1 mice. Collectively, these results identify that HDACi's display promising potential as pharmacological adjuncts in exposure-based therapy to rescue impaired fear extinction in a persistent manner.

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