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MEETING ABSTRACT

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Role of histone acetylation and dopaminergic signalling in promoting long-term and context-independent fear extinction

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Background: Anxiety disorders are associated with an inability to extinguish learned fear. Current treatments including exposure-based therapies are only partially effective as return of fear is commonly observed. Mirroring anxiety patients, 129S1/SvImJ (S1) mice exhibit profound resistance to induce fear extinction, which is rescued by dietary zinc restriction (ZnR). Here, we show that dietary ZnR can also protect against spontaneous return of fear and fear renewal in a novel context; revealing a treatment to identify key factors leading to sustained and context-independent fear extinction. To elucidate the underlying molecular mechanisms, we assessed gene expression changes following successful ZnR-induced fear extinction. In addition, as acetylation of lysine residues on histone proteins are important steps in promoting gene expression and classical histone deacetylases are Zn-dependent enzymes, we measured lysine acetylation changes following fear extinction in ZnR S1 mice.

Methods: S1 mice were subjected to multi-trial cued fear conditioning/extinction paradigms to measure the ability of ZnR to promote long-term and context-independent protection against the return of fear (spontaneous recovery/fear renewal). Gene expression changes following successful ZnR-induced extinction were quantified 2 h post extinction training using microarrays. Lysine acetylation changes following fear extinction in ZnR S1 mice were measured by fluorescent immunohistochemistry and it was assessed whether the extinction-induced increases in histone acetylation are present in the promoter regions of the differentially regulated genes using chromatin immunoprecipitation.

Results: Gene microarray analysis following successful ZnR-induced fear extinction identified a selective cohort of differentially regulated genes in the amygdala, a brain area known to be involved in extinction. Strikingly, many differentially regulated genes were related to dopaminergic signalling, e.g. dopamine receptor D_1 and D_2 genes, suggesting that the dopaminergic system can be one possible mechanism via which dietary ZnR leads to persistent fear extinction. Indeed, pharmacological enhancement of dopaminergic signalling via L-DOPA following extinction training rescued the impaired extinction consolidation in S1 mice. The results obtained by fluorescent immunohistochemistry and chromatin immuno-precipitation revealed a significant increase in lysine acetylation in the medial prefrontal cortex (mPFC) of extinguishing ZnR S1 mice as compared to non-extinguishing control-fed S1 mice; this was correlated with enhanced histone acetylation in the promoter region of the extinction-regulated dopamine D_1 and D_2 receptor genes in the mPFC of extinguishing ZnR S1 mice.

Discussion: The current data show that ZnR induces extinction of learned fear in a psychopathological animal model and promotes sustained and context-independent fear inhibition, which is an important clinical aim. Changes in gene expression and histone acetylation following successful ZnR-induced fear extinction suggest that the dopaminergic system can be one possible molecular mechanism via which dietary ZnR leads to persistent fear extinction. This is further confirmed as pharmacological enhancement of dopaminergic signalling rescued the extinction consolidation deficits in S1 mice. Collectively, these results suggest that histone deacetylase (HDAC) inhibitors and dopaminergic agents mediate the preservation and context-independency of rescued fear extinction in S1 mice and thus represent promising targets for the development of pharmacological adjuncts for exposure therapy in human anxiety disorders.

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