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Study: Increased acetylation of histones promotes fear extinction in mice

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The targeted modulation of gene activity and cellular signaling pathways could provide a new approach to the treatment of fear and anxiety states according to the recent findings of a project sponsored by the Austrian Science Fund FWF.

Fear extinction is a classical method used in anxiety therapy: memories of negative – anxiety-producing – experiences can be "overwritten" by new learning involving positive (safe) associations. If you have ever been bitten by a dog, you are bound to be afraid of dogs. But if you subsequently have repeated encounters with dogs with no ill effects, the fear will fade. As simple as this method sounds and as effective as it may be, it does not work equally well for everyone. In an FWF project entitled "Epigenetic Mechanisms of Disturbed Memory Regulation" within the Special Research Programme (SFB) of "Cell Signaling in Chronic CNS Disorders", Nicolas Singewald set out to find out why that is so and how extinction can be boosted.

ACETYLATION COUNTERING ANXIETY

Singewald's team focussed specifically on epigenetic effects, i.e. changes in the genome that are acquired in the course of life. Specifically, the team investigated a chemical change (acetylation) of certain DNA-associated proteins (histones) that are believed to have a positive influence on fear extinction. The team succeeded in showing that such chemical modifications can augment and correct impaired fear extinction. Together with SFB and international colleagues, they also identified key cellular mechanisms underlying this effect.

SCAREDY CATS AMONG THE MICE

Singewald's team used a special mouse strain (129S1/SvImJ) which they had previously identified together with the US brain researcher Andrew Holmes. Like anxiety patients, these mice exhibit a reduced capacity for fear extinction and are therefore an ideal model for identifying cellular and molecular mechanisms that can promote anxiety therapy. In fact, the researchers found that increased acetylation of histones promotes fear extinction in these mice, thus establishing a clear relationship between epigenetic modifications and the correction of impaired extinction. In further convincing experiments, the group then identified cellular and molecular processes that contribute to this mechanism.

ORPHAN RECEPTORS

The team showed that, following histone acetylation, specific genes are recruited for fear extinction. "In fact, we revealed that for fixing of impaired extinction the involvement of certain genes and their gene products known to influence the plasticity of nerve endings, or synapses is important. We also discovered a number of genes for hitherto unknown receptors to play a role. The search for compounds that could interact with these receptors is now ongoing," says Singewald, explaining the results. Other molecular players suspected of influencing fear extinction were discovered in further studies, namely specific RNAs. These molecules are usually responsible for translating the genetic code into protein structures. However, it has long been known that some RNAs have other functions as well. It was precisely such RNAs (ncRNAs and miRNAs) that Singewald and his cooperation partners within the SFB found to be involved in facilitating fear extinction.

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THERAPEUTIC CONCEPT

The team found that receptors activated by classical neurotransmitters such as dopamine are also involved and formulated an approach to treating impaired extinction that may be beneficial in humans. "To investigate this therapeutic concept, we took advantage of the fact that an approved drug (for Parkinson's disease) exists that has an activating effect

on dopamine-dependent signaling pathways," Singewald says. Together with international colleagues, the team obtained convincing results. "We were able to show in both mice as well as in healthy humans that this therapeutic concept had sustained fear-inhibiting effects," Singewald reports.

The results of the FWF project indicate that the augmentation of certain cellular and (epi)genetic processes could offer new approaches to the treatment of fear and anxiety. This could provide hope for more effective treatment of pathological fear in the future for individuals in whom treatment concepts based on fear extinction, e.g. exposure therapy, do not work optimally.

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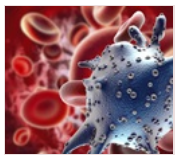
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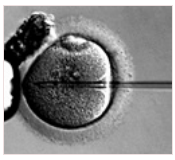
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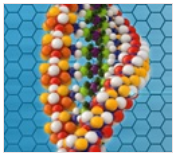
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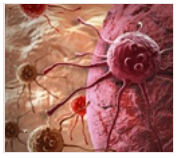
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