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TRANSLATIONAL PERSPECTIVE

# Histone-deacetylation inhibitors – old tools in new applications may ameliorate the consequences of social isolation on mental health

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'Happiness is only real when shared' marks the end of the motion picture *Into the Wild*, named after the corresponding book by Jon Krakauer. Conversely, the lack of social interaction causes adverse effects. This relationship has been subject to a vast number of psychological studies. A new study led by Zhen Yan and colleagues at the State University of New York Buffalo's Jacobs School of Medicine and Biomedical Sciences (Yan et al., 2024) now provides important insights into how early-life social isolation affects the mammalian genome, hence potentially the human genome, shaping stress responses and stress-related aggression. In their study, Yan et al. (2024) identified an epigenetic mechanism underlying heightened aggression in mice that experienced the stressor of social isolation early in life compared with animals housed in groups. They revealed increased deacetylation of histones in neurons of the prefrontal cortex, which is ultimately considered to change the expression of genes without altering the DNA sequence. In humans, epigenetics has already been identified to play a role in psychiatric disorders such as major depressive disorder. The present data provide important new insights into how early-life social stress might also alter gene expression in humans and underlie maladaptation in the stress response.

In a series of elegant experiments ranging from slice electrophysiology to animal behaviour, Yan et al. (2024) find that the altered histone acetylation is accompanied by an increased excitatory postsynaptic current in socially isolated male mice upon exposure to acute stress, putatively resulting in a change of prefrontal activity underlying the behavioural phenotype. This is very well in line with a role for histone deacetylation in synaptic plasticity, in addition to the effect of stress to modulate prefrontal activity rapidly in mice and humans (Gräff & Tsai, 2013). Thus, their data strongly point towards early-life social isolation leading to a hyperactivity within frontal networks, putatively underlying the impulsive action and heightened aggressive behaviour in response to the acute stressors.

Importantly, using histone-deacetylation inhibitors to treat these behavioural symptoms pharmacologically resulted in a vast attenuation of the aggressive stress response in mice that were socially isolated in early life. Consistent with improved animal behaviour, the group found the increased excitation upon acute stress in frontal regions in socially isolated mice to be reduced to baseline levels, highlighting not only the effects of epigenetics on synaptic plasticity and finally animal behaviour, but also the effectiveness of pharmacological interventions targeting epigenetics.

These results contribute to earlier and recent findings in which epigenetic changes, such as DNA methylation and histone deacetylations, were described in response to social isolation stress and where the use of histone-deacetylation inhibitors was shown to facilitate extinction learning in animals that went through fear conditioning experiments (Bludau et al., 2023). Including the present study by Yan et al. (2024) in this issue of *The Journal of Physiology*, this epigenetic mechanism has now been observed in several brain regions involved in the response to stress and fear, potentially assigning histone deacetylation to be a general mechanism in the precipitation of stressful situations during life. Collectively, this corroborates not only the significance of epigenetics for social stress, but also the use of histone-deacetylation inhibitors in the treatment of stress-related psychiatric manifestations.

Histone-deacetylation inhibitors constitute known tools in the treatment of various cancers, where they are able to suppress the rapid growth of tumour cells and, in combination with other drugs, reveal effectiveness in a broad range of different tumour classes. The two drugs used by Yan et al. (2024), romidepsin and MS-275, which target histone-deacetylation pharmacologically, are already in use in the context of cancer therapies (Bondarev et al., 2021). Romidepsin is already approved by the United States Food and Drug Administration, and MS-275 is currently in clinical trials and might show less side effects than romidepsin. Collectively, this raises the possibility of histone-deacetylation inhibition to constitute a new prominent avenue in the treatment of stress-related psychiatric disorders.

This is of particular interest for a post-pandemic society, in which adolescents ranging from kids to teenagers have been suffering from social isolation, and in a changing society that facilitates a lack of social interaction of human beings at any age. The costs of social isolation in the context of the coronavirus disease 2019 pandemic measures are yet to be calculated. In a society of rapidly growing cities with rapidly increasing anonymity, mankind consequently encounters elevated levels of social isolation, and the effects on mental health and well-being are already well described. Therefore, to tackle the disadvantages and the consequences of social isolation, identification of new tools and targets in the treatment of stress-related psychiatric disorders is particularly relevant. Collectively, the present research by Yan et al. (2024) will further strengthen the focus of the field on epigenetics and how to modulate and target the consequences of social stress on gene expression by the use of histone-deacetylation inhibition. It also illustrates the necessity to develop drugs targeting epigenetic modifications of gene expression with high specificity and minimal side effects (Park & Kim, 2020).

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## Additional information

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## Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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