学位論文内容の要旨
（Summary of dissertation）

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学 位 論 文 題 名（Title of dissertation）
The neurobiological basis of the antidepressant-like effect of exercise
(運動の抗うつ様効果の神経生物学的基盤に関する研究)

Introduction

Exercise, or physical activity, improves stress coping and reduces depression in humans and rodents. However, the underlying neurobiological mechanism remains unclear. Rarely has any research examined the causality between the observed neurobiological changes and the beneficial outcomes by exercise. This is further complicated by a 'side effect' of exercise: it increases basal glucocorticoid (CORT), the stress hormone, which has been shown to be a mediator linking stress to depressive disorders. For instance, basal CORT is typically elevated by chronic stress and in depression, and elevated basal CORT has been shown to predict the onset of depression. Here we aimed to explore the effects of exercise on CORT and various neurotransmitters in the medial prefrontal cortex (mPFC) and identify how exercise exerts antidepressant-like effect despite potentially increasing CORT, employing in vivo microdialysis and microinjection.

Methods and results

Experiment 1 The behavioral and neurobiological effects of exercise

Rats were randomly allocated to exercise (EX) or control (CON) group, both raised in the same cage box while only EX rats had free access to a running wheel attached on the side of the box. Three weeks later, one subset of rats was subjected to the forced swim test (FST), while another subset was subjected to the FST under microdialysis. We found that three weeks of voluntary wheel running reduced immobility time in the FST, an antidepressant-like effect. Monitoring extracellular fluids in the mPFC we found that, compared to CON, EX rats had significantly higher bassal CORT, but lower CORT overall-exposure after FST. Further, exercise rats had higher DA both at baseline and after FST. There was no significant effect of wheel running on other neurotransmitters measured, including NA, 5-HT, alanine, glycine, taurine, glutamine, and glutamate. Nor was there significant effect of wheel running on the protein expression density of glucocorticoid receptor (GR), DA D1R, D2R, or 5-HT1AR.

Experiment 2 The role of medial prefrontal DA in the antidepressant-like effect of exercise

This experiment aimed to examine whether the upregulated DA observed in experiment 1 plays a causal role in the antidepressant-like effect of wheel running, by intra-mPFC pre-microinjection of a D1R or D2R antagonist. 25-30 min (27.23±0.33) before the FST, EX rats were injected a D1R or D2R antagonist while CON rats received only the vehicle. In the meantime, we monitored the general motor activity of a subset of EX and CON rats using an apparatus with an infrared sensor that detects thermal radiation from animals. We observed that, the antidepressant-like effect of wheel running in the FST was completely abolished by intra-mPFC pre-microinjection of a D2R but not D1R antagonist, at a dose that does not affect normal rats' performance in the FST. Further, wheel running did not affect the general motor activity of rats.

Experiment 3 The role of elevated medial prefrontal CORT in the antidepressant-like effect of exercise

Experiment 3 was designed to test the hypothesis that the elevated basal CORT in the mPFC is responsible for the upregulated DA and thus plays a causal role in the antidepressant-like effect of wheel running. A GR antagonist was injected into the mPFC of EX rats 30 min before the FST, while CON rats only received the vehicle. One subset of rats underwent the FST only, while another subset of rats underwent the FST under microdialysis. We found that the antidepressant-like effect of three weeks of

wheel running in the FST was abolished by intra-mPFC pre-microinjection of a GR antagonist. In the meantime, intra-mPFC pre-microinjection of the GR antagonist also downregulated the basal DA as well as the FST-responsive DA in the mPFC of exercise rats, without any effect on the 5-HT in the mPFC.

Discussion

Consistent with previous reports that exercise reduces depression and improves stress coping, we observed that wheel running reduced immobility in the FST, without affecting general motor activity. This antidepressant-like effect was accompanied by overall upregulated DA in the mPFC. More interestingly, intra-mPFC pre-microinjection of a D2R but not D1R receptor antagonist completely abolished the antidepressant-like effect of wheel running. These results suggest that exercise exerts antidepressant-like effect through upregulating DA in the mPFC and in a D2R-dependent way. It has been shown that chronic stress reduces while antidepressants increase DA in the mPFC and that DA in the mPFC is associated with animal's performance in the FST and effortful behavior. Our research, for the first time, provides causal support for the essential role of DA in the mPFC for active coping and antidepressant-like effect.

In the meantime, we observed that EX rats also showed higher basal CORT but overall lower FST-responsive CORT. Further, intra-mPFC pre-microinjection of a GR antagonist abolished the antidepressant-like effect of wheel running and blocked the originally upregulated basal and FST-responsive DA by wheel running. This suggests that the elevated basal CORT may be responsible for the upregulated DA. This is consistent with recent evidence that CORT increases DA efflux in the mPFC through activating GR but that DA in the mPFC acts to suppress stress-responsive CORT.

These results suggest a causal pathway linking CORT, GR, DA, and D2R, to the antidepressant-like effect of exercise. Returning to the CORT paradox we discussed in the introduction, a second comparison of chronic stress and exercise reveals fundamental differences. Although both elevate basal CORT, chronic stress reduces while exercise increases DA in the mPFC. This might be the key why the former is detrimental while the latter is beneficial to stress coping and depression.

Conclusion

Exercise achieves antidepressant-like effect through the CORT-GR-DA-D2R pathway and that the increased CORT by exercise itself is beneficial rather than detrimental.