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Brain-derived neurotrophic factor and exercise-induced reversal of cognitive deficits of relevance to schizophrenia in the sub-chronic phencyclidine rat model

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Introduction: Cognitive deficits in schizophrenia remain an unmet clinical need, these have a significant impact on outcome and quality of life for patients and carers (1). The sub-chronic phencyclidine (scPCP) rat model and novel object recognition (NOR) task have been well validated for relevance to schizophrenia (2,3). Exercise increases hippocampal and plasma levels of brain-derived neurotrophic factor (BDNF), a growth factor protein that modulates synaptic plasticity and long-term potentiation (4), thus providing a hypothesis for its therapeutic effects on cognitive deficit symptoms of the illness. Our aim is to investigate the mechanisms by which aerobic exercise reverses cognitive deficits in the scPCP model, with a focus on BDNF.

Methods: Four groups of adult female Lister Hooded rats (n=10 per group) were used: vehicle control, vehicle exercise, scPCP control, and scPCP exercise. Rats were treated with saline or PCP (2mg/kg i.p.) twice a day for 7 days, followed by 7 days washout then given access to running wheels in individual cages for 1 hour a day, 5 times a week, for 6 weeks. Control groups had access to immobilised running wheels. NOR tasks (with a 1 minute inter-trial interval) were conducted pre-exercise, post-exercise, 2 weeks post-exercise, and 4 weeks post-exercise. Blood samples were taken pre-exercise and post-exercise. Plasma BDNF levels were quantified by ELISA. Data were analysed by ANOVA and post-hoc student's t-test.

Results: Pre-exercise vehicle, but not scPCP groups, successfully discriminated the novel from familiar object ($p<0.05$). The exercise regimen reversed this cognitive deficit ($p<0.05$), while the scPCP control group remained unable to complete the task and vehicle groups successfully discriminated the novel from familiar object ($p<0.05$). The cognitive deficit reversal was sustained 2 weeks post-exercise ($p<0.05$), but the deficit returned 4 weeks post-exercise. Plasma analysis did not show significant changes in plasma BDNF levels. Subsequent studies will measure BDNF (protein and mRNA) in the hippocampus, prefrontal cortex, and frontal cortex.

Conclusions: This work demonstrates that exercise therapy reverses a robust cognitive deficit in a well validated pharmacological rat model of relevance to schizophrenia. Our work to evaluate potential mechanisms of this effect through BDNF could inform future therapeutic strategies in patients.

References:

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