Brain function and glucocorticoids in obesity and type 2 diabetes including effects of lifestyle interventions

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Akademisk avhandling

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Background Obesity and associated metabolic dysregulation are linked to impaired cognitive function and alterations in brain structure, which increases the risk of age-related dementia. Increased glucocorticoid (GC) exposure may be a potential mediator of these negative effects on the brain. Methods and results In paper 1, we tested the relationship between cortisol levels, brain morphology and cognitive function in 200 women and men. Salivary cortisol levels were negatively related to cortical surface areas in prefrontal brain regions in both sexes. In participants with type 2 diabetes, high salivary cortisol levels were associated with lower memory performance. In paper 2, we tested in 70 overweight women the effects on tissue-specific GC metabolism of a Paleolithic diet or a diet following the Nordic nutrition recommendations. The 24-month interventions led to decreased expression of the GC-activating enzyme 11βHSD1 in adipose tissue, interpreted as a normalization of an obesity-related disturbance in GC metabolism. Furthermore, GC metabolism by 5α-reductase increased substantially after 2 years, an unexpected and novel result. The outcomes did not differ by diet. In paper 3, 20 women included in paper 2 were examined with functional magnetic resonance imaging (fMRI) while performing a memory task at baseline and after 6 months. Memory performance improved and functional brain responses increased in the hippocampus. Once again, the results were similar in both diet groups. In paper 4, 24 overweight participants with type 2 diabetes were examined with fMRI, using the same memory test as in paper 3, at baseline and after 12 weeks of intervention with a Paleolithic diet with or without exercise training. Functional brain response increased in the hippocampus, but memory was not improved. The addition of physical exercise did not alter the results. Conclusion Cortisol levels are linked to prefrontal brain structure and, at least in type 2 diabetes, lower memory performance. Furthermore, the dysregulated GC metabolism in obesity can be reversed by long-term diet-induced weight loss. Finally, dietary interventions with associated metabolic improvements alter functional brain responses during memory testing, including increased activation of the hippocampus. Whether these changes are linked to alterations in GC exposure and mediate improved cognition requires further study.

Keywords Obesity, type 2 diabetes, glucocorticoid, cortisol, 11beta hydroxysteroid dehydrogenase type 1, episodic memory, functional magnetic resonance imaging, paleolithic diet, exercise