Epigenetic regulation of the endocannabinoid system in Activity-based model of Anorexia nervosa

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Abstract

Aims: Anorexia nervosa (AN) is a psychiatric disorder characterized by dramatic reduction in caloric intake by excessive dieting and irrational fears of gaining weight, often accompained by over-exercise. The endocannabinoid system (ECS) has been proven to play a role in the regulation of feeding behaviour and its impaired signaling in AN makes it a promising treatment target[1,2].

Methods: Activity-based anorexia (ABA) model mimics key sympotms of AN in rodents where animals housed with running wheels and subjected to daily food restriction show reductions in food intake and increases in running wheel activity[3]. We investigated the transcriptional regulation of endocannabinoid system (ECS) genes in ABA rat model with two critical time-points: 3 and 6 days. In comparison, the ECS was studied in the same fashion in the genetic, *anx/anx* model of the disease.

Results: In ABA model we observed selective down-regulation of cannabinoid type-1 receptor gene (*Cnr1*) after 6 days induction period in rats nucleus accumbens. Consistently, pyrosequencing has revealed increased DNA methylation levels at *Cnr1* promoter. Reduced

Cnr1 gene expression levels were also accompanied by decreased protein expression. No changes were observed in other brain regions studied for any of ECS genes, besides a down-regulation of *Cnr1* in the hypothalamus. On contrary, in the genetic animal model the only relevant change detected was down-regulation of *Cnr1* gene in prefrontal cortex.

Conclusion: Our findings demonstrate selective and time-dependent epigenetic modulation of *Cnr1* in ABA rats in relevant brain regions and therefore support the central role played by *Cnr1* in food intake.

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