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Effects of physical exercise on metabolic syndrome-associated hypothalamic and testis alterations in the rabbit

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Metabolic Syndrome (MetS) is a cluster of clinical conditions, associated to an increased cardiovascular (CV) and metabolic risk along with hypogonadism (HG). Lifestyle modifications (including physical exercise, PhyEx) are well-known treatments for this condition [1]. We previously established a rabbit model of MetS that recapitulates the human phenotype, including HG [2]. We now report studies on the effects of PhyEx on hypothalamus-pituitary-testis (HPT) axis. MetS was induced in adult male rabbits fed a high-fat diet (HFD). Rabbits fed a regular diet were used as controls (RD). RD and HFD rabbits were exercise-trained to run on a treadmill for 12 weeks (RD + PhyEx and HFD+ PhyEx). HFD rabbits showed typical metabolic and CV features of MetS along with hypogonadotropic HG (reduced testosterone and LH plasma levels). Within the hypothalamus (preoptic region) a significant reduction of GnRH- and KISS1R-positive neurons, along with the increase of genes related to inflammation (COX2, IL6, CD68), glucose metabolism (GLUT1, GLUT4, IRS-1) and estrogen action (ERb, GPR30) was detected in HFD rabbit, as compared to RD group. Immunohistochemistry analysis confirmed the HFD-induced hypothalamic inflammation. Interestingly, genes encoding for inhibitory factors for GnRH, such as NPY, were also increased in HFD hypothalamus. Within the testis, HFD down-regulated LH receptor and all the steroidogenic enzymes leading to T synthesis. PhyEx completely restored T and LH plasma levels and GnRH/KISS1R immunostaining. All the aforementioned HDF-induced increase of inflammatory markers were significantly reduced in HFD+ PhyEx, with the exception of IL6. Moreover, at hypothalamic level, PhyEx decreased orexigenic and GnRH-inhibiting factors (dinorphin and its receptors OPRD1 and OPRK1), whereas increased anorexigenic ones (POMC). Within the testis, genes related to T formation (17βHSD3) and metabolism (5α-reductase 1) were increased by PhyEx. In conclusion, in this experimental model, endurance training (PhyEx) completely reverted MetS-induced hypogonadotropic hypogonadism, exerting beneficial effects on the HPT axis. Particularly, in the hypothalamus PhysEX reduced HFD-induced inflammation. Hence, aerobic exercise training can be regarded an interesting strategy to combat MetS-associated alterations of the HPT axis.

References

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Key words

GnRH neurons, hypogonadism, inflammation, hypothalamus.