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tytuł pracy: ***„Genetic and environmental interactions in the acquisition of the brown adipocyte phenotype during postnatal development”***

Abstract

The brown adipocyte phenotype (BAP) in white adipose tissue (WAT) from mice appears transiently at 21 days of age, it subsequently involutes, but it is induced in adult mice in response to stimulation of the sympathetic nervous system (SNS). Under-nutrition during the perinatal period suppressed the induction of brown adipocytes in WAT at 21 days of age, caused hypoglycemia, hypoinsulinemia and hypoleptinemia, and reduced adiposity in the pre-weaning and adult mice within an obesogenic environment. If induction of a negative energy balance can prevent or reverse obesity, then increasing energy expenditure with reduced ambient temperature may be an effective anti-obesity strategy.

To determine the effects of variation in ambient temperature during early postnatal period on the BAP, two genetic mouse models, C57BL/6J (B6) and AxB8/PgJ (AxB8) mice, with variable capacity for brown adipocyte induction in WAT, were reared at 17^{o}C or 29^{o}C from birth until weaning at 21 days of age. Then, mice were shifted to 23^{o}C for a period of 5 weeks and either exposed to 4^{o}C for an additional week or fed a high fat diet for 8 weeks. Reduced ambient temperature during early postnatal period suppressed the development of diet-induced obesity in 112 day-old mice from both strains indicating that 17^{o}C during the pre-weaning period influenced adiposity and the overall metabolism throughout life. Morphological and molecular analyses of brown adipocyte-specific biomarkers in inguinal WAT (iWAT) indicated that 17^{o}C did not stimulate the BAP in WAT at 10 days of age. Microarray analysis of global gene expression in iWAT from 10 day-old B6 mice reared at 17^{o}C and 29^{o}C demonstrated that stimulation of sympathetic activity in WAT is not detected at 10 days of age. In contrast, reduced ambient temperature significantly increased the expression of *Ucp1*, *Dio2*, *Pgc1a* and *Ppara* in 21 day-old mice from both strains. However, the BAP was induced also in WAT from 21 day-old mice reared at thermoneutrality indicating that the appearance of brown adipocytes in WAT is determined genetically. Global gene expression analysis in iWAT from 21 day-old B6 mice maintained at 17^{o}C and 29^{o}C revealed that decreased ambient temperature influenced the expression of transcripts involved in regulation of thermogenesis, mitochondrial function and glucose and lipid metabolism. Comparative microarray analysis revealed that the majority of changes in the expression

of genes in iWAT between 10 and 21 days of age occurred independently of the ambient temperature and were involved in the formation of neural structures and WAT remodeling that enabled the subsequent response to sympathetic stimulation by 17^{o}C. The BAP found in WAT at 21 days of age disappeared post-weaning with a complete involution of brown adipocytes observed in WAT from 56 day-old mice. The BAP was re-induced in response to 7 days of cold exposure in a manner indicating equal thermogenic activity irrespective of the ambient temperature during early postnatal development demonstrating that the effect of reduced ambient temperature during the pre-weaning period was transient.

In conclusion, a concept for a genetic model for brown adipocyte development, which involves a spontaneous appearance of brown adipocytes in WAT and a mechanism of involution in which the BAP is degraded when a demand for thermogenesis has ceased, was introduced. The BAP in WAT appears as soon as WAT acquires its mature structure. The post-weaning involution of brown adipocytes in traditional white fat is relevant for dynamic changes in the BAP upon environmental requirements.