

## Social stress alters hepatic gene expression with reference to lipid metabolism and induces obesity in mice

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It has been reported that daily exposure to social and psychological stress is associated with life-style related diseases such as hyperinsulinemia, hyperglycemia, cardiovascular diseases and cancer, as well as mental disorders. The stress is considered to link to obesity. However, the mechanisms of the relationship between them remain unclear. In this study, we evaluated changes in the hepatic gene expression profile using a DNA microarray in mice that were exposed to isolation stress for 30 days. And we also investigated whether isolation stress induces obesity or not.

Male BALB/c mice (4 weeks old, Japan SLC, Shizuoka, Japan) were housed at 5 mice per cage. After acclimatization for 10 days, the mice were exposed to isolation stress (1 mouse per cage). All cages were placed in a foamed polystyrene box in order to avoid social contact. To enhance the feeling of isolation, the bed volume in each cage for the isolated mice was reduced to about 2 g per cage. Both control and stress groups were composed to 5 mice each. Hepatic RNA was sampled and subjected to DNA microarray analysis. We employed a method for extracting the differentially expressed genes more effectively and used gene function enrichment analysis according to Gene Ontology. On the other hand, after acclimatization for 10 days, male C57B/L mice were exposed to isolation stress for 3 months with normal diets. The food intake and body weight were measured. After the feeding period, the 6 hr-fasted mice were sacrificed to collect blood, liver, adrenal, and abdominal adipose tissue. Serum biochemical indices were measured by EIA kits etc.

Gene Ontology analysis of these differentially expressed genes indicated that the stress remarkably down-regulated the lipid metabolism-related pathway through peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ), while the lipid biosynthesis pathway controlled by sterol regulatory element binding factor 1(SREBP1) was significantly up-regulated. Significant increase of body and adipose tissue weight was observed in the mice isolated for 3 months compared with control mice. Serum adiponectin level was significantly lower in isolated mice, while significant increase of serum cholesterol was observed. These results suggest that a mild and consecutive social stress affects the systems for lipid metabolism and induces obesity.

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