



AIR POLLUTION PARTICIPATES IN THE GENESIS OF OBESITY THROUGH THE ACTIVATION OF HYPOTHALAMIC TLR4

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Abstract

Air pollution is involved in several processes harmful to health. PM_{2.5} is the most associated with the induction of chronic inflammation. Hypothalamus regulates the energy homeostasis through metabolic, neural and hormonal signals. Leptin signaling participates in this process, and hypothalamic inflammation may induce leptin resistance. TLR4 is an innate immune receptor capable of triggering subclinical inflammation, and one of its agonists is LPS, which is known to be present in the PM_{2.5} composition. Polluted C57 mice had increased adiposity due to hyperphagia and lower energy expenditure, caused by leptin resistance. The TLR4 gene expression was elevated in the hypothalamus of polluted C57. The TLR4 deletion protected the animal from obesity, glucose intolerance, and leptin resistance when exposed to PM_{2.5}. Together, these results suggest that air pollution induces hypothalamic leptin resistance by the activation of inflammatory pathways, probably involving TLR4.

Key words: Air pollution, hypothalamic leptin action, Obesity.

Introduction

Exposure to air pollution has unfavorable cardiometabolic effects contributing to the increase in mortality. Particulate matter 2.5 (PM_{2.5}) is the most associated with these effects and is known for its ability to develop chronic inflammation in many tissues.¹ PM_{2.5} may trigger inflammation by the activation of toll-like receptor 4 (TLR4) since PM_{2.5} contains lipopolysaccharide (LPS) in its composition.^{3,4} Leptin signaling in the hypothalamus participates in the maintenance of energy homeostasis. Leptin resistance may occur due to low-grade hypothalamic inflammation in obese models.² Therefore, the aims of the present study were to investigate the TLR4 gene expression in the hypothalamus of C57BL/6J mice (C57) exposed to PM_{2.5} (polluted) compared to C57 exposed to filtered air (FA) as well as the changes in energy homeostasis in C57 and TLR4-knockout mice (TLR4KO) exposed to PM_{2.5} or FA. Six-weeks-old male mice were exposed to PM_{2.5}/FA in the Harvard Ambient Fine Particles Concentrator at the University of Sao Paulo. Afterward, we measured food intake, O₂ consumption, and heat. Besides, we performed: intraperitoneal leptin sensitivity test and glucose tolerance tests (GTT). At the end of all in vivo experiments, mice were sacrificed, and hypothalamus and epididymal adipose tissue were dissected and kept under -80°C.

Results and Discussion

Polluted C57 mice had increased body weight, adipose mass, and serum insulin concentration. The GTT was altered in the polluted C57 compared to C57 FA. Food intake was elevated in the polluted

C57; however, the oxygen consumption was significantly lower in polluted C57 compared to FA mice, suggesting lower energy expenditure and hyperphagia in this group. Polluted C57 mice presented leptin resistance in the hypothalamus because body weight and food intake in response to leptin only decrease in the FA C57 mice, not in polluted C57 mice. TLR4 gene expression levels were elevated in the hypothalamus of polluted C57 mice. The TLR4KO exposed to PM_{2.5} did not present changes in body weight or adipose mass. Consistent with this result, hypothalamic leptin sensitivity was similar to C57 exposed to FA. Heat (kcal/h) measurement was increased in the TLR4KO exposed to PM_{2.5} compared to C57 exposed mice, which might contribute to the leanness in this group.

Conclusions

Together, the data suggest that the air pollution participates in the genesis of obesity and glucose intolerance. The increase in adiposity may be due to hyperphagia and reduced energy expenditure. Hypothalamic inflammatory pathways may be involved in leptin resistance induced by air pollution because the TLR4 deletion protected the polluted mice from obesity and glucose intolerance.

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