The flavonoid compound luteolin prevents endothelial dysfunction in a mouse model of high fat diet-induced obesity

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Background. Endothelial dysfunction is a proposed early mechanism whereby obesity is associated with cardiovascular disease. The flavonoid luteolin is suggested to exert beneficial effects in the prevention of comorbidities associated with obesity. However, the putative effects of luteolin on obesity-associated endothelial dysfunction remain undetermined. This study examined the effects of luteolin on endothelial dysfunction in a mouse model of diet-induced obesity.

Methods. Male C57BL/6J mice were fed with standard diet (SD) or high-fat diet (HFD). SD or HFD mice were treated with luteolin (10 mg/Kg/day). After 8 weeks, body and epididymal fat weight, as well as blood cholesterol, triglycerides and glucose levels were evaluated. Functional experiments were performed on resistance mesenteric vessels, mounted on a pressurized myograph. Endothelium-dependent relaxation was assessed by a concentration-response curve to acetylcholine, repeated upon infusion of L-NAME or ascorbic acid to investigate the availability of nitric oxide (NO) and reactive oxygen species (ROS), respectively. Intravascular ROS production was measured by the dihydroethidium (DHE) fluorescent dye. Endothelial NO synthase (eNOS) expression and microRNA (miRNA)-214-3p (a miRNA with protective effects against endothelial senescence/apoptosis) were examined by Western blot and RT-PCR assays, respectively.

Results. When compared to SD mice, HFD animals displayed significant increments of body weight, epididymal fat weight and metabolic indexes. Mesenteric vessels from HFD mice displayed a reduced endothelium-dependent relaxation, which was resistant to L-NAME and potentiated by ascorbic acid, which also restored the inhibitory effect of L-NAME, indicating the presence of a reduced NO availability, secondary to an increased ROS generation. Such changes were associated with an intravascular increase in superoxide anion production and a decreased vascular eNOS expression. Furthermore, miRNA-214-3p expression was reduced in HFD mesenteric vessels, as compared to SD mice. In HFD mice, luteolin counteracted the increase in body and epididymal fat weight, as well as the alterations of metabolic indexes. Luteolin also restored the endothelial NO availability, decreased the intravascular ROS production and increased the vascular eNOS expression. In addition, luteolin normalized miRNA-214-3p expression in mesenteric vessels.

Conclusions. These results suggest that luteolin can prevent systemic metabolic alterations and vascular dysfunction associated with obesity, likely through antioxidant properties.