

## RESVERATROL IMPROVES SYSTEMIC OXIDATIVE STRESS AND LOWER URINARY TRACT DYSFUNCTION IN OBESE MICE

### Hypothesis / aims of study

The polyphenol resveratrol is produced in plants and is present in many plant-based foods, such as grapes, peanuts, or berries. Preclinical studies have identified a number of mechanisms and targets by which resveratrol exerts benefits against cardiovascular diseases, including vascular dysfunction, hypertension, inflammatory states, cardiac injury, platelet hyperaggregability and oxidative stress. In addition, resveratrol activates lipolysis in rat and human adipocytes, reduces white adipose tissue and liver lipogenic activity, increases liver fatty acid oxidation, and enhances brown adipose tissue and skeletal muscle thermogenesis (1).

Clinical studies have implicated obesity as a major contributing factor for voiding dysfunction and overactive bladder (OAB). Recent studies carried out in high-fat fed obese mice showed degradation of soluble guanylate cyclase and reduction of cGMP production in detrusor (2) and urethra smooth muscle (3). This study aimed to evaluate whether chronic oral intake with resveratrol prevents obesity-induced OAB.

### Study design, materials and methods

C57BL/6 male mice fed for 12 weeks with standard chow (n=20) or high-fat diet (n=22) were used. Control and obese mice were treated with vehicle (water) or resveratrol (100 mg/kg/day for 2 weeks). The metabolic profile was assessed by measuring body weight, epididymal fat mass, fasting glucose, total cholesterol, LDL and HDL. The oxidative stress status was evaluated by using TBARS assay kit in plasma. In separate experiments, bladder and urethra smooth muscle from control and obese mice were mounted in 5-ml organ bath chambers containing Krebs solution (95% O<sub>2</sub> / 5% CO<sub>2</sub>, pH 7.4, 37°C). Contractile responses to the muscarinic agonist carbachol (CCh; 0.001 - 100 µM) and electrical-field stimulation (EFS; 1 - 32 Hz) were obtained in the bladder smooth muscle. Relaxant responses to the NO donor glyceryl trinitrate (GTN; 0.001 - 100 µM) were obtained in the urethra.

### Results

Obese mice showed increased body weight, epididymal fat mass, fasting glucose, total cholesterol and HDL (P<0.05) compared to lean mice. Oral treatment with resveratrol reduced epididymal fat mass and blood glucose. There was no difference in LDL between groups (Table 1). TBARS assay showed a 71% higher lipid peroxidation in plasma of obese mice when compared to lean mice, which was reversed by resveratrol (Table 1).

**Table 1.** Body weight, epididymal fat mass, blood glucose, total cholesterol, LDL and HDL in lean and obese mice treated with resveratrol.

	Lean + Vehicle	Lean + Resveratrol	Obese + Vehicle	Obese + Resveratrol
<b>Body weight (g)</b>	30.3 ± 3.3	28.1 ± 3.1	40.6 ± 4.8*	35.5 ± 1.1
<b>Epididymal fat mass (g)</b>	0.25 ± 0.01	0.27 ± 0.01	1.72 ± 0.12*	1.36 ± 0.08#
<b>Blood glucose (mg/dL)</b>	103.6 ± 3.2	103.0 ± 9.2	170.0 ± 5.7*	139 ± 7.6#
<b>Total cholesterol (mg/dL)</b>	90.0 ± 1.2	89.1 ± 1.2	108.0 ± 3.4*	106.2 ± 1.7
<b>LDL (mg/dL)</b>	48.9 ± 1.0	44.8 ± 1.1	50.4 ± 2.1	50.3 ± 2.3
<b>HDL (mg/dL)</b>	29.0 ± 0.7	33.4 ± 0.35	46.3 ± 1.6*	44.2 ± 1.8
<b>TBARS</b>	12.2 ± 1.1	10.5 ± 1.6	20.9 ± 1.6*	15.6 ± 0.7#

\*P<0.05 – compared with lean+vehicle; #P<0.05 – compared with obese+vehicle.

Carbachol-induced bladder contractions were significantly greater in obese compared with lean mice (E<sub>max</sub>: 3.7 ± 0.4 and 2.2 ± 0.3 mN/mg, respectively), which was fully normalized by resveratrol. Likewise, EFS-induced bladder contractions were greater in obese compared with lean mice (8 Hz: 4.2 ± 0.8 and 1.9 ± 0.2 mN/mg, respectively), which was normalized by resveratrol. Urethral relaxations induced by were lower in obese compared with lean group (E<sub>max</sub>: 31.5 ± 1.8 and 46 ± 3.5 %, respectively), which was also restored by resveratrol.

### Interpretation of results

Obese mice show increased body weight, epididymal fat mass, fasting glucose, total cholesterol and HDL levels, as well as increased oxidative stress. Obese mice also displayed bladder hypercontractility associated with impaired NO-mediated urethral relaxations. Resveratrol treatment reduced epididymal fat mass and blood glucose, and improved systemic oxidative stress in obese mice. Resveratrol reversed the functional alterations in bladder and urethra.

### Concluding message

Resveratrol treatment improved lower urinary tract dysfunction in obese mice probably due to improvement of systemic oxidative stress.

### References

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Disclosures

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