THE ROLE OF SUCCINATE IN THE TREATMENT OF VOIDING DYSFUNCTION ASSOCIATED WITH METABOLIC SYNDROME

Hypothesis / aims of study
Metabolic syndrome is closely associated with overactive bladder syndrome (OAB) in both men and women, affecting a large population in Western societies. Metabolic syndrome and OAB are linked through common risk factors such as atherosclerosis, ischemia and a pro-inflammatory state. Increased succinate production is detected in the presence of hyperglycemia and hypoxemia, as with diabetes mellitus and metabolic syndrome, and was recently identified as a major metabolic switch controlling metabolic functions in the body through its receptor GPR91 (SUCNR1). Our goal is to determine the role of succinate in the generation of bladder overactivity in a metabolic syndrome animal model associated with insulin resistance.

Study design, materials and methods
This novel study assessed the voiding pattern of rats known for insulin resistance and salt-induced hypertension. A group of Dahl-salt sensitive rats (Dahl-SS), of SS2BN rats (Dahl-SS rat with chromosome 2 of the Brown-Norway rats) and of Spontaneously Hypertensive Stroke Prone rat (SHRSP) were assessed in with conscious cystometry, with instillation of normal saline or saline with succinate. Succinate was measured in plasma and urine samples using an enzymatic method (Megazyme kit). Fasting glycemia was also determined in these animals. Bladder samples were fixed in paraformaldehyde 1% and processed for immunohistochemistry.

Results
Succinate receptor GRP91 was detected by immunohistochemistry of the urothelial and smooth muscle cells of the whole bladder (Figure 1). Immunoblotting confirmed the presence of the receptor as well. Measure of fasting glucose confirmed moderate hyperglycemia in SS2BN and SHRSP rats (Figure 2). Succinate levels were increased in the plasma of insulin-resistant rats compared to controls, while urinary succinate concentrations were significantly decreased (Figure 3).

Cystometry carried out in conscious rat revealed that SS2BN, Dahl-SS and SHRSP male rats have a lower bladder capacity, lower micturition volume and lower micturition interval than their controls Wistar. Other parameters were similar (Table 1).
Cystometry revealed that intra-vesical instillation of succinate (10 mM) displays a relaxing effect on the bladder, increasing micturition volume (0.54±0.04 to 0.68 ± 0.04 ml), intercontraction intervals (187±11 to 222±6 sec), and bladder capacity (0.52 ± 0.03 to 0.62 ± 0.02 ml) in SHRSP rats and intercontraction intervals (223±33 to 338±39 sec) and bladder capacity (0.62 ± 0.09 to 0.94 ± 0.11 ml) in DAHL/SS rats (P<0.05) (Figure 4).

Figure 4. Sample cystometric tracings of Dahl-SS rat with saline instillation (top panel) and succinate 10 mM instillation (bottom panel).

Interpretation of results
The presence of the succinate receptor GPR91 on urothelial and smooth muscle cells suggests a physiological role of succinate in voiding function. Low levels of succinate in urine of insulin-resistant rats suggest a link between insulin signaling, glucose metabolism and succinate release. Indeed, intra-vesical succinate administration partially corrects bladder overactivity suggesting an essential role of succinate in detrusor contraction.

Concluding message
Succinate receptor GPR91 is expressed in smooth muscle and urothelial cells of the bladder. Succinate partially reverses the bladder overactivity in rats by promoting bladder relaxation. This effect might be mediated by its receptor GPR91 and by acting at the level of the Krebs cycle.

Disclosures
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