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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).

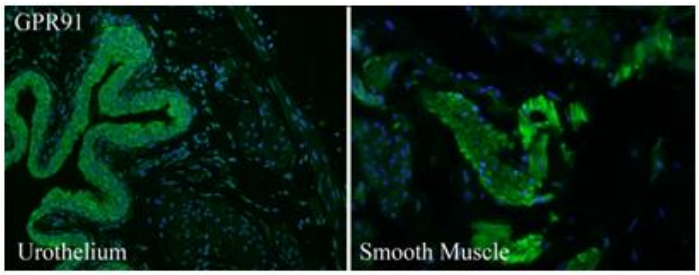

Figure 1. Immunohistochemistry of GPR91 in whole bladder tissue.

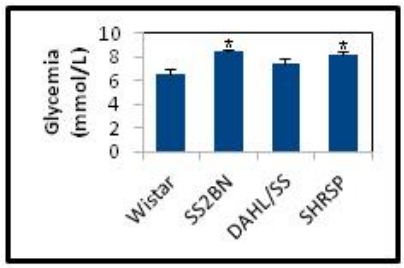

Figure 2. Fasting glycemia (* P<0.05)

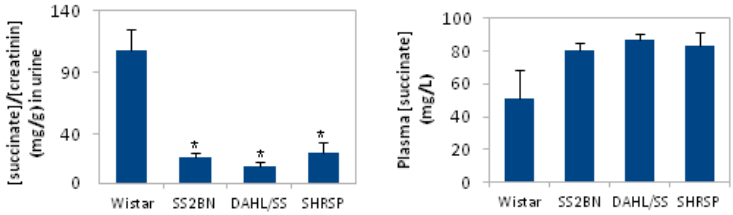

Figure 3. Plasma and urine succinate levels in animal groups. A. Urinary succinate levels standardized to urinary creatinine (* P<0.05). B. Plasma succinate concentrations in plasma of rats.

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).

	maximal pressure	threshold pressure	basal pressure	intermict. Pressure	spontan. activity	Intercont. interval	Bladder capacity	micturition volume	residual volume	bladder complian.
	MP	TP	BP	IP	SA	ICI	Bcap	MV	RV	Bcom
Units	cm H_2O	cm H_2O	cm H_2O	cm H_2O	cm H_2O	seconds	mL	mL	mL	mL/cm H_2O
Wistar (n=5)										
Mean	117.0	41.7	11.4	27.6	16.2	555.7	1.5	1.5	0.113	0.065
SEM	12.7	14.2	2.8	10.8	13.0	96.6	0.3	0.4	0.107	0.019
SS2BN (n=7)										
Mean	105.3	38.5	18.6	27.4	8.8	**206.1***	**0.572****	**0.557***	0.035	**0.031***
SEM	10.6	3.6	3.8	4.8	1.3	35.3	0.1	0.1	0.025	0.006
DAHL/SS (n=6)										
Mean	83.1	50.0	14.4	26.5	12.0	**222.8***	**0.619****	**0.625***	0.034	0.041
SEM	24.9	19.1	4.6	6.0	4.9	33.2	0.1	0.1	0.016	0.018
SHRSP (n=6)										
Mean	128.8	46.9	17.0	23.6	6.6	**186.9***	**0.5****	**0.538***	0.016	0.027
SEM	29.2	9.5	5.9	7.5	3.2	11.2	0.0	0.0	0.010	0.026

Table 1. Bladder characteristics of control Wistar rats and hypertensive insulin-resistant rats. (*P<0.05, **P<0.005).

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).

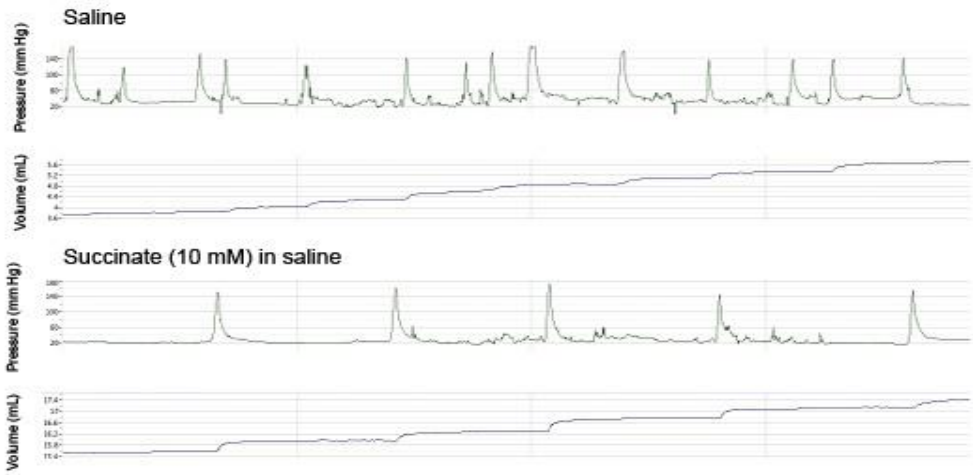

Figure 4. Sample cystometric tracings of Dahl-SS rat with saline instillation (top panel) and succinate 10 mM instillation (bottom panel).

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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