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THE ROLE OF SUCCINATE IN VOIDING DYSFUNCTION ASSOCIATED WITH METABOLIC SYNDROME

Hypothesis / aims of study

Overactive bladder syndrome (OAB) is common among patients with metabolic syndrome. Disruption in energy homeostasis, the main factor driving metabolic syndrome, may also be responsible for the development of bladder dysfunction. An important step in energy metabolism, the Kreb's cycle, is a target site for dysregulation. Succinate, an intermediate of this cycle, has been implicated in multiple pathologies, and it is possible that its role could extend to the bladder. We aim to show that succinate, increased in metabolic syndrome, is responsible for changes in bladder function that lead to the development of bladder overactivity.

Study design, materials and methods

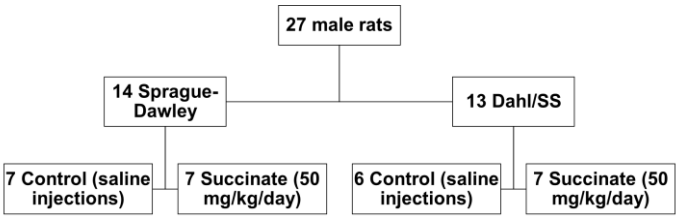

Figure 1. Study set-up. 27 4-month-old rats were included in this study.

Intraperitoneal injections of saline or succinate were administered daily for a period of 5 weeks to Sprague-Dawley rats and Dahl/SS rats, a model of metabolic syndrome (Fig. 1). Three days after bladder catheter implantation, conscious cystometry was performed involving an infusion of saline, followed by 5 mM succinate, 10 mM succinate, and saline again (each for one hour at a rate of 10 mL/hour). On the next day, the animals were sacrificed and their bladders were collected for organ bath experiments. Bladder detrusor strips were stimulated with KCl and carbachol to measure their contractile response. The strips were also stimulated with either a 30 mM KCl or 1 uM carbachol solution. Once the response stabilized, the strips were subjected to increasing concentrations of succinate (3-100 mM). Finally, the strips were subjected to EFS (1–32 Hz). Repeated-measures one-way ANOVA with Bonferroni post-hoc test was used to measure differences during cystometry of each group. One-way ANOVA with Bonferroni post-hoc test was used to measure differences between all groups. $p<0.05$ was considered significant.

Results

Within each group, administration of succinate resulted in an increase in three parameters: Intercontraction Interval (ICI), Bladder Capacity (Bcap), and Micturition Volume (MV), with significant increase seen specifically in the SD succinate, Dahl control, and Dahl succinate groups (Fig. 2).

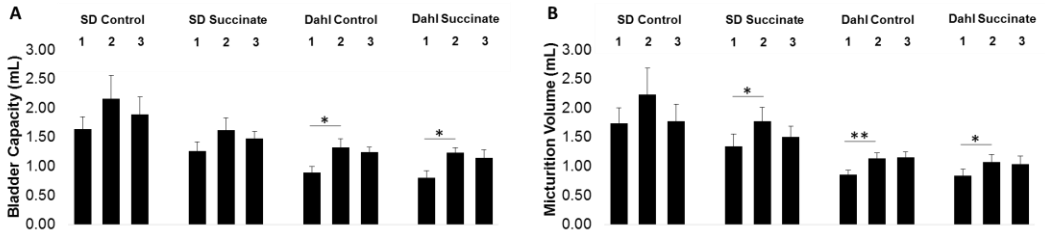

Figure 2. Selected cystometry values (A: Bcap; B: MV) for each animal group during infusions of saline (1), followed by 10 mM succinate (2) and saline again (3). Results are expressed as mean values ± SEM, *$p<0.05$; **$p<0.01$.

Comparisons between baseline values (1st saline infusion) of all groups showed that the parameters mentioned above were significantly lower in both Dahl groups compared to the SD control group (Fig. 3).

Organ bath data showed that the response to KCl and carbachol was significantly increased in detrusor strips from Dahl control rats compared to the other three groups (Fig. 4A-B). Dahl succinate rats had similar responses as SD control and SD succinate rats. Similar results were observed with EFS.

Finally, in all groups, strips stimulated with 1 uM carbachol showed an increase in relaxation with increasing concentrations of succinate (Fig. 4C). However, after 30 mM succinate, the strips regained their initial contractile response.

The strips showing the most relaxation were those from SD control rats; the strips with the least relaxation were those from Dahl control rats (41±4% vs. 10±8% relaxation, respectively; $p<0.01$). No significance was observed between groups when stimulated with KCl.

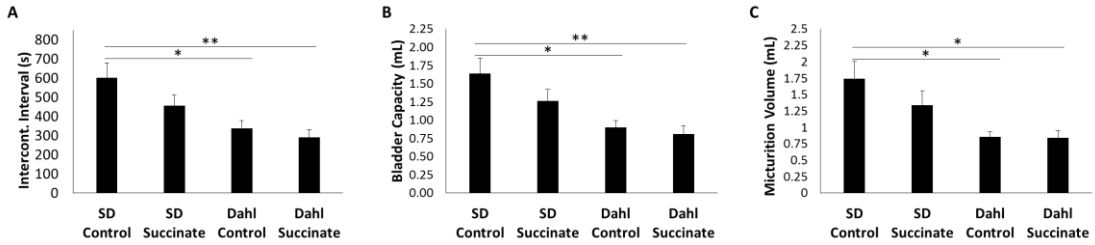

Figure 3. Baseline cystometry parameters for which significance was observed. A: Intercontraction interval; B: Bladder capacity; C: Micturition volume. Results are expressed as mean values ± SEM, *p<0.05; **p<0.01.

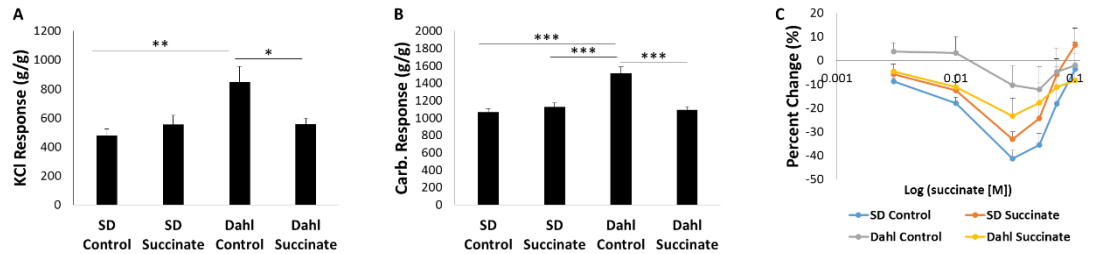

Figure 4. Organ bath results. A: Contractile response to 60 mM KCl; B: Maximal response to carbachol situmlation (3 nM–100 uM); C: Response to succinate (3–100 mM) after preincubation with 1 uM carbachol. Results are expressed as mean values ± SEM, *p<0.05; **p<0.01; ***p<0.001.

Interpretation of results

Our models of metabolic syndrome (Dahl/SS rats) have shorter intercontraction intervals, smaller bladder capacities and lower micturition volumes. Chronic administration of succinate does not seem to have an impact on these parameters. Acute effects of succinate, however, are observed as these parameters are increased when succinate is infused at 5 mM and even more at 10 mM, suggesting a relaxing effect of succinate on the bladder. Unlike in cystometry, chronic effects of succinate are observed in organ bath experiments. Detrusor strips from Dahl rats with daily saline injection (Dahl control) have the highest contractile response to KCl, carbachol, and EFS. However, those strips taken from Dahl rats with daily succinate injections (Dahl succinate) show a lower contractile response, similar to those strips from SD rats. Furthermore, upon stimulation with 1 uM carbachol, the addition of succinate to the bath relaxes all strips, with Dahl control strips showing the least relaxation.

Concluding message

In both *in vivo* and *in vitro* experiments, acute administration of succinate has a relaxing effect on the bladder. Models of metabolic syndrome have obvious differences in bladder function compared with normal rats. Chronic administration of succinate, as observed *in vitro*, seems to alter detrusor contractility of our model of metabolic syndrome, steering it towards a normal phenotype.

Disclosures

Funding: FRQS **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** McGill University Animal Care Committee