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Succinic acid relaxes bladder strips in a NO/cGMP -independent, ATP-dependent way.

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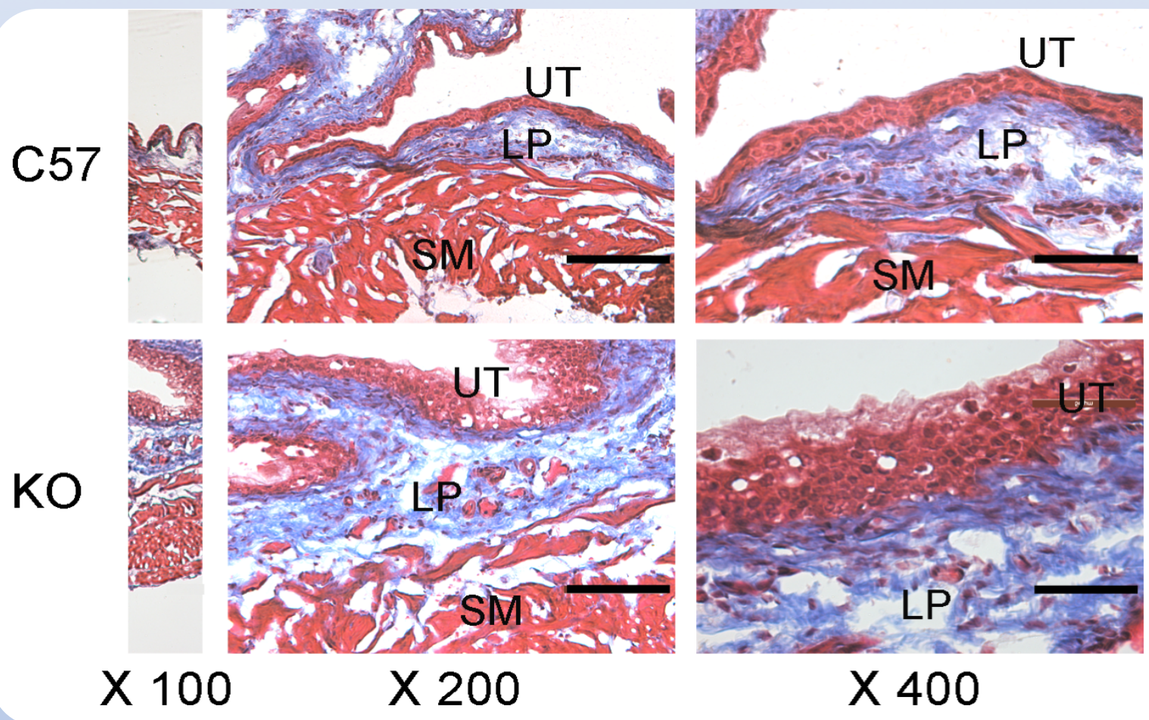
Background and aims

- The bladder urothelium and detrusor layer express the succinate receptor, GPR91, for which the pathophysiological function is not fully described.
- We found previously that immediate succinate administration causes relaxation in bladder strips from Sprague Dawley rats in organ bath.
- The aim was to identify the mechanisms of succinate relaxation using a mouse model with specific deletion of the GPR91 receptor.

Methods

- Conscious cystometry on C57BL/6 and GPR91(-/-) mice with and without succinate intravesical instillation.
- Contractile properties of bladder strips for both strains by organ bath.
- Bladders characteristics by Masson's trichrome.
- Primary urothelial cell culture for nitric oxide secretion (colorimetric assay), ATP and cGMP levels (commercial kits).

Results

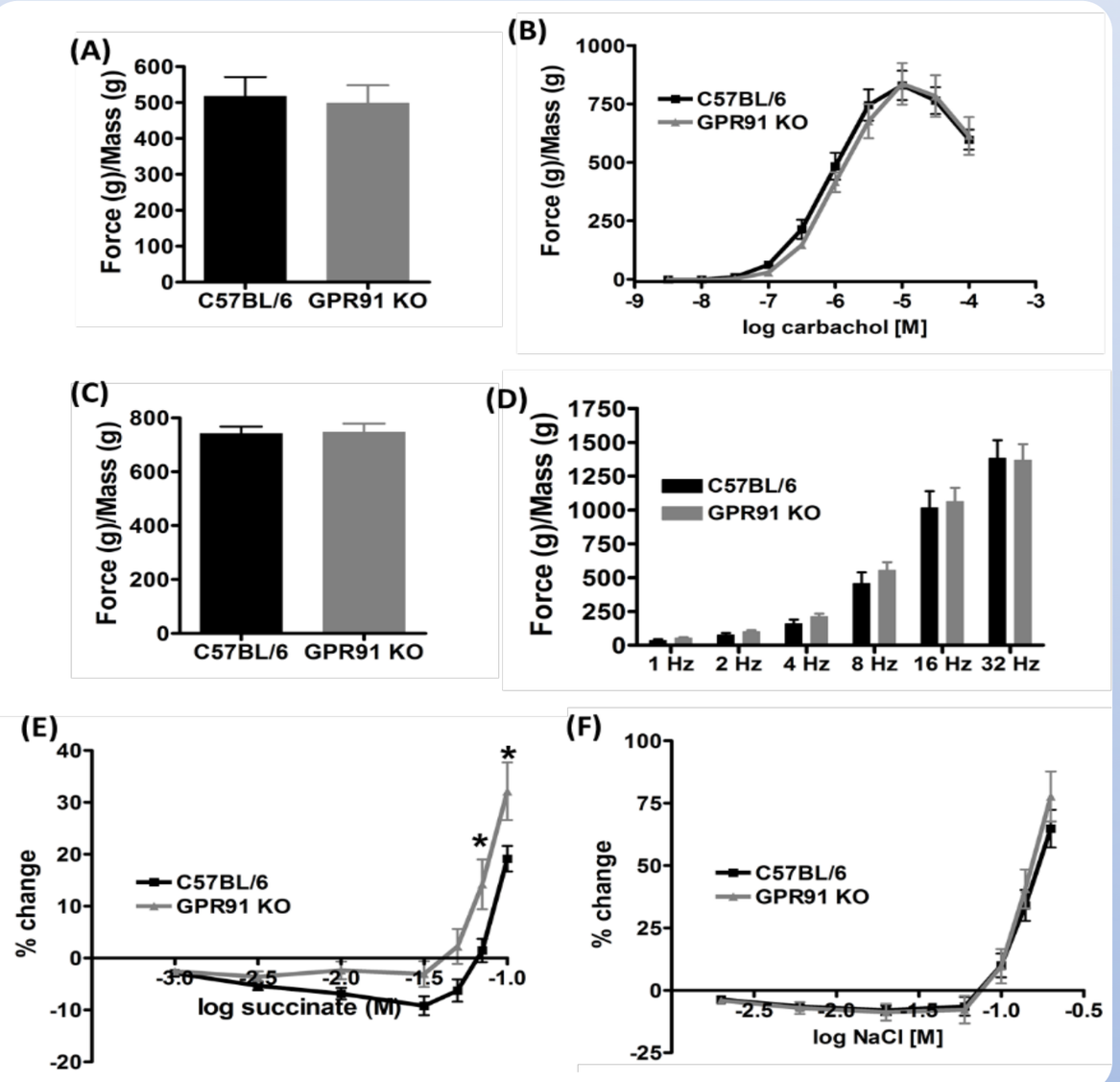


The bladder mass was higher in GPR91(-/-) mice yet the body weight was not different from C57BL/6. Masson's trichrome showed a thicker urothelium and lamina propria in GPR91(-/-) mice.

Parameter	Strain	Saline	Succ 10 mM
Intercontraction Interval (s)	C57BL/6	453.8 ± 85.0	528.3 ± 88.7**
	GPR91 KO	277.5 ± 69.6	242.3 ± 58.0
Bladder Capacity (ml)	C57BL/6	0.23 ± 0.04	0.26 ± 0.04 **
	GPR91 KO	0.14 ± 0.03	0.12 ± 0.03
Micturition Volume (ml)	C57BL/6	0.21 ± 0.05	0.27 ± 0.05 **
	GPR91 KO	0.11 ± 0.02$	0.10 ± 0.01

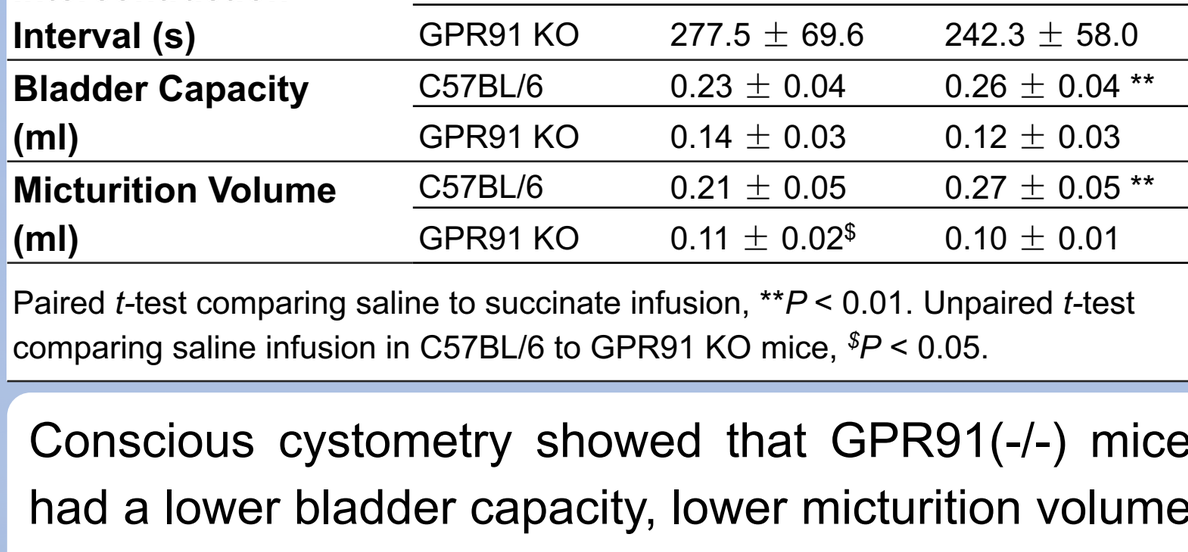
Paired *t*-test comparing saline to succinate infusion, $^{**}P < 0.01$. Unpaired *t*-test comparing saline infusion in C57BL/6 to GPR91 KO mice, $^{\$}P < 0.05$.

Conscious cystometry showed that GPR91(-/-) mice had a lower bladder capacity, lower micturition volume and lower intercontraction interval. Intravesical instillation of succinate (10 mM) increased the bladder capacity in C57BL/6 mice only.



In organ bath, no contractile response difference was noticed between C57BL/6 and GPR91(-/-) mice for 60 mM KCl (A), 3nM-100uM carbachol (B), carbachol E_{max} (C) and electrical field stimulation (D).

Succinate administration [1mM-100mM] relaxed carbachol-stimulated strips [1uM] in C57BL/6 mice only (E). The contraction phase at the end of succinate curve is mainly due to NaCl as seen in the NaCl curve (2–200 mM) with strips precontracted with 1 µM carbachol (F). *p<0.05 simple t-test.



Conclusion

These results suggest that succinate modulates the relaxation-contraction of the detrusor through its action on its receptor GPR91, possibly by decreasing ATP synthesis in the urothelium. The lack of GPR91 receptor has structural and functional effects on the bladder.

Secretion of nitric oxide by urothelial cells incubated with 10mM succinate for 10 and 30 minutes was not different between C57BL/6 and GPR91(-/-) mice (A). Succinate decreased ATP synthesis by urothelial cells (B) pre-incubated for 30 min with or without succinate (10 mM) then with or without carbachol (50 uM), ATP levels in supernatant were decreased by succinate. ANOVA One-way, **P<0.01, *P<0.05..

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