Null leptin receptor mice as a translational model of type II diabetes-induced erectile dysfunction.

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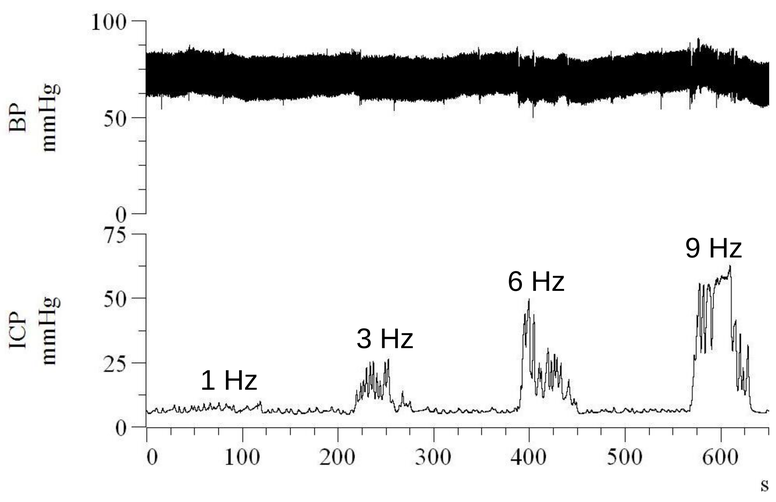
Objectives

Erectile dysfunction (ED) is highly prevalent and difficult to treat in type 2 diabetic patients[1,2]. The use of translational preclinical models would be an advantage for the development of *ad hoc* drug treatment of ED in this patient population. BKS(D)-Lepr^{db}/JOrlRj mice (db/db mice) are homozygous for a mutation in the leptin receptor gene that results in null leptin receptor activity. This affects hypothalamic responses, leading to the development of obesity and diabetes. Despite being the most widely used translational model for the study of type 2 diabetes-related pathophysiological processes, only few studies investigated ED in db/db mice[3-5].

The aim of the present study was to further characterise the erectile dysfunction reported in db/db mice and to assess the proerectile effect of sildenafil citrate in this experimental model.

Methods

- 13-16 weeks-old BKS(D)-Lepr^{db}/JOrlRj (Janvier SAS, France) male mice and age matched control littermates (DB and CT respectively) were anaesthetised with pentobarbital.
- Carotid artery, corpus cavernosus and jugular vein were catheterised for blood samples, intracavernous pressure recording (BP and ICP) and drug injection respectively. The right cavernous nerve was mounted on bipolar silver stimulating electrode.
- Electrical stimulations (ES) were performed at 1, 3, 6 and/or 9 Hz for 1 min (see illustration below of ICP and BP recording in DB mice).

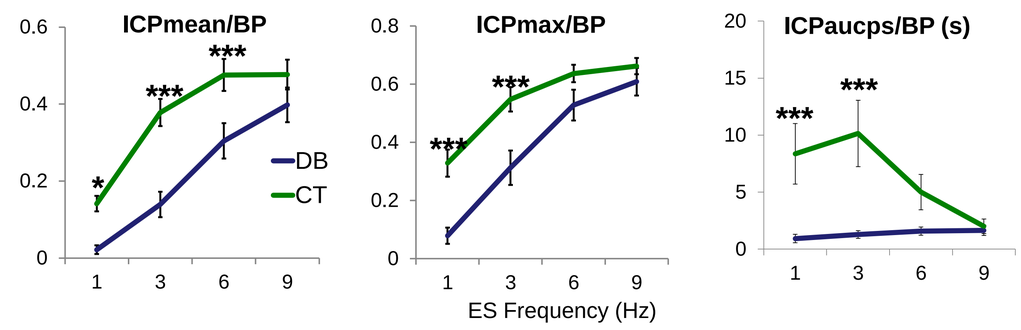


- Mean and maximal values of the ICP were measured during ES (ICPmean and ICPmax respectively). The area under the ICP curve was measured for 1 min post ES (ICPaucps). All parameters were expressed relative to the corresponding BP.

Results

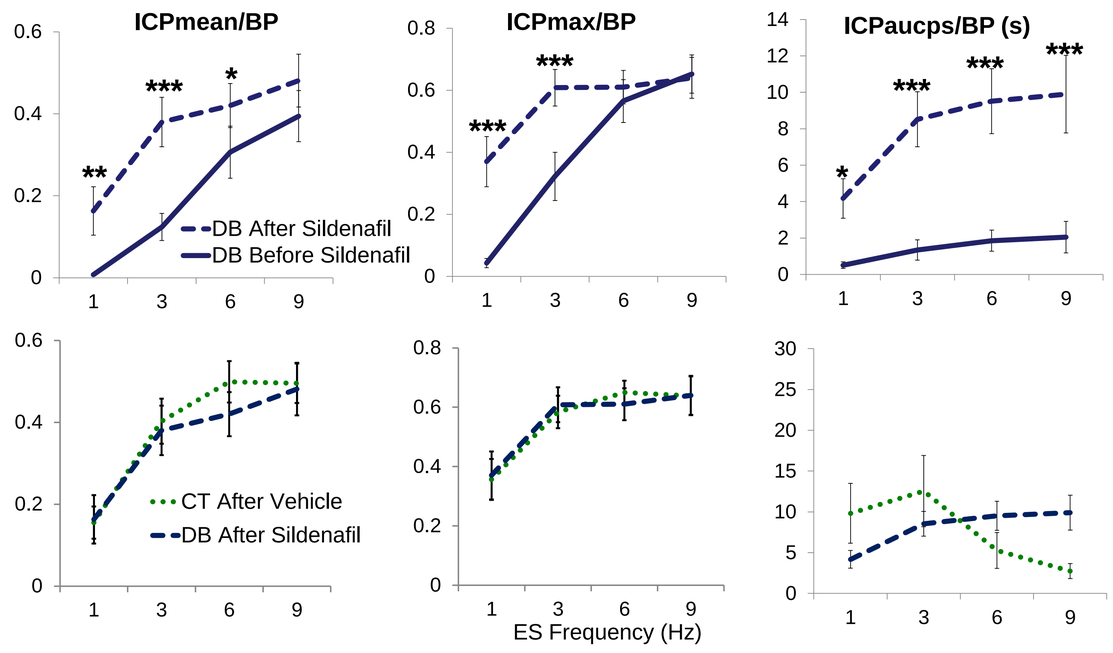
DB mice display consistent erectile dysfunction

- DB mice were significantly heavier (49.3±0.5 vs 25.4±0.6 g) with higher glycemia (32.6±0.5 vs 7.4±0.5 mmol/l) compared with CT mice (P<0.001) .
- Erectile responses were generated in 12 and 14 DB and CT mice respectively.
- All parameters characterising erectile responses elicited at 1 and 3 Hz were significantly lower in DB compared to CT mice.
- ***:P<0.001;**P<0.01;*: P<0.05.



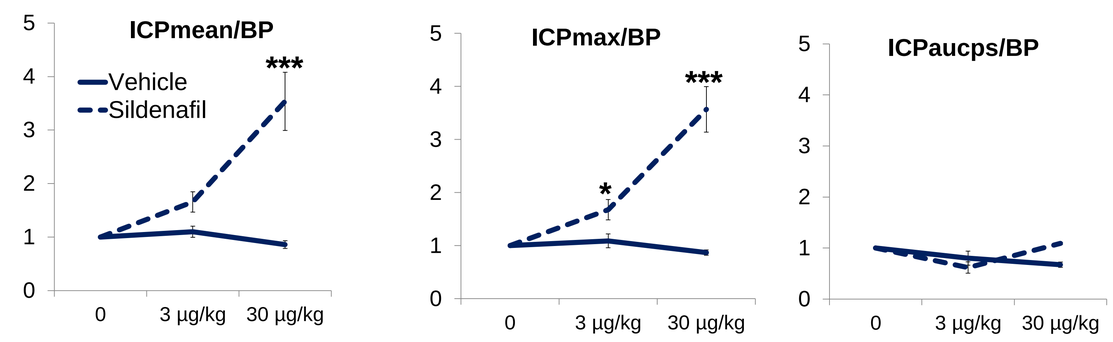
Sildenafil restores erectile responses in DB mice towards control levels

- Erectile responses were generated before and after the injection of 1 mg/kg sildenafil or saline in 2 independent groups (n=7).
- Erectile responses were similar before and after saline injection in CT and DB mice (not shown).
- The effect of sildenafil was more pronounced with ES at 1 and 3 Hz compared to 6 and 9 Hz.
- ***:P<0.001; **:P<0.01;
- *:P<0.05.



Dose–response study demonstrate measurable effect of sildenafil from 3 ug/kg in DB mice

- Erectile responses were measured at baseline and after successive injections of 3 and 30 µg/kg sildenafil or the corresponding vehicle in 2 independent groups (n=7).
- Results of quantification were expressed as ratio over baseline response.
- *:P<0.05; ***:P<0.001



Conclusions

We confirmed that erectile responses are significantly impaired in obese and diabetic BKS(D)-Lepr^{db}/JOrlRj mice. In contrast to previous observations, our data show a pronounced impairment at low (1 and 3 Hz) but not at high frequency (9 Hz) of ES, a discrepancy likely explained by differences in experimental conditions and/or background strains[3,5]. The present experiment also demonstrate that the proerectile activity of sildenafil could be evidenced in DB mice from 3 ug/kg iv, and that 1 mg/kg restored erectile responses to almost control levels.

The present study suggests that db/db mice is an adequate model to test drugs aiming at treating ED in diabetic patients. Further studies are necessary to confirm that the pathophysiological basis of ED in db/db mice and human patients with type 2 diabetes are similar.

References

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