Effects of sitagliptin on cardiac metabolism in mice

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Background

- Type 2 diabetes is associated with an increased risk of cardiac complications.
- Diabetic cardiomyopathy increases the risk of heart failure, independently of co-existing coronary artery disease and hypertension.
- The effects of inhibition of dipeptidylpeptidase 4 (DPP-4) on myocardial metabolism have not been studied in detail.
Physiology of incretin hormones

Sitagliptin has no effect on body and heart weight, fasting glucose in healthy C57Bl6 mice

C57Bl6 mice, sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 3 additional weeks (n=6 for control; n=8 for sitagliptin)
Sitagliptin reduces weight gain in \( \text{db/db} \)-\(-/-\) mice

\( \text{db/db} \)-\(-/-\) mice at age 6, 8 and 10 weeks, sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks (n=9-12; ***p<0.001)

**Body Weight [g]**

- 6 weeks: Control - Sita
- 8 weeks: Control - Sita
- 10 weeks: Control - Sita

**-18.6±3.5%**
Fasting glucose and post-prandial glucose impair age-dependent in db/db-/- mice

5, 6, 8 and 10 weeks old db/db-/- db/db-mice; peritoneal glucose tolerance test; (**p<0.001; ††p<0.01; †††p<0.001)

** Fasting glucose [mg/dl]

** Blood glucose [mg/dl]

p<0.001 for linear trend
Sitagliptin improves postprandial glucose in db/db-/- mice

db/db-/- mice at age 8 and 10 weeks; peritoneal glucose tolerance test; sitagliptin (16mg/d, p.o.) or control chow for 2 and 4 weeks (*p<0.05; **p<0.01; ***p<0.001)

Blood glucose [mg/dl]

- db/db- 8 weeks
- db/db- 8 weeks + 2 weeks Sita

Blood glucose [mg/dl]

- db/db- 10 weeks
- db/db- 10 weeks + 4 weeks Sita
Myocardial hypertrophy in db/db-/- is not altered by sitagliptin

db/db-/- mice at age 6 and 10 weeks; hematoxylin and eosin staining; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; **p<0.01
DPP-4 inhibition prevents the development of myocardial fibrosis in db/db-/- mice

db/db-/- mice at age 6 and 10 weeks; sirius red staining; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; *p<0.05
Fatty acid oxidation and uptake in the heart are regulated by acetyl-CoA carboxylase (ACC) and fatty acid translocase (FAT/CD36).
Sitagliptin prevents elevated fatty acid oxidation and uptake in myocardium of db/db-/- mice

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; *p<0.05; **p<0.01; ***p<0.001

Phosphorylation of ACC [% db/db-/- 6 weeks]

FAT/CD36 Mem./Cyt.-ratio [% db/db-/- 6 weeks]
Sitagliptin decreases glucose uptake in db/db-/- mice

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; ***p<0.001

**Phosphorylation of PFK2**
[%. db/db-/- 6 weeks]

**GLUT-4 Mem./Cyt.-ratio**
[%. db/db-/- 6 weeks]

**Sitagliptin decreases glucose uptake in db/db-/- mice**

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; ***p<0.001
AMP-activated protein kinase – a key metabolic regulator
AMP-activated protein kinase – a key metabolic regulator
DPP-4 inhibition prevents phosphorylation of AMPK in db/db-/- mice

* * p<0.05; ** p<0.01

**Phosphorylation of AMPK [% db/db-/- 6 weeks]**

**α2-AMPK [% db/db-/- 6 weeks]**
AMP-activated protein kinase – a key metabolic regulator
AMP-activated protein kinase – a key metabolic regulator
Sitagliptin reduces increased phosphorylation of TSC

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; **p<0.01

Phosphorylation of TSC [% db/db-/- 6 weeks]

** **

db/db-/- 6 weeks  db/db-/- 10 weeks  db/db-/- 10 week + 4 weeks Sita

P-TSC GAPDH
Working heart analysis of db/db-/- mice
No difference between 6 and 10 week old db/db-/- mice in working heart analysis

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; n=7-12

Cardiac output [ml/min]  Ejection fraction [%]  End-diastolic volume [µl]
No difference between 6 and 10 week old db/db-/- mice in working heart analysis

db/db-/- mice at age 6 and 10 weeks; western blot analysis; sitagliptin (16mg/d, p.o.) or control chow starting at age 6 weeks for 4 additional weeks; n=7-12

db/db-/-
6 weeks

db/db-/-
10 weeks

db/db-/-
10 week + 4 weeks Sita

Pressure [mmHG]

Volume [µl]

Pressure [mmHG]

Volume [µl]

Pressure [mmHG]

Volume [µl]
Conclusion

- DPP-4 inhibition has no effect on body-, heart weight and glucose tolerance in healthy C57Bl6 mice.

- Inhibition of DPP-4 improves glucose tolerance and weight gain in diabetic db/db/-/- mice.

- Inhibition of DPP-4 leads to a reduction of myocardial fibrosis in db/db/-/-mice.

- Increased myocardial fatty acid oxidation and uptake is reduced by DPP-4 inhibition.

- Increased activation of AMP-activated protein kinase is reduced by treatment with sitagliptin.

These observations suggest a potential beneficial myocardial metabolic effect of DPP-4 inhibition in diabetic and obese mice that warrants further research.