Stiftung Tierärztliche Hochschule Hannover
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Effects of dietary niacin supplementation on hepatic expression of FoxO1 and genes involved in glucose production in dairy cows during the transition period

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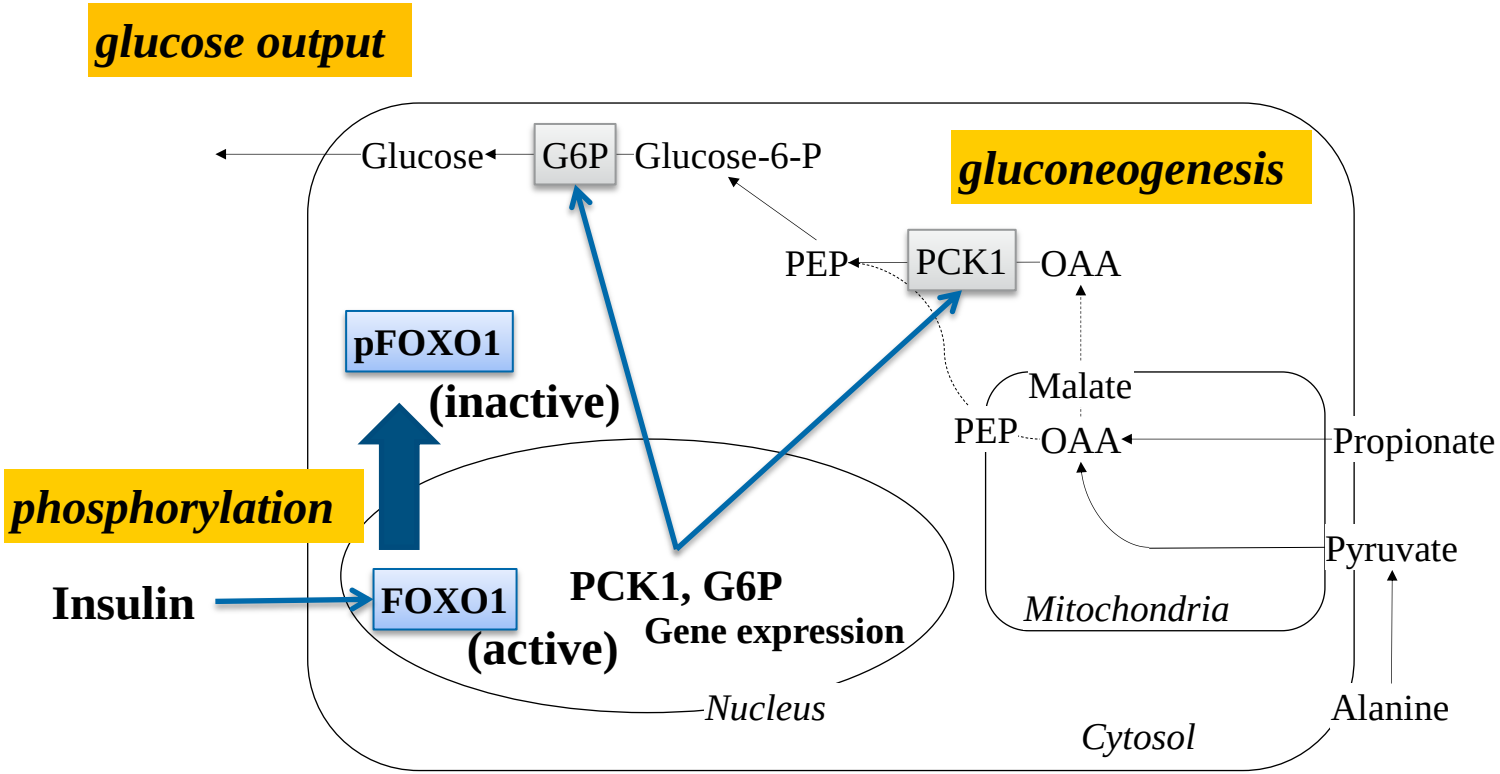
Background

Forkhead box protein O1 (FoxO1)

Transcriptional factor for G6P, PCK1 (Barthel et al., 2005)

Inactivated by phosphorylation as a target of insulin signaling (Barthel et al., 2005)

Background


glucose output
Glucose
G6P
Glucose-6-P
gluconeogenesis
PEP
PCK1
OAA
pFOXO1
(inactive)
Malate
PEP
OAA
Propionate
phosphorylation
Pyruvate
Insulin
FOXO1
PCK1, G6P
Gene expression
(active)
Mitochondria
Nucleus
Alanine
Cytosol

Background

Forkhead box protein O1 (FoxO1)

Transcriptional factor for G6P, PCK1(Barthel et al., 2005)

Inactivated by phosphorylation as a target of insulin signaling (Barthel et al., 2005)

Nicotinic acid (NA)

Substrate for NAD, NADH (Niehoff et al., 2009)

Lipid-lowering effect (Pires et al., 2009, Titgemeyer et al., 2011, Kenez et al., 2014)

Affects translational and transcriptional regulation (Khan et al., 2013, 2013)

Reduced phosphorylation of FoxO1 in rats (Choi et al, 2011)

Hypothesis & aims

Hypothesis:

NA supplements and **onset of lactation** affect **FoxO1-mediated regulation** of hepatic glucose production and the **expression of downstream genes** in dairy cows in transition period

Aimes:

To investigate the effects of dietary **NA** supplements and **onset of lactation** on expression and extent of phosphorylation of **FoxO1** as well as mRNA expression of **genes involved in glucose metabolism** in dairy cows in transition period fed with diet with high or low concentrate portions

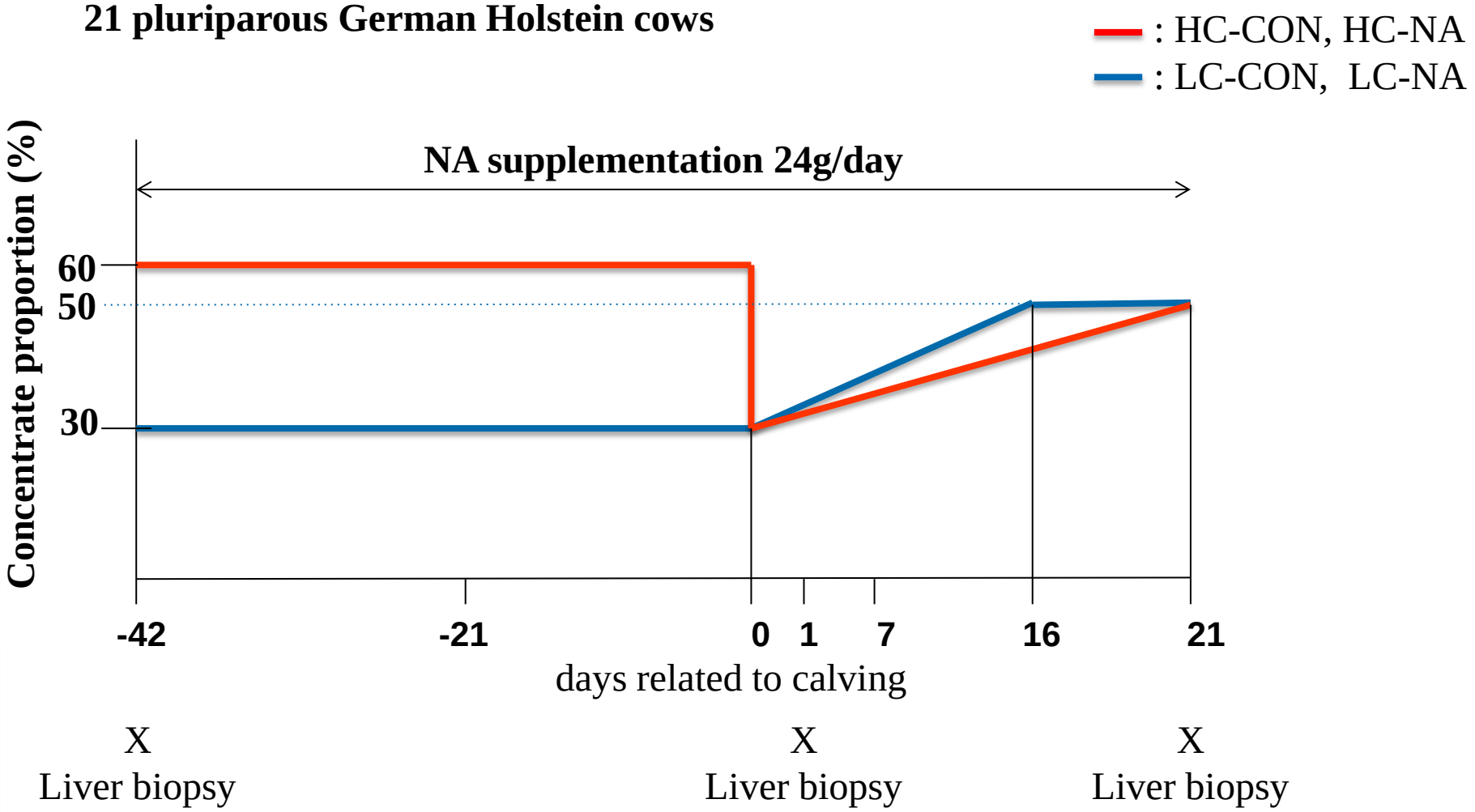
Study design

21 pluriparous German Holstein cows

	Nicotinic acid (NA) supplementation (d-42 – d+21)	
	NA (24g/day; N=11)	Control (0g/day; N = 10)

Study design

21 pluriparous German Holstein cows



Study design

21 pluriparous German Holstein cows

	Nicotinic acid (NA) supplementation (d-42 – d+21)	
	NA (24g/day)	Control (0g/day)
Prepartum: LOW concentrate proportion (30% in DM basis)	**LC-NA (n=5)**	**LC-CON (n=5)**
Prepartum: HIGH concentrate proportion (60% in DM basis)	**HC-NA (n=6)**	**HC-LOW (n=5)**

Analysis of liver biopsy samples

Protein expression (Western Blot)

tFoxO1: Total protein of FoxO1
pFoxO1: Extent of phosphorylation of FoxO1 at serine 256

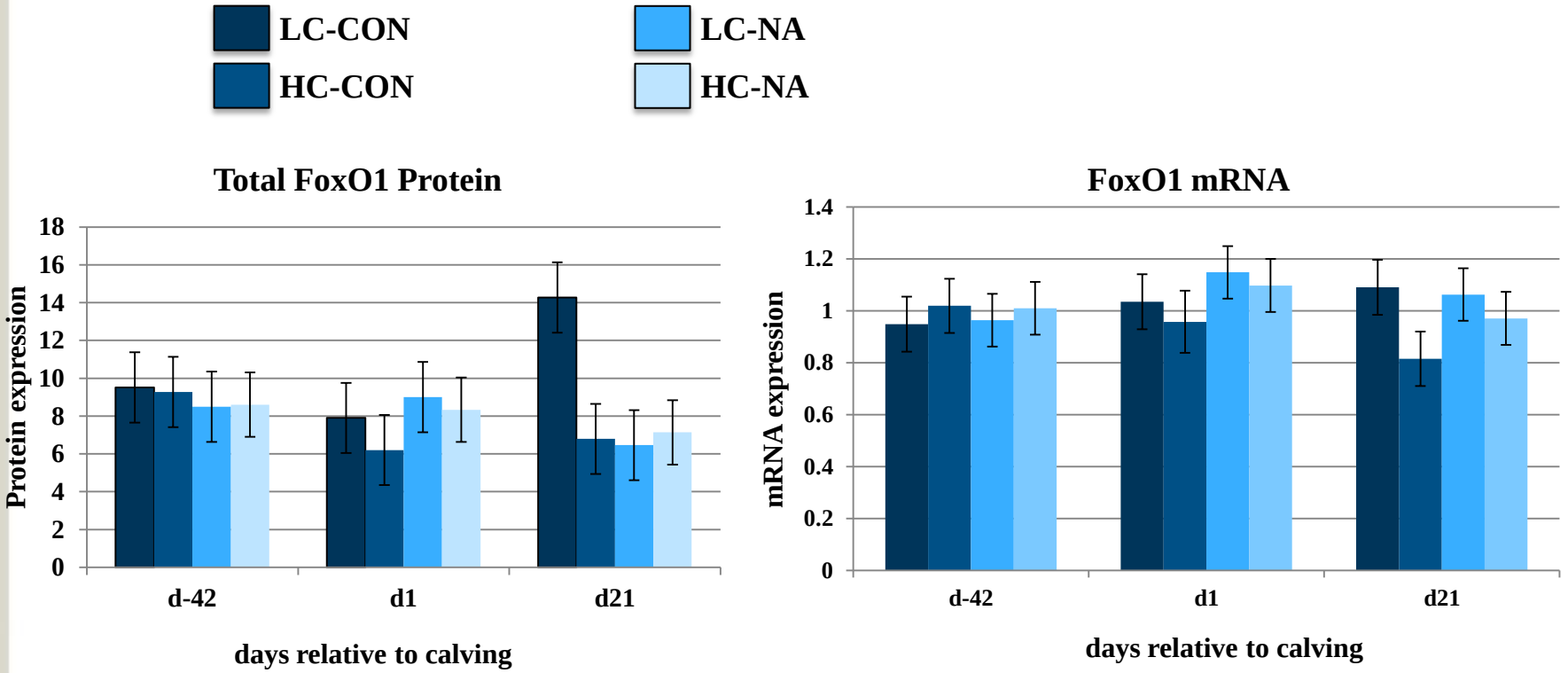
mRNA expression (real time-qPCR)

FoxO1
Insulin Receptors (IRA, IRB)
GLUT2
G6P, PCK1, PC, PCCA

Data evaluation

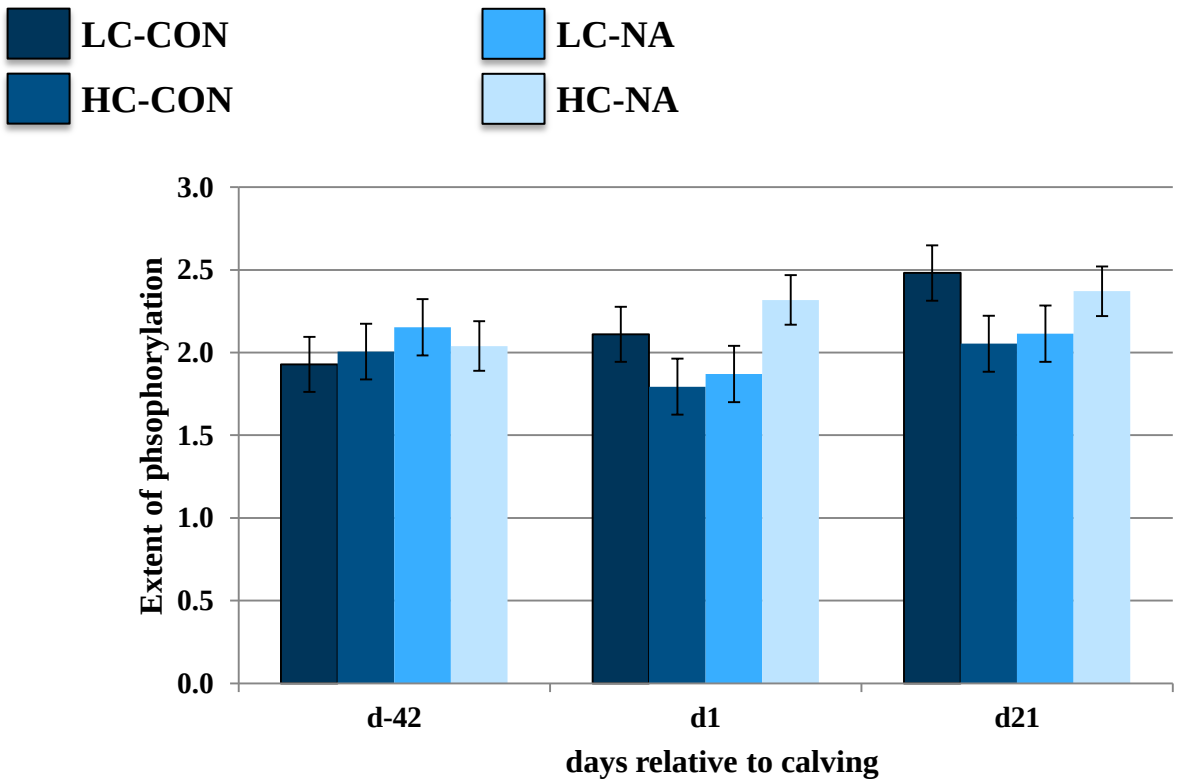
SAS mixed model for repeated measures
for effects of NA, time, and concentrate

FoxO1 Protein and mRNA expression



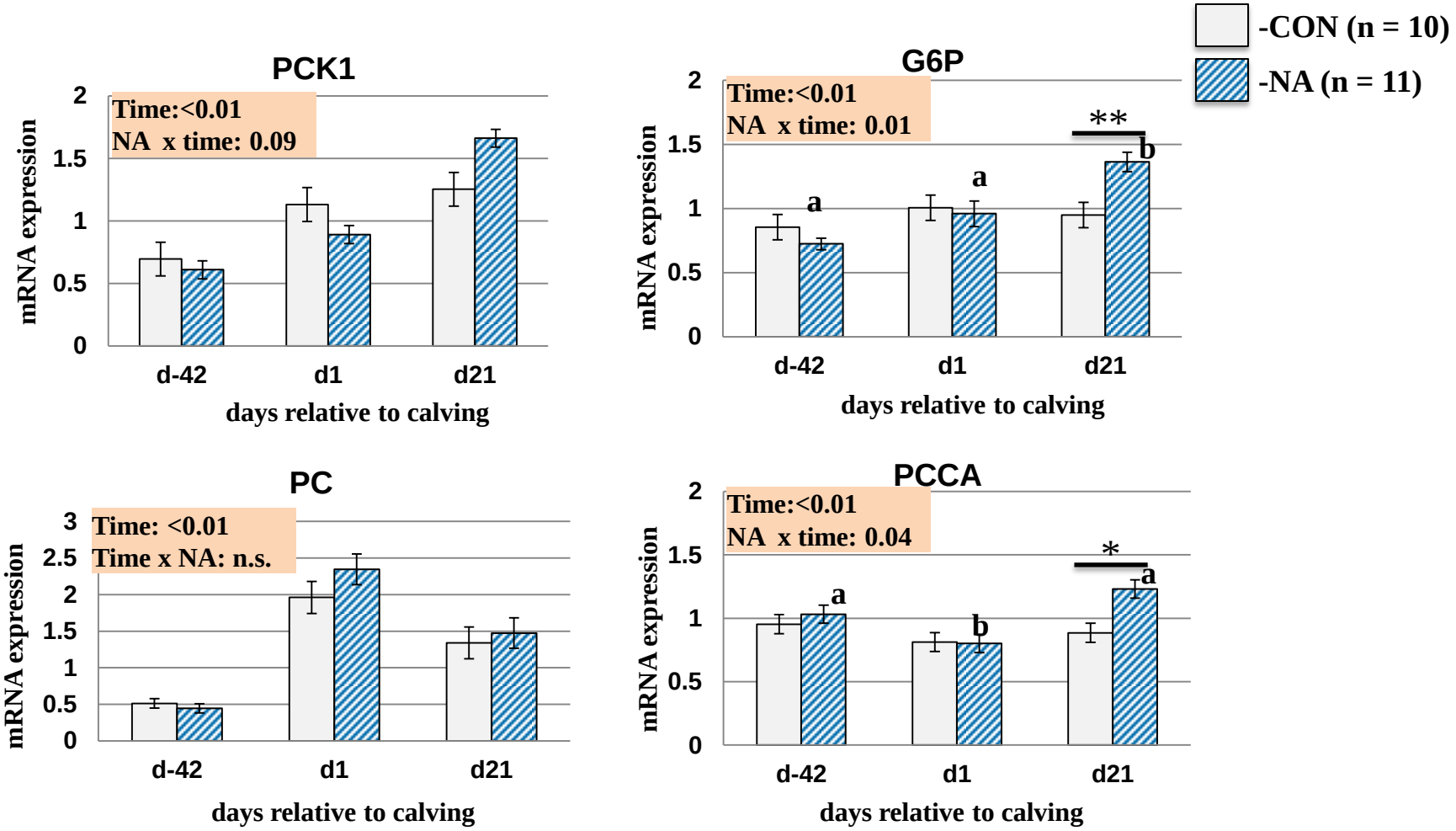
Time : n.s.
NA : n.s.
Concentrate : n.s.

Extent of phosphorylation of FoxO1 at ser256

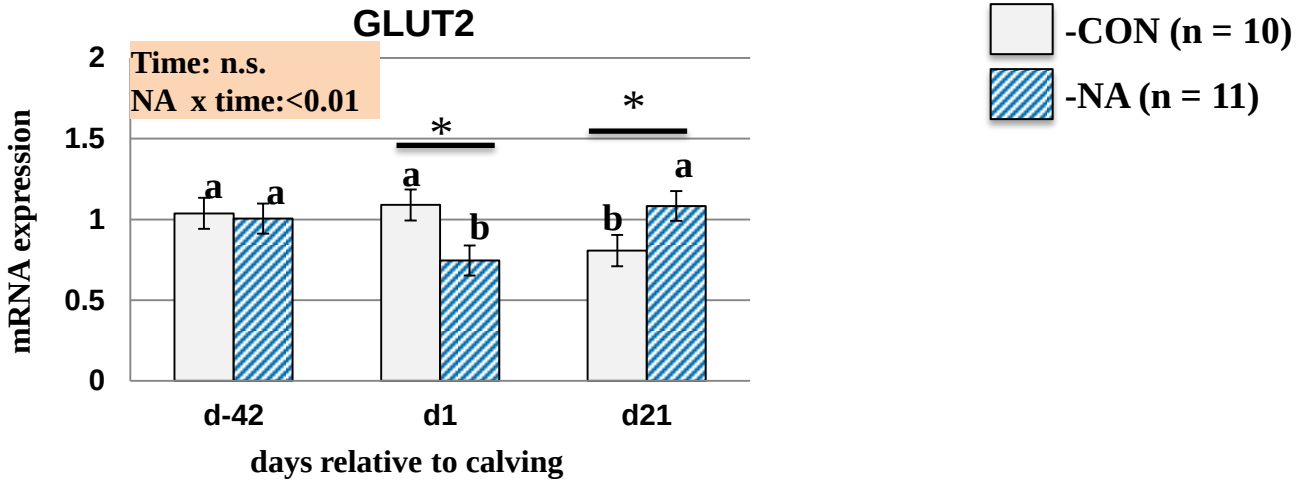


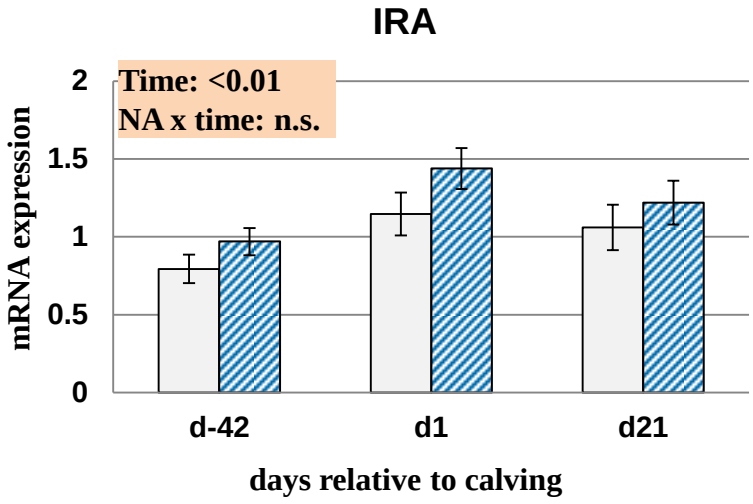
Time	**:0.08**
NA	**: n.s.**
Concentrate	**: n.s.**
NA x Concentrate	**: 0.04**
NA x Concentrate x time	**: 0.08**

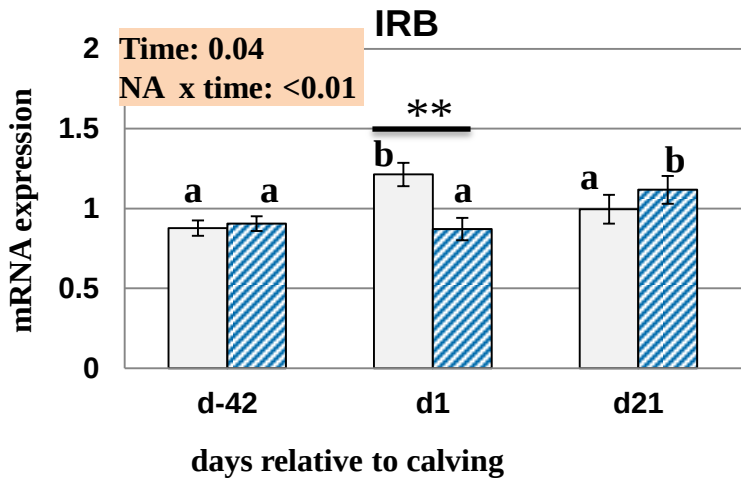
mRNA expression of gluconeogenic enzymes



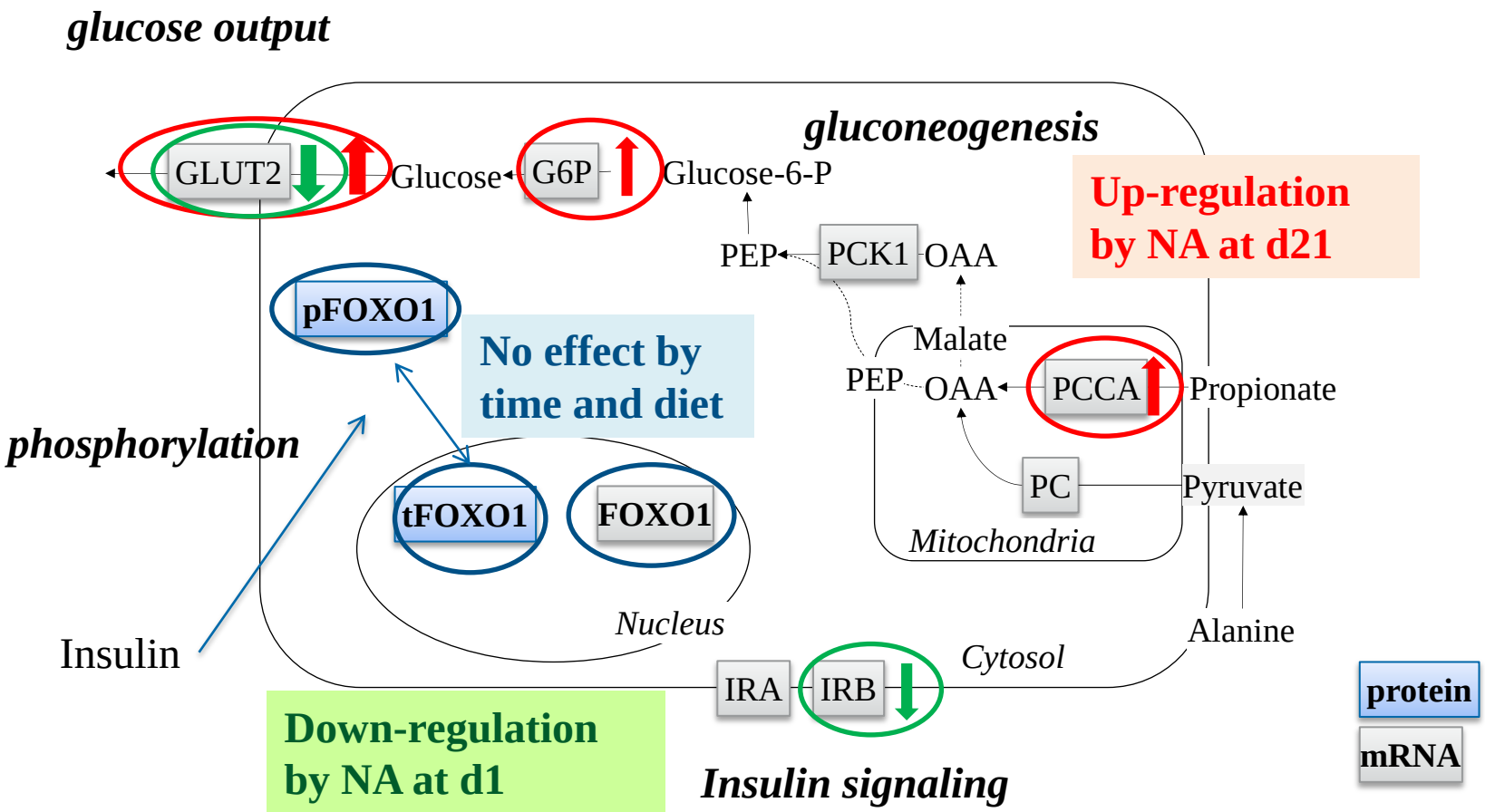
mRNA expression







Summary


glucose output
gluconeogenesis
GLUT2
Glucose
G6P
Glucose-6-P
PEP
PCK1
OAA
Up-regulation
by NA at d21
pFOXO1
No effect by
time and diet
Malate
PEP
OAA
PCCA
Propionate
phosphorylation
PC
Pyruvate
tFOXO1
FOXO1
Mitochondria
Nucleus
Alanine
Insulin
Cytosol
IRA
IRB
protein
mRNA
Down-regulation
by NA at d1
Insulin signaling

Conclusion

- NA supplements appeared to induce a reduced insulin sensitivity and increased hepatic gluconeogenesis in dairy cows in transition period
- Prepartal concentrate portion in the diet had only a marginal effect on the NA action on gene expression
- Regulation of hepatic gluconeogenesis by FoxO1 appeared to be less important at the levels of transcription, translation and phosphorylation

Thank you for your attention

This study was supported by Deutsche Forschungsgemeinschaft