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Veterinary Physiology

The reduction of feed intake and gluconeogenesis during hyperketonemia in dairy cows indicates a signal of abundant energy availability

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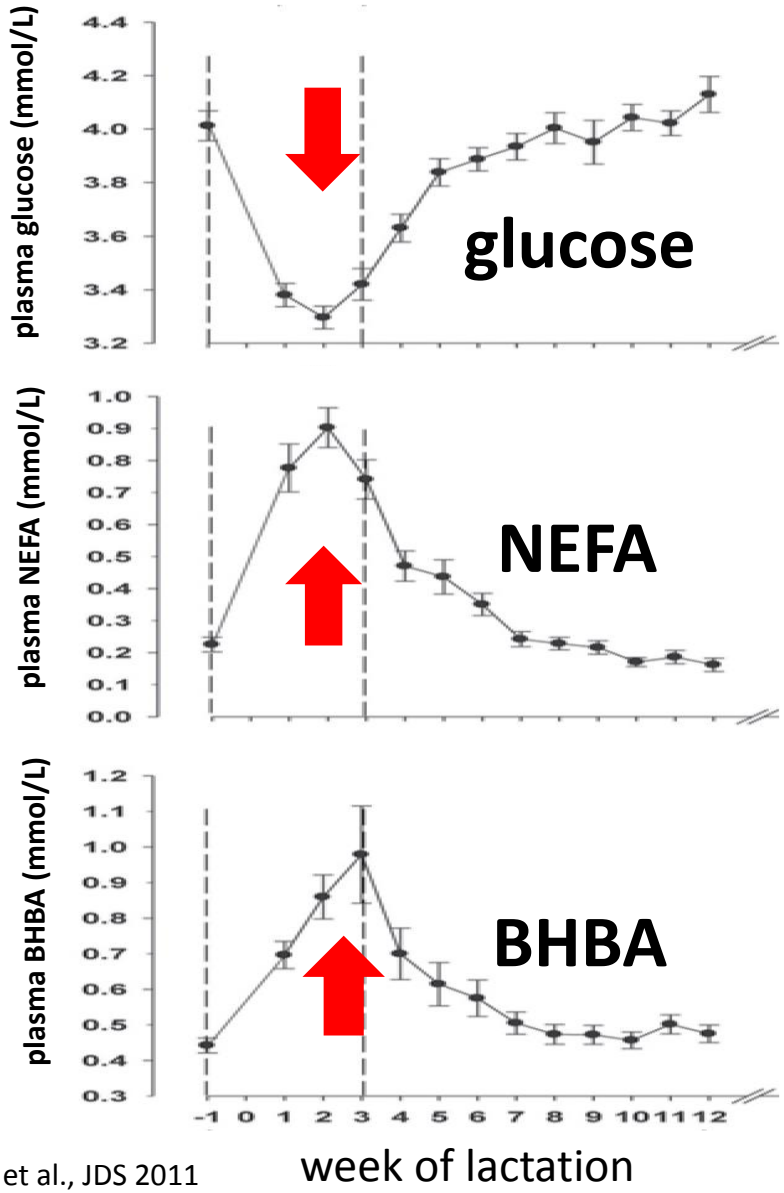
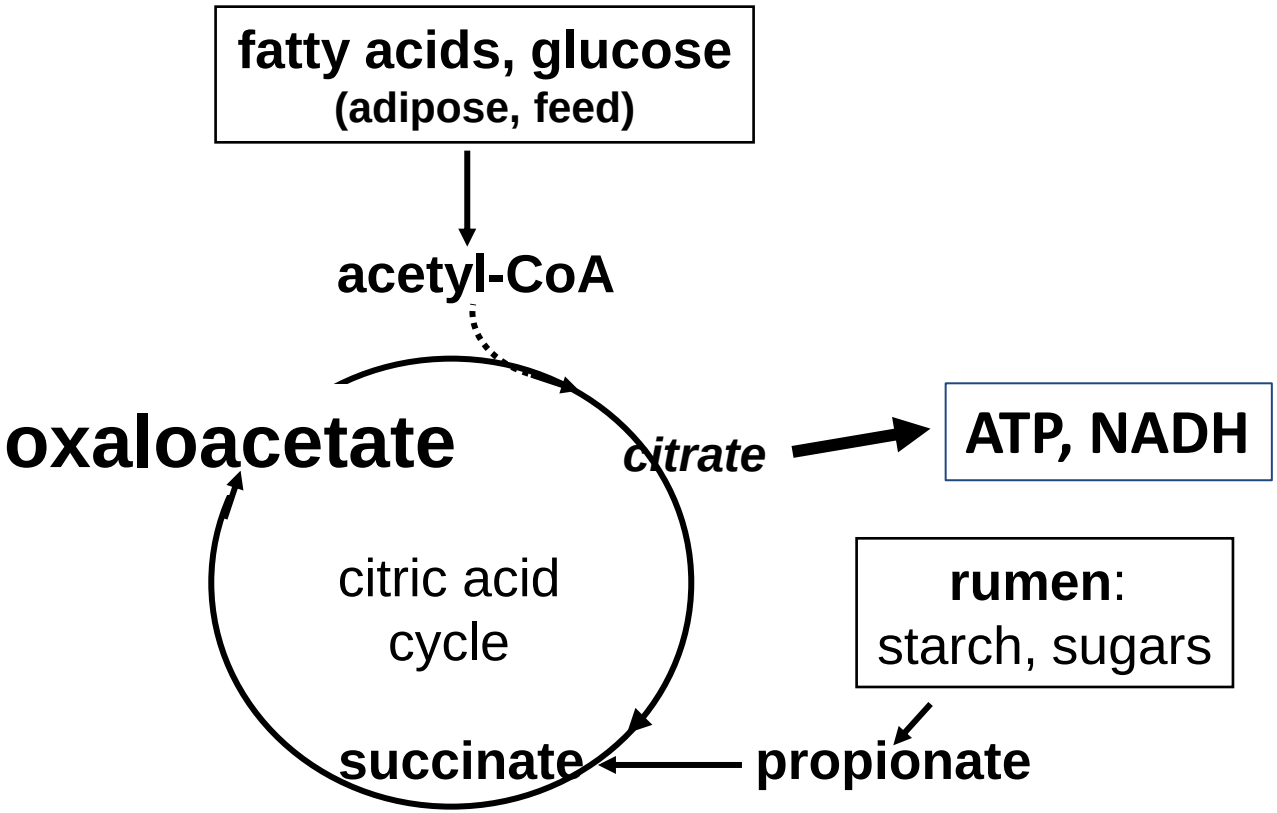
Background

Typical metabolic changes during negative energy balance in early lactation

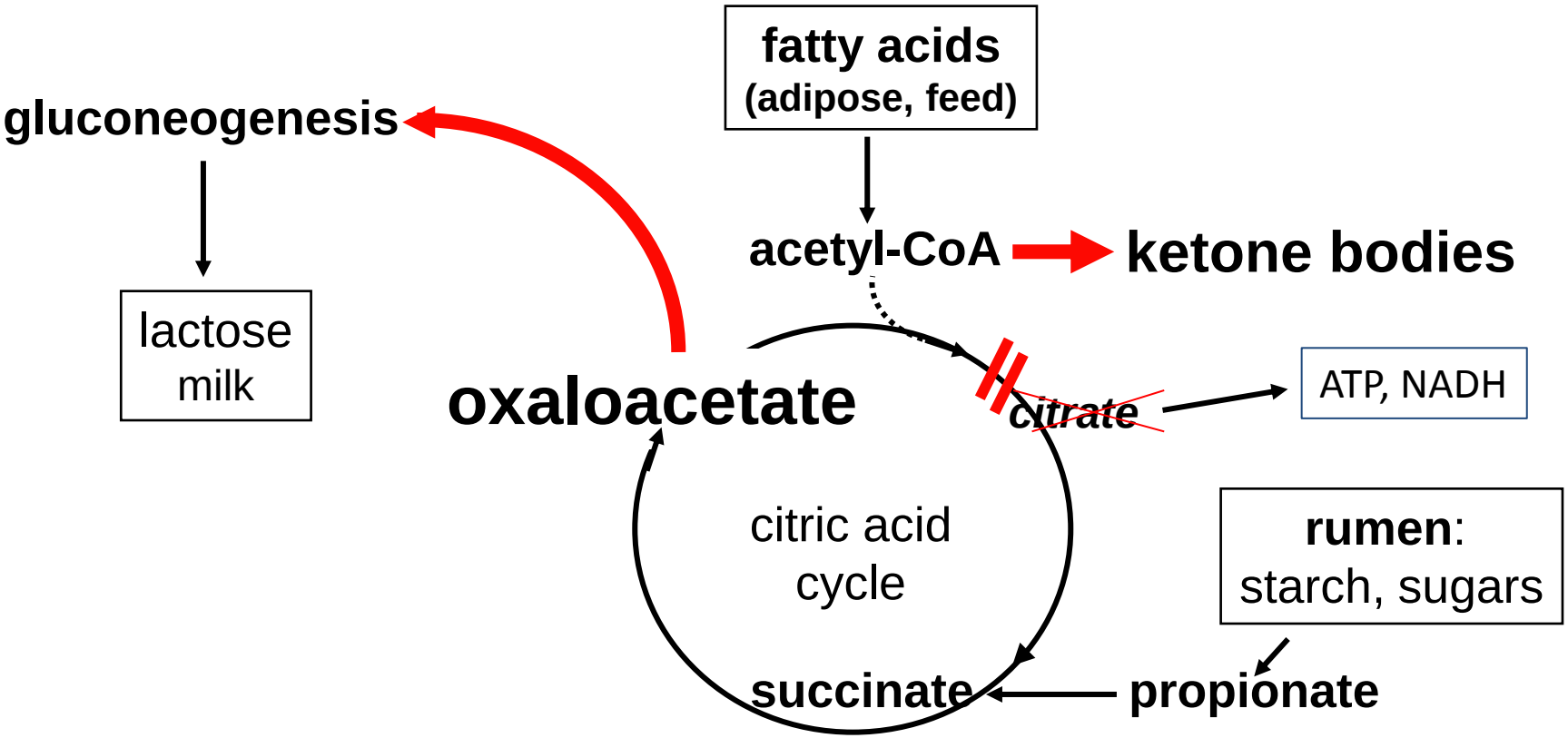


Gross et al., JDS 2011

Citric acid cycle



Generally accepted model



Ketone bodies are increasingly synthesized because of depletion of the citric acid cycle through the use of oxaloacetate for gluconeogenesis.

Experiments

During high ketone body concentration:

- reduced feed intake
- disturbed immune function

Questions:

- are the effects caused directly by ketone bodies?
- why this regulation?

Experimental approach:

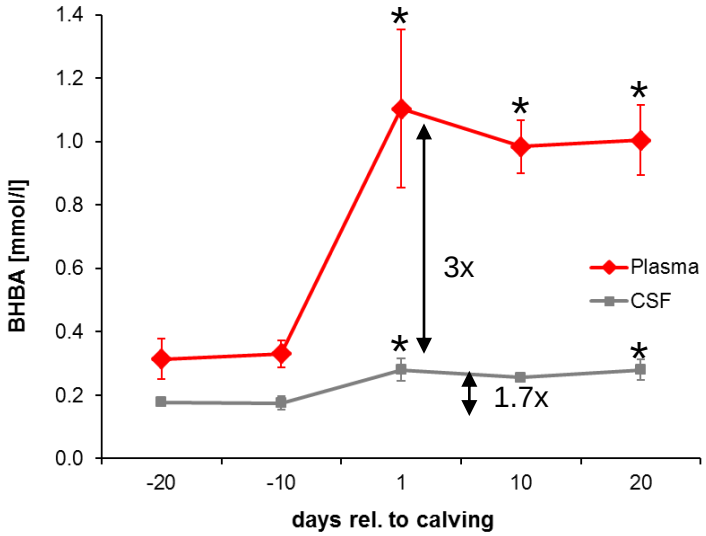
Administration of BHBA to study effects

- on feed intake (Dummerstorf)
- on metabolism and immune response (Bern)

Studies in Dummerstorf

Effects of BHBA on feed intake

BHBA in Plasma and CSF in Early Lactation

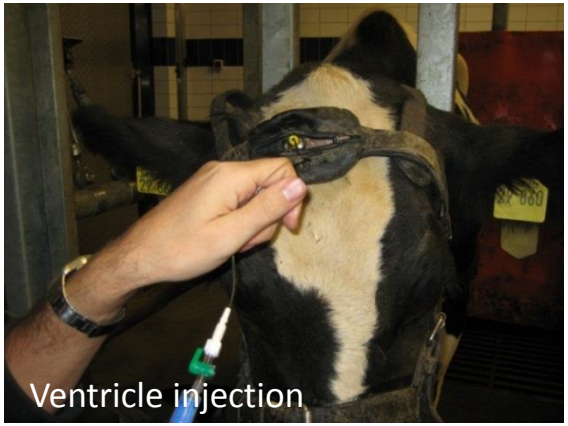


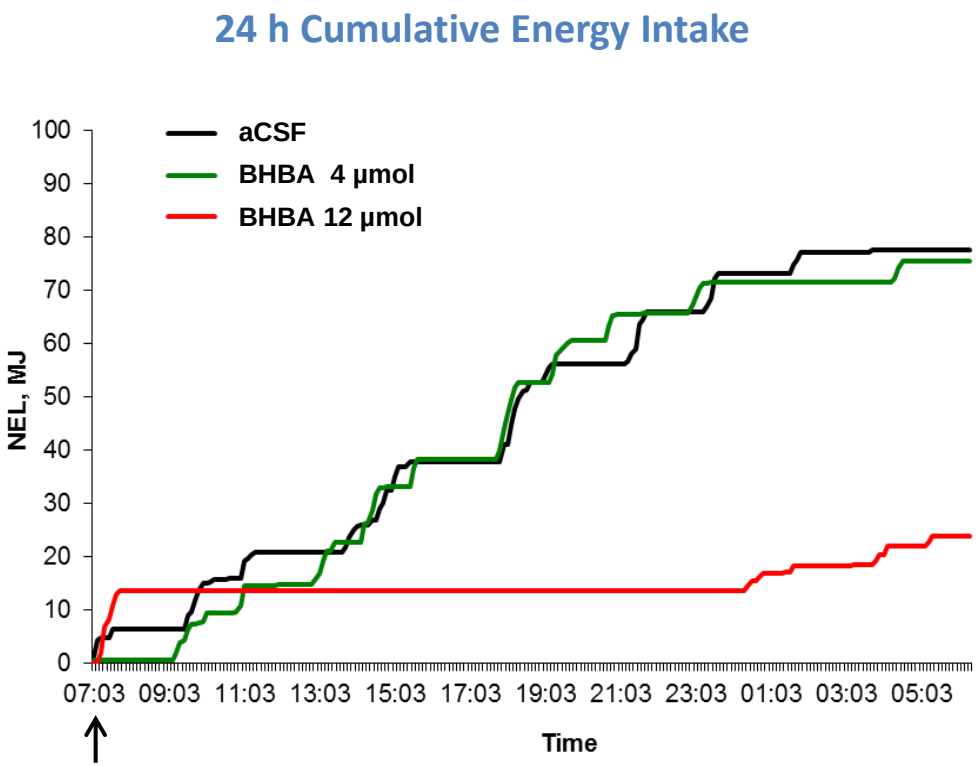
$p<0.05$

The increase of plasma BHBA is partially also transferred to CSF.

Laeger *et al.*, JDS 2013

BHBA injection into lateral brain ventricle (in vivo)

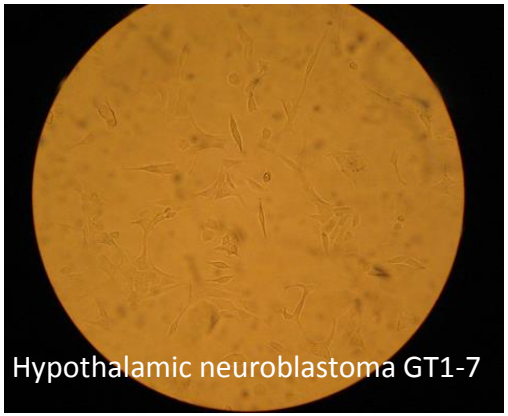




BHBA at a high dosage caused an inhibition of feed intake.

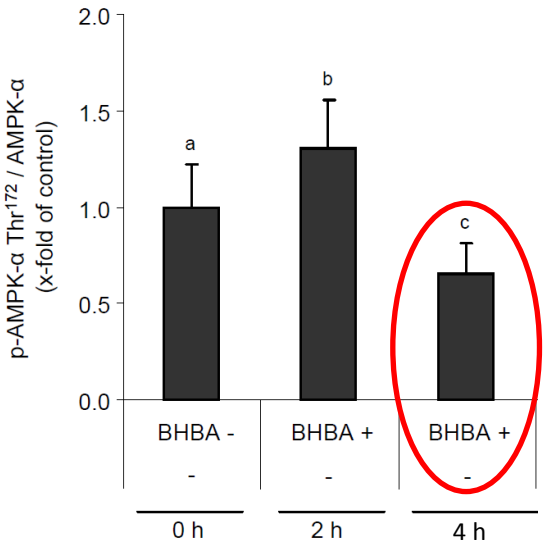
Kuhla *et al.*, JDS 2011

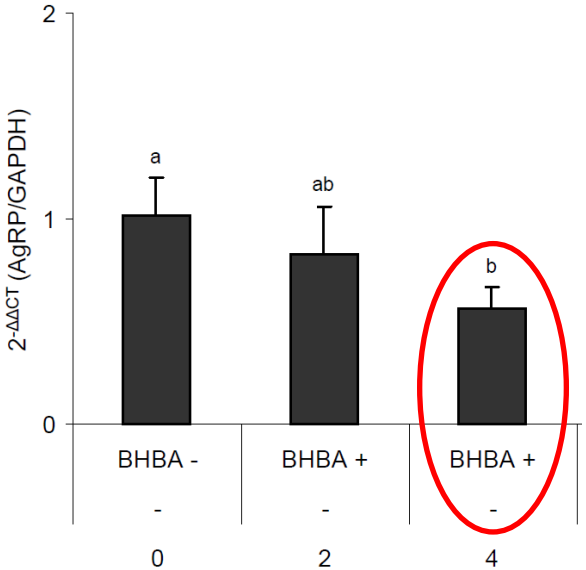
BHBA application to hypothalamic neurons (in vitro)

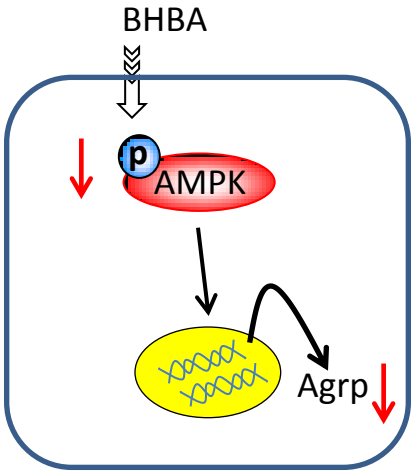


Hypothalamic GT1-7 cells

Incubation with BHBA (6 mM)







Laeger et al., J. Endocrinology 2012

BHBA reduced the expression of AGRP likely via inhibition of AMPK.

Studies in Bern

Effects of elevated plasma BHBA concentration through BHBA infusion

(during mid-lactation, at a non-negative energy status)

on

metabolism

and

immune response during LPS-induced mastitis

Treatments

- **Beta- hydroxybutyrate** (HyperB, n=5 animals)

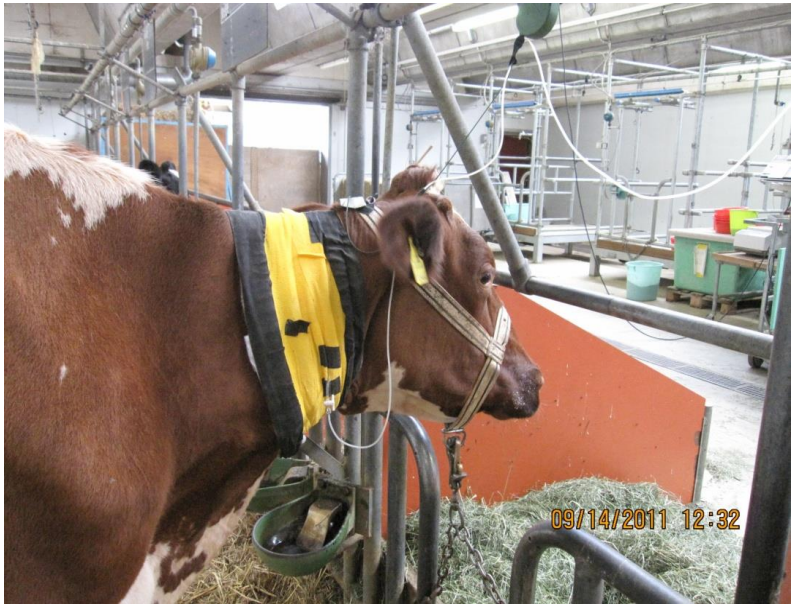
Clamped infusion for 56 h:

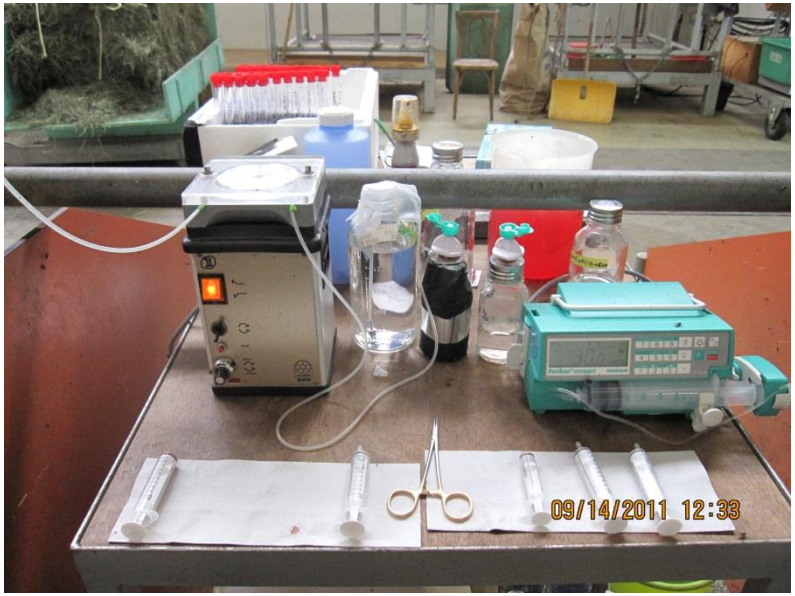
BHBA concentration measured every 15 min, and infusion rate adjusted accordingly

Goal → plasma BHBA concentration: 1.5 to 2.0 mmol/L

- **NaCl** (control, n=8 animals)

  0.9 % saline solution

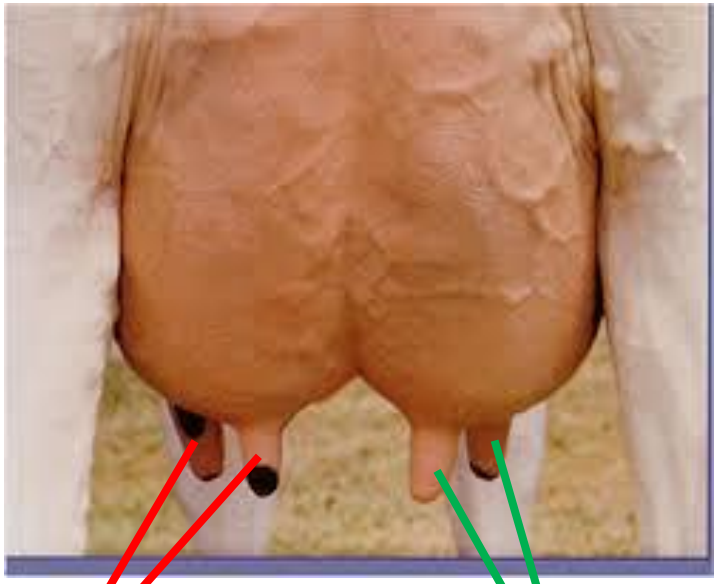




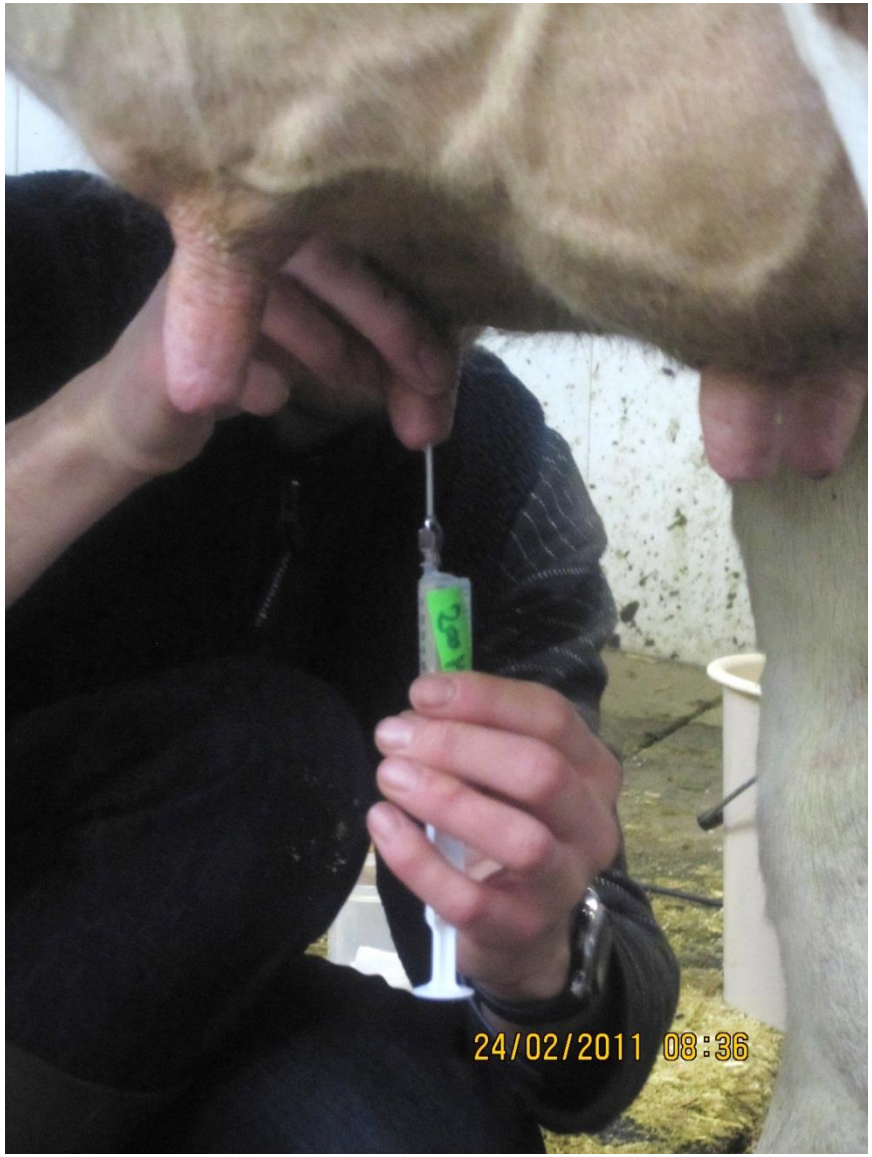
LPS challenge

48-56 h of infusion:

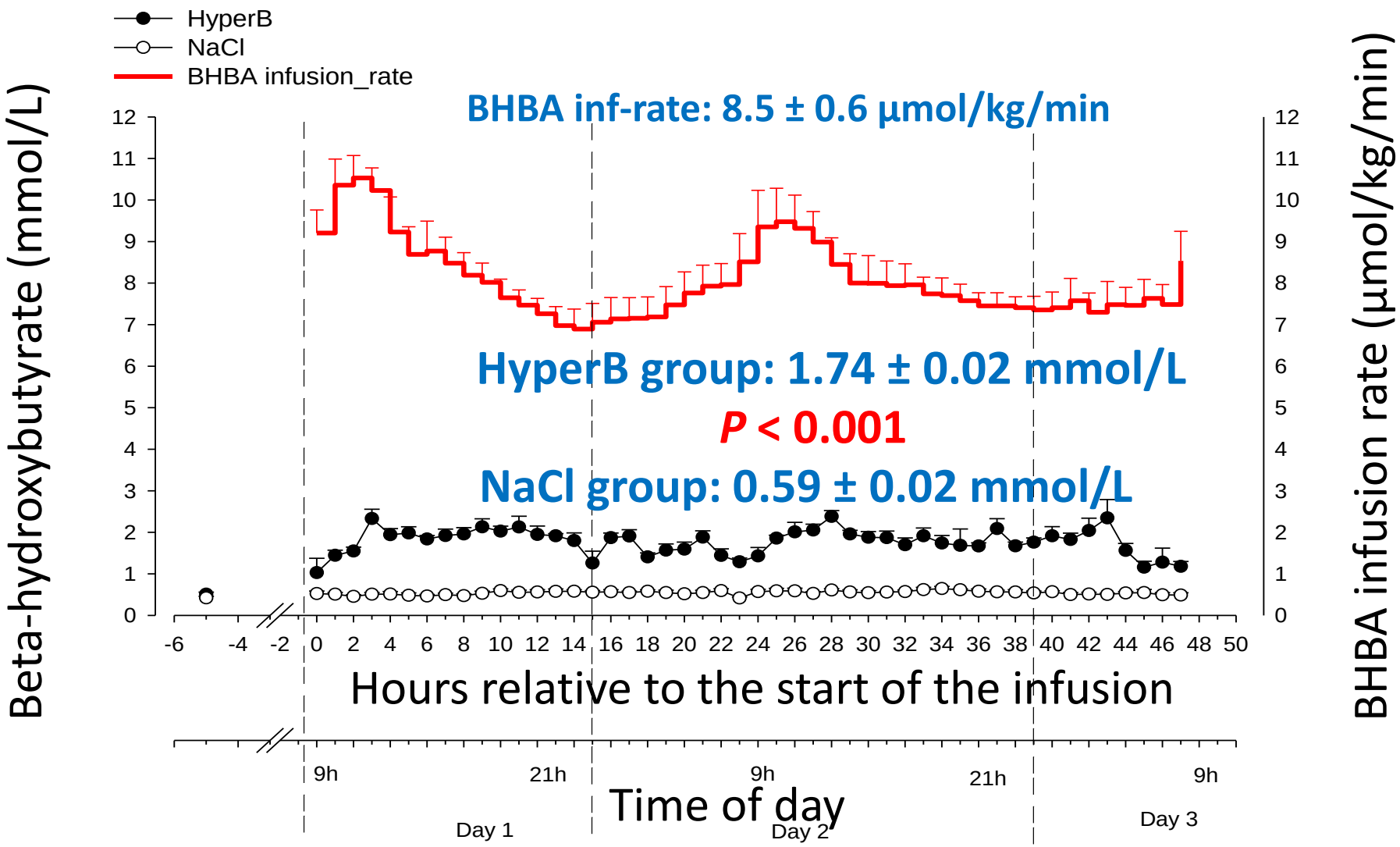
200 µg of *Escherichia coli* LPS



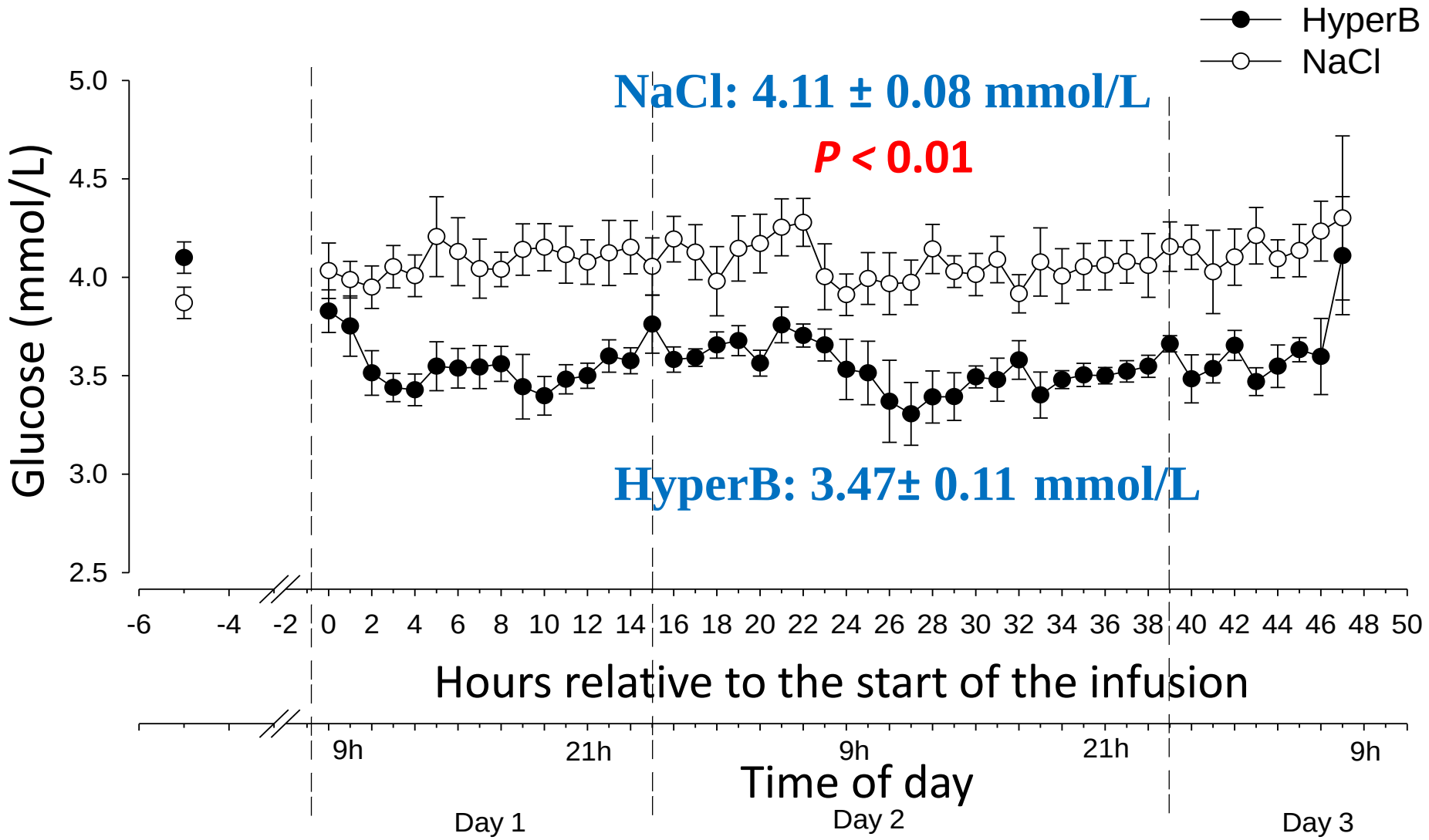
LPS **0.9% NaCl**



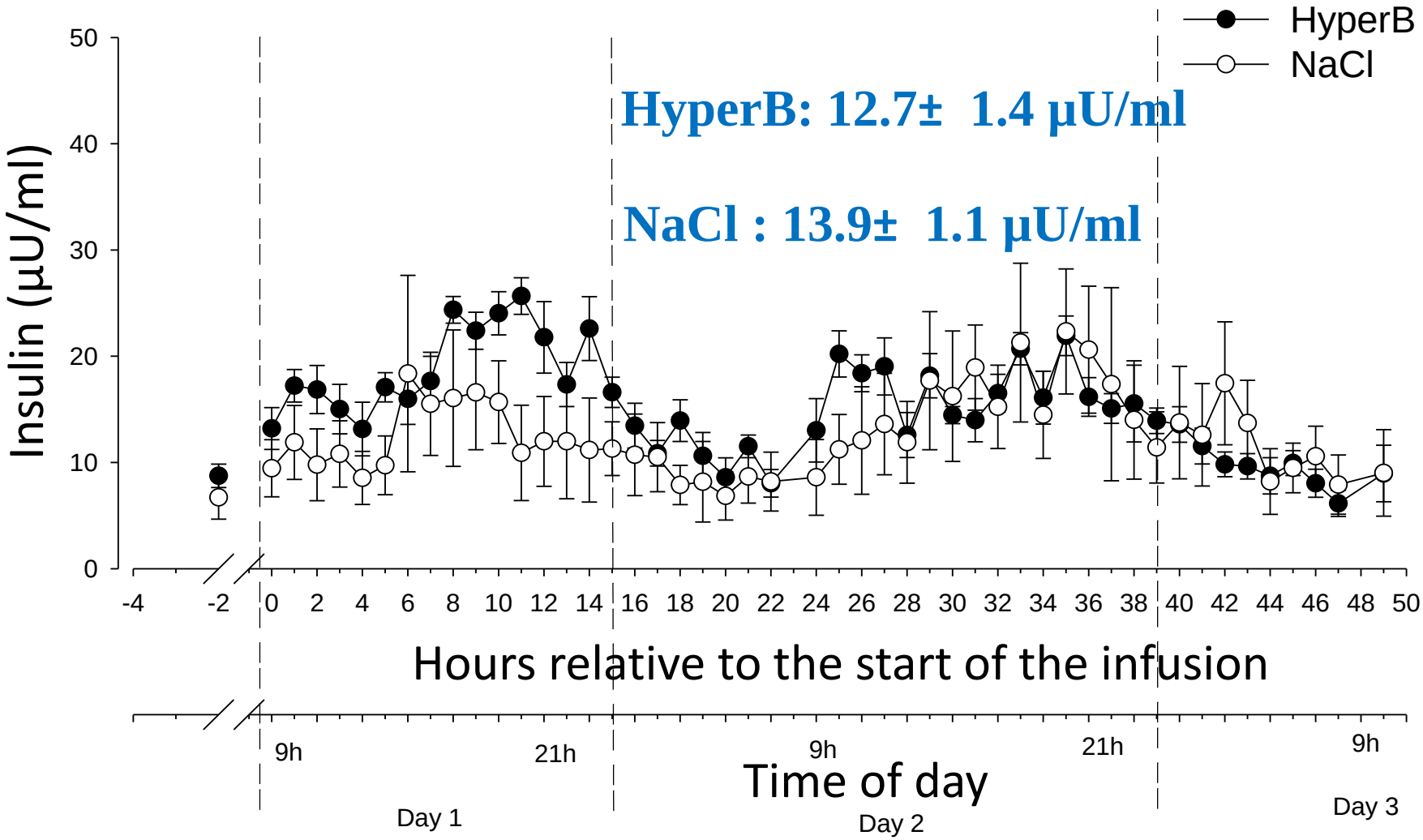
BHBA (48 h)


HyperB
NaCl
BHBA infusion_rate
BHBA inf-rate: 8.5 ± 0.6 µmol/kg/min
HyperB group: 1.74 ± 0.02 mmol/L
P < 0.001
NaCl group: 0.59 ± 0.02 mmol/L
Beta-hydroxybutyrate (mmol/L)
BHBA infusion rate (µmol/kg/min)
Hours relative to the start of the infusion
Time of day
9h
21h
9h
21h
9h
Day 1
Day 2
Day 3

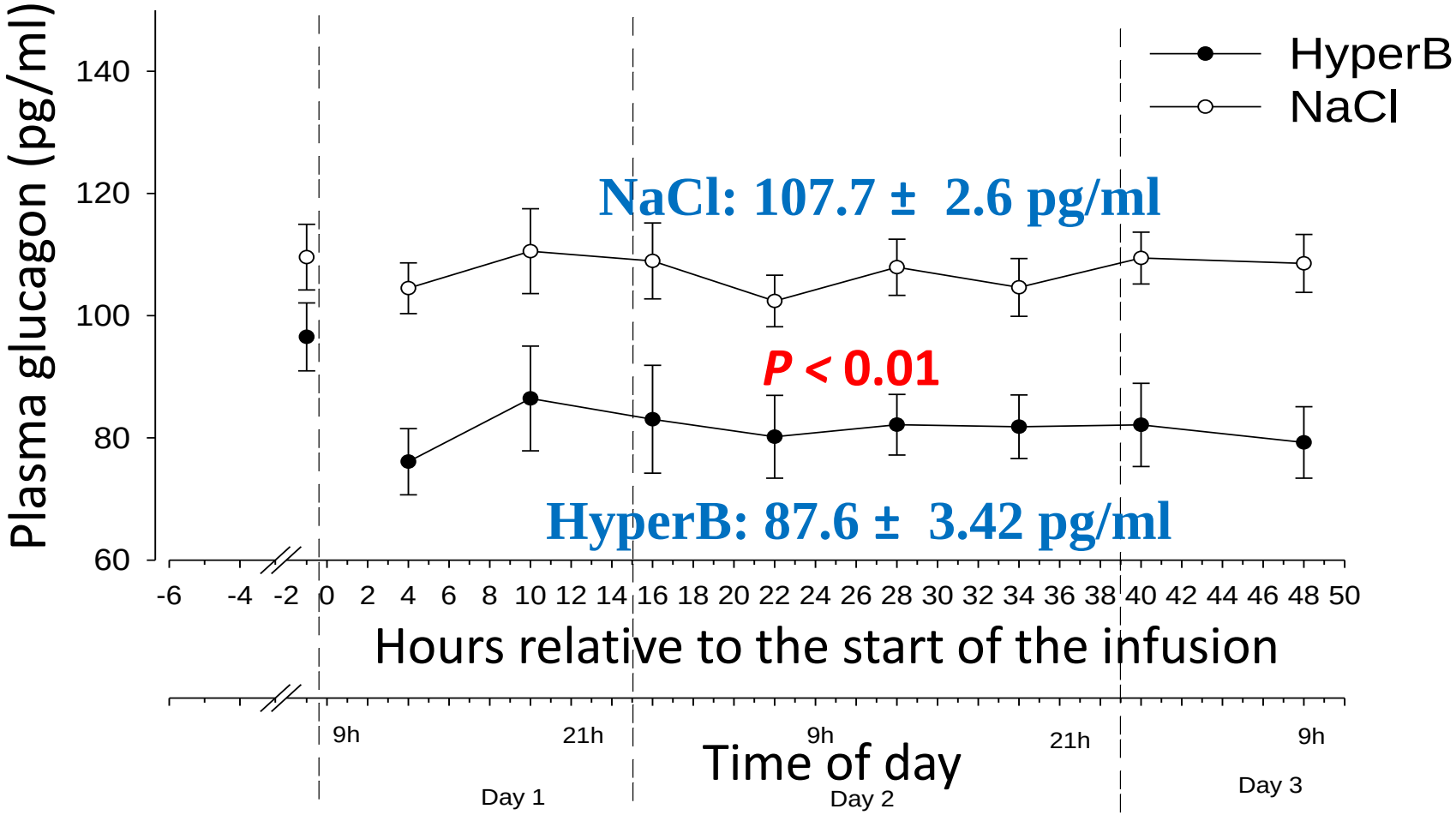
Glucose (48 h)


HyperB
NaCl
NaCl: 4.11 ± 0.08 mmol/L
P < 0.01
HyperB: 3.47± 0.11 mmol/L
Glucose (mmol/L)
5.0
4.5
4.0
3.5
3.0
2.5
-6 -4 -2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
Hours relative to the start of the infusion
9h 21h 9h 21h 9h
Time of day
Day 1
Day 2
Day 3

Insulin (48 h)


HyperB
NaCl
HyperB: 12.7± 1.4 µU/ml
NaCl : 13.9± 1.1 µU/ml
Insulin (µU/ml)
0
10
20
30
40
50
-4
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48
50
Hours relative to the start of the infusion
9h
21h
9h
21h
9h
Time of day
Day 1
Day 2
Day 3

Glucagon (48 h)



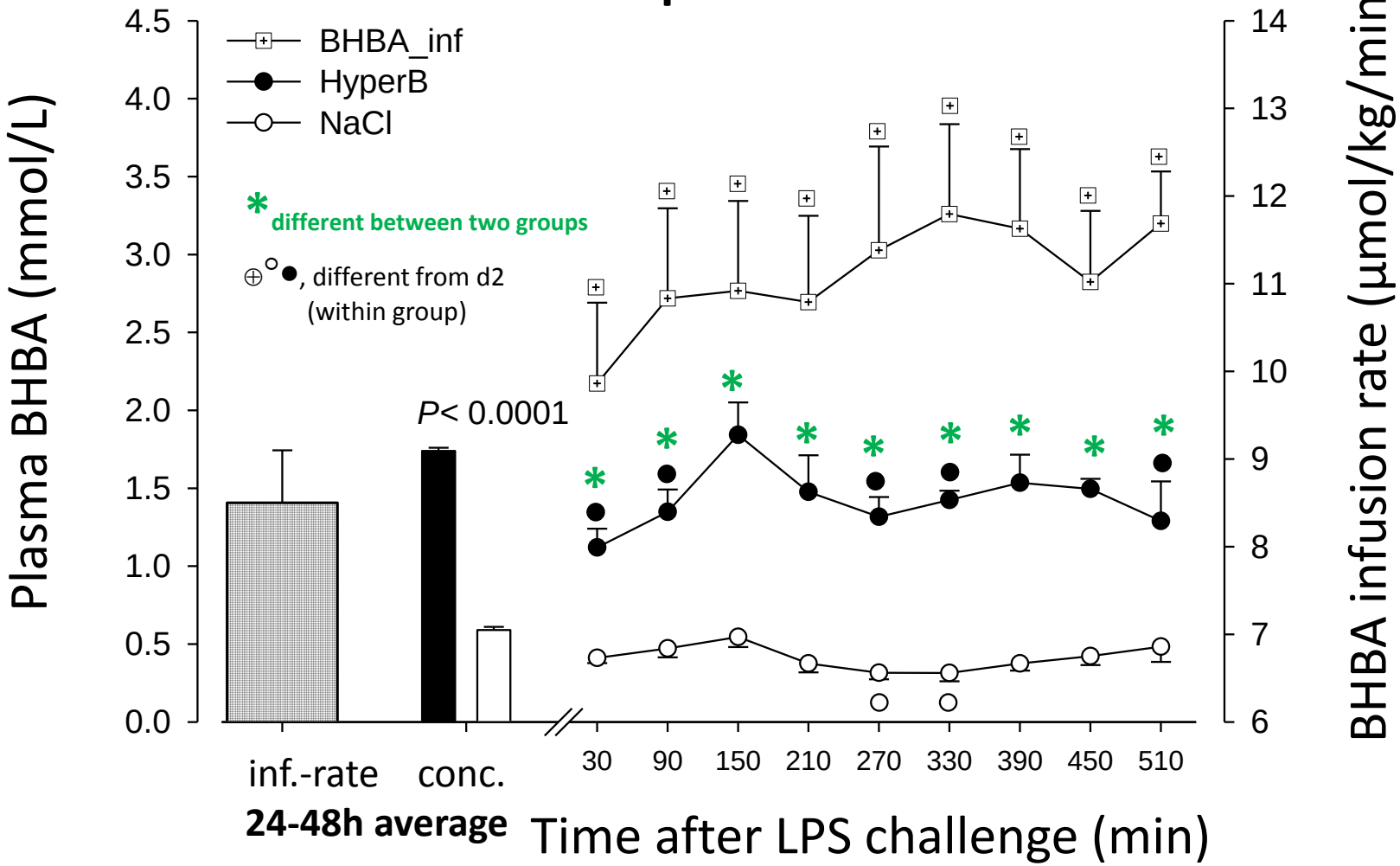
Results

Hormones and metabolistes (means ± SEM of AUC)

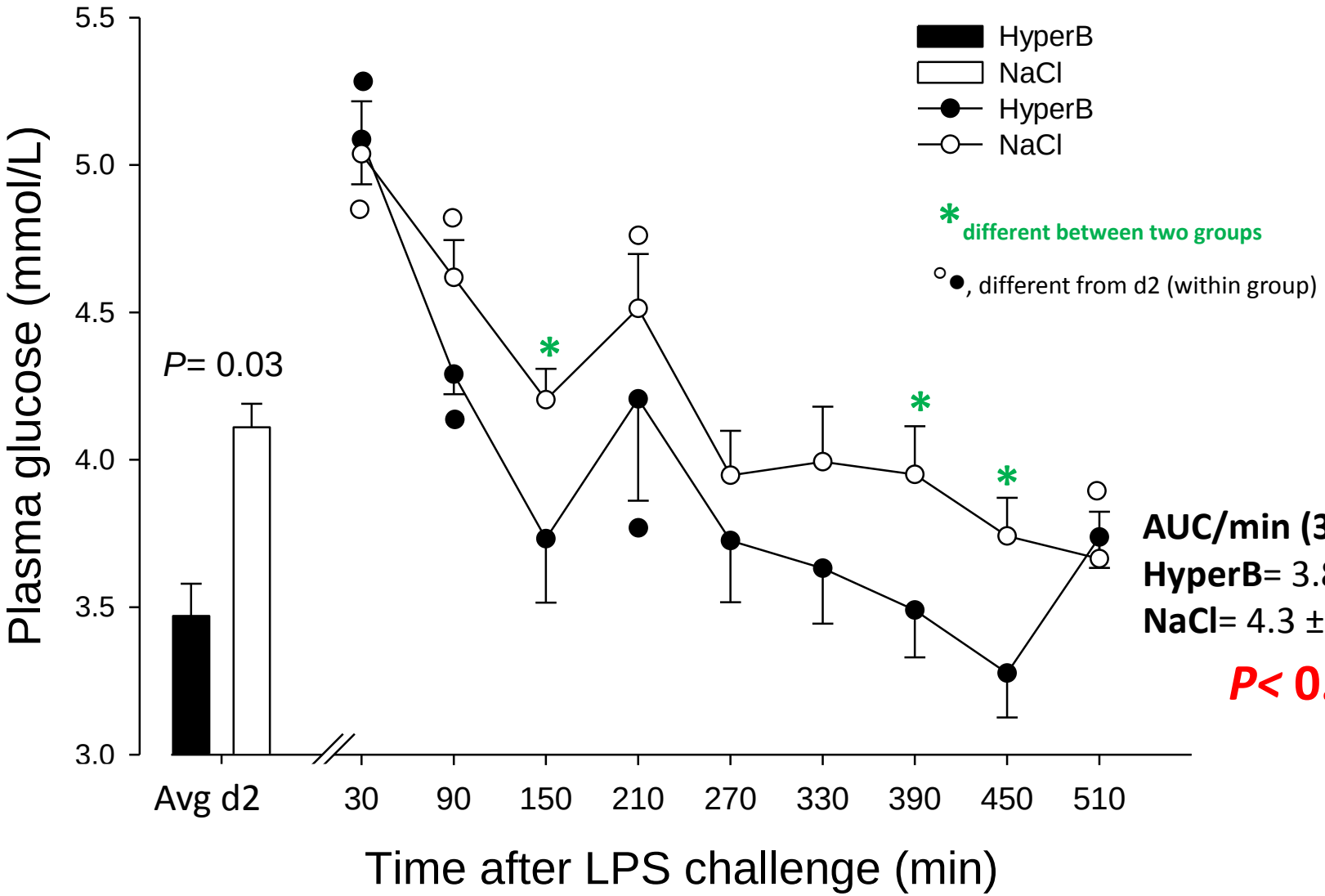
Variable	Group	day 2, (means ± SEM)			ANOVA, (P-Value, group)
Glucose, mmol/L	HyperB	3.47	±	0.11	< 0.01
	NaCl	4.11	±	0.08	
INS, mU/L	HyperB	12.7	±	1.4	0.54
	NaCl	13.9	±	1.1	
BHBA, mmol/L	HyperB	1.74	±	0.02	< 0.001
	NaCl	0.59	±	0.02	
NEFA, mmol/L	HyperB	0.06	±	0.03	0.51
	NaCl	0.09	±	0.02	
Urea, mmol/L	HyperB	3.77	±	0.31	0.63
	NaCl	3.97	±	0.24	
Glucagon, pg/ml	HyperB	97.4	±	3.3	< 0.05
	NaCl	107.7	±	2.6	
IGF-1, ng/mL	HyperB	90	±	4.5	0.11
	NaCl	80	±	3.6	
TG, mmol/L	HyperB	0.15	±	0.01	0.58
	NaCl	0.14	±	0.01	
Cortisol, ng/mL	HyperB	2.41	±	0.55	0.78
	NaCl	2.62	±	0.43	

Results (plasma)

Beta-hydroxybutyrate (BHBA): infusion rate and plasma concentration



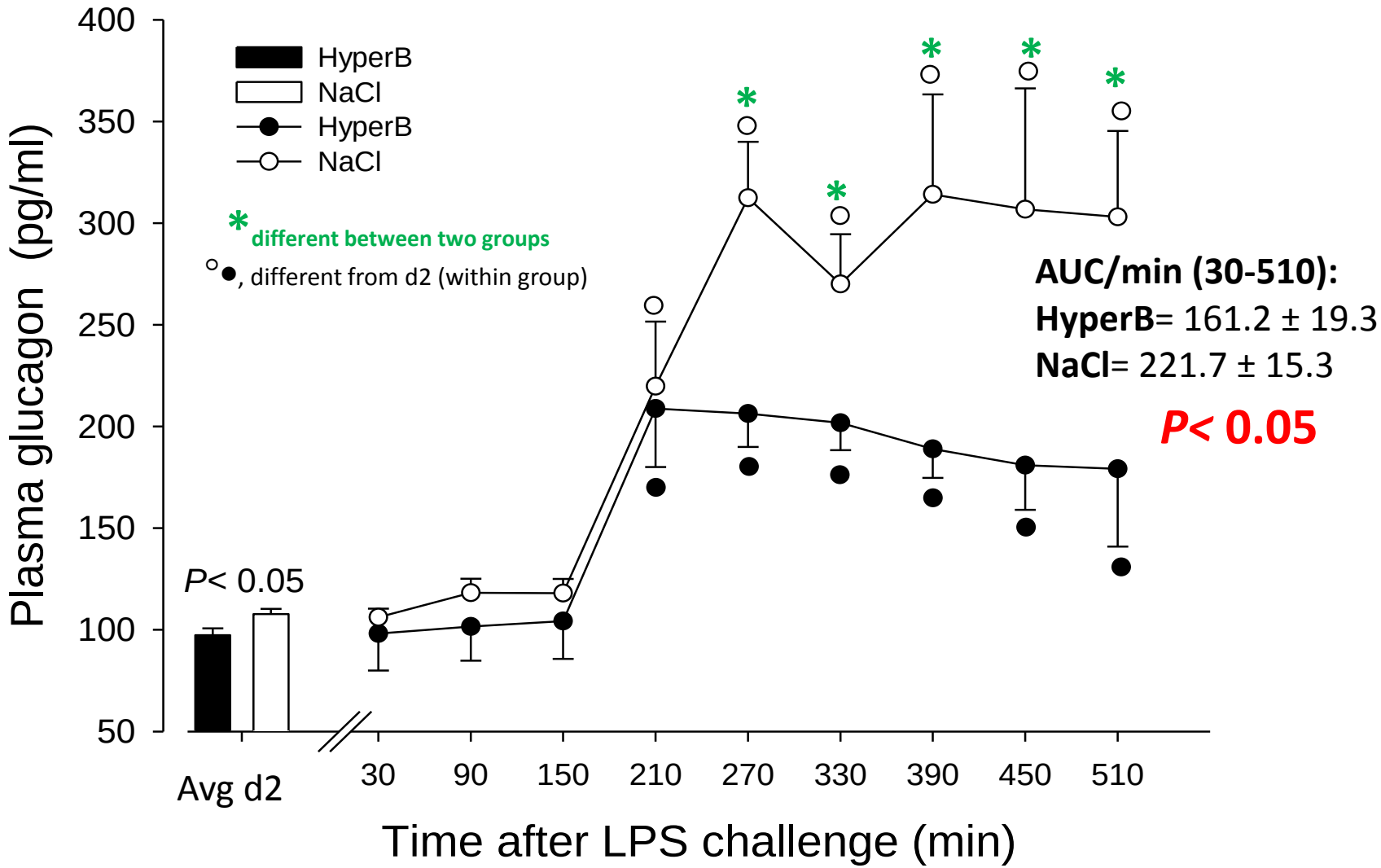
Glucose (LPS challenge)



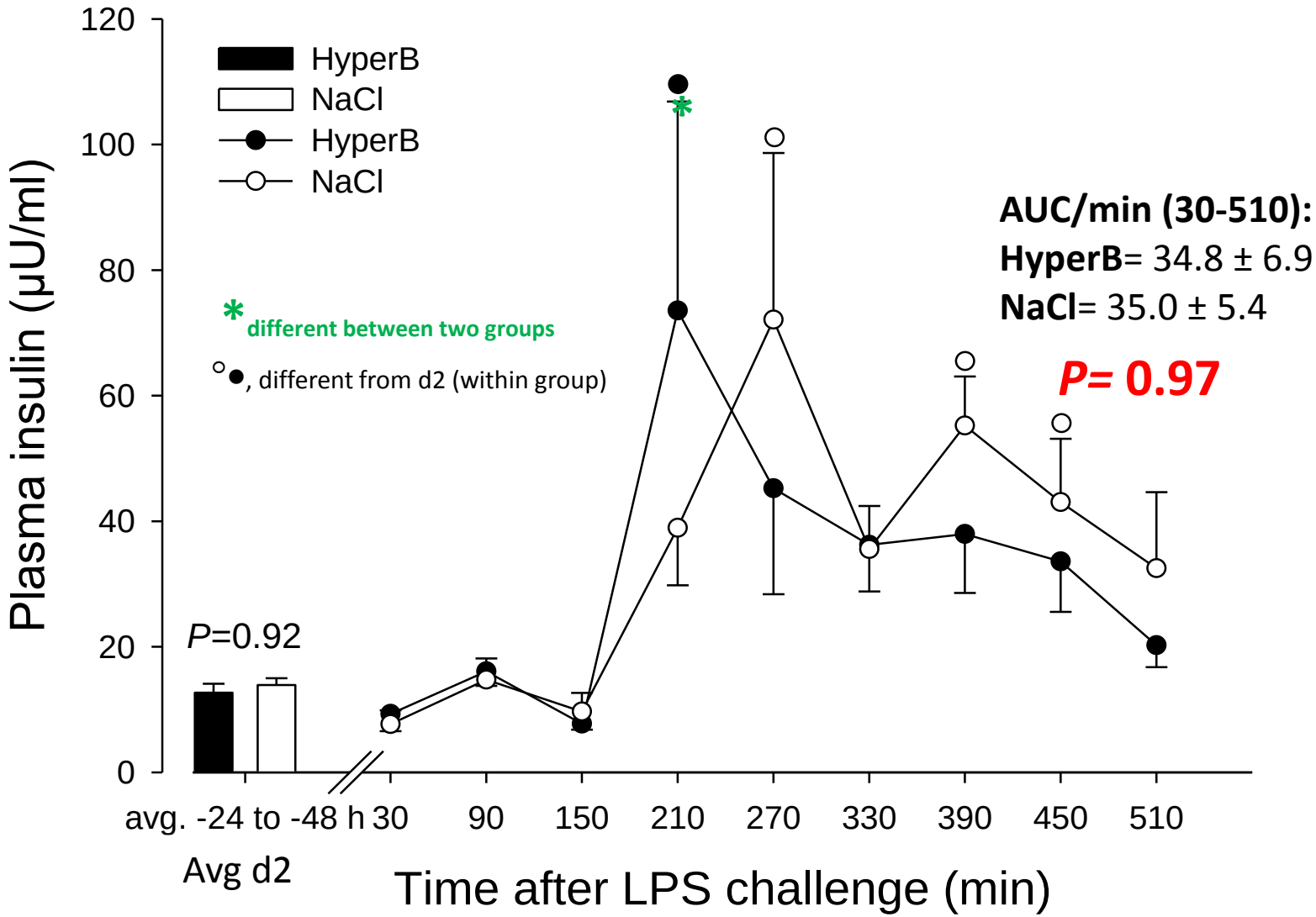
AUC/min (30-510):
HyperB= 3.8 ± 0.1
NaCl= 4.3 ± 0.1

***P*< 0.05**

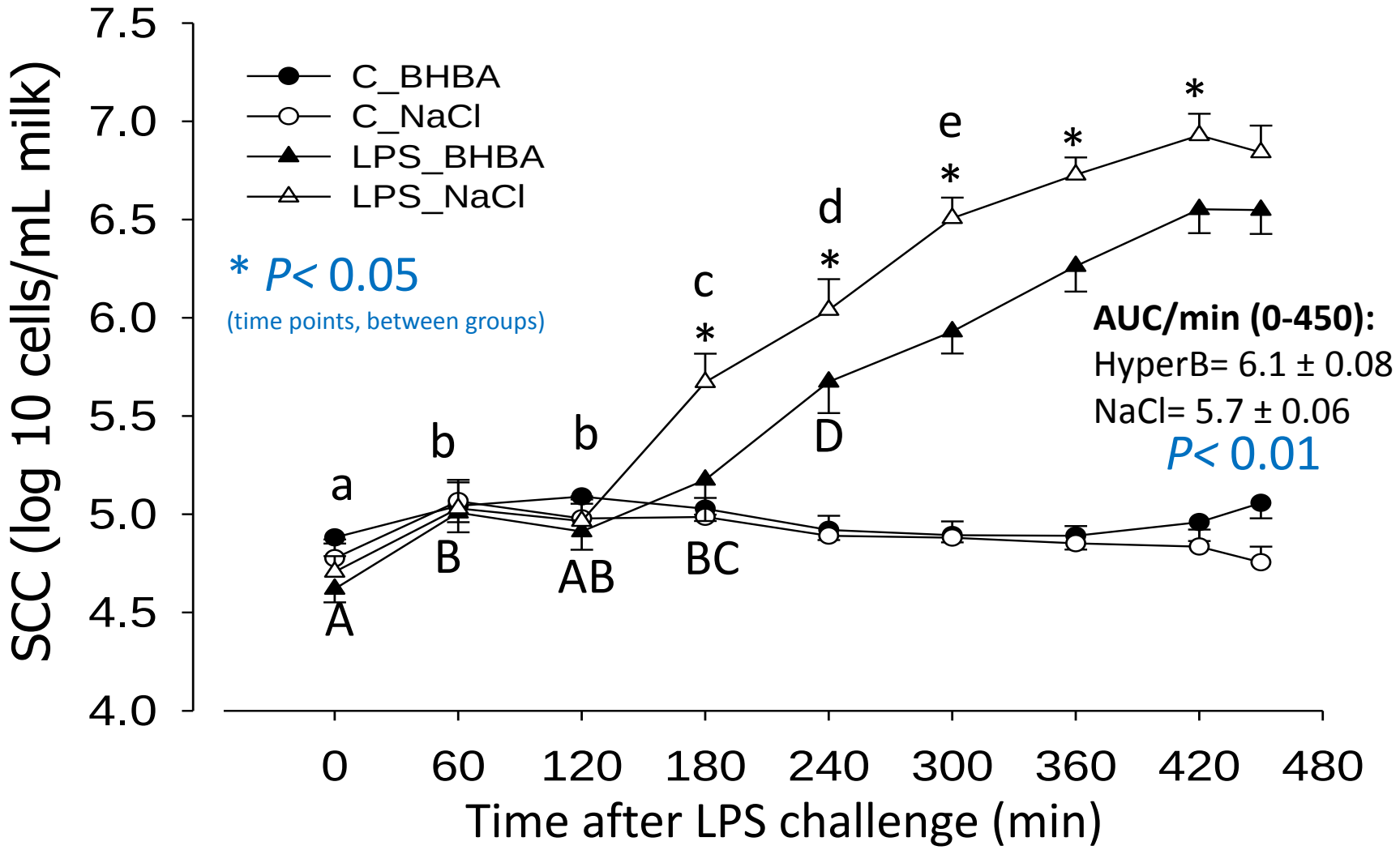
Glucagon (LPS challenge)



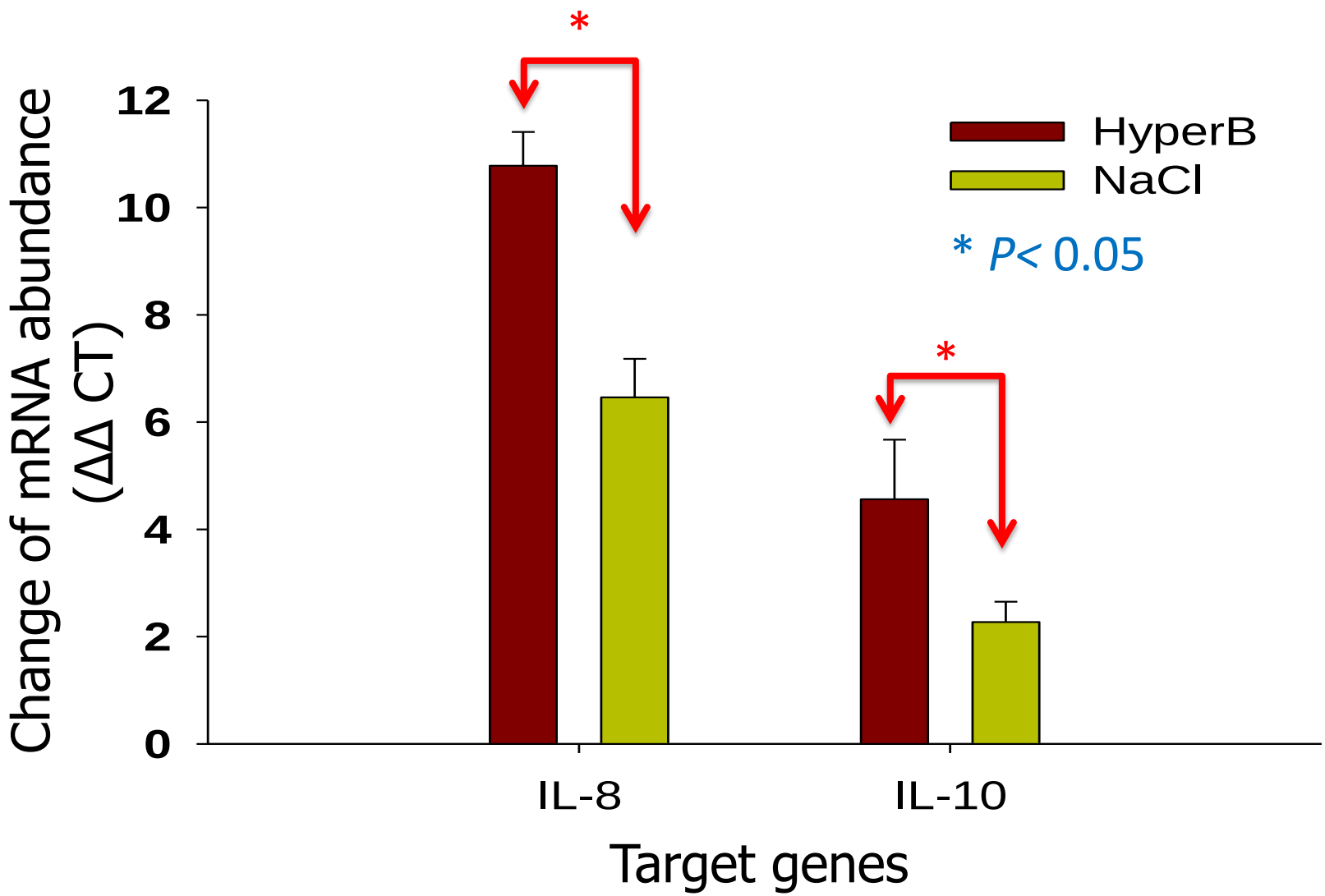
Insulin (LPS challenge)



SCC (LPS challenge)



mRNA abundance (LPS)



Conclusions

Reduced feed intake and gluconeogenesis during hyperketonemia:
a paradox reaction to a signal of abundant energy availability?

Metabolization of ketone bodies instead of using other energy sources and to save oxaloacetat for the citric acid cycle?

If so, this adaptation does not consider the specific needs of glucose for lactose synthesis in lactating dairy cows.

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Thank you for your attention!

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