# Tradeoff between production and survival under stress: Role of glucose sparing by the mammary gland


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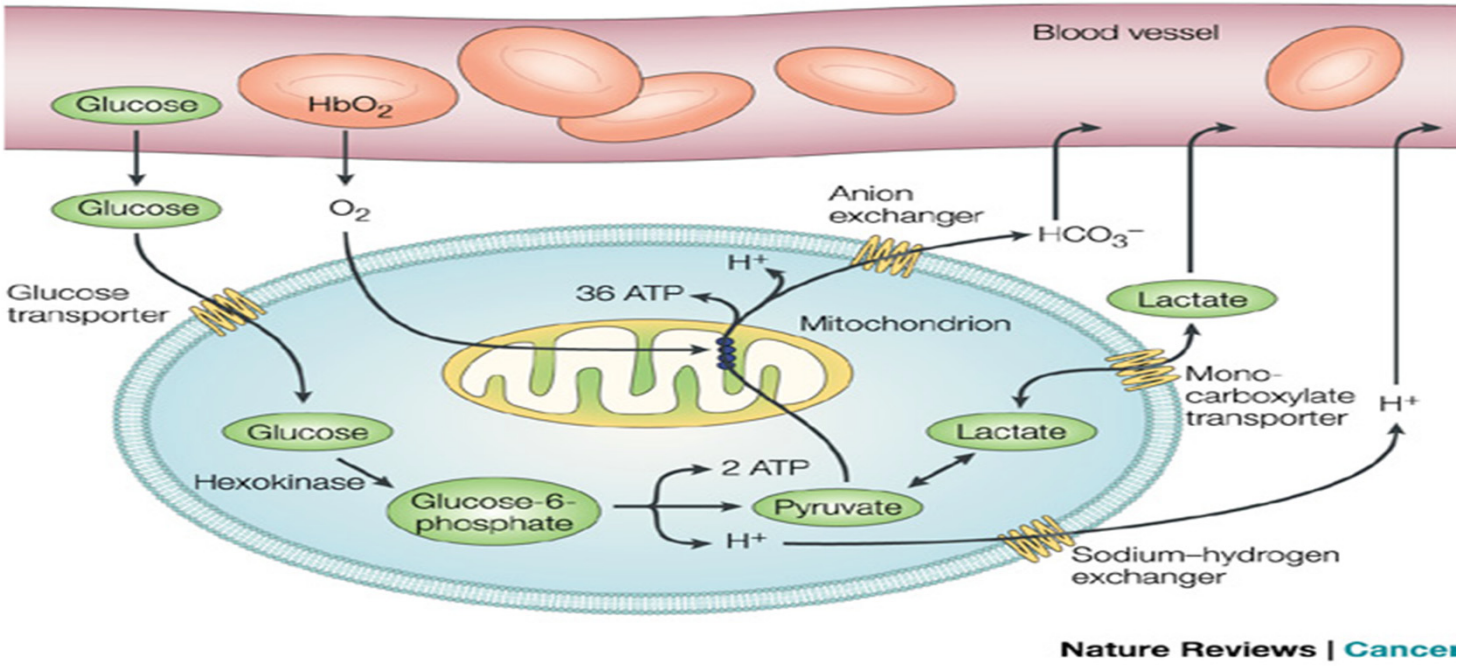
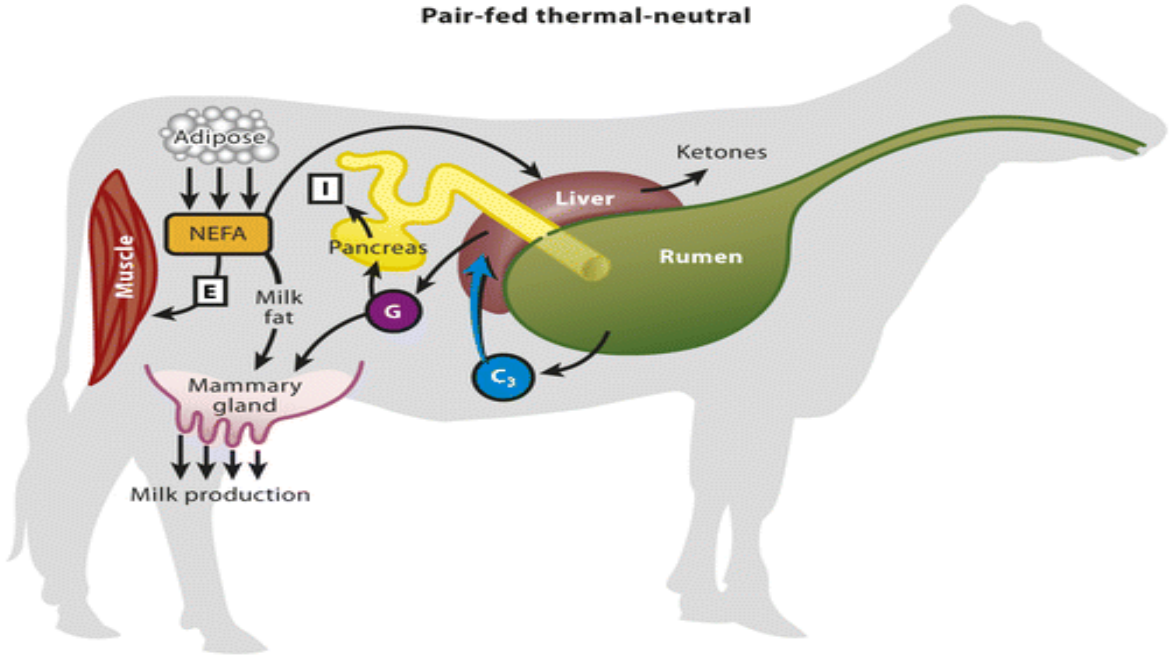
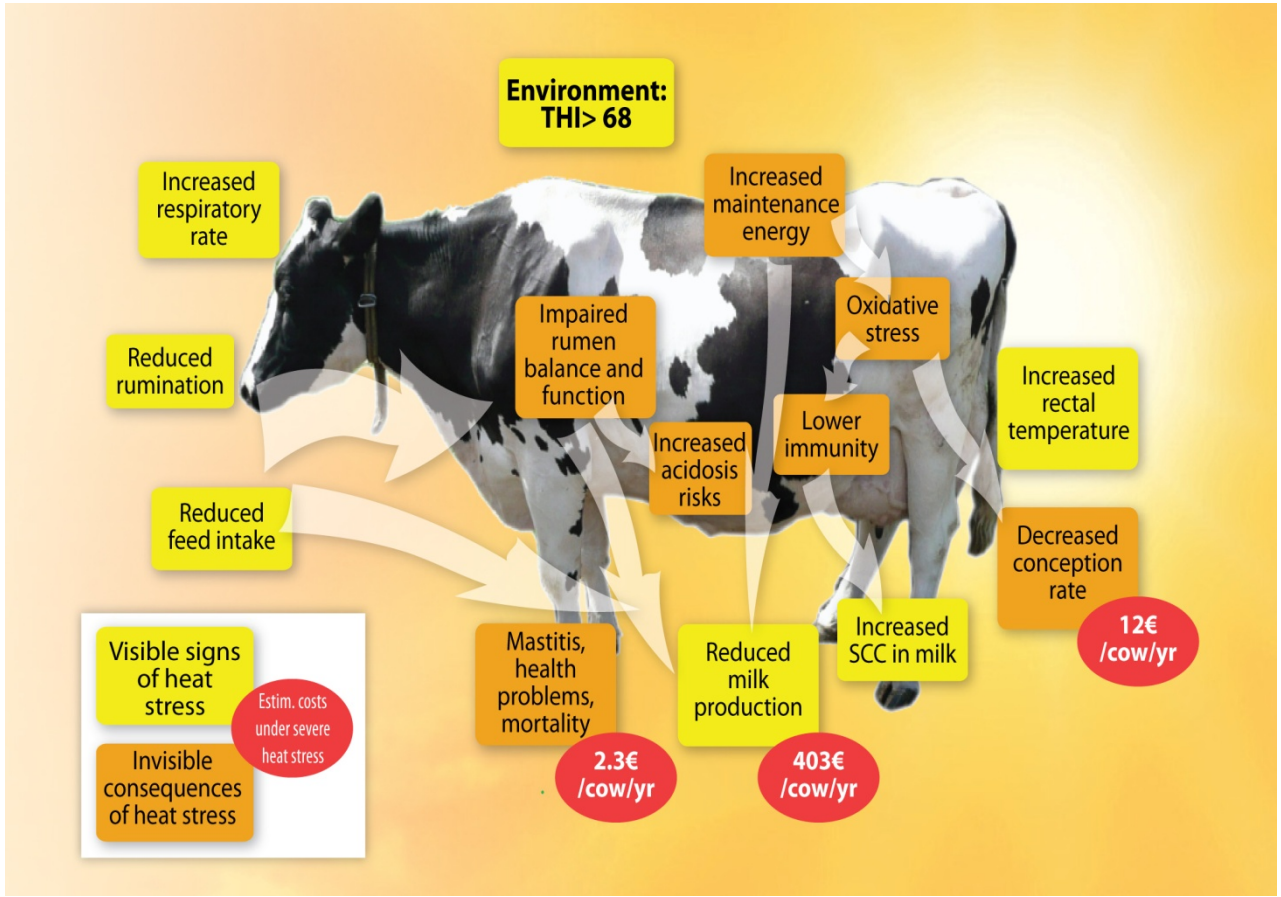


In modern high-producing dairy cows most (70-80%) of glucose synthesized (around 3 kg per day) by **gluconeogenesis** in the liver from VFA is diverted to the mammary gland

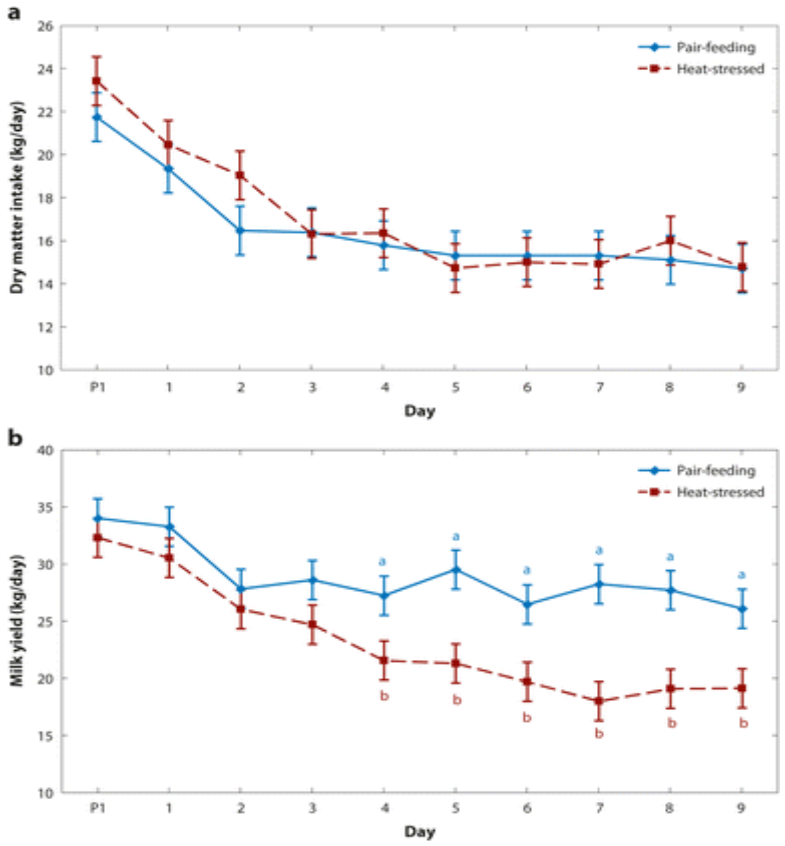



Baumgard LH and Rhoads Jr. RP. 2013.
Annu. Rev. Anim. Biosci. 1:311–337

# First: The effect of heat stress is considered



# Pair-feeding experiments show that the reduction in milk yield exceed the reduction in feed intake

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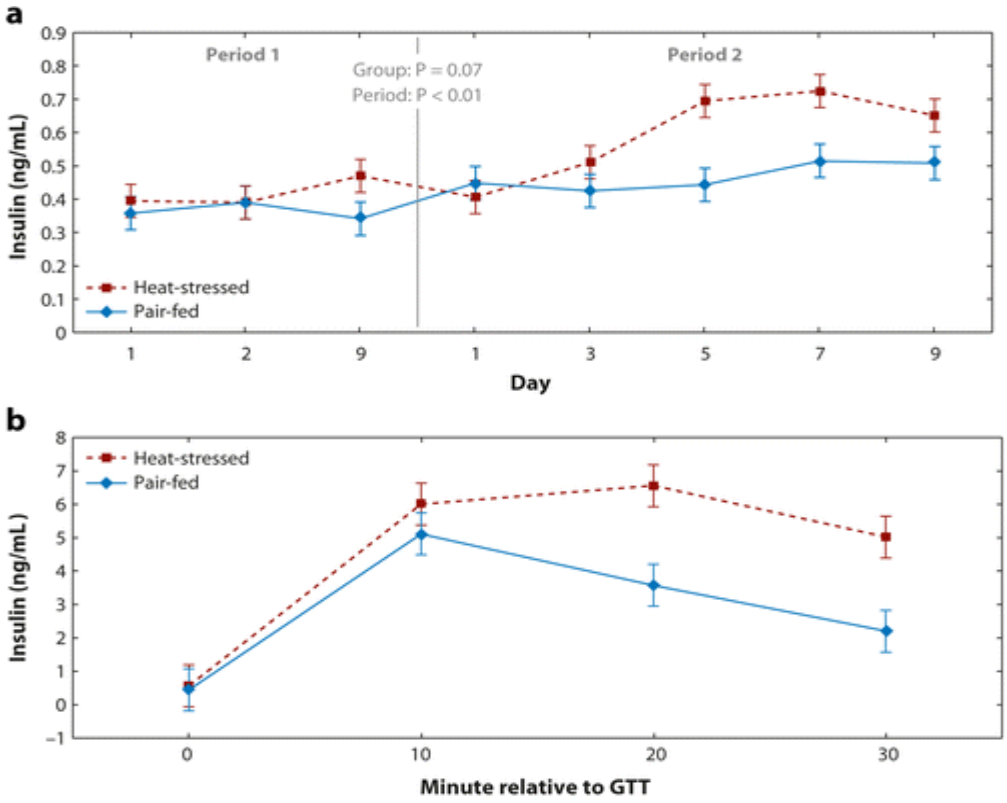
# Heat stress is associated with increase in insulin sensitivity

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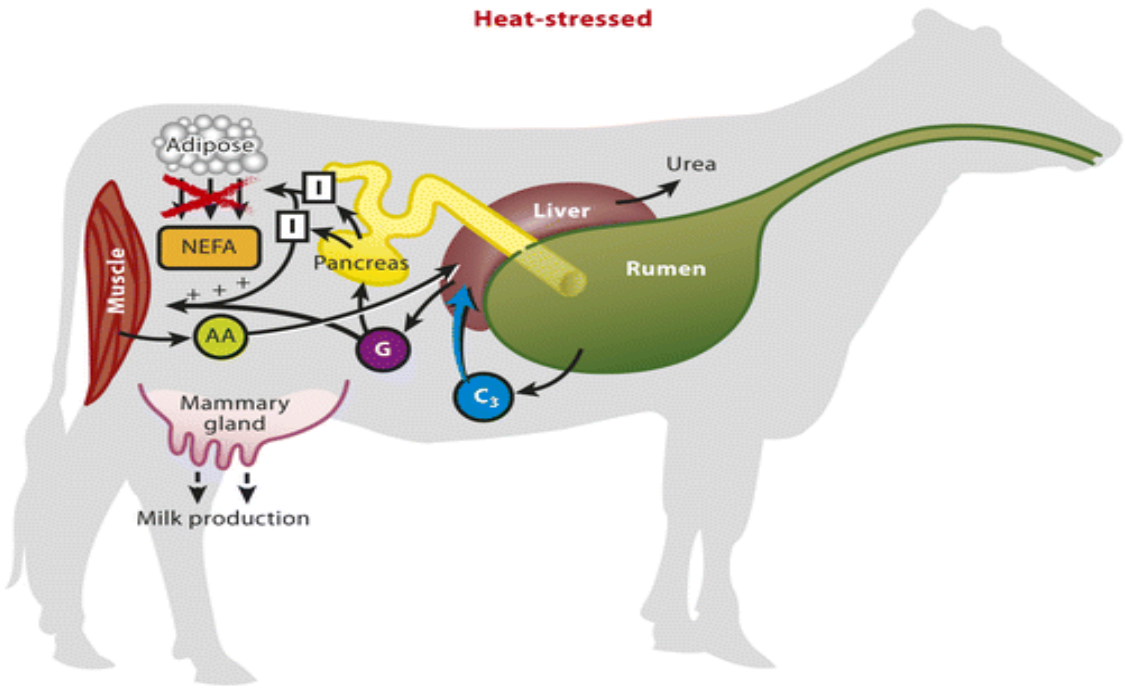
Heat stress is associated by diminished uptake of glucose by the mammary gland (by up to 1 kg out of 3 kg) and almost complete stop of NEFA release fro fat (hence their supply to the mammary gland)

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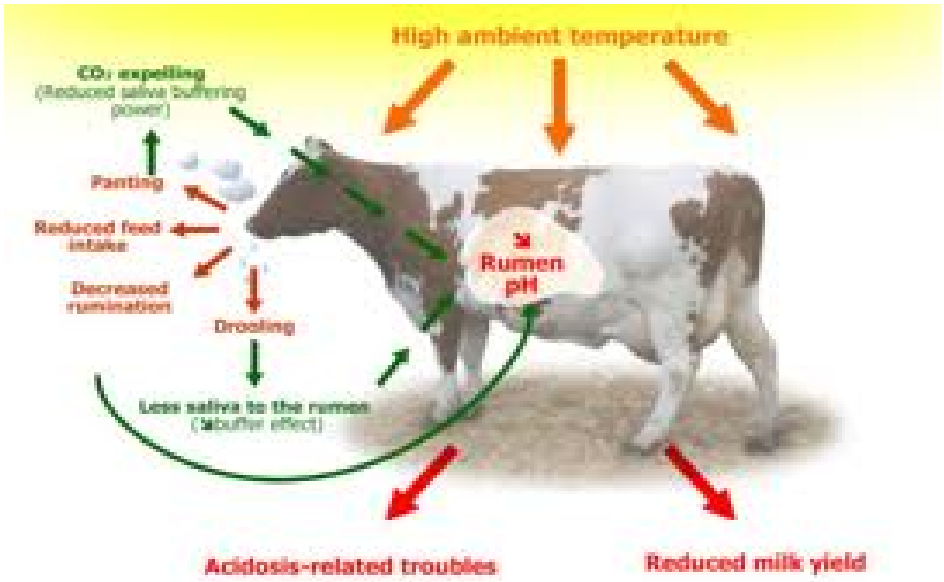
# What are the conclusions from the per-feeding experiments under heat stress?



-“The primary difference between a thermal-neutral and a heat-stressed animal in a similar energetic state is the inability of the hyperthermic beast to employ glucose-sparing mechanisms to homeorhetically prioritize product (milk and meat) synthesis”.

-In other words, a glucose sparing mechanism is needed to preserve essential body functions and maintaining their homeostasis.

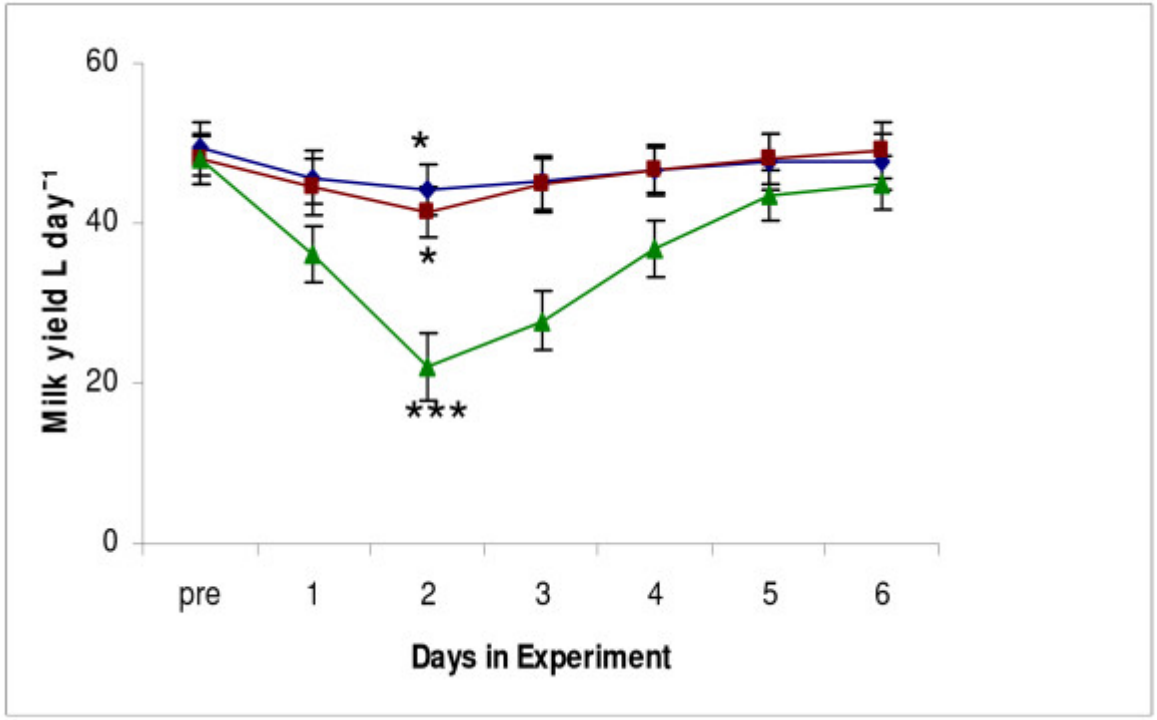
-“From an animal agriculture standpoint, these survival strategies reduce productivity and seriously jeopardize farm economics. “

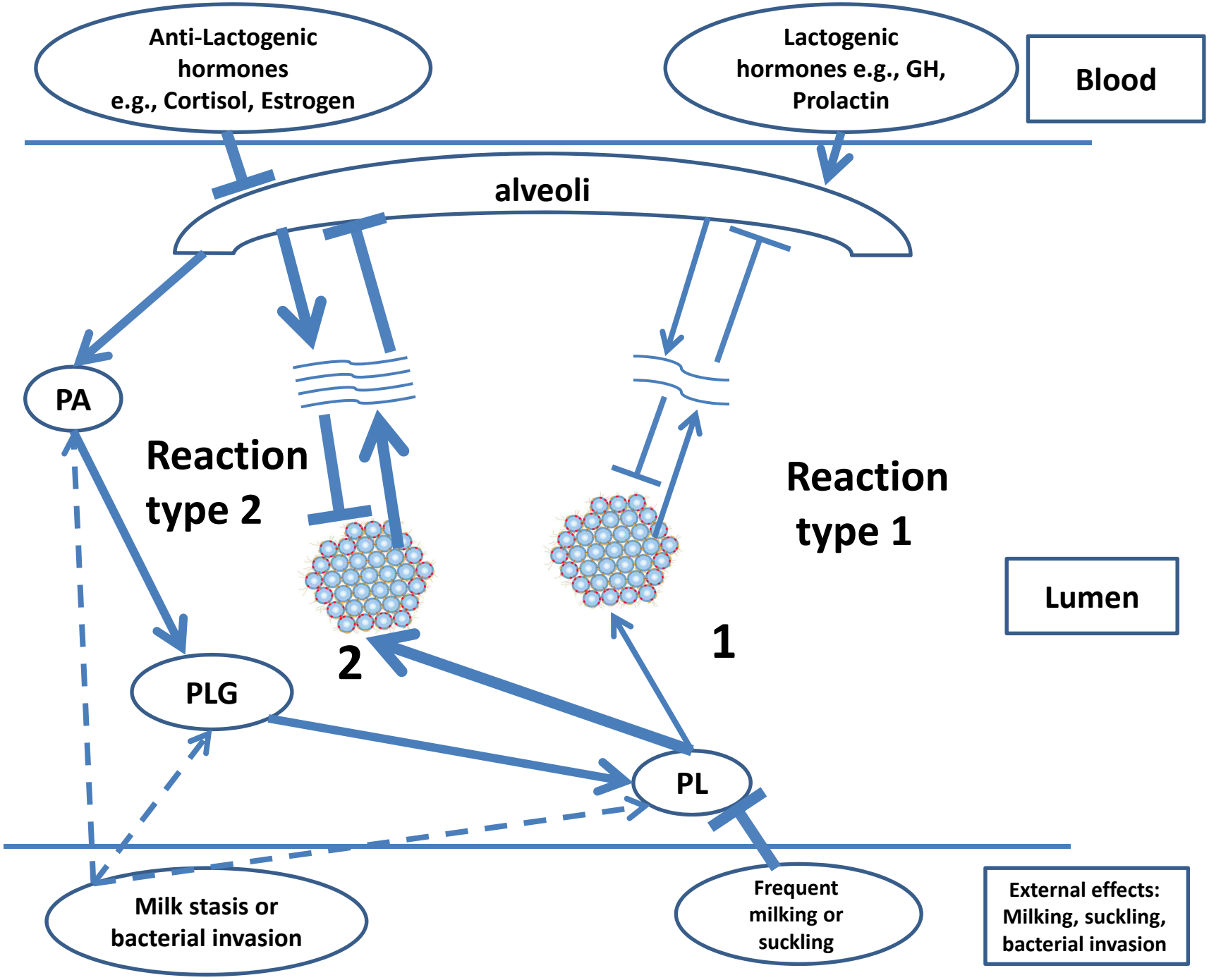
-“Defining the biology and mechanisms of how HS threatens animal health and performance is critical in developing approaches to ameliorate current production issues and is a prerequisite for generating future mitigating strategies to improve animal well-being, performance, and agriculture economics.”

What is the physiological basis for the non-feed intake basis for reduction in milk yield under stress?

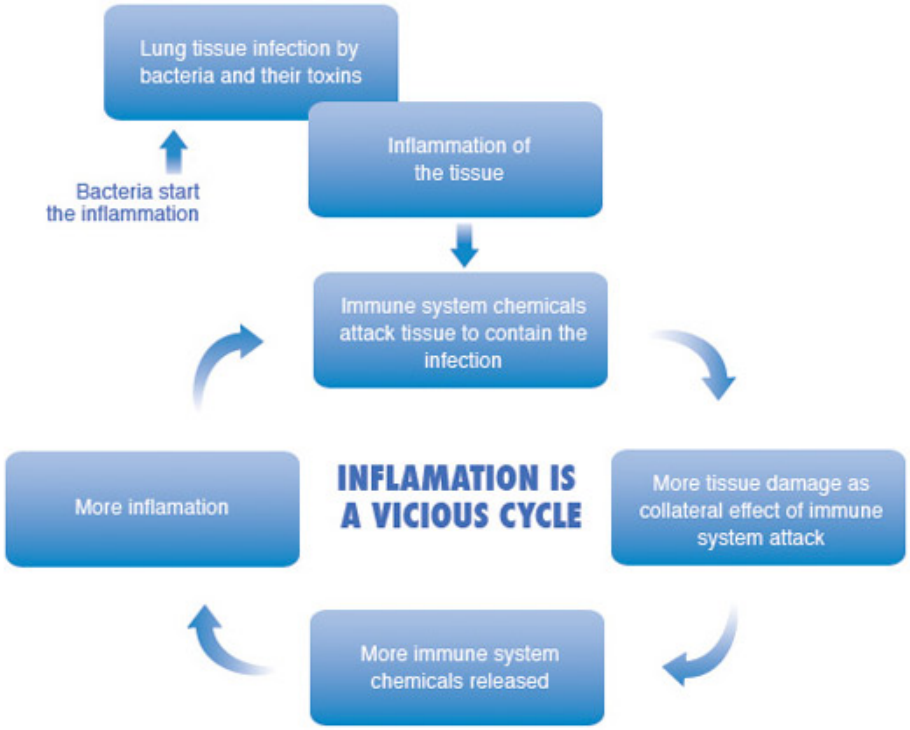
The role of milk-born negative feed-back mechanism

Comparing the effects of prevention of cooling (sprinkling) and shade and prevention of shade on milk yield of high-producing cows in the middle of the summer (THI around 90)

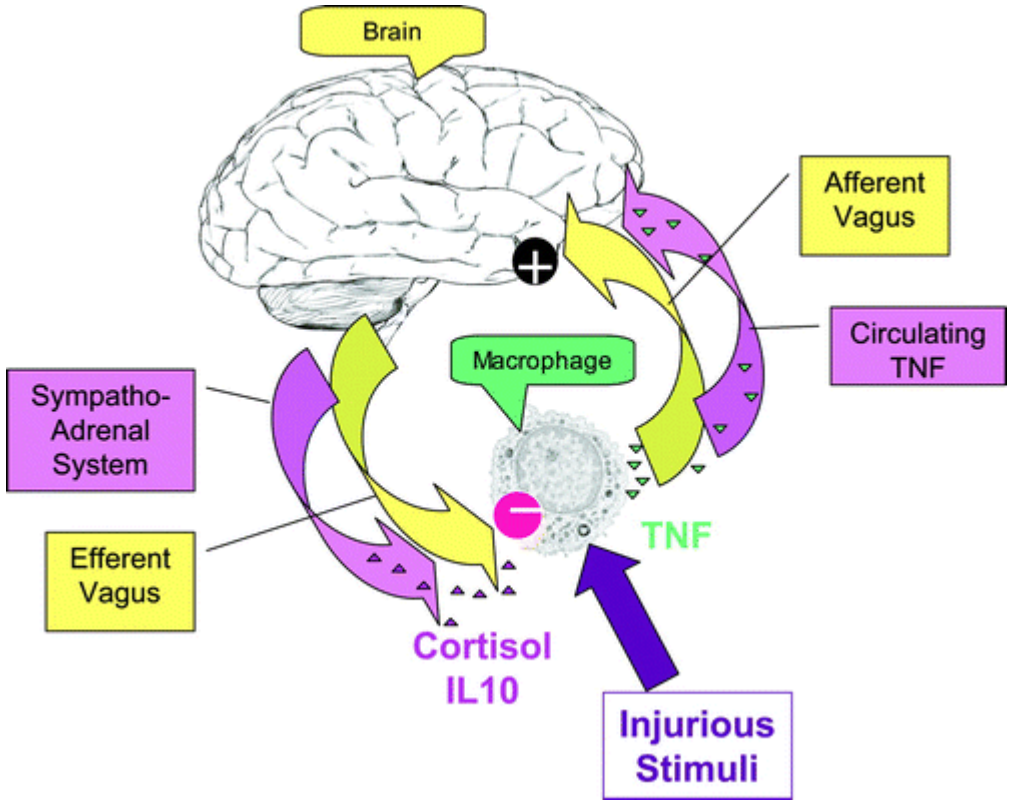



Anti-Lactogenic hormones e.g., Cortisol, Estrogen
Lactogenic hormones e.g., GH, Prolactin
Blood
alveoli
PA
Reaction type 2
Reaction type 1
Lumen
2
1
PLG
PL
Milk stasis or bacterial invasion
Frequent milking or suckling
External effects: Milking, suckling, bacterial invasion

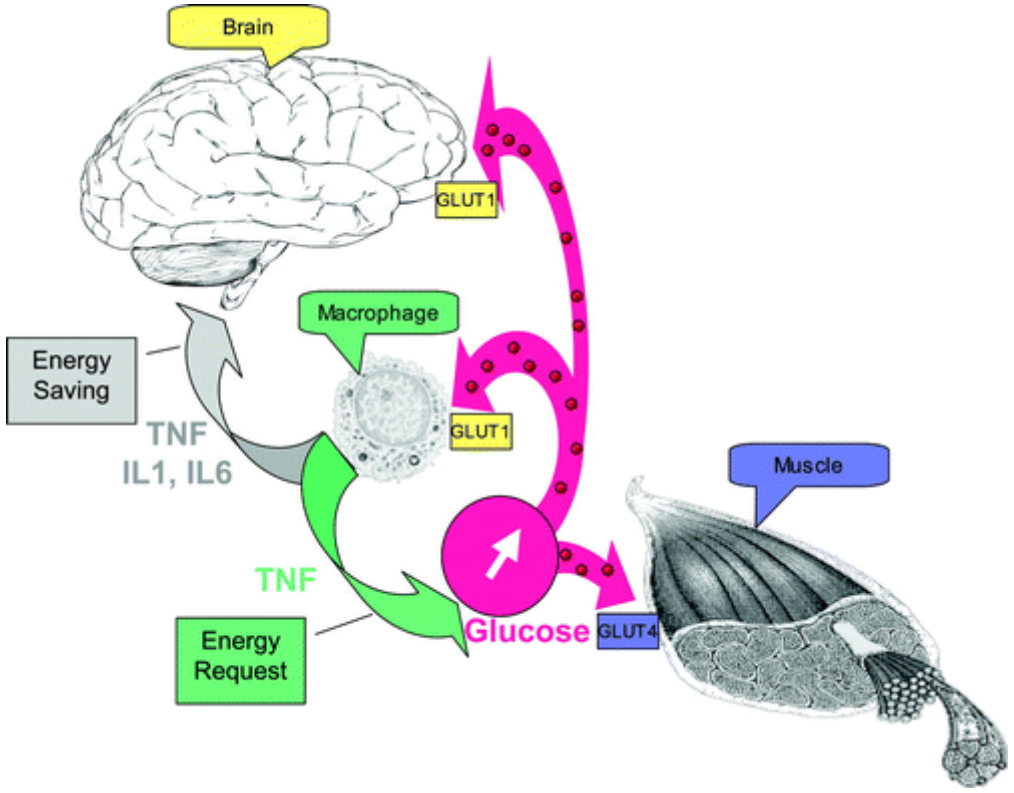
Secondly: the effect of inflammatory stress is considered. During acute inflammation, the demand of the immune system for glucose may increase by up to 1 kg

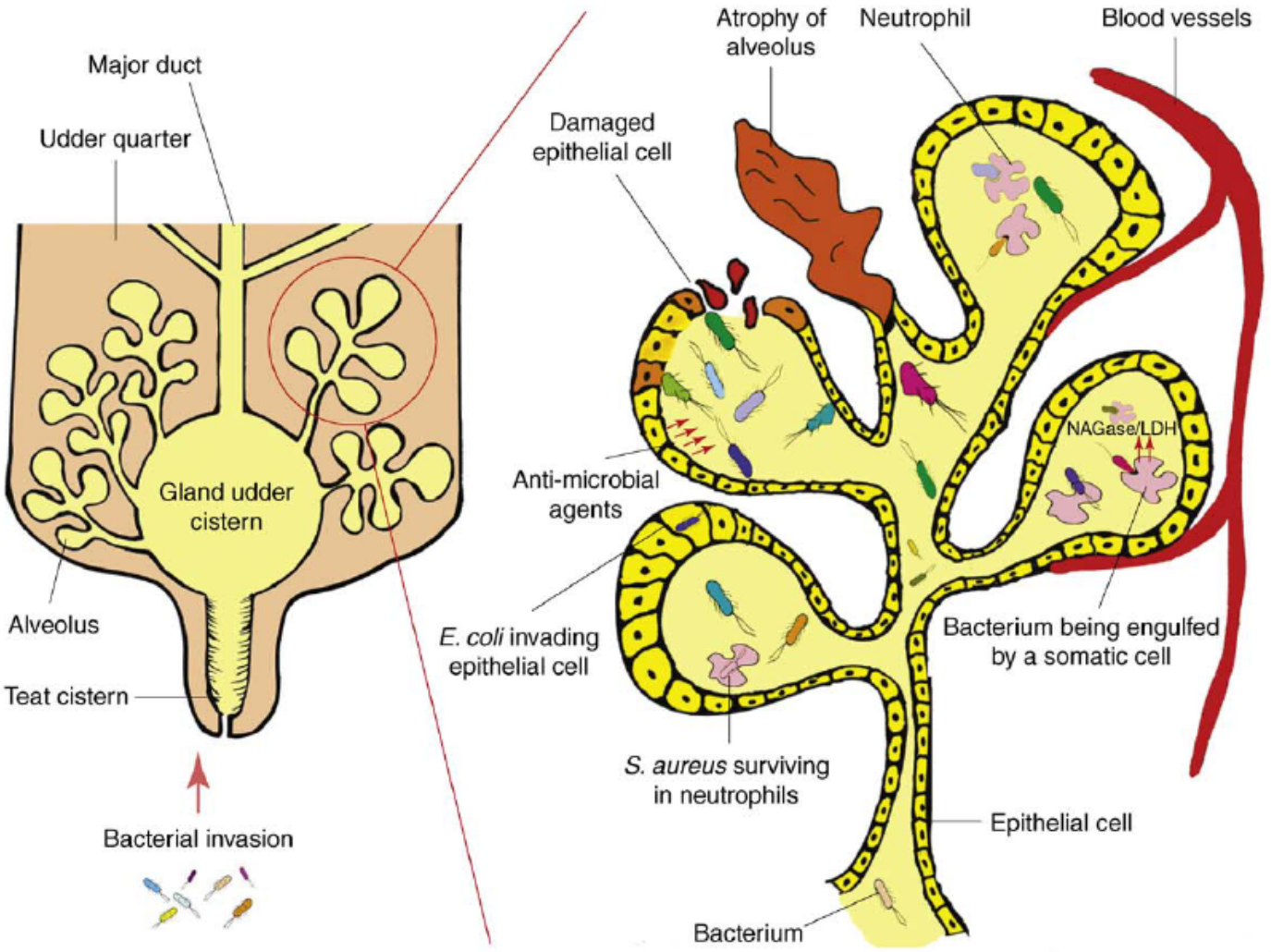


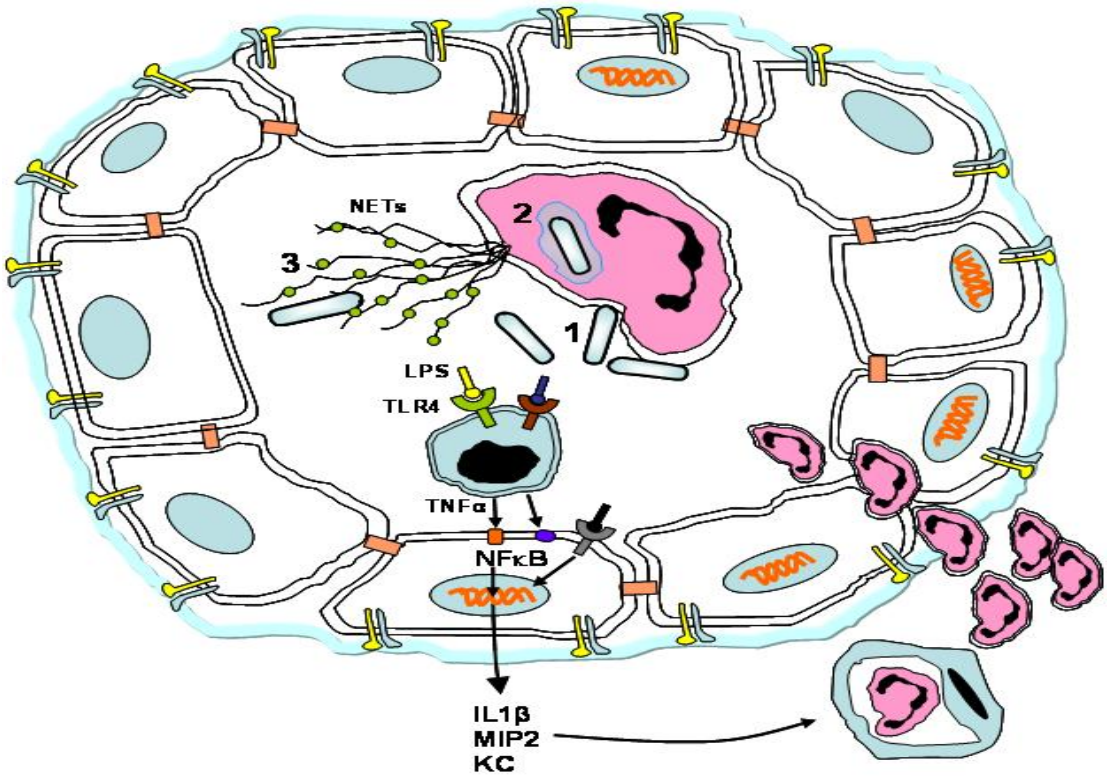
Bidirectional communication between immunologically competent cells and the brain. Upon release of TNF by macrophages, both humoral and neural signaling initiates brain responses that in turn exert feedback inhibition on macrophage activity.

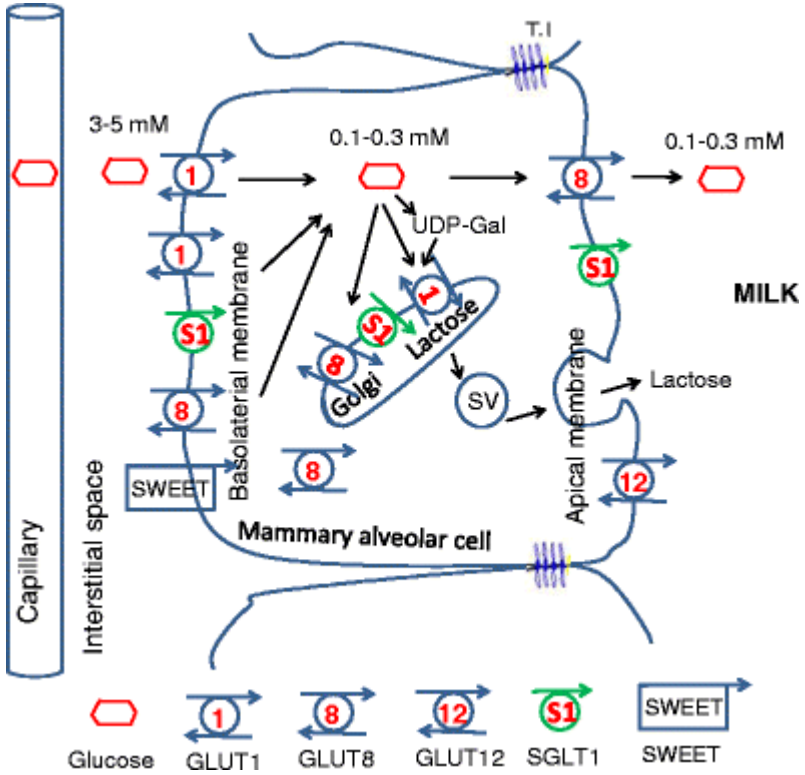


**Glucose fluxes during inflammation. The activated macrophage releases TNF and in so doing allocates glucose preferentially to itself. Glucose enters macrophages and the brain via GLUT-1, whereas it enters muscle cells via GLUT-4. Released TNF enhances GLUT-1 and decreases GLUT-4 transport. TNF, IL-1, and IL-6 released from the macrophage centrally initiate energy-saving sickness behavior.**

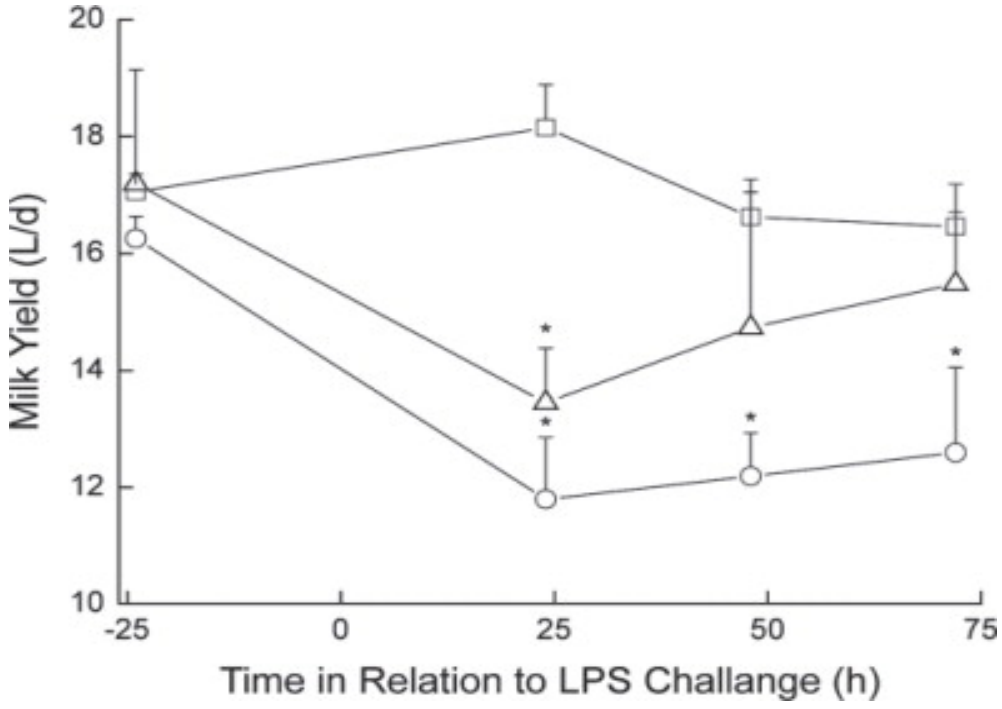



Major duct
Udder quarter
Gland udder cistern
Alveolus
Teat cistern
Bacterial invasion
Atrophy of alveolus
Neutrophil
Blood vessels
Damaged epithelial cell
NAGase/LDH
Anti-microbial agents
E. coli invading epithelial cell
Bacterium being engulfed by a somatic cell
S. aureus surviving in neutrophils
Epithelial cell
Bacterium

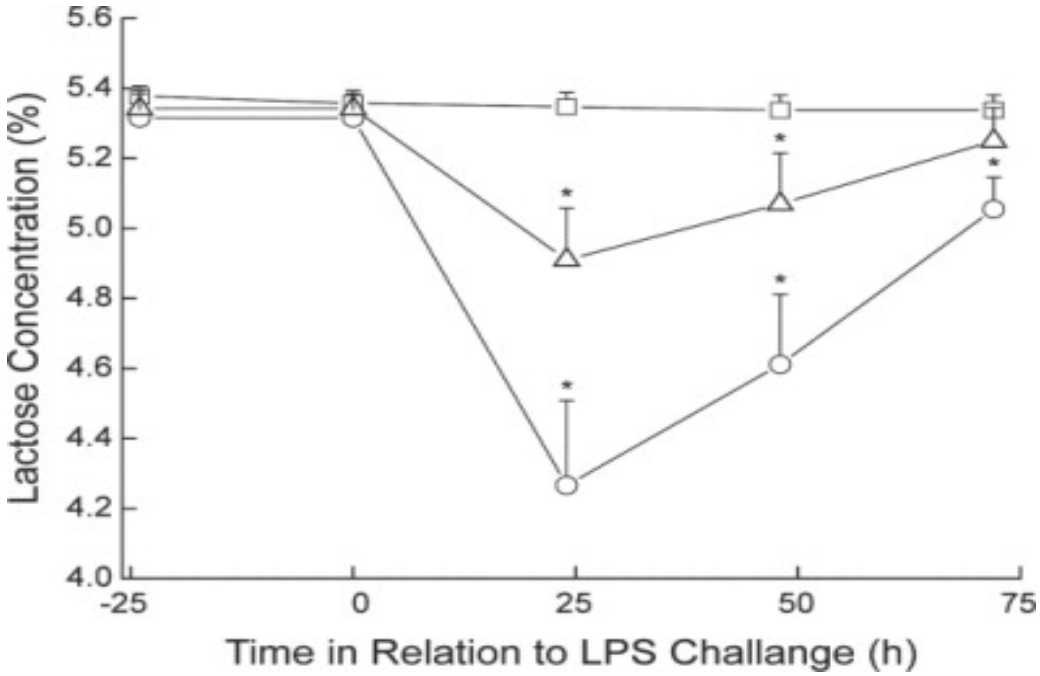

NETs
2
3
1
LPS
TLR4
TNFα
NFκB
IL1β
MIP2
KC


T.I
3-5 mM
0.1-0.3 mM
0.1-0.3 mM
UDP-Gal
MILK
Lactose
Golgi
SV
Lactose
Capillary
Interstitial space
Basolateral membrane
Apical membrane
SWEET
Mammary alveolar cell
Glucose
GLUT1
GLUT8
GLUT12
SGLT1
SWEET
SWEET

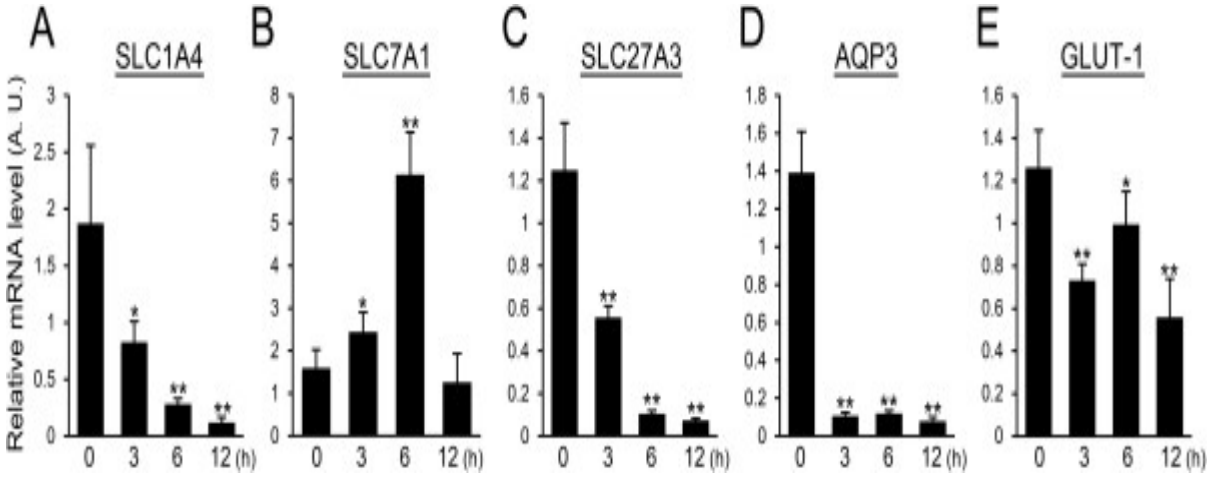
Effect of LPS on milk yield (L/d) in treated (circles), control-LPS (triangles), and control-control (squares) quarters. The results are presented as mean ± SD. Values marked by asterisk are significant at $P < 0.001$ or lower



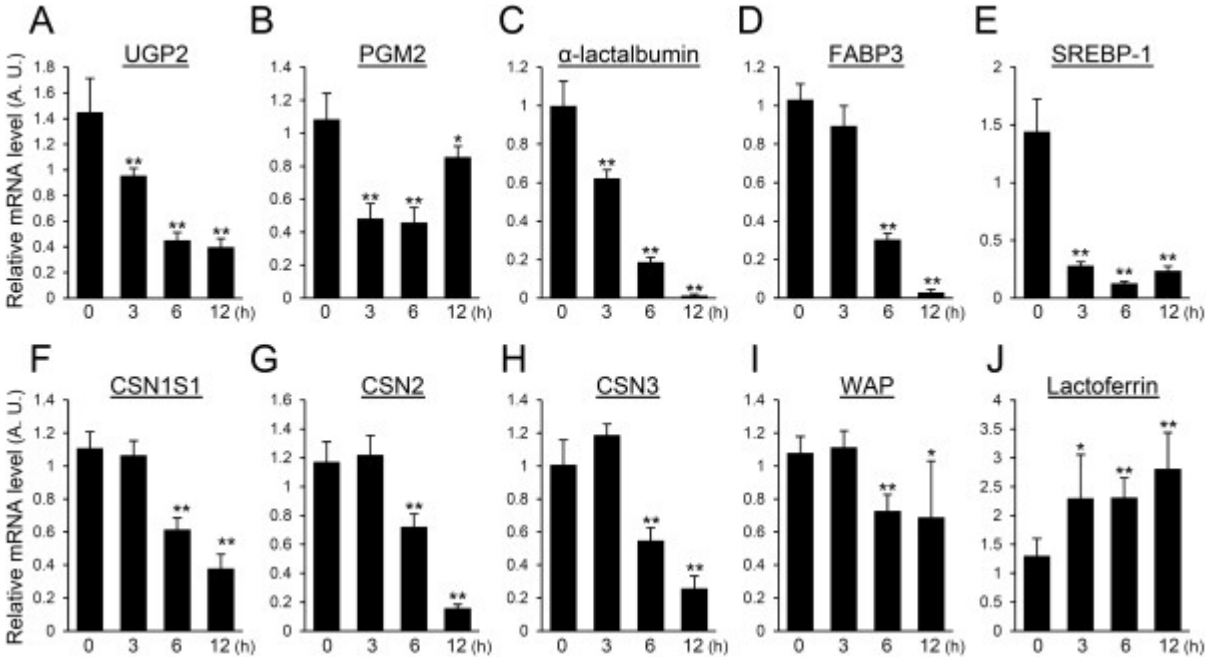
Effect of LPS on lactose (%) concentration in treated (circles), control-LPS (triangles), and control-control (squares) quarters. Values marked by asterisk are significant at $P < 0.001$ or lower.

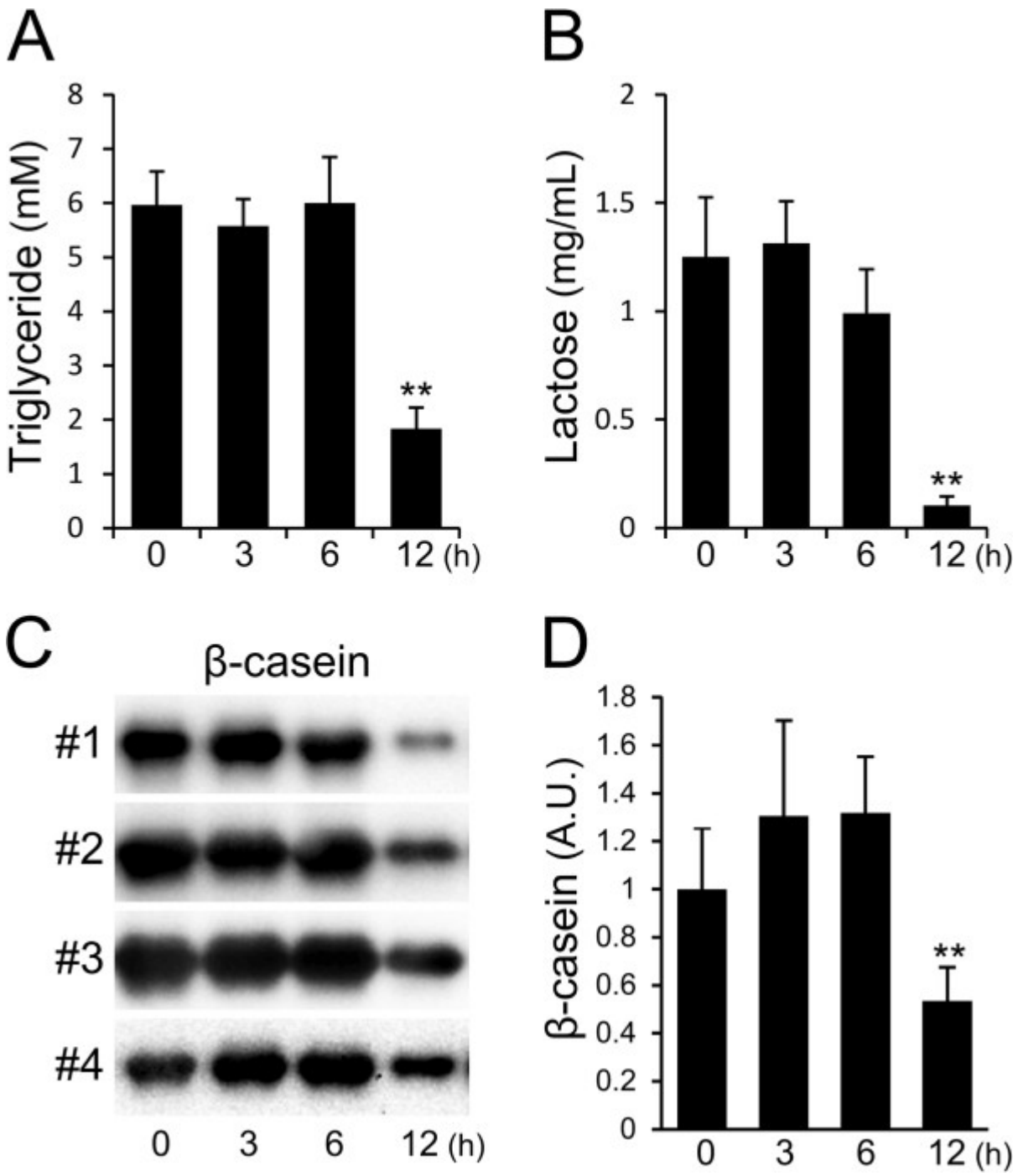


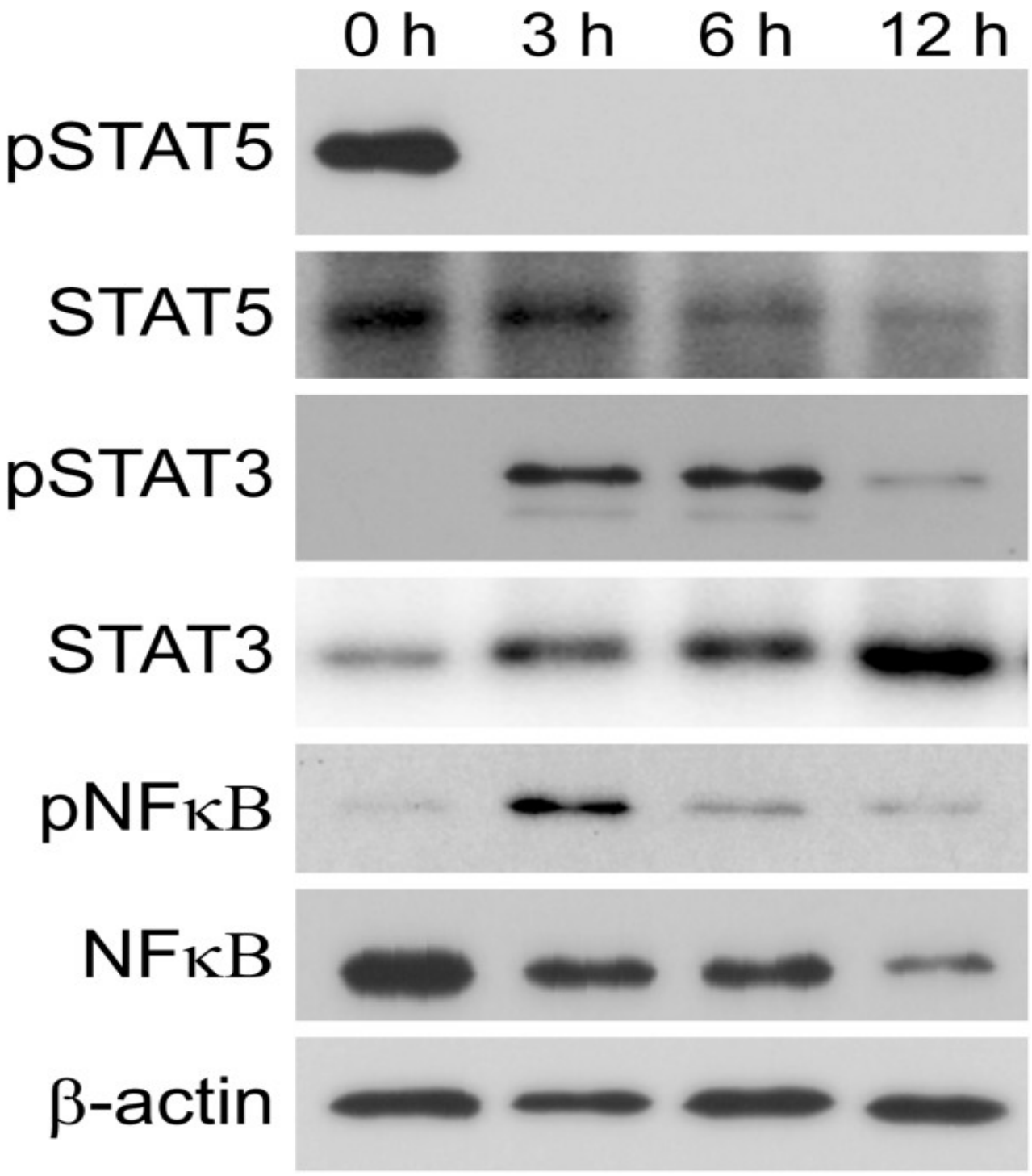
**Influence of LPS on the gene expression of transport proteins and channel proteins required to supply raw materials for milk.** Expression levels of SLC1A4 **(A)**, SLC7A1 **(B)**, SLC27A3 **(C)**, AQP3 **(D)**, and GLUT-1 **(E)** in mammary glands non-treated (0 h) and at 3, 6, and 12 h after LPS injection were quantified by real-time PCR. Data represent the mean (SD) ($n$ = 6). *, $p < 0.05$; **, $p < 0.005$ vs. 0 h.
Kobayashi *et al. Veterinary Research* 2013



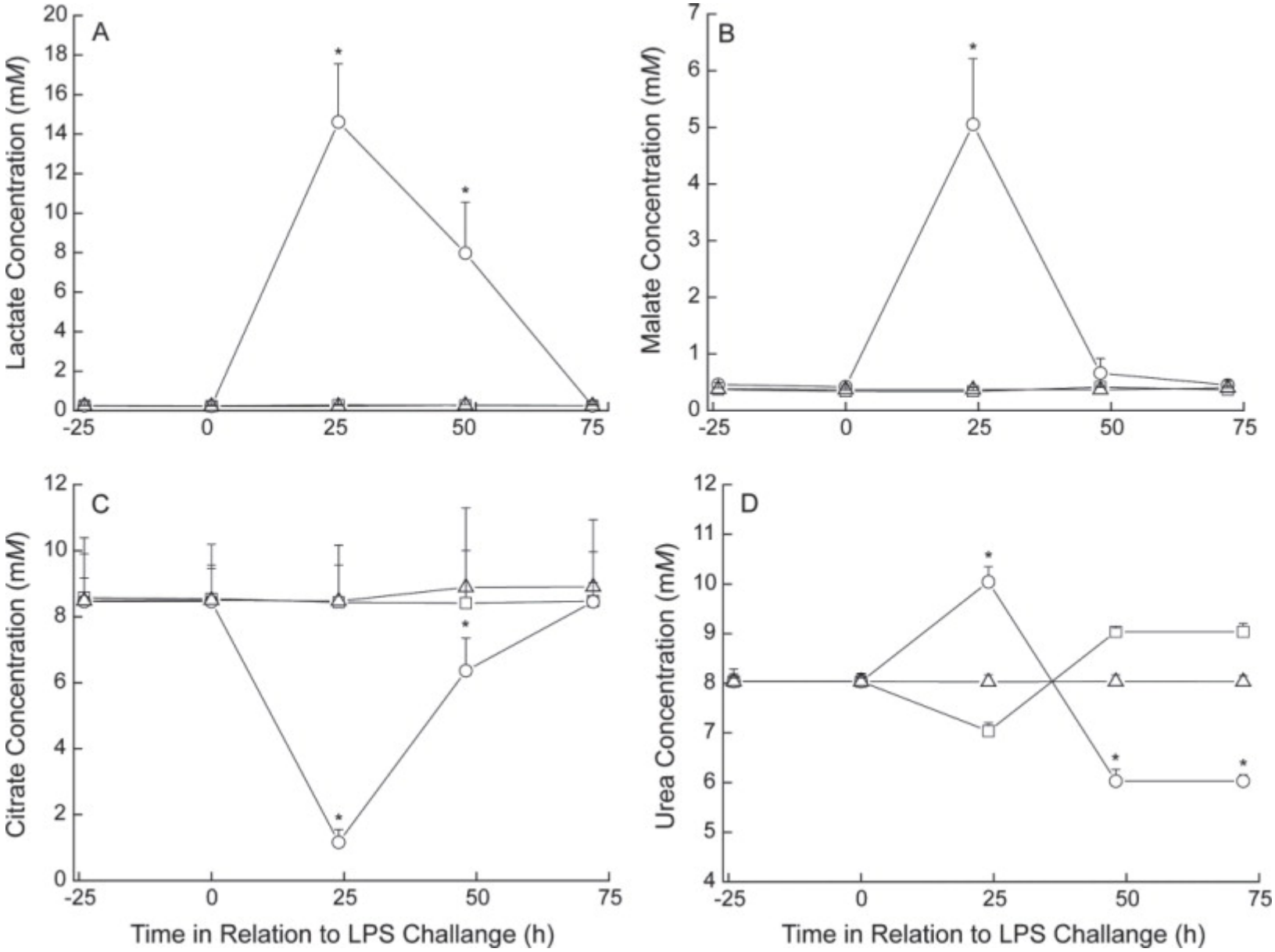
**Influence of LPS on the expression of genes related with milk component synthesis.**
Expression levels of UGP2 **(A)**, PGM2 **(B)**, α-lactalbumin **(C)**, FABP3 **(D)**, SREBP-1 **(E)**, CSN1S1 **(F)**, CSN2 **(G)**, CSN3 **(H)**, WAP **(I)**, and lactoferrin **(J)** in mammary glands non-treated (0 h) and at 3, 6, and 12 h after LPS injection were quantified by real-time PCR. Data represent mean (SD) ($n$ = 6). *, $p < 0.05$; **, $p < 0.005$ vs. 0 h.
Kobayashi *et al. Veterinary Research* 2013




A
Triglyceride (mM)
8
7
6
5
4
3
2
1
0
**
0
3
6
12 (h)
B
Lactose (mg/mL)
2
1.5
1
0.5
0
**
0
3
6
12 (h)
C
β-casein
#1
#2
#3
#4
0
3
6
12 (h)
D
β-casein (A.U.)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
**
0
3
6
12 (h)




**Influence of LPS on STAT3, STAT5, and NFκB phosphorylation in mammary glands.**


A
Lactate Concentration (mM)
20
18
16
14
12
10
8
6
4
2
0
-25
0
25
50
75
B
Malate Concentration (mM)
7
6
5
4
3
2
1
0
C
Citrate Concentration (mM)
12
10
8
6
4
2
0
Time in Relation to LPS Challange (h)
D
Urea Concentration (mM)
12
11
10
9
8
7
6
5
4
Time in Relation to LPS Challange (h)

Concentrations (mean ± SE) of lactate, malate, citrate, nitrite, lactoferrin, and albumin and activity of lactate dehydrogenase in milk of cows approaching natural involution (ANI) or forceful involution (AFI) before the induction of involution (milk cessation) and during the first 3 d after the induction of involution

| Treatment and time[2] | Lactate (μ*M*) | Malate (μ*M*) | Citrate (m*M*) | Citrate:(lactate + malate) | Nitrite (μ*M*) | Lactate dehydrogenase (U/mL) | Lactoferrin (μg/mL) | Albumin (μg/mL) |
|---|---|---|---|---|---|---|---|---|
| ANI | | | | | | | | |
| 0 d | 132 ± 22[c] | 294 ± 44[b] | 12.1 ± 1[a] | 28.4 ± 2.6[b] | 263 ± 41[b] | 242 ± 45[c] | 392 ± 52[bc] | 255 ± 39[d] |
| 1 d | 248 ± 40[b] | 356 ± 41[b] | 11.0 ± 1[a] | 18.2 ± 2.5[c] | 372 ± 31[ab] | 444 ± 58[b] | 610 ± 49[b] | 425 ± 49[c] |
| 2 d | 287 ± 52[b] | 306 ± 46[b] | 10.1 ± 1[a] | 17.0 ± 2.3[cb] | 541 ± 99[a] | 544 ± 99[b] | 990 ± 53[a] | 795 ± 51[b] |
| 3 d | 511 ± 28[a] | 864 ± 79[a] | 8.0 ± 2[b] | 5.8 ± 1.3[d] | 663 ± 65[a] | 1,699 ± 30[a] | 1,215 ± 63[a] | 1,110 ± 62[a] |
| AFI | | | | | | | | |
| 0 d | 115 ± 12[c] | 216 ± 32[c] | 13.1 ± 1[a] | 39.6 ± 3.3[a] | 225 ± 23[b] | 84 ± 6[d] | 179 ± 48[d] | 172 ± 39[d] |
| 1 d | 105 ± 8[c] | 297 ± 21[b] | 14.2 ± 1[a] | 35.3 ± 3.3[a] | 245 ± 27[b] | 113 ± 7[d] | 185 ± 38[d] | 174 ± 40[d] |
| 2 d | 147 ± 13[c] | 239 ± 15[b] | 14.1 ± 1[a] | 36.5 ± 2.6[a] | 233 ± 22[b] | 267 ± 6[c] | 187 ± 43[d] | 175 ± 41[d] |
| 3 d | 122 ± 9[c] | 255 ± 69[b] | 14.0 ± 1[a] | 37.1 ± 2.3[a] | 300 ± 31[ab] | 478 ± 38[b] | 182 ± 49[d] | 174 ± 51[d] |

Effect of subclinical mastitis by coagulase negative staphylococci (CNS) and Streptococci( Strep.) and previous clinical infection with Escherichia coli( Esch. coli) on milk yield, milk conductivity and somatic cell count (SCC) on the whole cow level

| Parameter | Uninfected | CNS | *Strep.* | *Esch. coli* | *P* [*F*] |
|---|---|---|---|---|---|
| *n* (cows) | 10 | 11 | 7 | 13 | |
| Lactation number | 4·78 ± 0·06 | 4·69 ± 0·07 | 4·61 ± 0·08 | 4·52 ± 0·05 | NS |
| Days in milk (d) | 222 ± 41 | 291 ± 39 | 280 ± 49 | 218 ± 37 | NS |
| Milk (L/d) | $39·1 \pm 2·8^{b}$ | $37·0 \pm 2·6^{b}$ | $34·4 \pm 3·3^{ab}$ | $31·3 \pm 2·5^{a}$ | 0·05 |
| Conductivity (units) | $9·7 \pm 0·51^{b}$ | $10·9 \pm 0·39^{ab}$ | $10·8 \pm 0·47^{ab}$ | $11·7 \pm 0·36^{a}$ | 0·025 |
| SCC ($\times 10^{3}$) | $236 \pm 30^{c}$ | $682 \pm 88^{b}$ | $1381 \pm 446^{ab}$ | $2203 \pm 577^{a}$ | 0·006 |

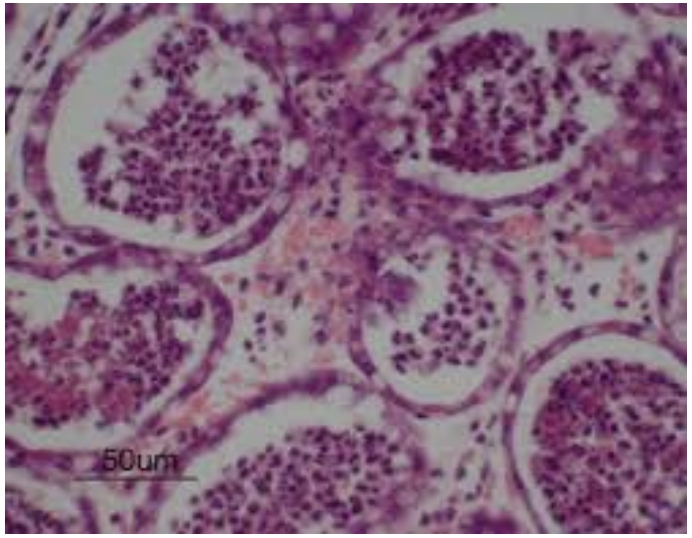
Effect of subclinical mastitis by coagulase negative staphylococci (CNS) and Streptococci( Strep.) and previous clinical infection with Escherichia coli( Esch. coli) on somatic cell count (SCC), gross milk composition (fat, protein and lactose), rennet clotting time (RCT), curd firmness (CF) and the concentrations of lactate, malate and citrate on a gland level

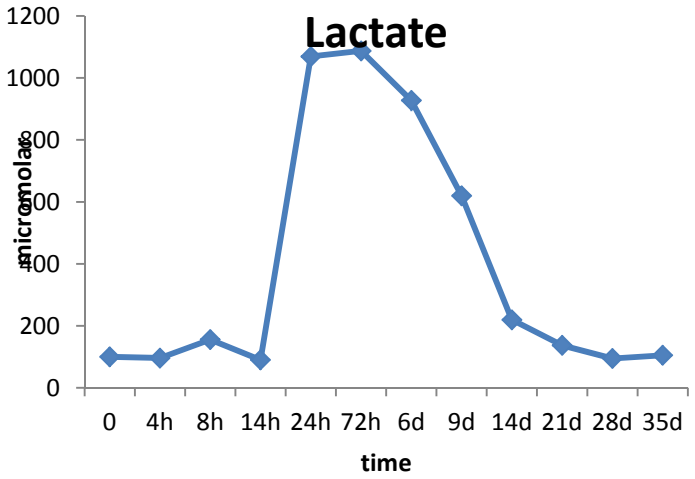
| Parameter | Uninfected | CNS | *Strep.* | *Esch. Coli* | $R^2$ | *P* [*F*] |
|---|---|---|---|---|---|---|
| *n* (cows)(glands) | 10 (40) | 11 (11) | 7 (7) | 13 (13) | | |
| SCC (cells/ ml × $10^3$) | $46 \pm 18^{b}$ | $971 \pm 177^{a}$ | $3272 \pm 1008^{a}$ | $3073 \pm 604^{a}$ | 0·441 | <0·001 |
| Log SCC | $4{\cdot}37 \pm 0{\cdot}2^{b}$ | $5{\cdot}92 \pm 0{\cdot}1^{a}$ | $6{\cdot}32 \pm 0{\cdot}2^{a}$ | $6{\cdot}37 \pm 0{\cdot}1^{a}$ | 0·801 | <0·001 |
| Fat (g/l) | $29{\cdot}6 \pm 7{\cdot}0$ | $30{\cdot}2 \pm 1{\cdot}7$ | $23{\cdot}6 \pm 2{\cdot}4$ | $25{\cdot}8 \pm 2{\cdot}9$ | 0·099 | NS |
| Protein (g/l) | $33{\cdot}7 \pm 0{\cdot}9$ | $34{\cdot}8 \pm 0{\cdot}1$ | $32{\cdot}3 \pm 0{\cdot}7$ | $35{\cdot}5 \pm 0{\cdot}1$ | 0·130 | NS |
| Lactose (g/l) | $50{\cdot}2 \pm 2{\cdot}4^{a}$ | $47{\cdot}0 \pm 2{\cdot}4^{ab}$ | $42{\cdot}6 \pm 2{\cdot}9^{ab}$ | $40{\cdot}5 \pm 2{\cdot}3^{b}$ | 0·229 | 0·033 |
| RCT (s) | $1277 \pm 112$ | $1886 \pm 286$ | $2133 \pm 468$ | $1752 \pm 236$ | 0·109 | NS |
| CF (V)† | $10{\cdot}0 \pm 1{\cdot}2^{a}$ | $5{\cdot}2 \pm 1{\cdot}2^{b}$ (9) | $4{\cdot}2 \pm 1{\cdot}5^{b}$ (4) | $1{\cdot}7 \pm 1{\cdot}1^{b}$ (6) | 0·417 | <0·001 |
| Lactic acid (μM) | $60{\cdot}2 \pm 38{\cdot}1^{c}$ | $246{\cdot}8 \pm 54{\cdot}1^{b}$ | $677{\cdot}1 \pm 114{\cdot}6^{a}$ | $616{\cdot}2 \pm 77{\cdot}8^{a}$ | 0·466 | <0·001 |
| Malic acid (μM) | $579{\cdot}6 \pm 33{\cdot}3$ | $521{\cdot}6 \pm 35{\cdot}6$ | $807{\cdot}0 \pm 192{\cdot}3$ | $1005{\cdot}6 \pm 141{\cdot}5$ | 0·152 | NS |
| Lactic + Malic (μM) | $639{\cdot}7 \pm 54{\cdot}2^{b}$ | $768{\cdot}4 \pm 75{\cdot}9^{b}$ | $1387{\cdot}3 \pm 275{\cdot}8^{ab}$ | $1621{\cdot}8 \pm 202{\cdot}4^{a}$ | 0·274 | 0·007 |
| Citric acid (mM) | $20{\cdot}9 \pm 1{\cdot}8$ | $19{\cdot}8 \pm 1{\cdot}7$ | $18{\cdot}1 \pm 2{\cdot}1$ | $18{\cdot}6 \pm 1{\cdot}5$ | 0·037 | NS |
| Citric/ Lactic + Malic | $34{\cdot}2 \pm 4{\cdot}2^{a}$ | $29{\cdot}2 \pm 4{\cdot}0^{ab}$ | $18{\cdot}8 \pm 3{\cdot}0^{b}$ | $18{\cdot}2 \pm 3{\cdot}7^{b}$ | 0·230 | 0·025 |
| Glucose (μM) | $253{\cdot}6 \pm 25{\cdot}2^{a}$ | $193{\cdot}9 \pm 25{\cdot}2^{ab}$ | $135{\cdot}4 \pm 30{\cdot}1^{b}$ | $108{\cdot}4 \pm 22{\cdot}1^{b}$ | 0·369 | <0·001 |
| Glu-6-p (μM) | $49{\cdot}5 \pm 7{\cdot}6^{b}$ | $45{\cdot}4 \pm 7{\cdot}2^{b}$ | $33{\cdot}0 \pm 8{\cdot}8^{a}$ | $44{\cdot}9 \pm 6{\cdot}6^{b}$ | 0·253 | <0·005 |
| Glu-6-p/Glu | $0{\cdot}22 \pm 0{\cdot}07^{b}$ | $0{\cdot}28 \pm 0{\cdot}07^{ab}$ | $0{\cdot}37 \pm 0{\cdot}08^{ab}$ | $0{\cdot}50 \pm 0{\cdot}06^{a}$ | 0·231 | 0·025 |

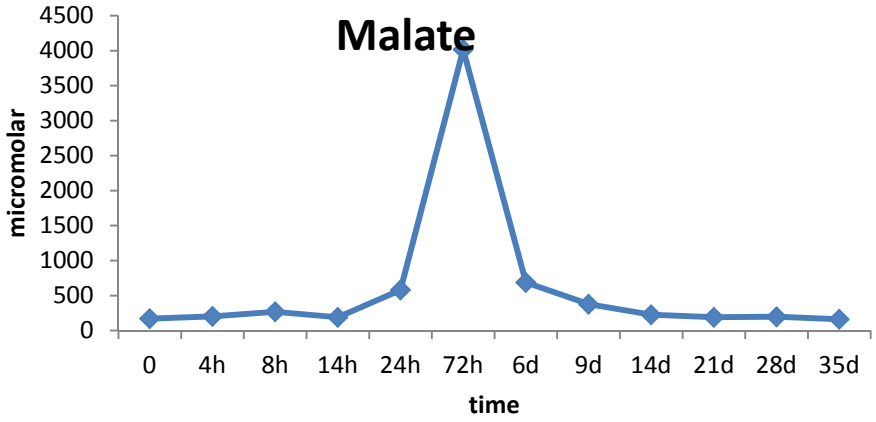
Linear correlations among glucose (Glu), lactose, glucose-6-phospate (Glu-6-p), citrate/lactate+malate (CA/LA+MA), Glu-6-p/Glu, log SCC and CF. All the data set on the gland level was applied

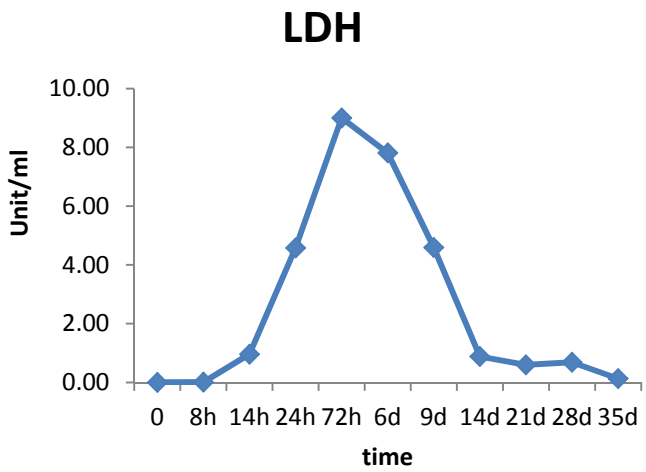
| Parameters | | | *r* | *P*[*r*] |
|---|---|---|---|---|
| Glucose | *v.* | CA/ LA + MA | 0·783 | <0·001 |
| CF | *v.* | Citric acid | 0·409 | 0·008 |
| CF | *v.* | CA/ LA + MA | 0·518 | <0·001 |
| CF | *v.* | Glucose | 0·630 | <0·001 |
| CF | *v.* | Log SCC | −0·546 | <0·001 |
| CF | *v.* | Glu-6-p | 0·395 | 0·011 |
| CF | *v.* | Glu-6-p/6 | −0·631 | 0·022 |
| Lactose | *v.* | Citric acid | 0·744 | <0·001 |
| Lactose | *v.* | CA/ LA + MA | 0·625 | <0·001 |
| Lactose | *v.* | Glucose | 0·706 | <0·001 |
| Lactose | *v.* | log SCC | −0·508 | 0·002 |
| Lactose | *v.* | Glu-6-p | −0·016 | NS |
| Lactose | *v.* | Glu-6-p/ Glu | −0·695 | <0·001 |

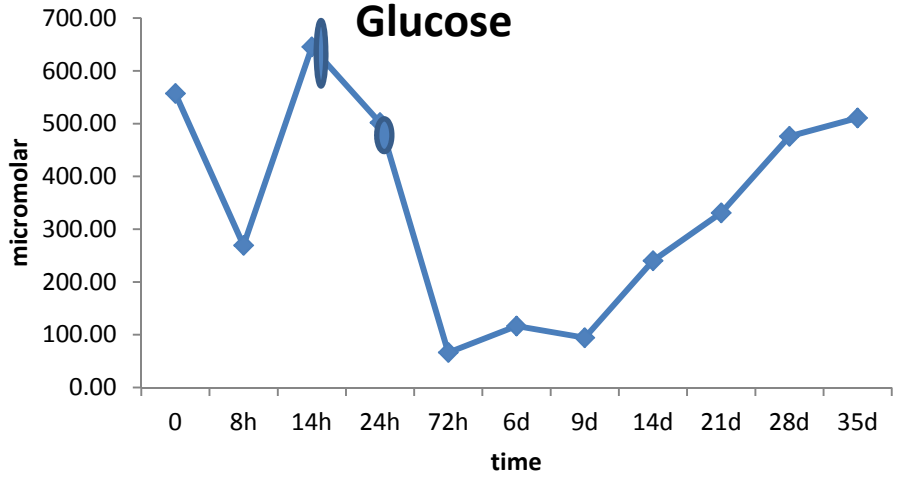
# Effect of intrammary infection with live strain of *E. coli* that cause transient acute mastitis



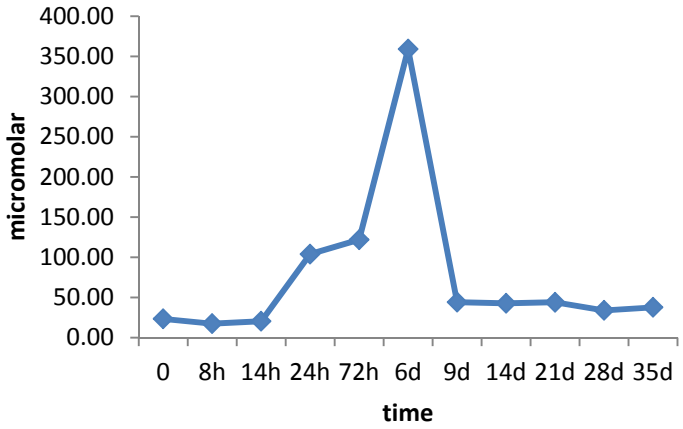

Lactate
micromolar
1200
1000
800
600
400
200
0
0 4h 8h 14h 24h 72h 6d 9d 14d 21d 28d 35d
time


Malate
micromolar
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0 4h 8h 14h 24h 72h 6d 9d 14d 21d 28d 35d
time

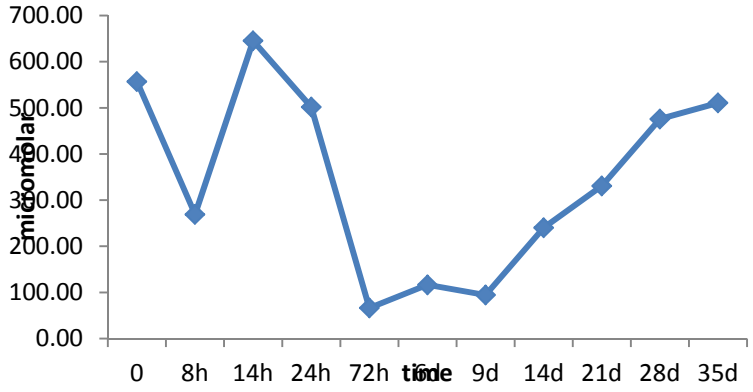

LDH
Unit/ml
10.00
8.00
6.00
4.00
2.00
0.00
0 8h 14h 24h 72h 6d 9d 14d 21d 28d 35d
time


Glucose
micromolar
700.00
600.00
500.00
400.00
300.00
200.00
100.00
0.00
0 8h 14h 24h 72h 6d 9d 14d 21d 28d 35d
time

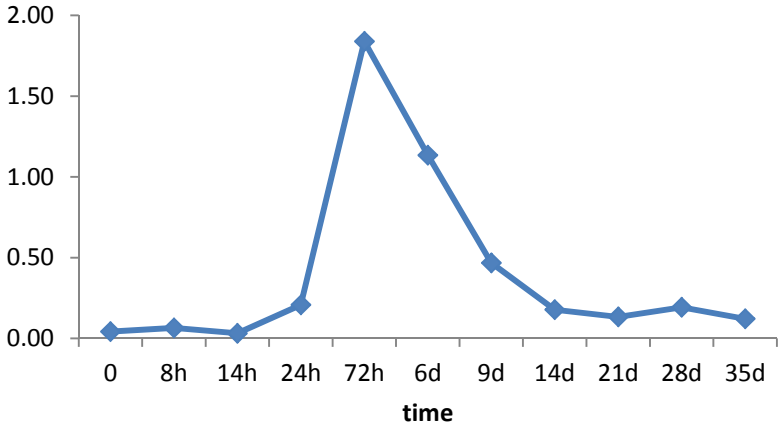
## Glucose-6-phosphate



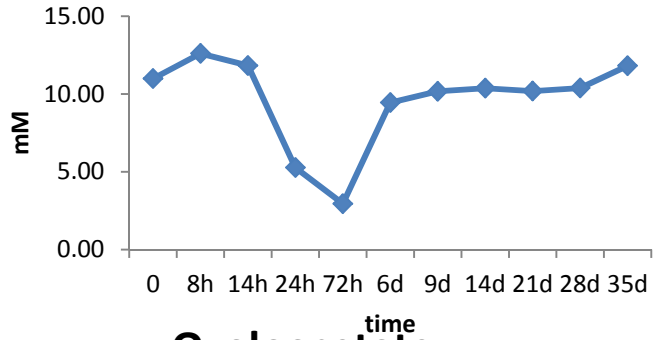

## Glucose



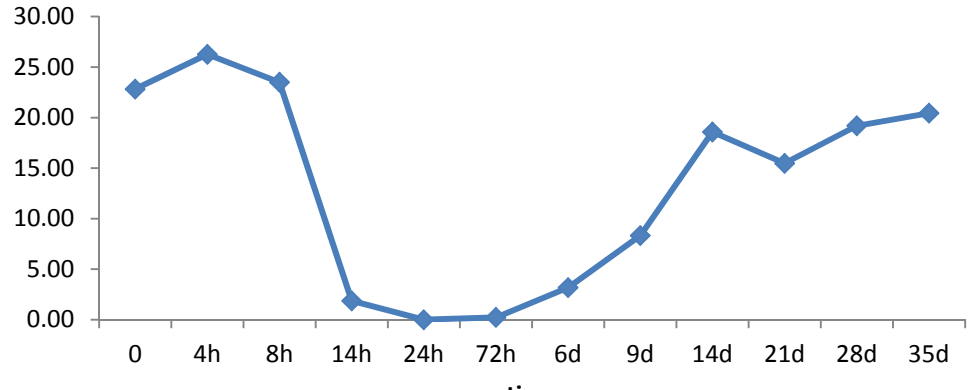

## Glu-6-p/glucose



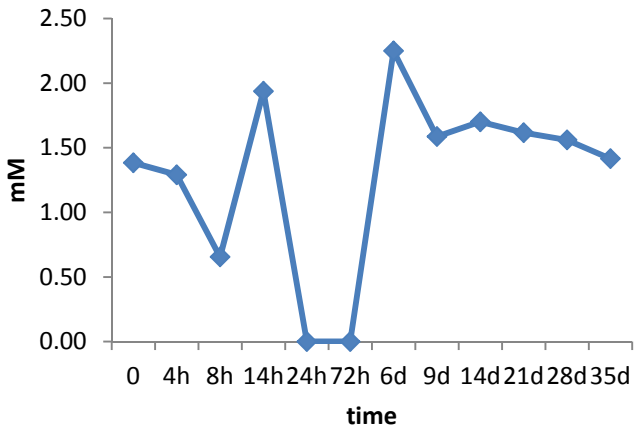
## Citrate



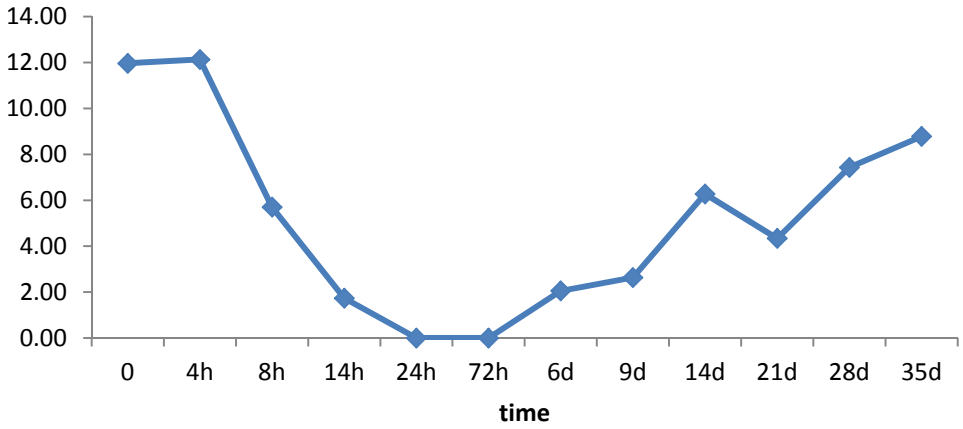

## Citrate/lact+mal



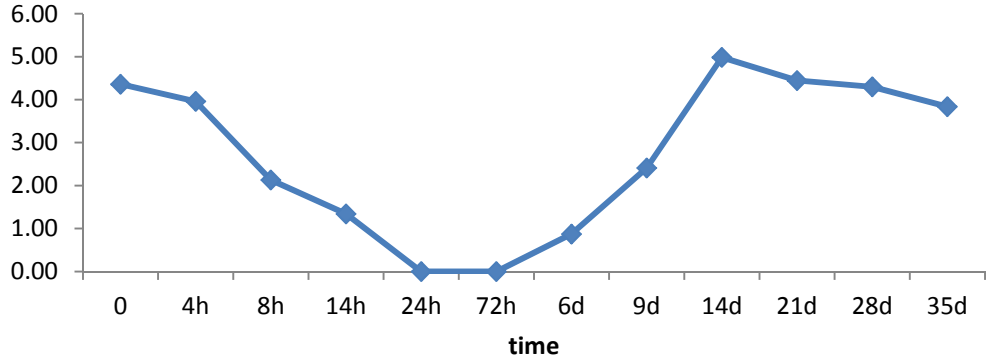

## Oxaloacetate

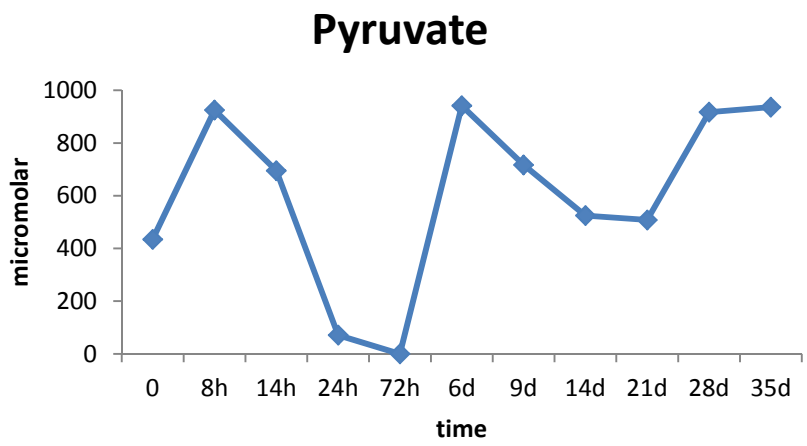


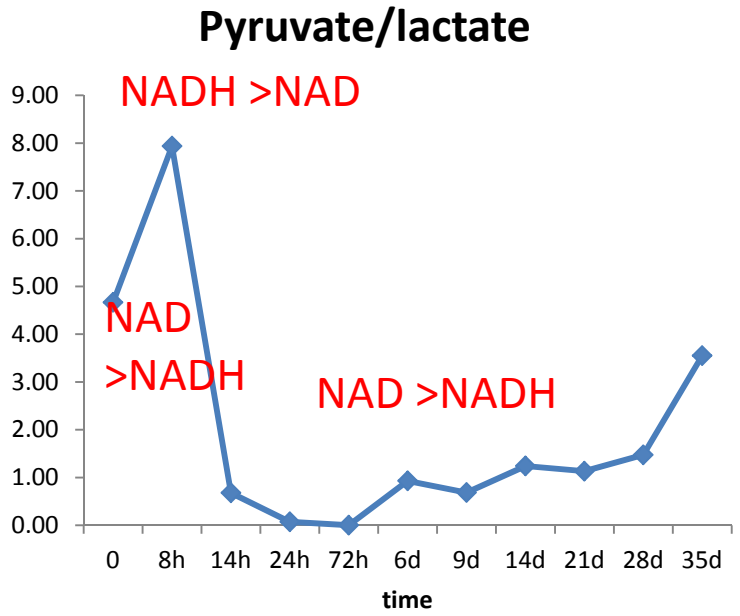

## Oxaloacetate/lactate

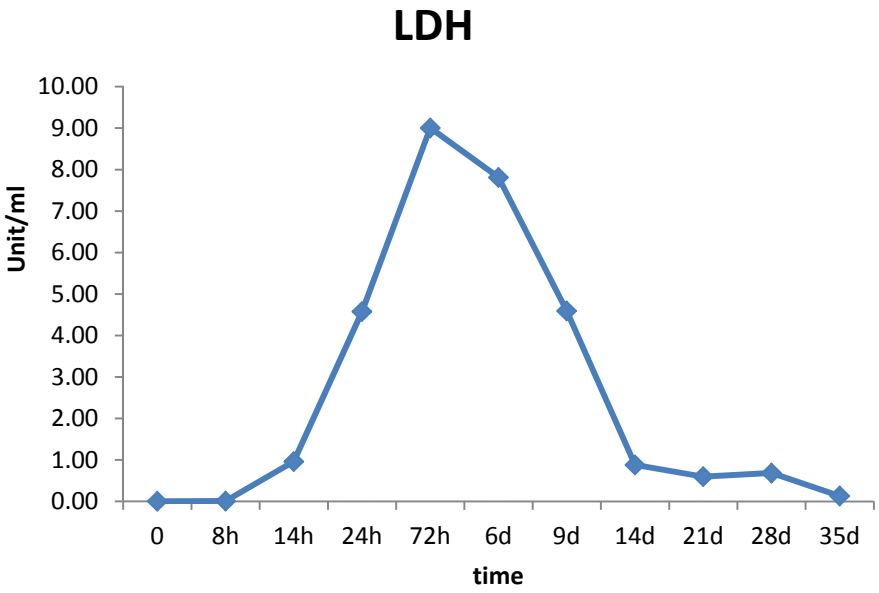


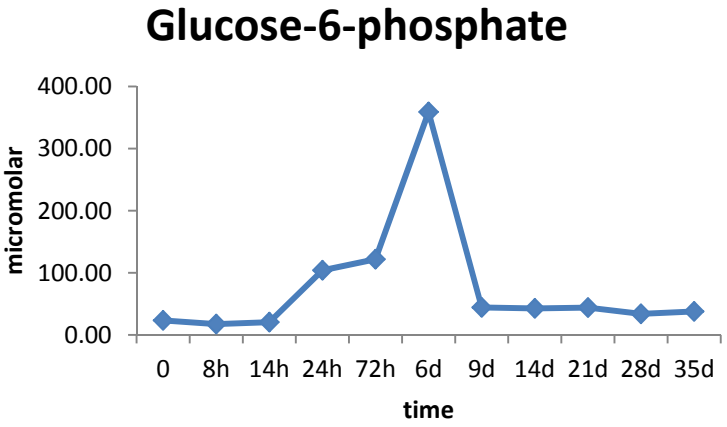

## Oxaloacetate/malate

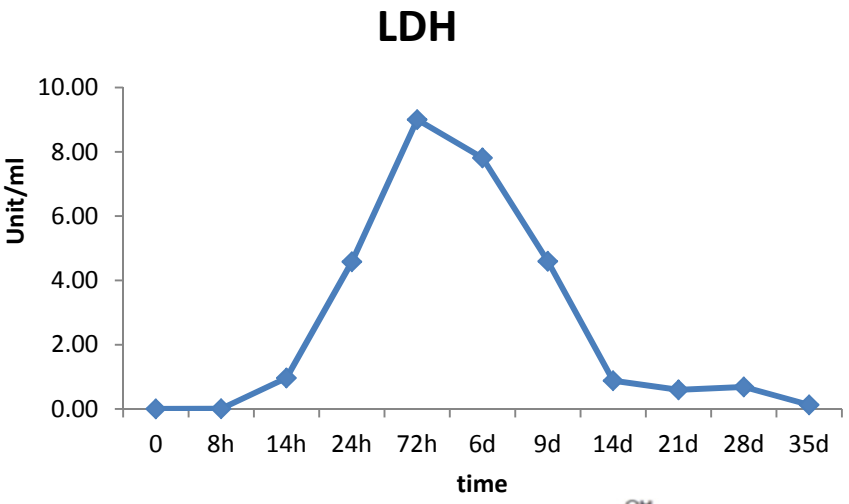


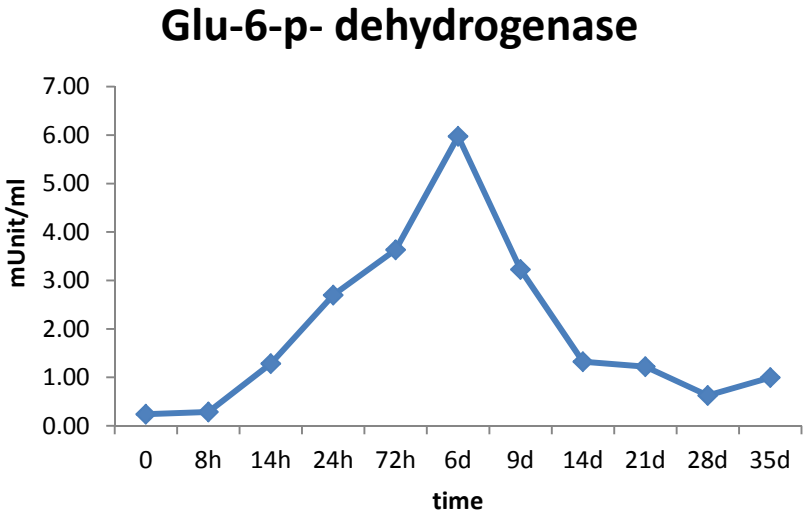

Pyruvate
micromolar
1000
800
600
400
200
0
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time

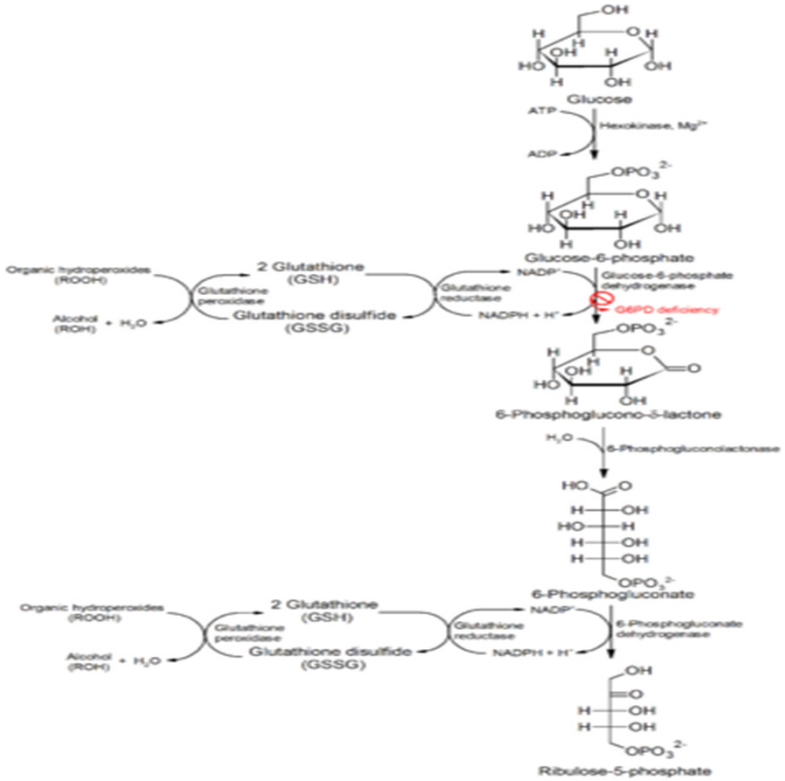

Pyruvate/lactate
NADH >NAD
NAD
>NADH
NAD >NADH
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time


LDH
Unit/ml
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time

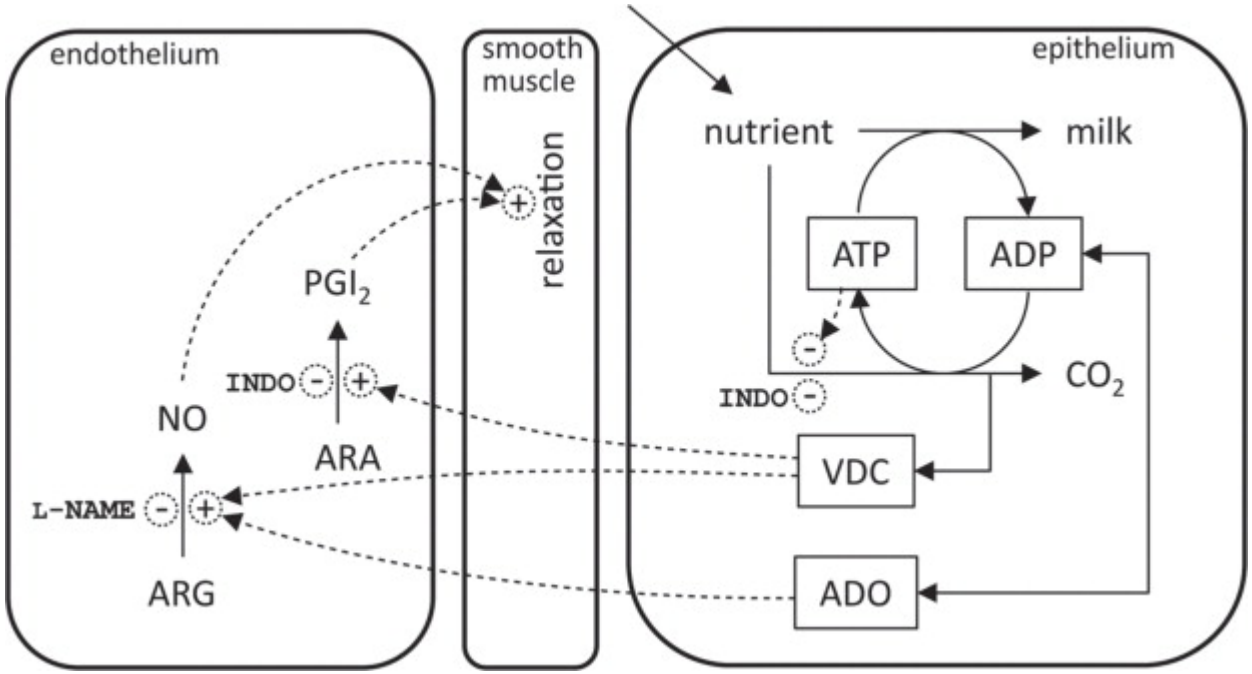

Glucose-6-phosphate
micromolar
400.00
300.00
200.00
100.00
0.00
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time

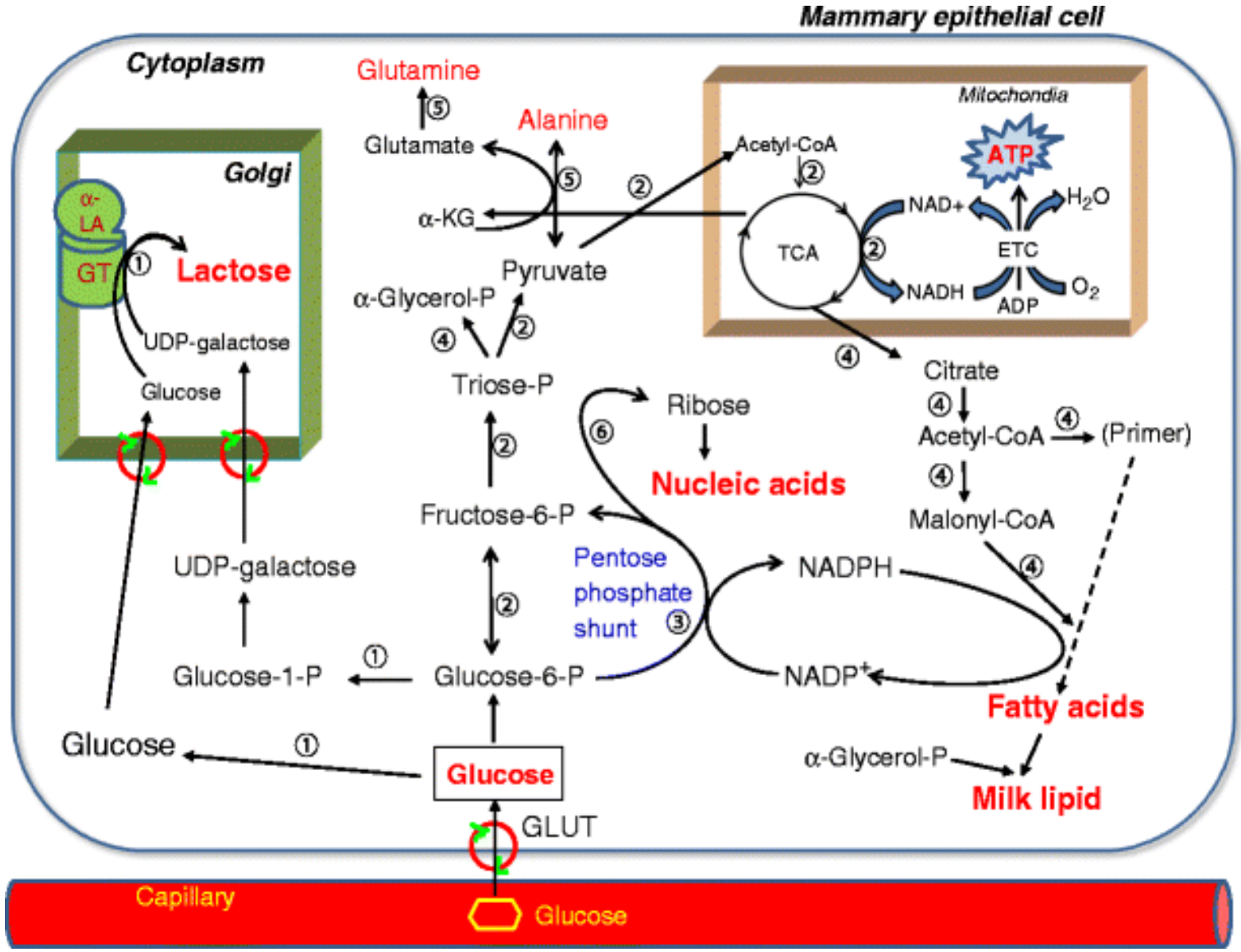

LDH
Unit/ml
10.00
8.00
6.00
4.00
2.00
0.00
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time


Glu-6-p- dehydrogenase
mUnit/ml
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
8h
14h
24h
72h
6d
9d
14d
21d
28d
35d
time


Glucose
ATP
ADP
Hexokinase, Mg2+
Glucose-6-phosphate
Glucose-6-phosphate dehydrogenase
G6PD deficiency
NADP+
NADPH + H+
2 Glutathione (GSH)
Glutathione disulfide (GSSG)
Glutathione peroxidase
Glutathione reductase
Organic hydroperoxides (ROOH)
Alcohol (ROH) + H2O
6-Phosphoglucono-δ-lactone
6-Phosphogluconolactonase
6-Phosphogluconate
6-Phosphogluconate dehydrogenase
Ribulose-5-phosphate

Proposed model of link between metabolic activity of mammary tissue and blood flow rate. Solid arrows represent mass flux and dashed arrows represent effector mechanisms; + and − represent activation and inhibition, respectively. ADO = adenosine, ARA = arachidonic acid, ARG = arginine, INDO = indomethacin, L-NAME = $N_{\omega}$-nitro-L-arginine methyl ester hydrochloride, NO = nitric oxide, $PGI_2$ = prostacyclin, VDC = vasodilatory compounds. **Cieslar et al., 2014, JDS**



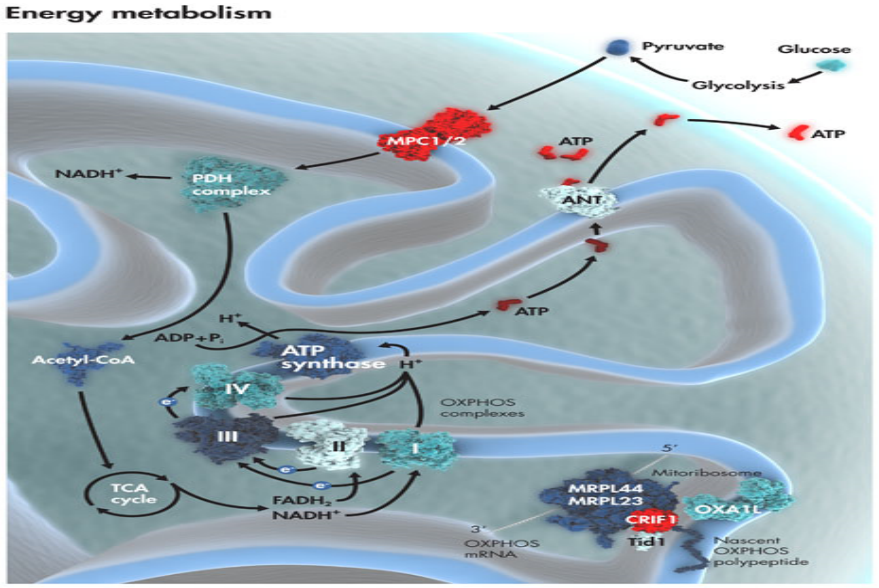

Mammary epithelial cell
Cytoplasm
Glutamine
Alanine
Glutamate
α-KG
Pyruvate
Mitochondia
Acetyl-CoA
ATP
NAD+
H2O
TCA
ETC
NADH
ADP
O2
Golgi
α-LA
GT
Lactose
UDP-galactose
Glucose
α-Glycerol-P
Triose-P
Ribose
Nucleic acids
Citrate
Acetyl-CoA
(Primer)
Malonyl-CoA
Fructose-6-P
Pentose phosphate shunt
NADPH
NADP+
Glucose-1-P
Glucose-6-P
Fatty acids
α-Glycerol-P
Milk lipid
Glucose
GLUT
Capillary
Glucose

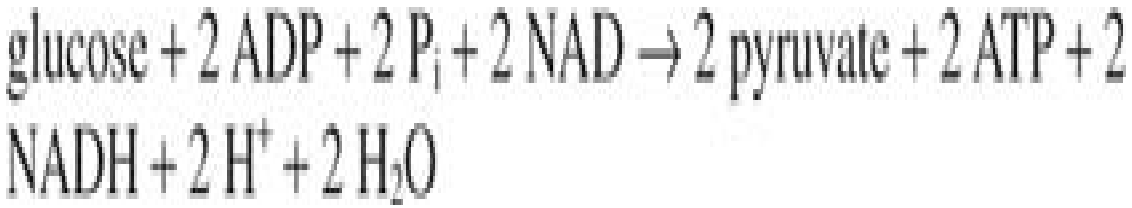
Blocking the pass of pyruvate to the mitochondria and increase in the activities of f cytosolic LDH and MDH explain the increase secretion of lactate and malate into milk. These changes are associated with dramatic reductions in NADH/NAD and ATP/ADP ratios


Pyruvate Lactate

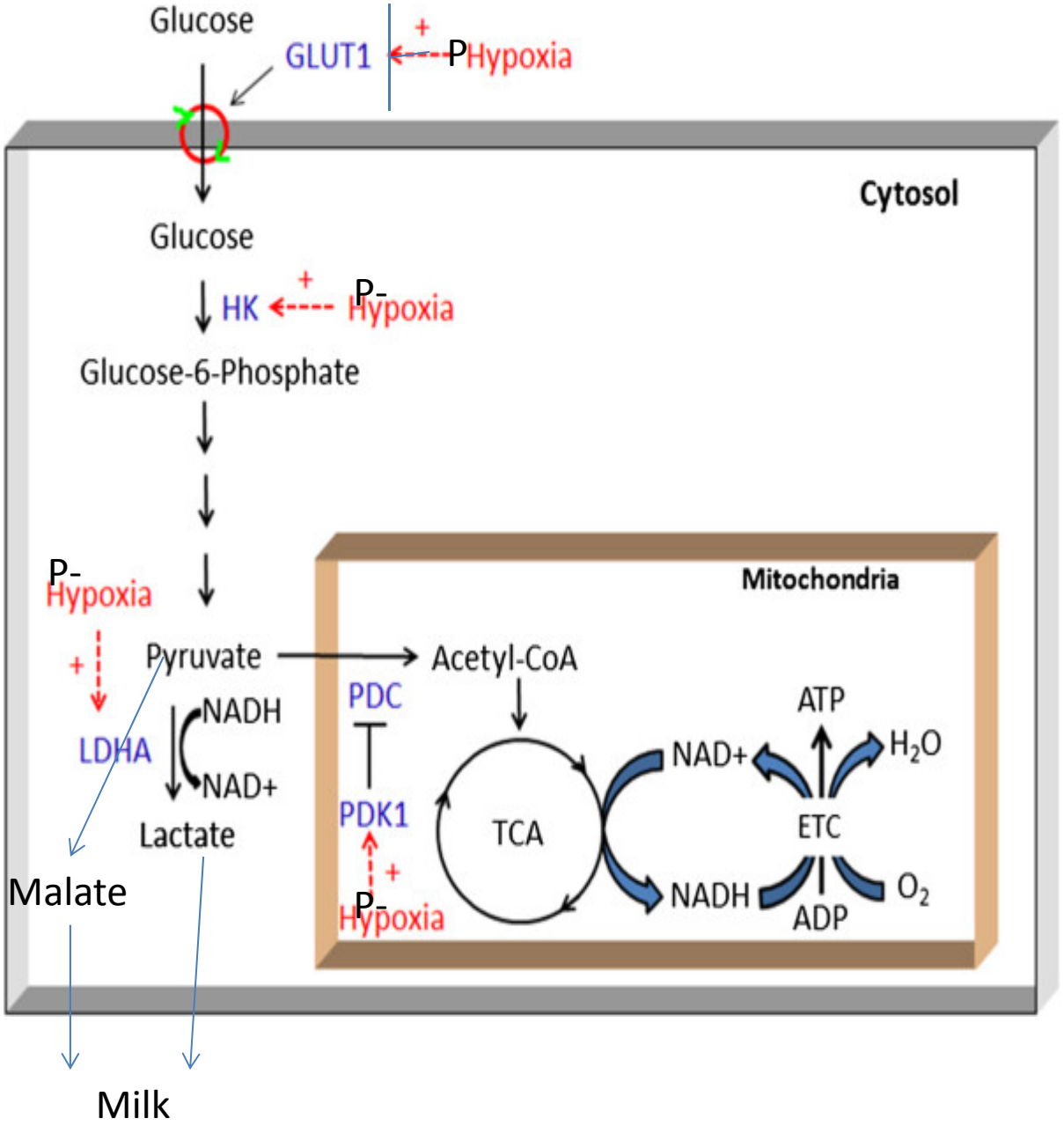
Two pyruvic acid + $CO_2$ + ATP —(Pyruvate carboxylase)→ Oxaloacetic acid + ADP

Oxaloacetic acid + NADH —(Malic dehydrogenase)→ Malic acid + $NAD^+$

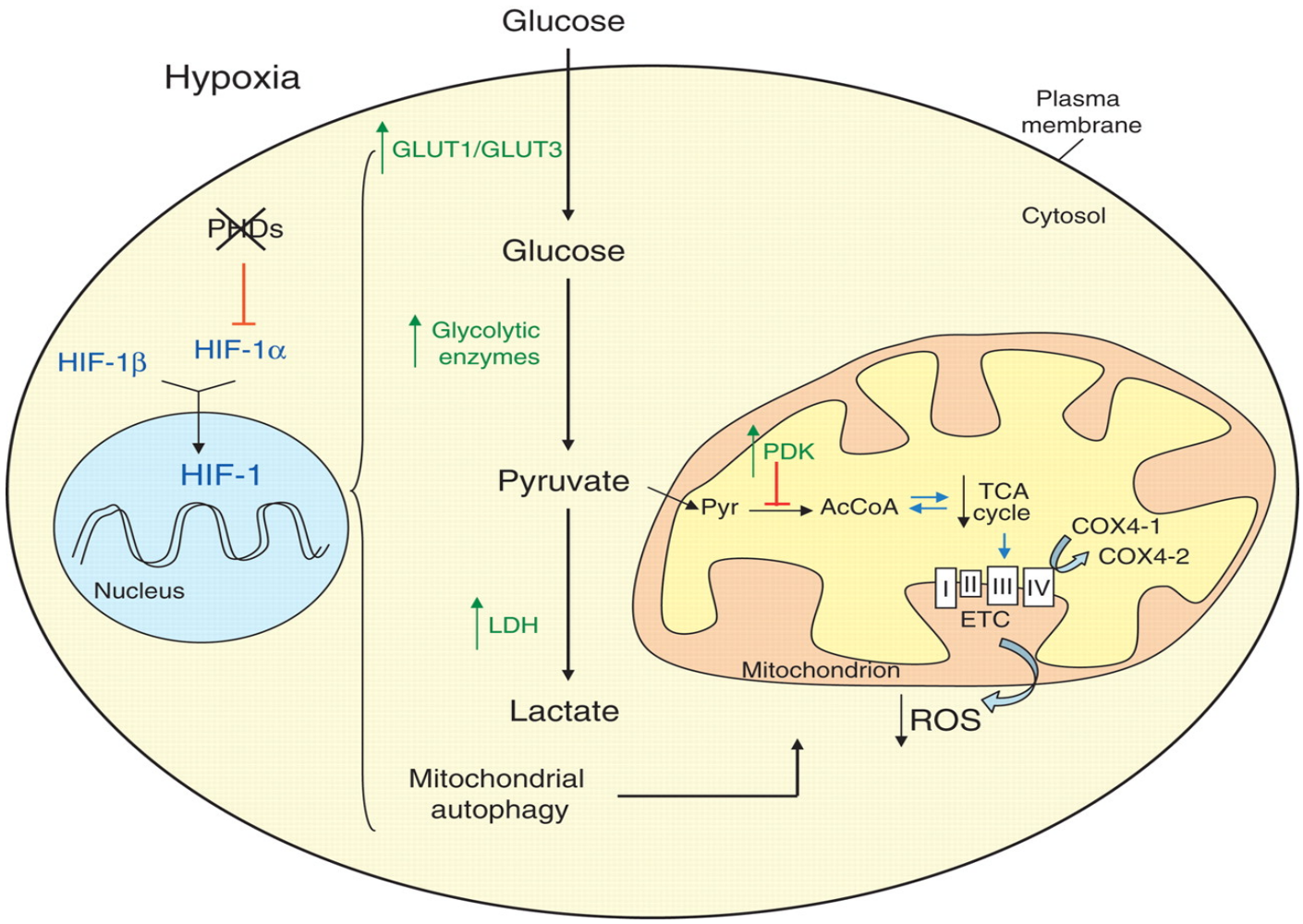





**Pseudohypoxia** refers to increased cytosolic ratio of free NADH to NAD in cells. Research has shown that declining levels of NAD+ in cancer cells and during aging cause pseudohypoxia, and that raising nuclear NAD+ in old mice reverses pseudohypoxia and metabolic dysfunction, thus reversing the aging process

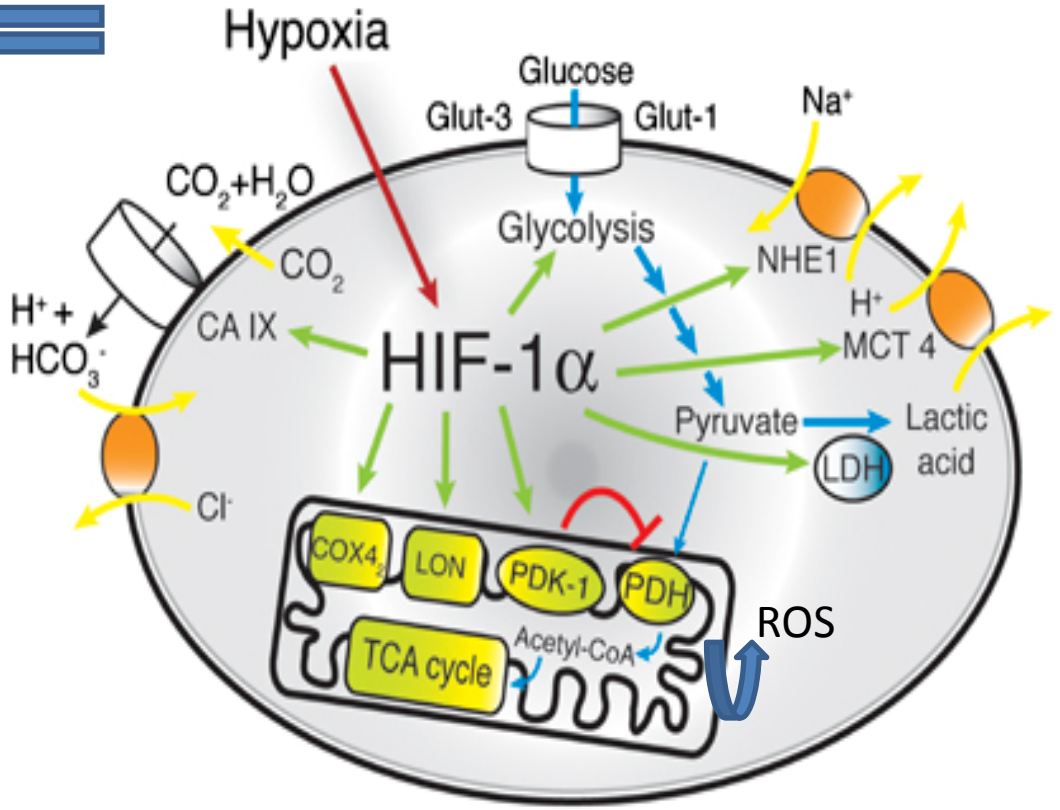

Glucose
GLUT1
+
P-Hypoxia
Cytosol
Glucose
HK
+
P-Hypoxia
Glucose-6-Phosphate
P-Hypoxia
+
Pyruvate
Acetyl-CoA
Mitochondria
LDHA
NADH
NAD+
Lactate
PDC
PDK1
+
P-Hypoxia
TCA
NAD+
ATP
H2O
ETC
NADH
ADP
O2
Malate
Milk

# Metabolic reprogramming induced by HIF-1.



# Metabolic reprogramming induced by HIF-1α.

Stress ⟶ inflammation



# Conclusions

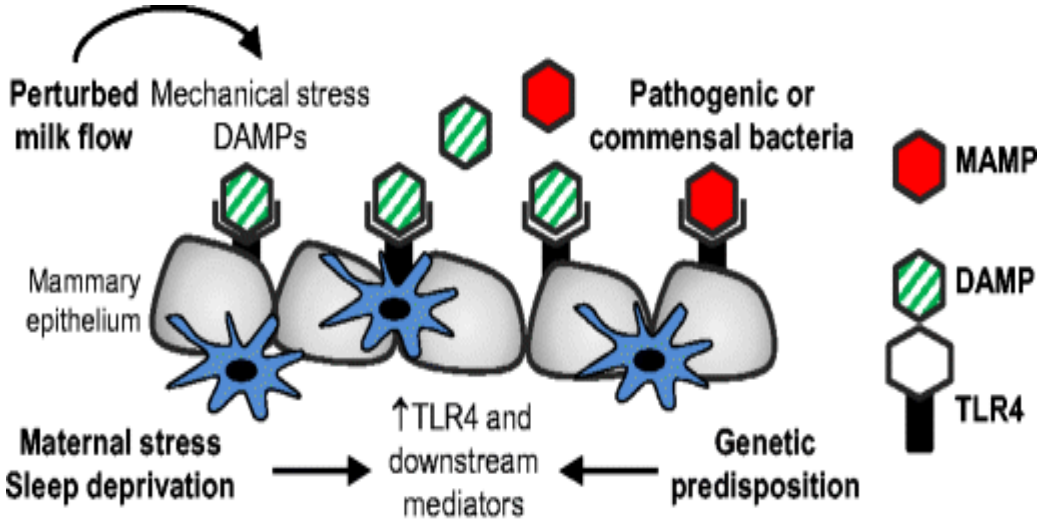
. The first response to stress is blocking the penetration of pyruvate into the mitochondria and consequently accumulation of pyruvate in the cytosol and conversion of the oxidative/reductive co-factor from high normal NAD/NADH ratio to high of NADH/NAD ratio in the cytosol and mitochondria

. High NADH/NAD ratio induce the conversion of the mammary gland epithelial cells metabolism into pseudohypoxic glycolysis (The Warburg effect). The increased formation of lactate and malate restore the oxidative/reductive co-factor into high NAD/NADH ratio and allow the resolution of the stress

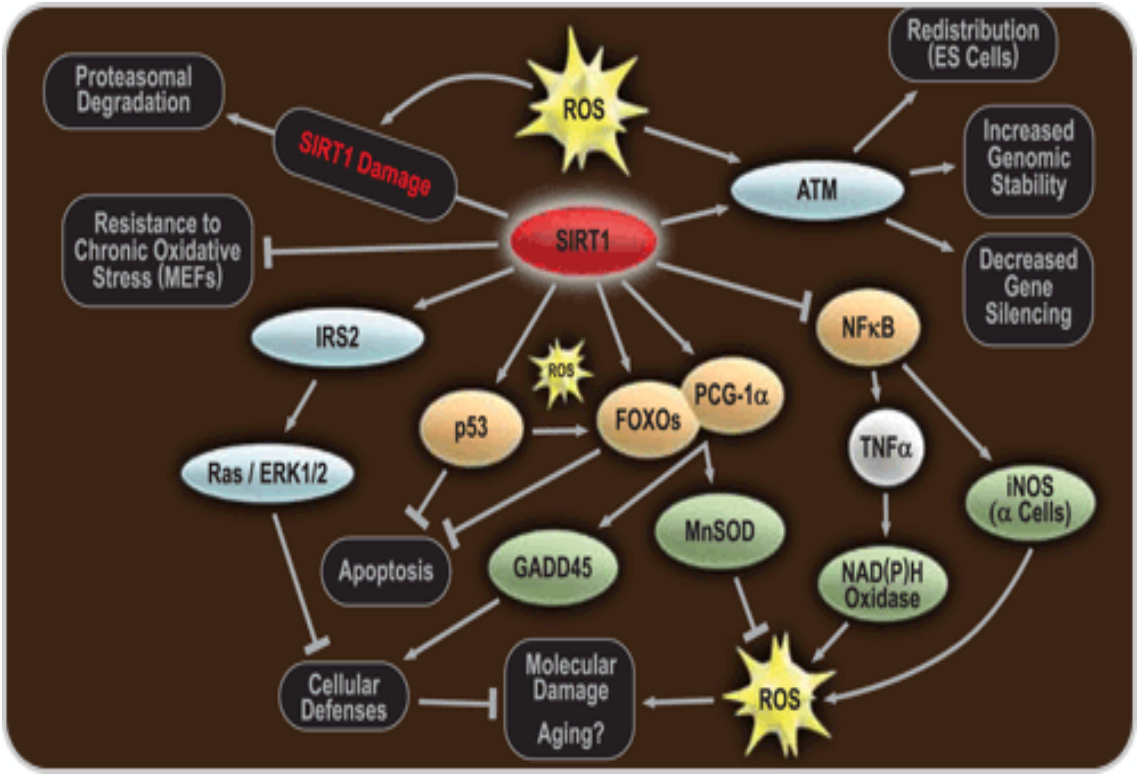
. The order of events can be revealed by the kinetics changes in the concentration of Glu, Glu-6-p, pyruvate, lactate, malate, citrate and oxaloacetate in milk and respective enzymes, LDH and Glu-6- p dehydrogenase

. The changes in the concentration of these metabolites is closely associated with milk production and quality (curdling)

TLR4-dependent inflammatory mediators affect lactation mastitis and milk supply. Perturbed milk flow, maternal stress, genetic predisposition and sleep deprivation can lead to accumulation of danger-associated molecular patterns (DAMPs) and heightened TLR4 signaling (or equivalent receptors) in the mammary gland, leading to increased susceptibility to mastitis and increased severity of the disease. Importantly, activation of NFkB could lead to partial mammary gland involution and may be responsible for the reduced milk supply associated with mastitis



Sirtuin enzymes are a conserved family of nictotinamide adenine dinucleotide (NAD)-dependent deacetylases and ADP-ribosyltransferases that regulate lifespan in lower organisms, and mediate responses to fasting and dietary restriction (DR) in mammals



# The Warburg effect is an essential homeostatic response for animal ability to survive under acute stress. Prevention of its development into chronic situations is important for maintaining health and productivity