Gluconeogenesis and Mammary Metabolism and their Links with Milk Production in Lactating Dairy Cows

Lemosquet, S.¹, Lapierre, H.², Galindo, C.E.² and Guinard-Flament, J.³, ¹INRA UMR1080, Dairy Production 35590 Saint Gilles, France, ²Agriculture and Agri-Food Canada, Sherbrooke, QC, J1M 1Z3, Canada, ³Agrocampus Ouest, UMR1080, dairy production 35062 Rennes, France; Sophie.Lemosquet@rennes.inra.fr

In dairy cows, whole (WB) glucose availability, measured as WB glucose rate of appearance (WBGRa), largely depends on gluconeogenesis or more precisely on WB glucose production, representing at least 62% of WBGRa. Glucose is mainly taken up by the mammary gland and plays an important role in regulating milk volume through lactose synthesis. However, the relationships between WBGRa, mammary glucose utilization, and milk volume are not clear. Neither lactose yield nor mammary glucose uptake represent a fixed proportion of WBGRa and varied between 39% to 59% and 59% to 84% of WBGRa, respectively, in mid lactating dairy cows. Increasing supply of glucogenic nutrients increased WBGRa indicating that glucose production responds to the push system. The apparent conversion of a single nutrient towards glucose production, however, does not appear to be constant. For example, a relative low apparent efficiency of conversion of propionate to glucose (30% to 40%) was observed when its infusion in the rumen increased its molar proportion above 17%. This variable efficiency of conversion of glucogenic nutrients to glucose could be explained if the demand for glucose utilisation is another driving force than the push system to regulate glucose production. Indeed, in cows receiving phlorizin which increased urinary glucose output, WBGRa increased probably to sustain milk yield that did not decrease. On the reverse, lactose yield and milk volume did not increase in parallel to WBGRa in response to increasing intestinal supply of non essential amino acids probably because mammary glucose uptake was not limited by WBGRa. In conclusion, glucose production and mammary glucose utilization for lactose synthesis could depend on the balance between glucogenic nutrient availability (push system) and mammary metabolic demand (pull system).
Gluconeogenesis and its Relation with Milk Production in Lactating Dairy Cows

S. Lemosquet\textsuperscript{1,2}, H. Lapierre\textsuperscript{3}, C.E. Galindo\textsuperscript{3}, J. Guinard-Flament\textsuperscript{2,1}

\textsuperscript{1}INRA, \textsuperscript{2}Agrocampus Ouest, \textsuperscript{3}UMR1080 Dairy Production, F-35590 Saint-Gilles, France

\textsuperscript{3}Agriculture and Agri-Food Canada, Sherbrooke, QC, Canada

Historically
- Glucose precursor of lactose (Grant, 1935, 1936)
- Glucose necessary for milk (Hardwich et al., 1961; Linzell, 1967)
- Lactose: osmotic nutrient (Linzell & Peaker, 1971)

A lot of glucose in dairy cows

(Galindo et al., 2011, in press)

Glucose mainly produced from liver gluconeogenesis

(Legg, 2005)

Liver 85%

Kidney 8-15%

VFA C3

Glucose

Lactose

Starch

Kidney

Liver

85%

Rumen

Intestine

Lactose 2.7 kg/d

Glucose 1.4 kg/d

Milk 31 kg/d

(Galindo et al., 2011, in press)

Glucose

Lactose

Milk volume

Historically
- Glucose precursor of lactose (Grant, 1935)
- Glucose necessary for milk (Hardwich et al., 1961; Linzell, 1967)
- Lactose: osmotic nutrient (Linzell & Peaker, 1971)
Historically first correlations between Energy supply and Whole Body Glucose flux \( \rightarrow \) Milk

\[
\text{Glucose (g/min) } = 0.013 + 0.029 \text{ ME (MJ/d)}
\]

\[
R = 0.90, P < 0.0001, n = 12
\]

\[
\text{Milk Yield (kg/d) } = 0.52 + 0.029 \text{ Glucose}
\]

\[
R = 0.74, P < 0.005, n = 12
\]

(Horsfield et al. 1974)

Future Feeding Systems based on Nutrient Fluxes?

\begin{itemize}
  \item Prediction of Fluxes …
  \item Gluconeogenesis precursors & Starch
  \item Gluconeogenesis flux
  \item Lactose
  \item Milk volume composition
\end{itemize}

(Nozière et al., 2010)

However correlations does not mean driving force …

Questions

Is gluconeogenesis the driving force or the reverse?

• Energy intake
• Nature of nutrients

Push factors

• Uptake
• Lactose

Pull factors

• Beginning of lactation
• Phlorizin
• Milking
Questions

1. How gluconeogenesis varies in response
   a. Push factors

2. Relations gluconeogenesis ↔ lactose
   a. Push factors
   b. Pull factors
   c. Push x Pull

Material & Methods

Two techniques to measure whole body glucose flux:
1. Glucose Rate of appearance (Ra)

\[ \text{Ra} \equiv \text{Ra} = \frac{\text{Lactose}}{\text{CO}_2, \text{ATP}} \]

Intermediary metabolism

Gluconeogenesis → Glycogen

Absorption → Lactose

Measured: Isotope dilution

Results - Part 1

Energy supply ⇔ Whole Body Glucose Ra

Net release of glucose (● glucose equivalent) in growing and lactating cattle (n = 311)

\[ y = 3.99e + 102 \quad R^2 = 0.89 \]

(Reynolds, 2006)
Nature of nutrients ⇒ Whole Body Glucose Ra

Dairy Production unit
- Digestive infusions
- 1 in supplement
- 3 in energy substitution

Mid lactation

A grass silage-based diet
(almost no intestinal starch)

Ra : [6,6-2H2]glucose
(0.7 µM/kg • 2 h⁻¹)

Results - Part 1

1- Glucose rate of appearance increased in response to intestinal glucose or glucogenic precursors

Ra (mmol C/h)

Ctrl
GLC iso E
C3 iso E
C3 suppl. E
NEAA
Casein
Casein+C3

(GLC+C3+AA (diet+infusion))

Results - Part 1

Different efficiencies of Ra increases depending on the nature nutrients

Ra (mmol C/h)

Ctrl, GLC, C3, NEAA

(a, b, c; P < 0.05)

(Lemosquet et al., 2009a)

Results - Part 1

Increasing total AA supply in ruminants increased whole body glucose rate of appearance

Whole Body Glucose Ra

Ra (g/dk kg BW⁻¹)

PDI (g/dk kg BW⁻¹)

Data corrected from experiment effect

(Lemosquet et al., 2007)

Results - Part 1

1- How whole body glucose rate of appearance varies in response to push factors?

- It increased in response to increased nutrient supplies (energy or nature of energy)
- However still variability to explore to predict glucose fluxes

Results - Part 2

2 – Relations between Lactose and Whole Body glucose Ra?

a. In response to dietary push factors, is the increased Ra the driving force of increased lactose?
When manipulating nature of nutrients in mid lactating dairy cows, no relationship? (a, b, c; P < 0.05) (Lemosquet et al., 2009a)

Propionate increased Ra not lactose

Results - Part 2a

Increased intestinal AA through casein infusion increased Ra and lactose

Results - Part 2a

In mid lactating cows, Ra per se did not always drive lactose production

Results - Part 2a

Yes! Is mammary glucose metabolism another key factor of lactose regulation?
- mammary glucose uptake
- mammary glucose partition
Propionate changed the partition of glucose utilization in the mammary gland

Casein changed the partition of glucose utilization in the mammary gland

Intestinal AA supplies increased lactose yield but not mammary glucose uptake

Intestinal AA supplies increased lactose yield but not mammary glucose uptake

With an increased metabolizable protein supply, gluconeogenesis is not the driving force of the increased milk yield

2a- In response to dietary push factors

Yes!

In mid lactating cows,
- Ra is not the driving force of lactose
- Changes in mammary glucose uptake and in glucose partition in the mammary gland also explain lactose

2 – Relations between Lactose and Whole Body glucose Ra?

b. In response to pull factors that increase Mammary glucose demand?
- Ra
- Glucose utilisation
**Increased whole body glucose demand through phlorizin increased gluconeogenesis from propionate**

- In steers: (long term: 19 d)

<table>
<thead>
<tr>
<th>Phlorizin, g/d</th>
<th>0</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLC urine excretion, mmol C/h</td>
<td>287</td>
<td></td>
</tr>
<tr>
<td>GLC Ra, mmol C/h</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>% Propionate → GLC, %</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

(Veenhuizen et al., 1988)

**Increased whole body glucose demand through increased glucose urinary loss increased gluconeogenesis and maintained milk yield**

- In dairy cows: (short term – 48 h)

<table>
<thead>
<tr>
<th>Phlorizin, g/d</th>
<th>0</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLC urine excretion, mmol C/h</td>
<td>0</td>
<td>312</td>
<td>468</td>
</tr>
<tr>
<td>DMI, kg/d of DM</td>
<td>17.4</td>
<td>17.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Milk yield, kg/d</td>
<td>30.2</td>
<td>29.8</td>
<td>29.6</td>
</tr>
<tr>
<td>Milk lactose, mmol C/h</td>
<td>2082</td>
<td>2054</td>
<td>2012</td>
</tr>
</tbody>
</table>

(Amaral-Phillips et al., 1993)

**In the beginning of lactation, parallel increases between lactose and post liver glucose fluxes**

![Graph](Reynolds et al., 2003)

**In the beginning of lactation, mammary glucose uptake was also a key point of regulation**

![Graph](Reynolds et al., 2003)

**At beginning of lactation, Ra efficiency increased**

- constant DMI

![Graph](Bennink et al., 1972)
At the beginning of lactation, milk yield and Ra increases did not parallel constant DMI (Bennink et al., 1972).

**Results - Part 2b**

2b- In response to pull factors?

- Mammary glucose demand could be a driving force of gluconeogenesis
- To respond to an important increase in glucose demand:
  - Gluconeogenesis efficiency increases
  - Utilisation of glucose is also regulated

Feed restriction x once daily milking

Mammary GLC uptake (mmol c/h)

Feed restriction 98% → 70% Milking 2/d → 1/d

Hypothesis: Feed restriction produced enough glucose for mammary uptake during 1/d milking

(Guinard-Flament et al., 2007)

A decreased portal flux decreased mammary glucose uptake independently of mammary demand

Mammary GLC uptake (mmol c/h)

Feed restriction 98% → 70% Milking 2/d → 1/d

Hyp. Rejected: additive response Feed restriction x Milking

Mammary GLC uptake (mmol c/h)

1/d Milking 98% Feed → 70% Feed

1051 → 23% 810

(Guinard-Flament et al., 2007)
In conclusions

1. Gluconeogenesis increases in response to nutrients
2. Not a positive linear relation

In response to push & pull factors
Milk also depends on:
- Mammary glucose uptake
- Glucose partition

1. Gluconeogenesis is not the driving force to increase milk yield:
   Except with Feeding restriction
2. Could Mammary Glucose demand be a driving force?
   For a part

Increase in gluconeogenesis is a NECESSARY CONDITION to increase milk yield not a sufficient

To take in account in future feeding system ...

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Thank you for your attention