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], [1]INRA UMR1080, Dairy Production 35590 Saint Gilles, France, [2]Agriculture and Agri-Food Canada, Sherbrooke, QC, J1M 1Z3, Canada, [3]Agrocampus 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).

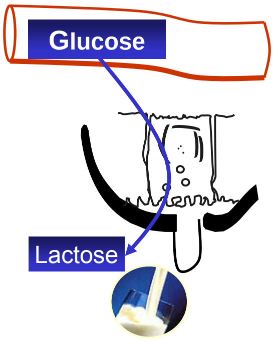
62nd Annual Meeting EAAP 2011
August 29th - September 2nd
Stavanger NORWAY

Gluconeogenesis and its Relation with Milk Production in Lactating Dairy Cows

S. Lemosquet[1,2],
H. Lapierre[3], C.E. Galindo[3], J. Guinard-Flament[2,1]

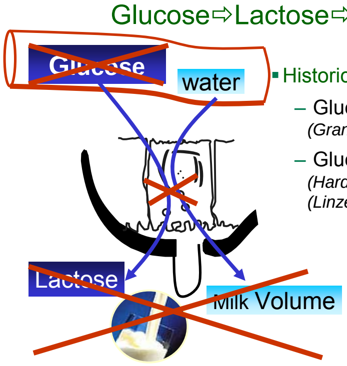
[1]INRA, [2]Agrocampus Ouest, [1,2]UMR1080 Dairy Production,
F-35590 Saint-Gilles, France
[3]Agriculture and Agri-Food Canada, Sherbrooke, QC, Canada

Glucose⇨Lactose⇨Milk volume



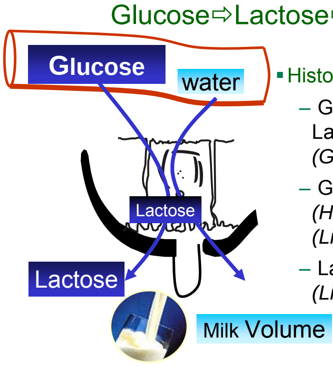
- Historically
  - Glucose precursor of Lactose
    (Grant, 1935, 1936)

Glucose⇨Lactose⇨Milk volume



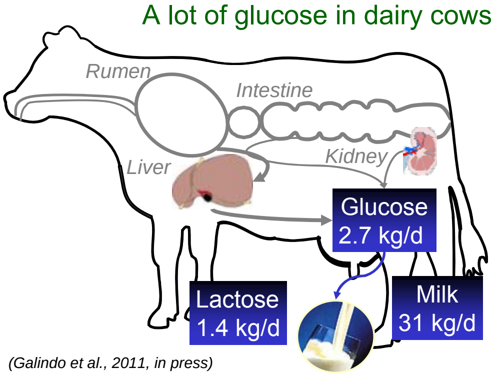
- Historically
  - Glucose precursor of lactose
    (Grant, 1935)
  - Glucose necessary for milk
    (Hardwick et al., 1961)
    (Linzell, 1967)

Glucose⇨Lactose⇨Milk volume



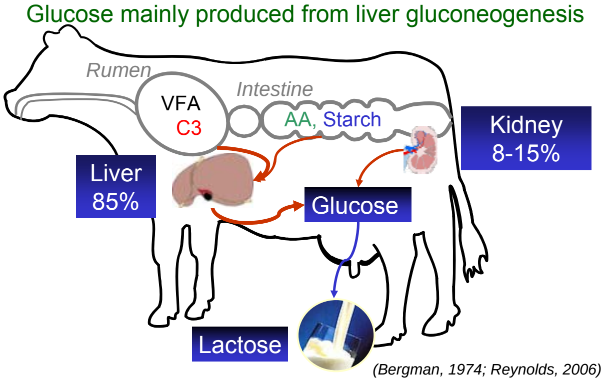
- Historically
  - Glucose precursor of Lactose
    (Grant, 1935)
  - Glucose necessary for milk
    (Hardwick et al., 1961)
    (Linzell, 1967)
  - Lactose: osmotic nutrient
    (Linzell & Peaker, 1971)

A lot of glucose in dairy cows



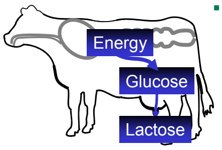
(Galindo et al., 2011, in press)

Glucose mainly produced from liver gluconeogenesis



(Bergman, 1974; Reynolds, 2006)

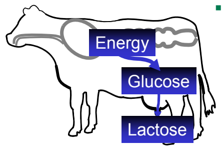
Historically first correlations between Energy supply ⇨ Whole Body Glucose flux ⇨Milk



- Glucose (g/min) = 0.013 + 0.029 ME (MJ/d)
  R = 0.90, P < 0.0001, n = 12
- Milk Yield (kg/d) = 0.52 + 0.029 Glucose
  R= 0.74, P < 0.005, n = 12

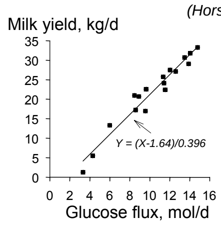
(Horsfield et al. 1974)

Historically first correlations between Energy supply ⇨ Whole Body Glucose flux ⇨Milk



- Glucose (g/min) = 0.013 + 0.029 ME (MJ/d)
  R = 0.90, P < 0.0001, n = 12
- Milk Yield (kg/d) = 0.52 + 0.029 Glucose
  R= 0.74, P < 0.005, n = 12

(Horsfield et al. 1974)



(Danfaer, 1994)

Future Feeding Systems based on Nutrient Fluxes?

- Prediction of Fluxes …

Gluconeogenesis precursors & Starch
⇩
Gluconeogenesis flux
⇩
Lactose
Milk volume
composition

(Nozière et al., 2010)

However correlations does not mean driving force …

gluconeogenesis
⇧
correlations
⇩
Lactose
Milk yield

Is gluconeogenesis the driving force or the reverse?

gluconeogenesis

Driving? Driving?

Mammary glucose demand
- uptake
- lactose

Is gluconeogenesis the driving force or the reverse?

Push factors
- Energy intake
- Nature of nutrients

gluconeogenesis

Driving? Driving?

Mammary glucose demand
- uptake
- lactose

Pull factors
- beginning of lactation
- Phlorizin
- Milking

Questions

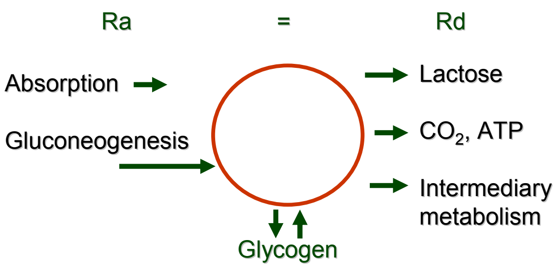
1. How gluconeogenesis varies in response
   a. Push factors
2. Relations gluconeogenesis ↔ lactose
   a. Push factors
   b. Pull factors
   c. Push x Pull

Questions

1. How gluconeogenesis varied in response
   a. Push factors (dietary)
2. Relations gluconeogenesis ↔ lactose
   a. Push factors
   b. Pull factors
   c. Push x Pull

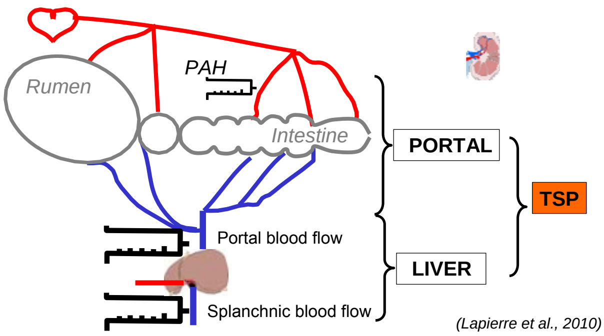
   • Mammary glucose uptake
   • mammary glucose metabolism

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



Measured: Isotope dilution

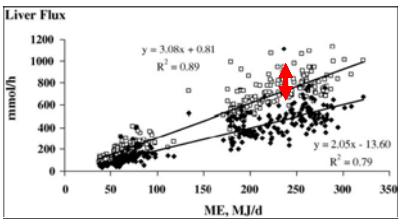
2- Net flux measurement on splanchnic area



(Lapierre et al., 2010)

1 – Whole body glucose Ra
in response to push factors ?

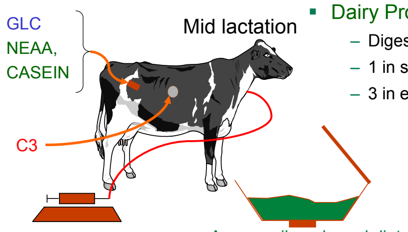
Energy supply ⇨ Whole Body Glucose Ra



Net release of glucose ☐ and removal of propionate
(♦ glucose equilivalent) in growing and lactating cattle (n = 311)

(Reynolds, 2006)

Nature of nutrients ⇨ Whole Body Glucose Ra

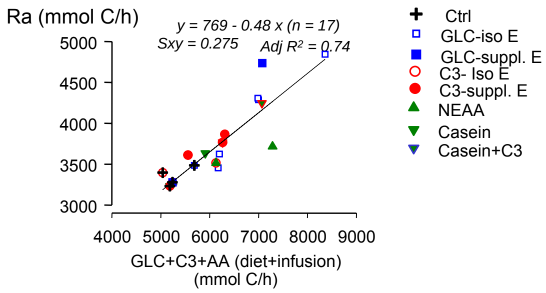


- Dairy Production unit
  - Digestive infusions
  - 1 in supplement
  - 3 in energy substitution

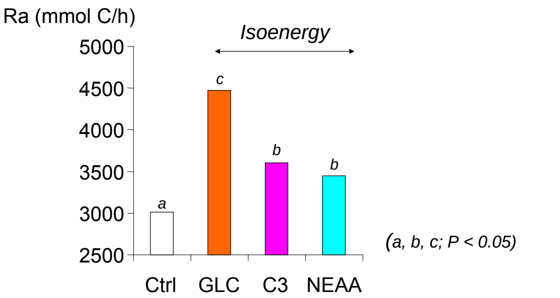
Ra : [6,6-$^2H_2$]glucose
(0.7 µM/kg - 2 h-4 h)

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

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



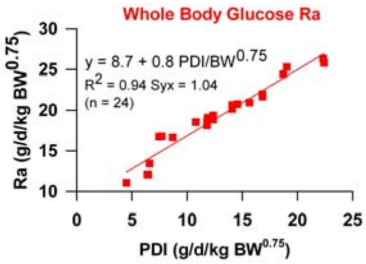
Different efficiencies of Ra increases depending on the nature nutrients



(a, b, c; P < 0.05)

(Lemosquet et al., 2009a)

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



(casein infusions or diets)
(Data corrected from experiment effect)

(Lemosquet et al., 2007)

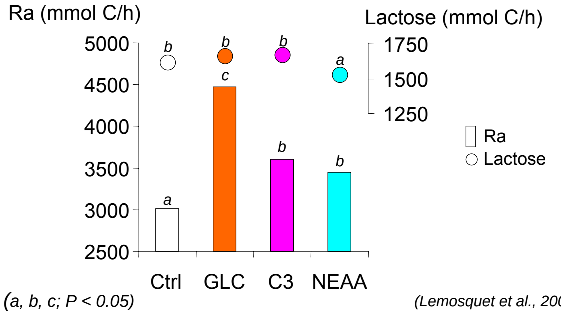
1- How whole body glucose rate of appearance varies in response to push factors?

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

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?

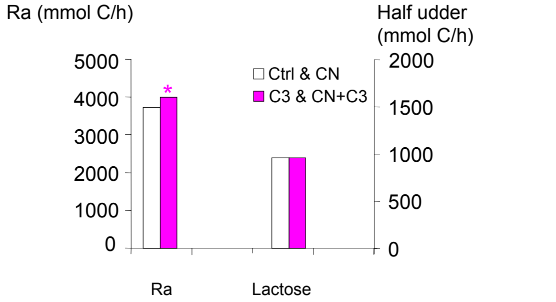
When manipulating nature of nutrients in mid lactating dairy cows, no relationship?



(a, b, c; P < 0.05)

(Lemosquet et al., 2009a)

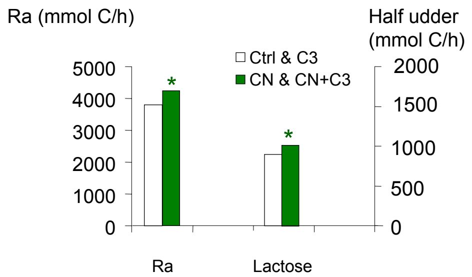
Propionate increased Ra not lactose



* P < 0.05 ; † P <0.10

(Lemosquet et al., 2009b)

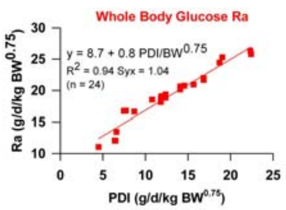
Increased intestinal AA through casein infusion increased Ra and lactose



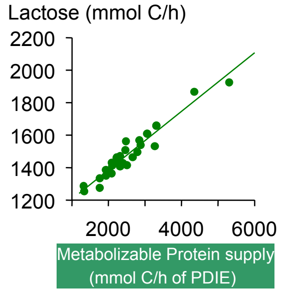
* P < 0.05 ; † P <0.10

(Lemosquet et al., 2009b)

Increased intestinal AA through casein infusions or diets increased Ra and lactose



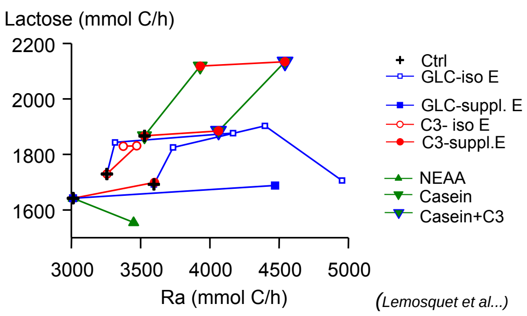
(Lemosquet et al., 2007)



(casein infusions or diets)
(Data corrected from experiment effect)

(Lemosquet et al., 2010)

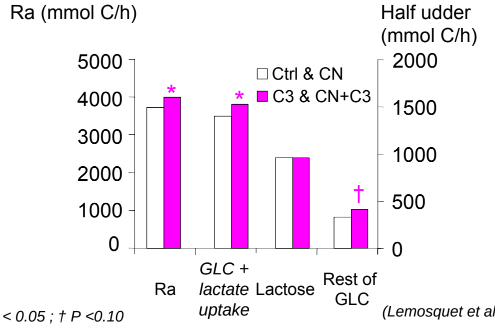
In mid lactating cows, Ra per se did not always drive lactose production



(Lemosquet et al...)

- Is mammary glucose metabolim another key factor of lactose regulation?
  - mammary glucose uptake
  - mammary glucose partition

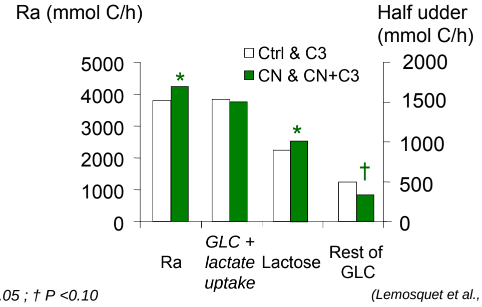
Propionate changed the partition of glucose utilization in the mammary gland



* P < 0.05 ; † P <0.10

(Lemosquet et al., 2009b)

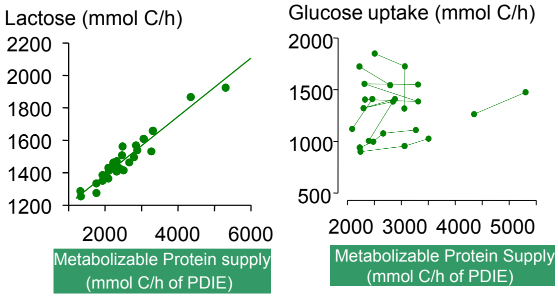
Casein changed the partition of glucose utilization in the mammary gland



* P < 0.05 ; † P <0.10

(Lemosquet et al., 2009b)

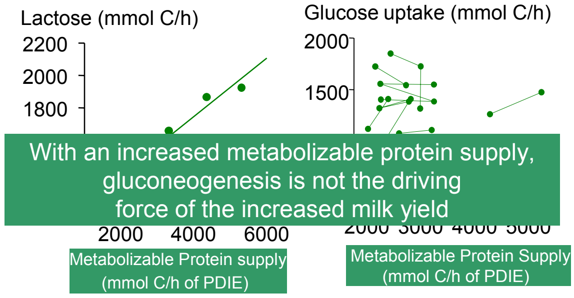
Intestinal AA supplies increased lactose yield but not mammary glucose uptake



(casein infusions or diets)

(Lemosquet et al., 2010)

Intestinal AA supplies increased lactose yield but not mammary glucose uptake



(Lemosquet et al., 2010)

2a- In response to dietary push factors

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)

Phlorizin, g/d	0	2
GLC urine excretion, mmol C/h	287 ↗	
GLC Ra, mmol C/h	188 ↗	
% Propionate → GLC, %	14 % ↗	

(Veenhuizen et al., 1988)

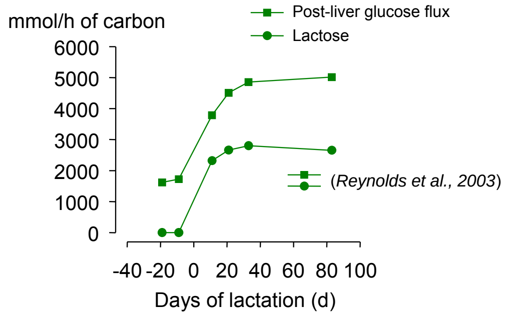
Increased whole body glucose demand through increased glucose urinary loss increased gluconeogenesis and maintained milk yield

- In dairy cows: (short term – 48 h)

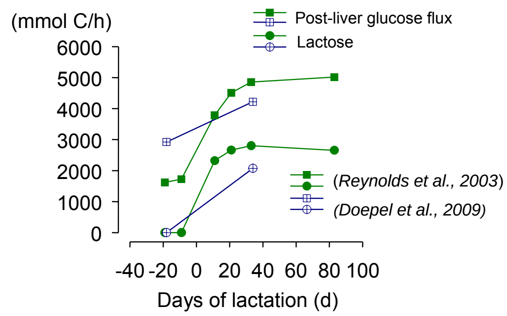
Phlorizin, g/d	0	2	4
GLC urine excretion, mmol C/h	0	312	468
DMI, kg/d of DM	17.4	17.6	17.9
Milk yield, kg/d	30.2	29.8	29.6
Milk lactose, mmol C/h	2082	2054	2012

(Amaral-Phillips et al. , 1993)

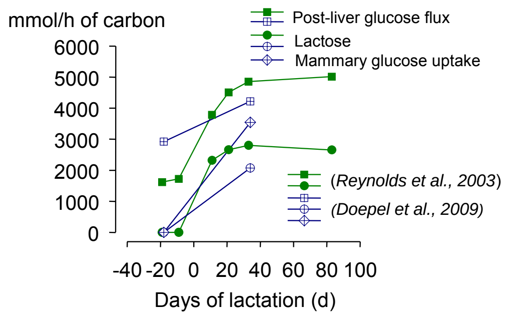
In the beginning of lactation, parallel increases between lactose and post liver glucose fluxes



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

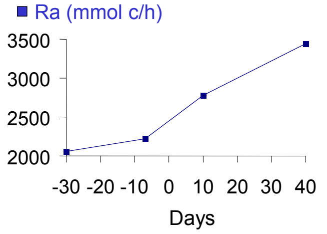


In the beginning of lactation, mammary glucose uptake was also a key point of regulation



At beginning of lactation, Ra efficiency increased

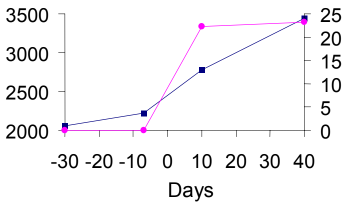
- constant DMI



(Bennink et al., 1972)

At beginning of lactation, milk yield and Ra increases did not parallel

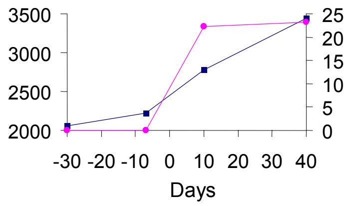
- constant DMI

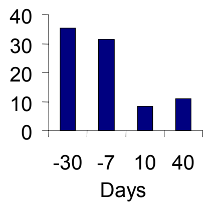


(Bennink et al., 1972)

At beginning of lactation, a decrease in whole body glucose oxidation also explained milk increase

- constant DMI





(Bennink et al., 1972)

2b- In response to pull factors

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

2c- In response to push x pull factors ?

- In a case of decreases

Feed restriction x once daily milking

	Feed restriction 98% → 70%	Milking 2/d → 1/d
Mammary GLC uptake (mmol c/h)	1187 → 945 (- 22%)	1211 → 930 (- 21%)

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

	Feed restriction 98% → 70%	Milking 2/d → 1/d
Mammary GLC uptake (mmol c/h)	1187 → 945 (- 22%)	1211 → 930 (- 21%)

Hyp. Rejected: additive response Feed restriction x Milking

	1/d Milking: 98% Feed → 70% Feed
Mammary GLC uptake (mmol c/h)	1051 → 810 (- 23%)

(Guinard-Flament et al., 2007)

In conclusions

Nutrients (push)

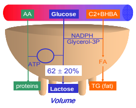
⇩

Gluconeogenesis

⇩

Milk volume

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

In conclusions

gluconeogenesis

Driving? → Milk

Driving?

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

In conclusions

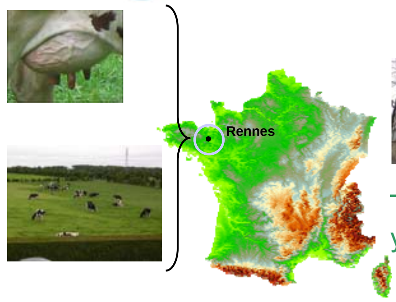
gluconeogenesis

Driving? → Milk

Driving?

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

To take in account in future feeding system ….



Thank you for your attention

A great thanks to our collaborators

Dr. C. Hurtaud (BIOLAIT team)
Drs. G. Raggio, E. Delamaire, S. Rigout
Drs. L. Delaby, J.L. Peyraud

C. Hurtaud and the 'LAB' dream team
P. Lamberton and the "Barn" dream team

Dr. J. Grisard

Thank you for your attention