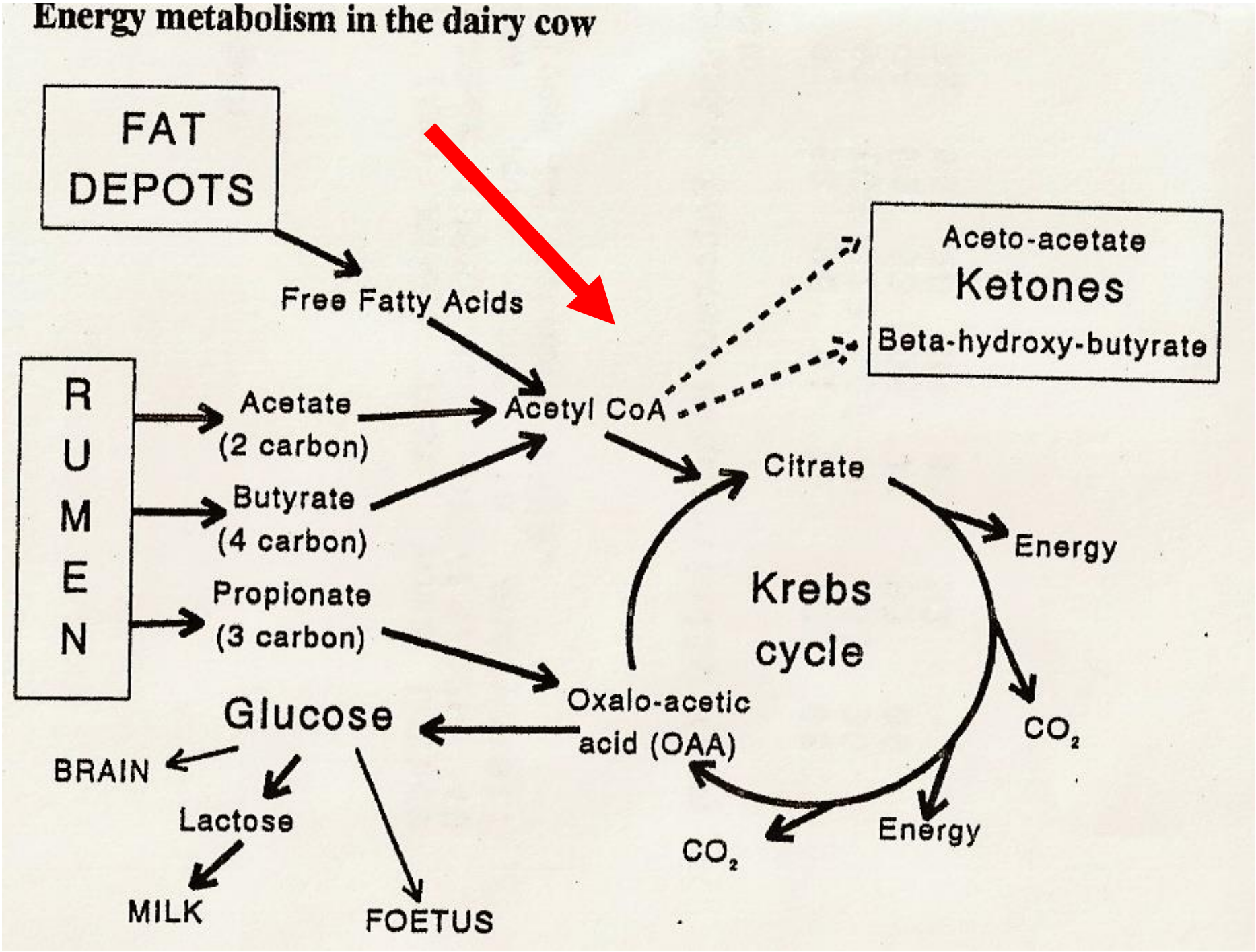
Ketosis

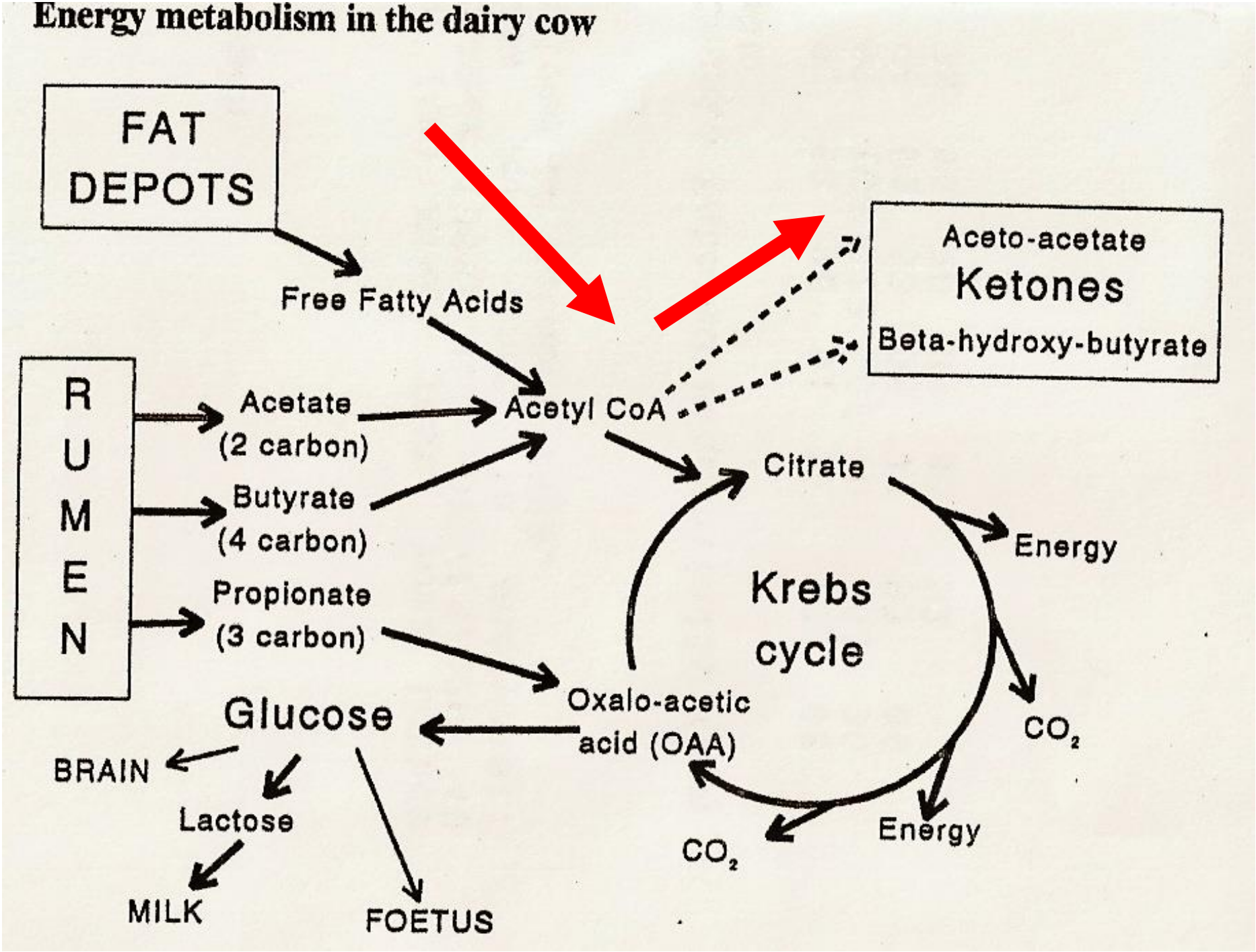
I don’t think its super simple even though its made out to be !

Though , Its mostly a condition of low dry matter intake which we can manage via diet



Cows loose Body fat

Body fat cant burn in liver fast enough

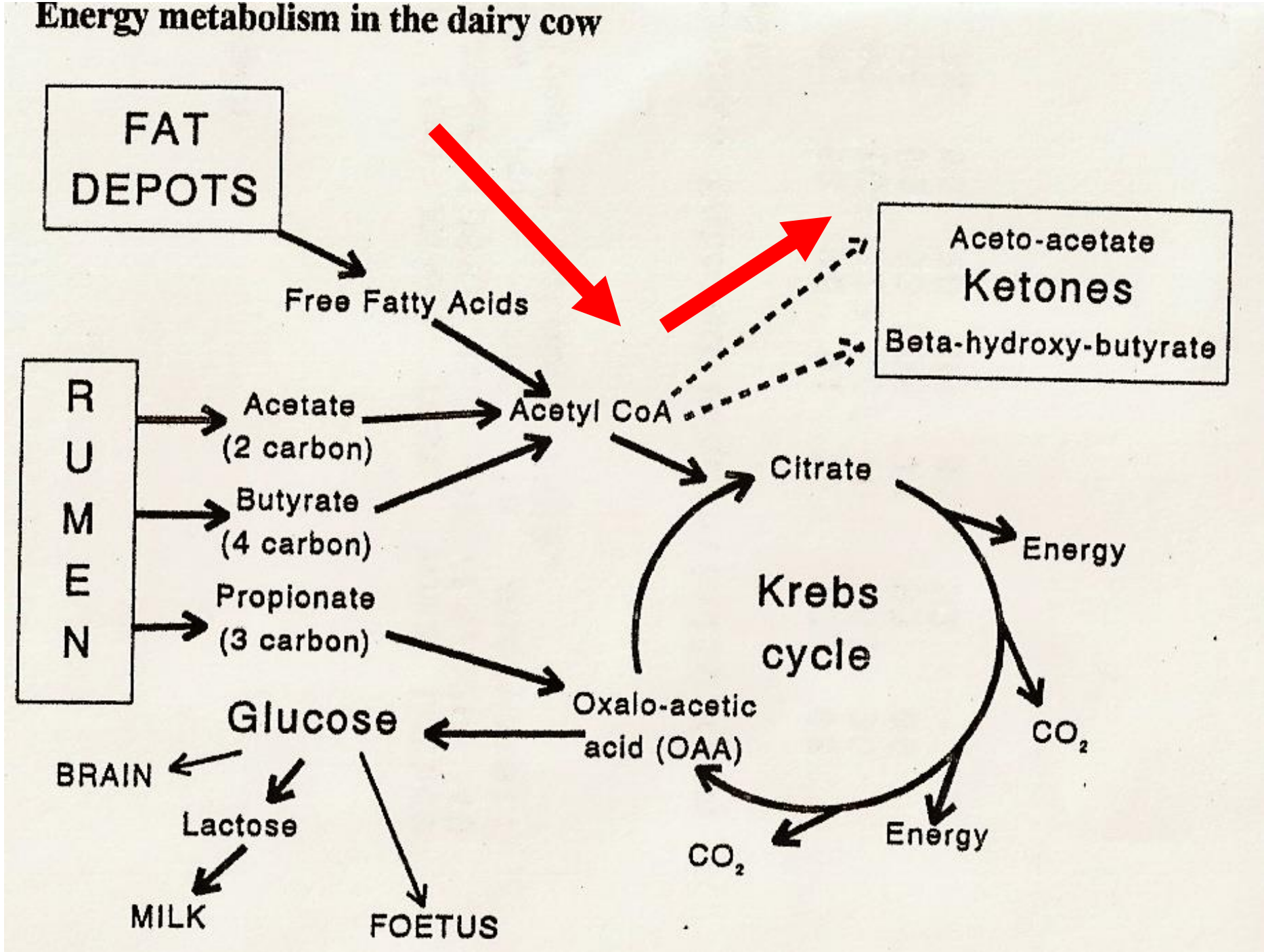


Cows loose Body fat

Body fat cant burn in liver fast enough

Ketones are created and build up in blood & tissue

Cows get crook



LETS GO FOR BEER !

Wish it were that simple right:
Billy cart v F1 in terms of the science position

A more nuanced approach would capture what’s really predicating the condition of Body fat loss … so lets get into it with that approach.

Lets start by saying that Ketosis is a FLAG of other significant things going on…

…its not the fundamental condition

All this stuff is inter related, starting with Body Fat loss

- low DMI (Hepatic oxidation of fat)
- Low milk yield (low DMI , low production of glucose
- Low gluconeogenisis and blood glucose
- Low ureagenosis (and hence high BUN levels)
- Low liver glycogen reserves
- ketosis
- Suppressed immune status
- Massive over inflammation status Poor fertility expressed in various ways
- Increased mastitis
- Increased lameness

Lets start by saying that Ketosis is a FLAG of other significant things going on…

…its not the fundamental condition

By the way This FLAG is a $3 billion dollar flag by my rough calculations

Ketosis is a FLAG…its not the fundamental condition

Give or take 12.5%

Still not bad though compared to us lot in Aus rugby …..current offers for equity rights to the wallaby flag stand at about $27.85…action is a bit slow too….

The Aus Rugby union have taken drastic measures

“Will consider swap for well maintained 1992 or later Toyota Coaster minibus”

(the boys have to get to games after all !)

“Will consider swap for well maintained 1992 or later Toyota Coaster minibus”

(the boys have to get to games after all !)

Lets define Ketosis to begin with….

- Ketotic at a sub clinical level at about 1.2 mmol/L BHB in blood
- Likely clinical ketosis signs at about 3.0 mmol/L BHB in blood

- 3-7% milk loss
- 3-19 times the chance of a DA
- 20-70% less chance of conceiving to first service
- 3 times the chance of being culled in first 30 days
- (Prof Garret Oetzal- DVM and Prof in Dairy Vet science at Wisconsin)

Two forms of Ketosis are “sort of” recognised

- Type 1- DIET DRIVEN: Simple stuff…We don’t feed them enough in early lactation with good milk flow , or we feed them the wrong stuff. They are placed in a big negative energy balance , and they peel body weight fast. NEFA > LIVER>BHB
- Normally as milk ramps up , weeks 3-6 of lactation

- Type 2-ANIMAL DRIVEN: the animal doesn’t make a metabolic adaptation to being in lactation , even if the diet looks “ok”. It’s a bit of head scratcher, and we will look at it more today, as its not as clear cut as “hungry cows”.
- Normally weeks 1-2 of lactation. (Even pre calving potentially, and diabolical at that stage)

- The prevention is the same …enough feed that is glucogenic and brings back insulin

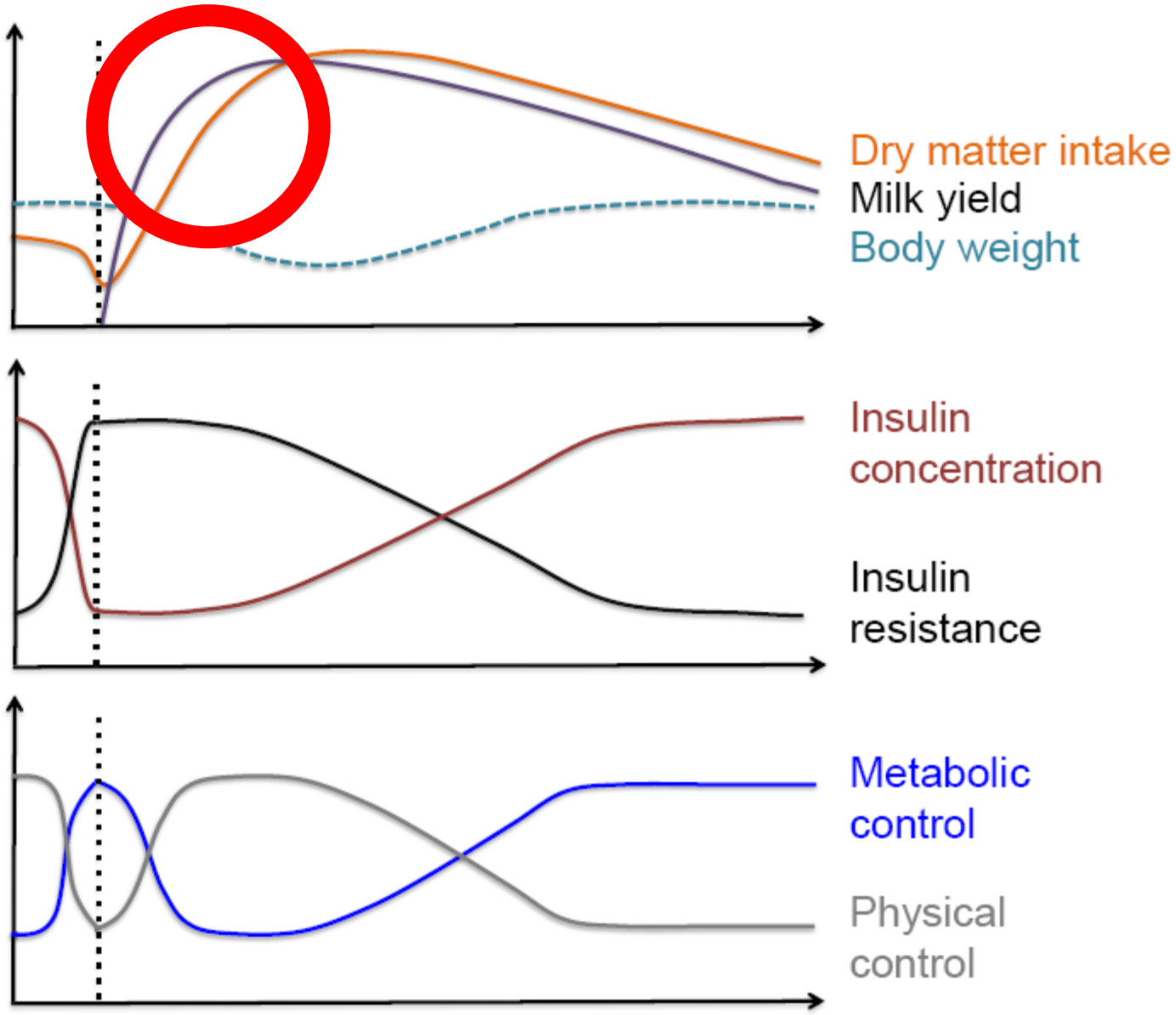
How do we get to having Ketosis ?

Type 1 = Its pretty clear why if we simply don't feed them !

- Type 2 = why does it happen to some beasties even when feed seems well available

We shout "eat you buggers"…but they don't seems to want to …so they loose weight/ mobilise NEFA/ hit liver/ make Ketones in XS

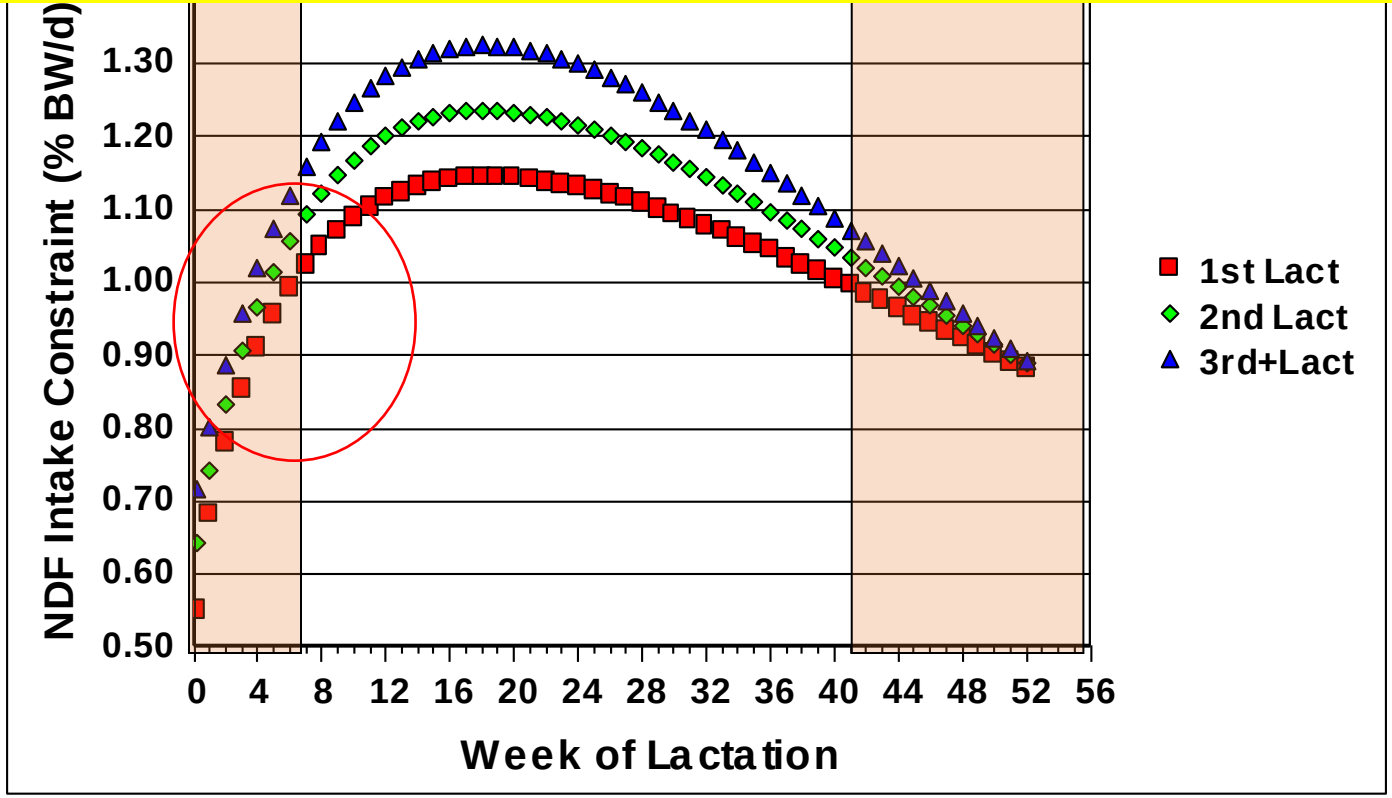
And it's the eating or not that makes a difference to experiencing Ketosis or not.
As that delivers the glucose we need



Put another way Stock clearly do not universally eat till they are full physically .
They do some times , but not other times.
What stops a cow on low quality grazing eating ? Gut fill
What stops a beef steer on 80% grain eating ? NOT gutfill
What stops a fresh dairy cow eating ? NOT Gut fill unless forage is poor
What stops a mid/late lactation cow eating? Gut fill

Intake is low and not limited by gut fill when fresh.

0.9% of Bwt as NDF in 600kg cow is about 15 kg DMI



Heptatic oxidation theory (HOT) may be the dominant regulator of intake in early and late lactation (Allen et al., 2009)

	Far-off	Close-up	Fresh	Peak-Mid	Late Maintenance
Physiological state					
Insulin	High	Low	Low	Med	High
Insulin sensitivity	High	Low	Low	Med	High
Glucose demand	Low	Med	High	Med	Low
Energy Partitioning	BC	BC	Milk	Milk	BC
Control of feed intake	GF	HO	HO	GF	HO
Grain amount	V-Low	Low	Med	High	Low
Ruminal starch digestibility	-	Low-med	Med	High	Med
Grazing intensity (leaves)	3+	3	3	2	2-3

BC = body condition, GF = gut fill, HO = hepatic oxidation

Situation summary of cow metabolism around calving: Gestational Diabetes

Situation

- Low insulin and insulin sensitivity of tissues
  - Fat mobilization: elevated plasma NEFA
  - Inflammation
- Fatty liver: compromised liver function
  - Gluconeogenesis
  - Detoxification of NH_3
- Grazing: excessive N intake
  - Energy cost to excrete
  - Depressed feed intake

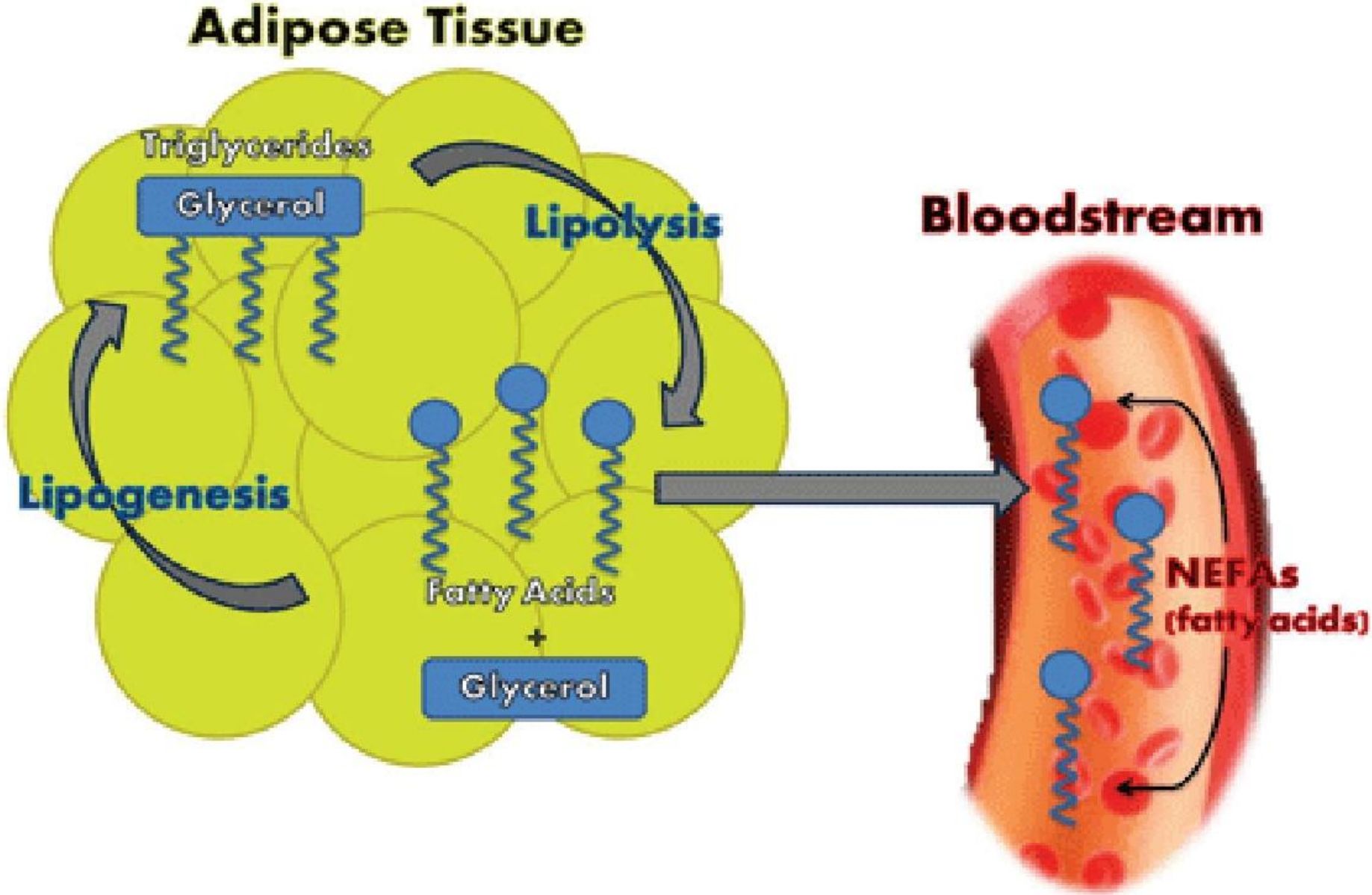
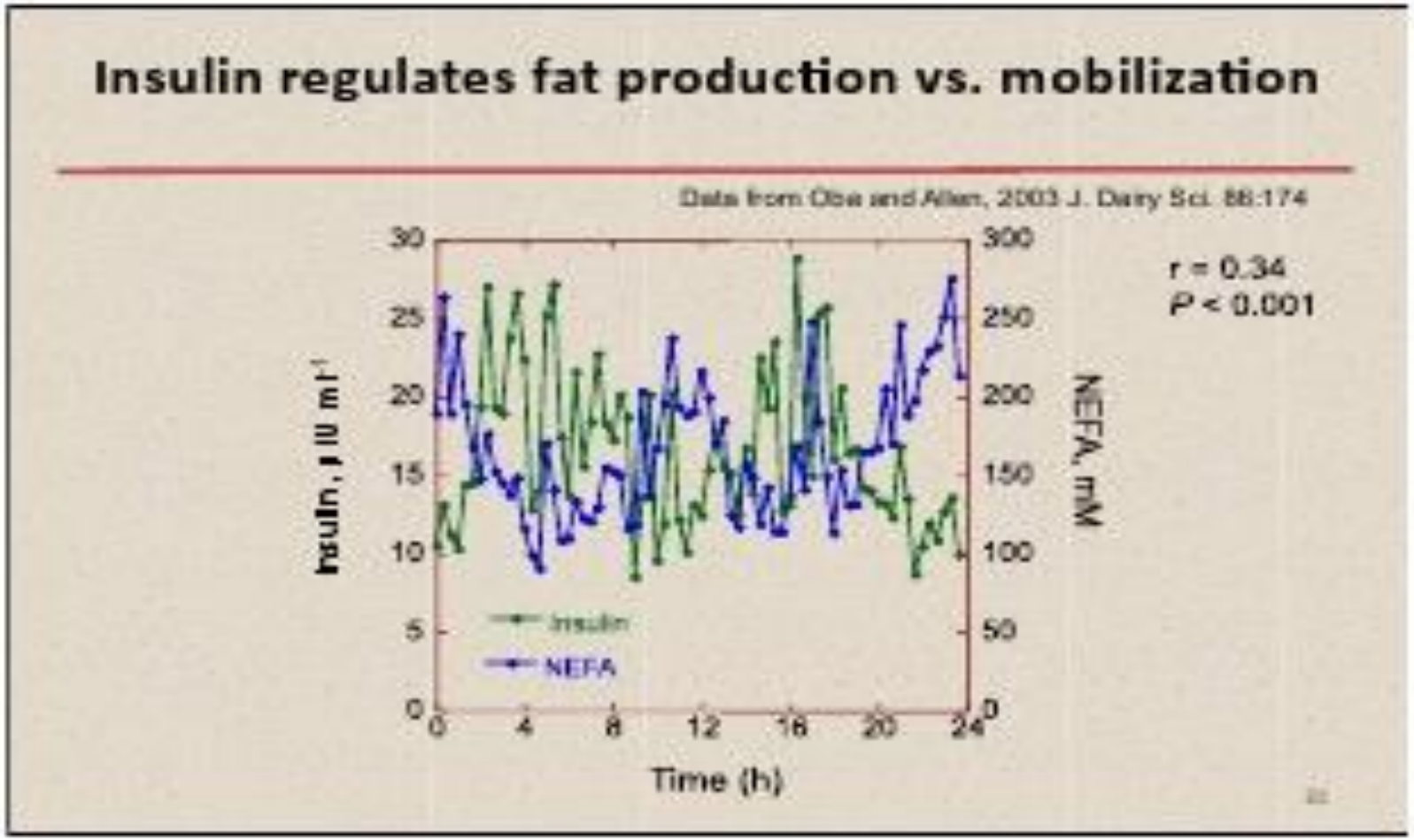


Figure 1. Fat mobilization process. Lipolysis releases fatty acids from triglyceride molecules in adipose tissue into the bloodstream. Lipogenesis assembles triglycerides from fatty acids and glycerol.

Insulin is the handbrake on NEFAs



Insulin will decline naturally pre birth in all female mammals …. And then NEFA climbs…why ?

- Cow drops insulin to maintain blood glucose for foetus in late gestation. It's a natural thing
- The Foetus is obligate glucose consumer , cow can run on several energy forms inc NEFA.
- NEFA also important right at calving to allow for colostrum with its raised fat content for calf at day 1-2
- We probably cant STOP NEFA increase, but we should LIMIT NEFA increase if possible

- So the big picture for ketosis management is promote dry matter intake

- Bridge the gap between energy draw down for lactation , and energy provision via DMI

Metabolic Control of Feed Intake

Implications for Metabolic Disease of Fresh Cows

Michael S. Allen, PhD[a,*], Paola Piantoni, Veterinaria, MS[b]

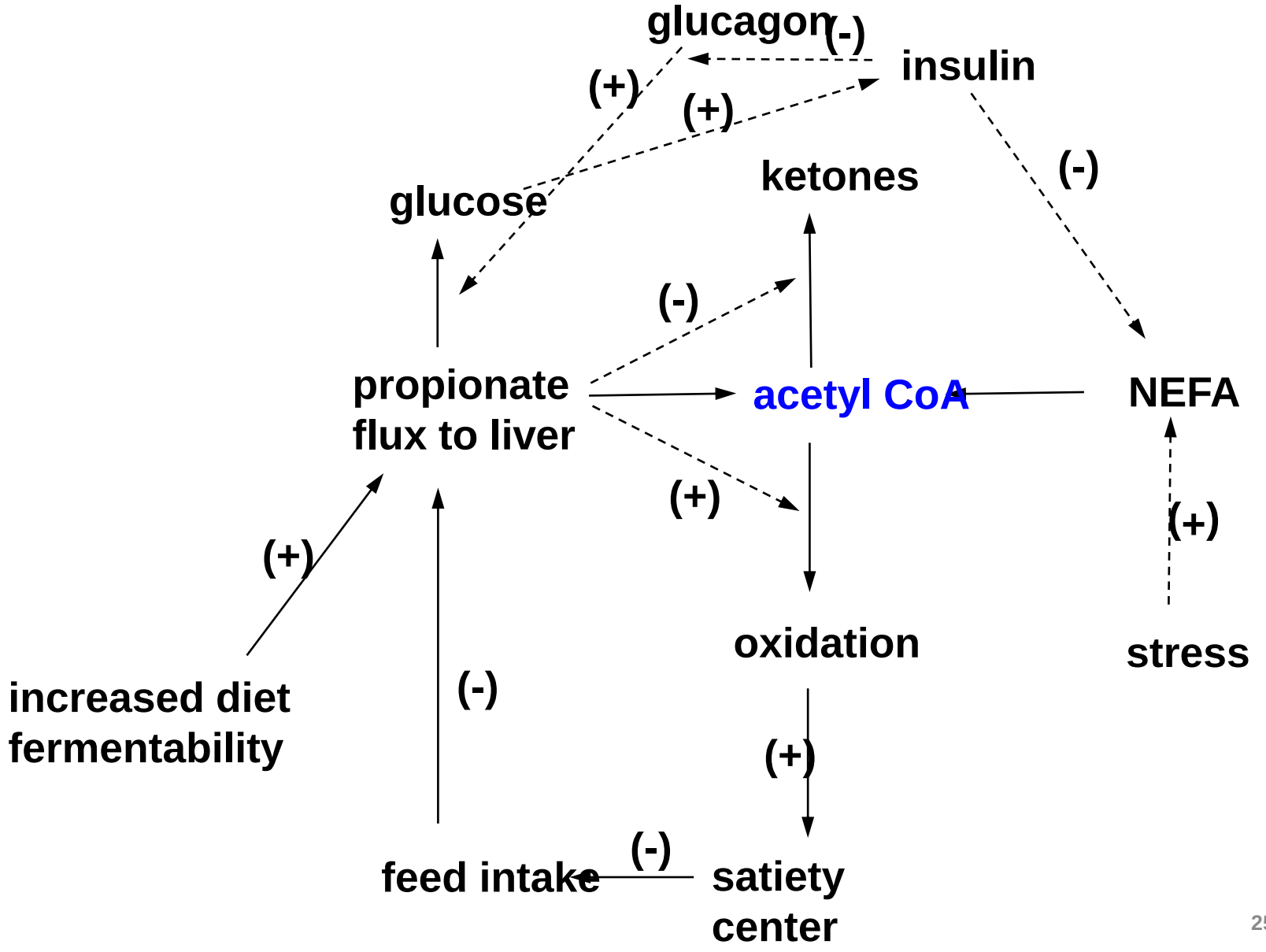
KEYWORDS

• Hepatic lipidosis • Hepatic oxidation • Insulin resistance • Ketosis • Lipolysis
• Metabolic disease • Propionic acid • Ruminal starch fermentability

KEY POINTS

- Metabolic diseases are associated with depression of feed intake in the peripartum period.
- Control of feed intake during the peripartum period is likely dominated by signals from hepatic oxidation of fuels.
- Cows are in a lipolytic state in the peripartum period that is initiated several weeks prepartum as insulin concentration in blood and insulin sensitivity of adipose tissue decrease.
- The continuous supply of NEFA to the liver during the lipolytic state at this time likely suppresses feed intake as they are oxidized.
- Diet interacts with the extent of lipolysis to affect feed intake.
- A better understanding of the metabolic control of feed intake can help implement strategies to reduce risk of metabolic disease.

Model by which propionate + NEFA may stimulate satiety more together….Ketosis can arise more in fresh cows



Hepatic oxidation Theory (HOT) as key driver of DMI around calving and early lactation with Huge nods to Prof Mike Allen at MSU

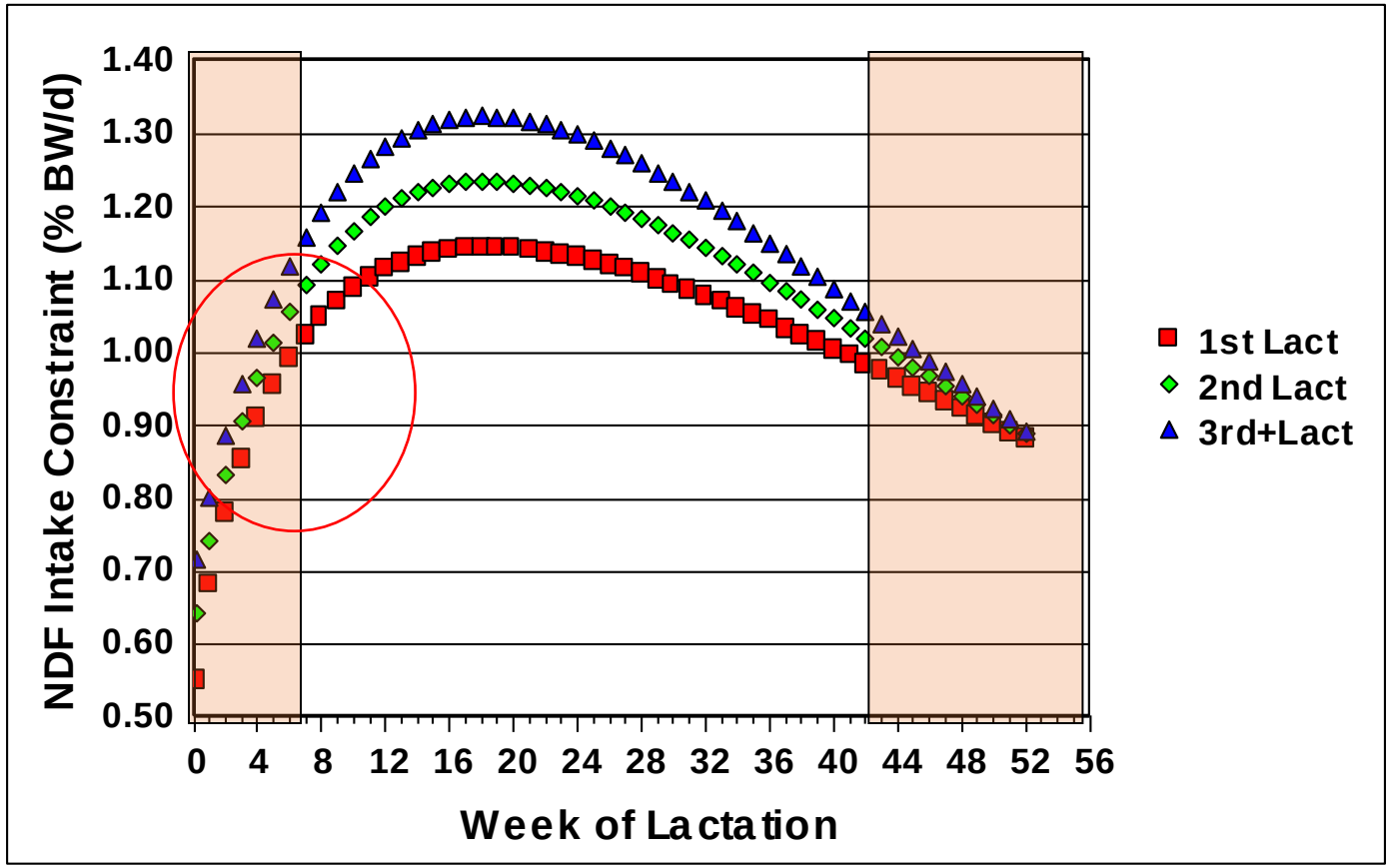
Guess what …they don't always eat to gut fill …and 1.2% of Bwt as NDF is actually a bit blunt (ask Dave Mertens…I did !)

NDF-Energy Intake System

Homeorrhetic control of NDFIC

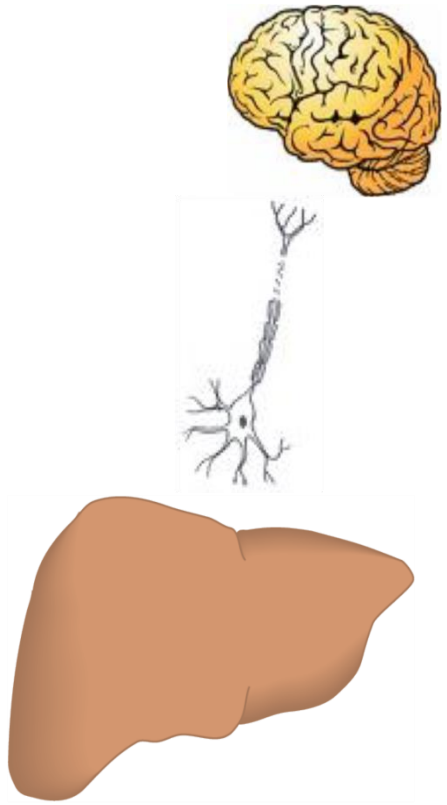
Intake is low and not limited by gut fill when fresh.

0.9% of Bwt as NDF in 600kg cow is about 15 kg DMI



Heptatic oxidation theory (HOT) may be the dominant regulator of intake in early and late lactation (Allen et al., 2009)

Liver is “hard-wired” to brain satiety centers…it effects appetite



Satiety

Hunger

HOT: hepatic oxidation theory

- **Liver is “hard-wired” to brain feeding centers via vagus nerve**
- **Feeding behavior is affected by firing rate of the nerve**
  - **Decreased firing rate causes satiety**
  - **Increased firing rate causes hunger**
- **Firing rate is affected by oxidation of fuels**
  - **Increased oxidation decreases firing rate causing satiety**
  - **Decreased oxidation increases firing rate causing hunger**
- **Great variation in oxidation of fuels over the short-term.**
- **Feed intake is affected by pattern of oxidation of fuels.**

- ***If I wont eat , it gets hard to reduce ketosis***

Prof Mike Allen

- **“Goal: maximize the amount of glucose produced or spared per unit of ATP generated in the liver over time”.**

- **Do that and I bring back insulin , slow NEFA , promote DMI , limit ketosis and make milk and fertility (yep the lot)**

Why not just more rapidly fermenting starch ? Why slow starch ?

- Whilst theoretically a glucose precursor via propionate, “fast starch” in early lactation produces a pronounced negative feedback on DMI from a wave of propionate hitting a liver that is not “fit” to handle it .
- It also increases oxidation of acetyl CoA in the liver and further depresses DMI
- Slow starch gives glucose more effectively, and with less pressure on liver

So NEFA + Propionate surges hitting liver bring additive crash in appetite and DMI

- It’s the real time propionate flux/surge that impacts liver and satiety
- Produces impact about 30-40 min post consumption or less
- Probably impacting grazing behaviour and keenness
- Means we must consider starch TYPE !

Grain starch levels and breakdown rates (Nocek&Tamminga 1991)

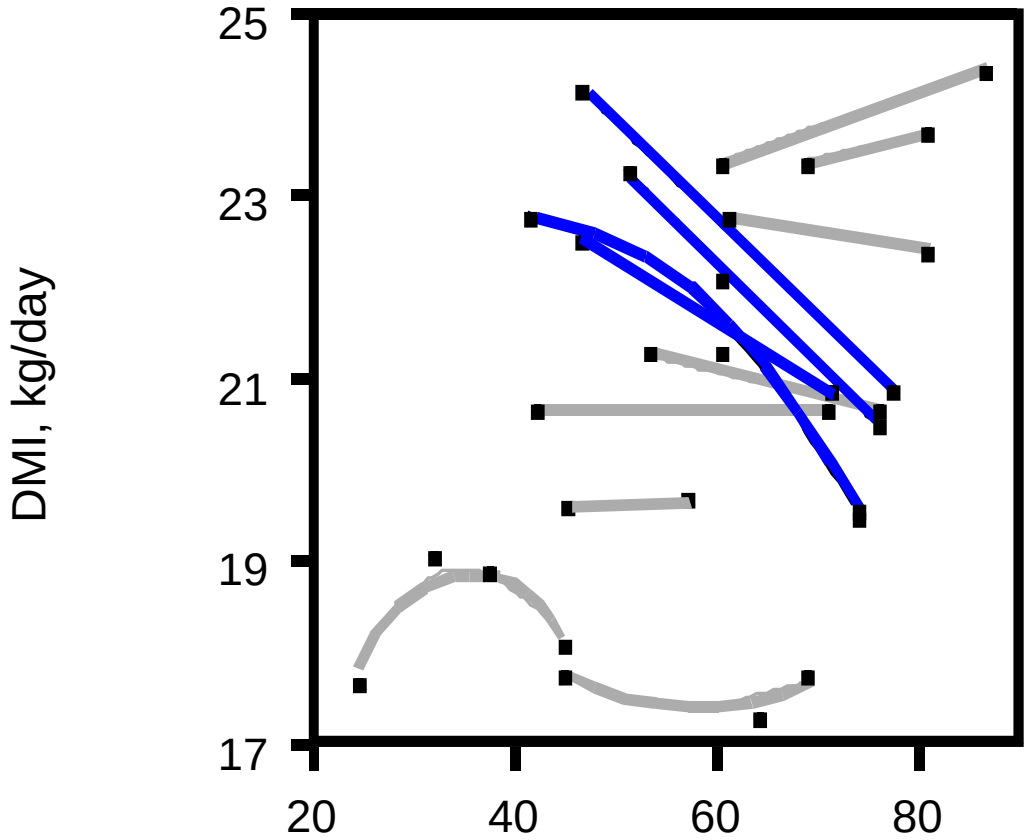
Grain	Starch %	Kd % /hour
Wheat	66	25
Barley	57	19
Rice	84	8
Rice bran	20	13
Sorghum	65	4
Corn	68	4
Millrun	23	25

Cerneau and Dorneau 1991

Grain type	% starch	Grind mm	Rapid degradation	slow but potential	Rumen degradability
Barley	57	0.8	82%	18%	98%
Barley	57	3	51%	49%	95%
Barley	57	6	47%	53%	91%
Corn	68	0.8	30%	70%	61%
Corn	68	3	26%	74%	58%
Corn	68	6	0%	99%	44%

We need glucose; but Excessive fast ruminal starch digestion can depress DMI of lactating cows

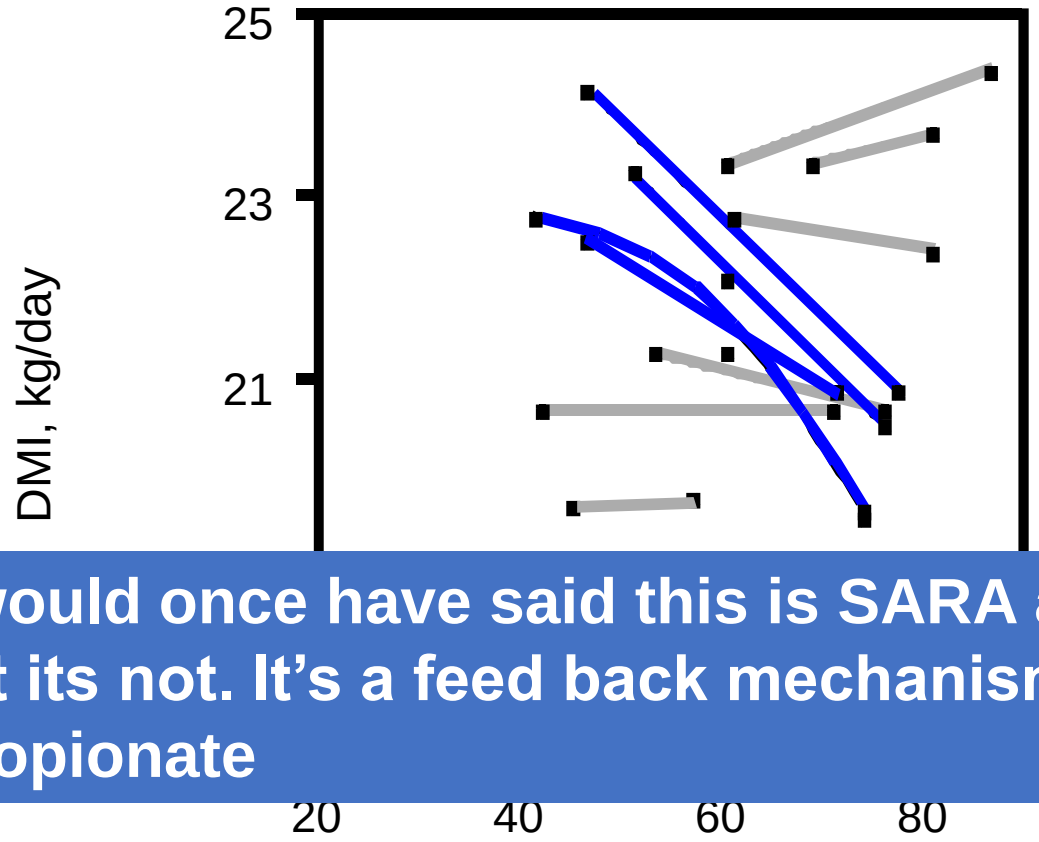
Allen, 2000, J. Dairy Sci. 83:1598



Grains differing in ruminal degradation

Excessive fast ruminal starch digestion can depress DMI of lactating cows

Allen, 2000, J. Dairy Sci. 83:1598

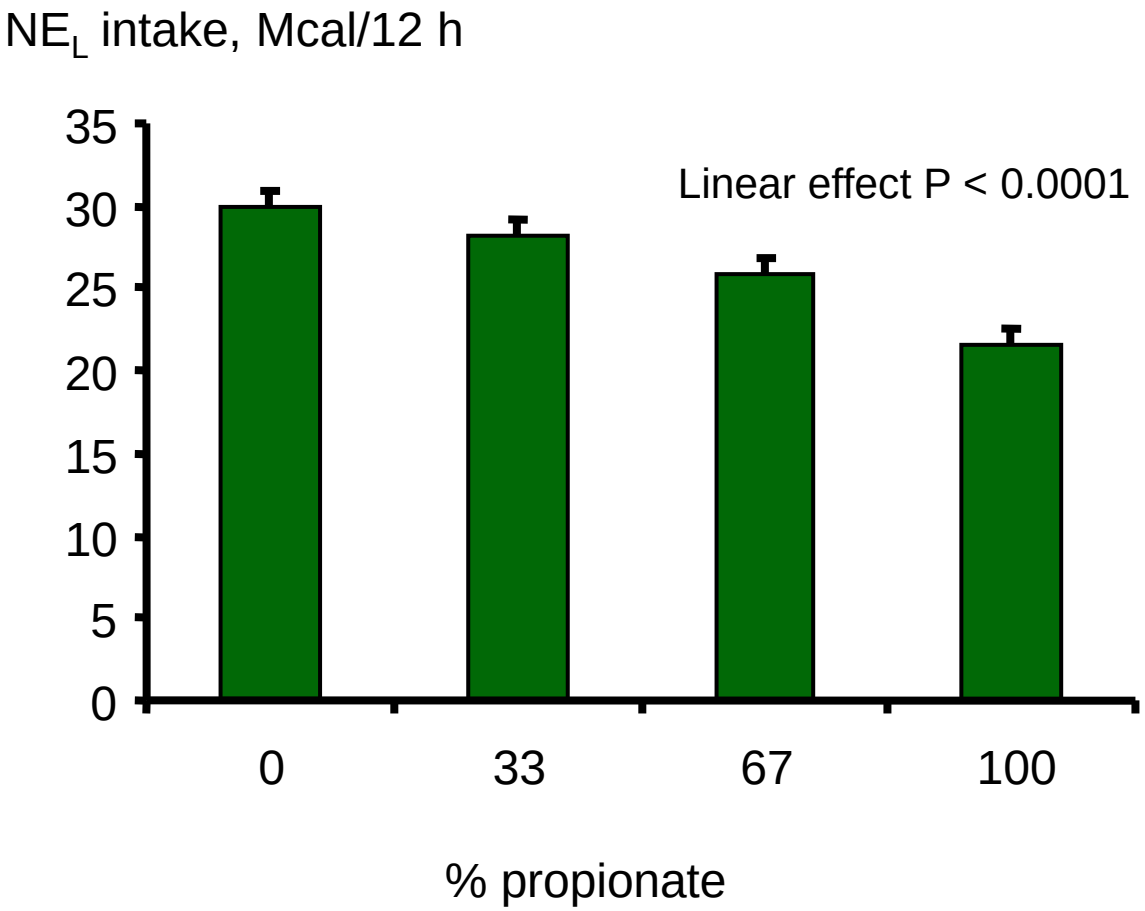


Grains differing in ruminal degradation

We would once have said this is SARA as an explanation …but its not. It's a feed back mechanism via HOT specific to Propionate

Propionate vs. acetate

Oba and Allen, 2003 J. Nutr. 133:1094



Infusion of mixtures of propionate and acetate at 25 mmol/min from 2 h before feeding until 12 h after feeding

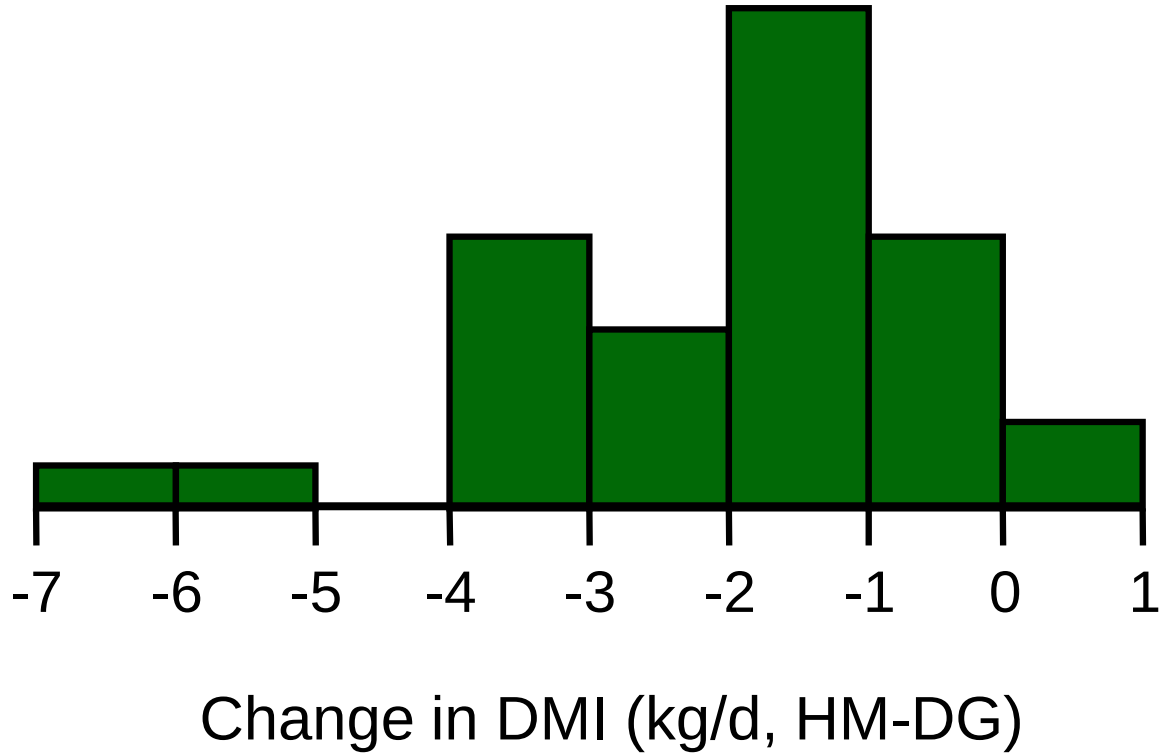
NE_L intake intake = feed + VFA

Effect of ruminal starch fermentation on eating behavior

Oba and Allen, 2003 J. Dairy Sci. 86:174

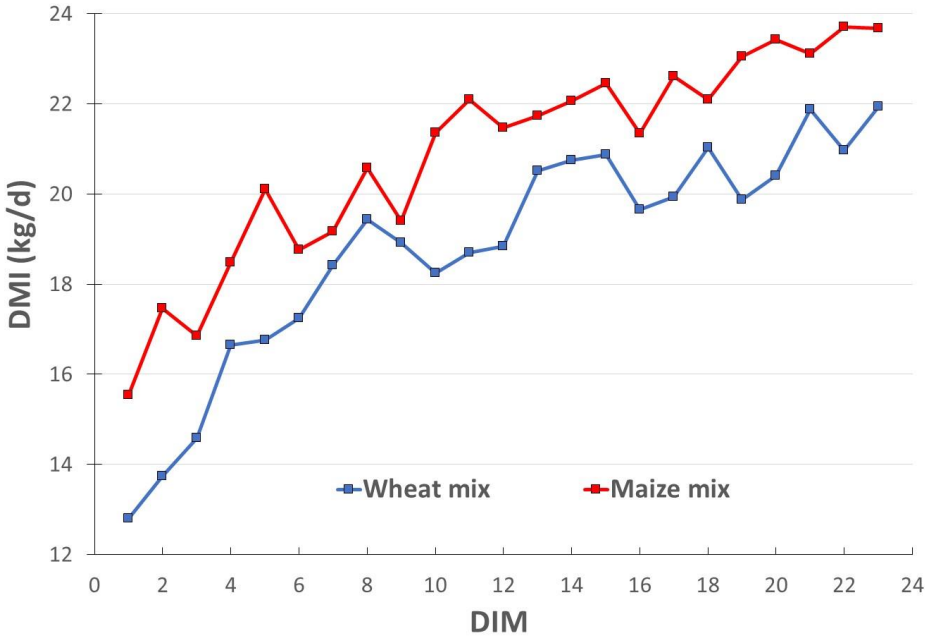
	Fast fermenting	slow ferment
	High Moisture	Dry
DMI, kg/d	20.8[b]	22.5[a]
RFOM, kg/d	11.3	10.3
Meal size, kg	1.9[b]	2.3[a]
Intermeal interval, min	93.9	105.0

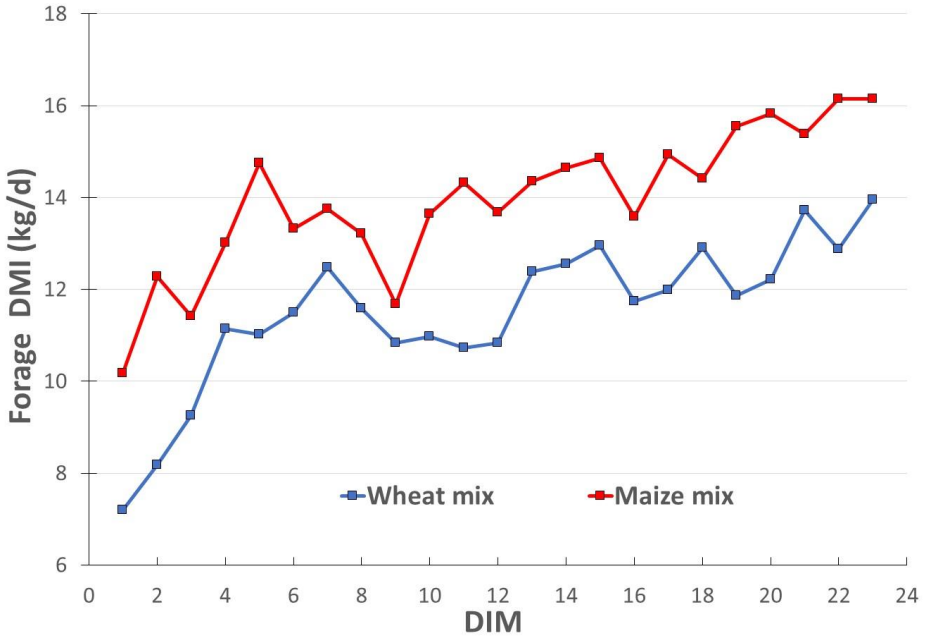
Variation among cows in DMI response to a change in diet fermentability



Data from Bradford and Allen, 2004 J. Dairy Sci. 87:3800

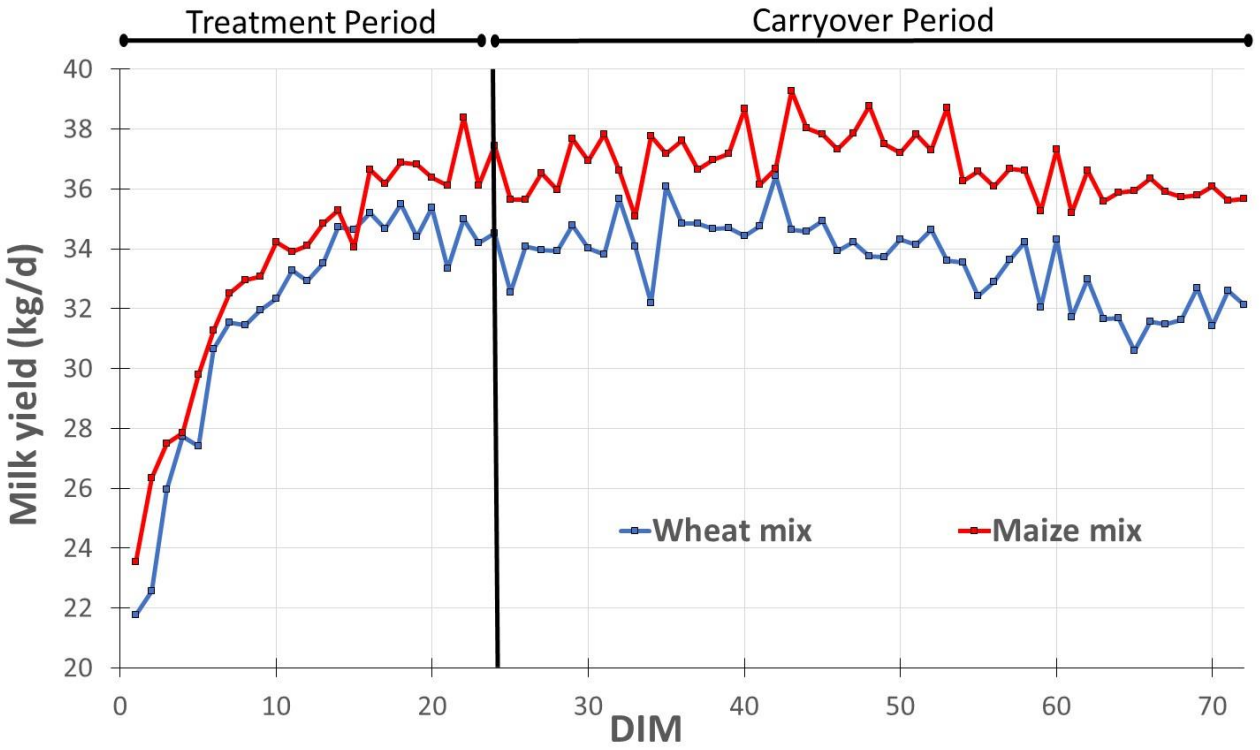
Ellinbank Fresh Cow Study 2020





Who had more chance of ketosis do you think ?

Fresh Cow Study 2020



Ammonia and propionate together are double whammy- implications with XS NPN from pasture

Excessive NPN can reduce DMI!

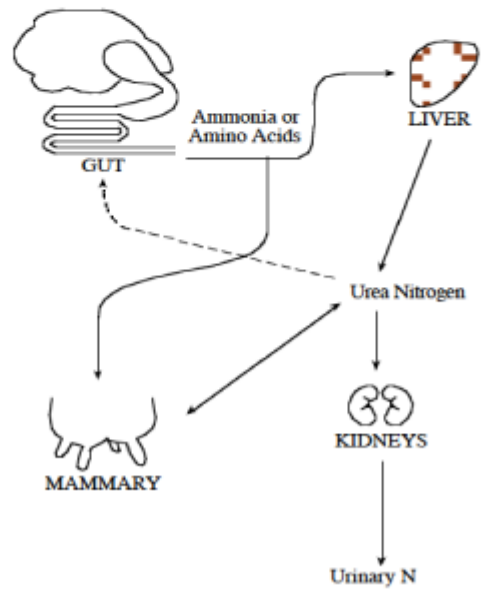
Oba and Allen 2003 J. Nutr. 133:1100

	Acetate		Propionate		Significance, *P*		
	Na	NH_3	Na	NH_3	VFA	Salt	Int.
DMI, kg/12 h	15.3	13.1	12.1	4.3	<0.001	<0.001	<0.01
ME intake, MJ/12 h	185	159	156	68	<0.001	<0.001	<0.01
Milk Urea N, mmol/L	5.4	15.6	5.3	15.4	NS	<0.01	NS
Meal size, kg	2.3	2.1	1.7	1.3	<0.01	NS	NS
Intermeal interval, min	64.6	80.8	70.5	96.1	NS	0.19	NS
Meals /12 h	7.0	6.6	7.2	3.9	0.03	<0.01	<0.01

Plus here is the hard maths on the energy cost of XS nitrogen excretion

Excessive nitrogen consumption

- Potential reduction in hepatic glucose production
- Potential reduction in feed intake
- Energy cost to excrete as urea
  - 4.4 kcal NE_L per g N (Tyrrell et al., 1970)
  - 450 kg cow, 20 kg DMI, 30 kg milk, 4.5% Fat, 3.5% Prot
  - 16 kg pasture @ 28% CP = 4.48 kg CP &
    4 kg concentrate @ 14% CP = 0.56 kg CP
  - Protein consumed: 5.04 kg CP /d
  - Protein required: 3.33 kg CP /d
  - Difference: 1.71 kg CP /d = 274 g N /d
  - 274 g N x 4.4 kcal/g N = 1,204 kcal NE_L
  - 1,204 kcal NE_L / 672 kcal NE_L /kg FCM
    = 1.78 kg FCM equivalent

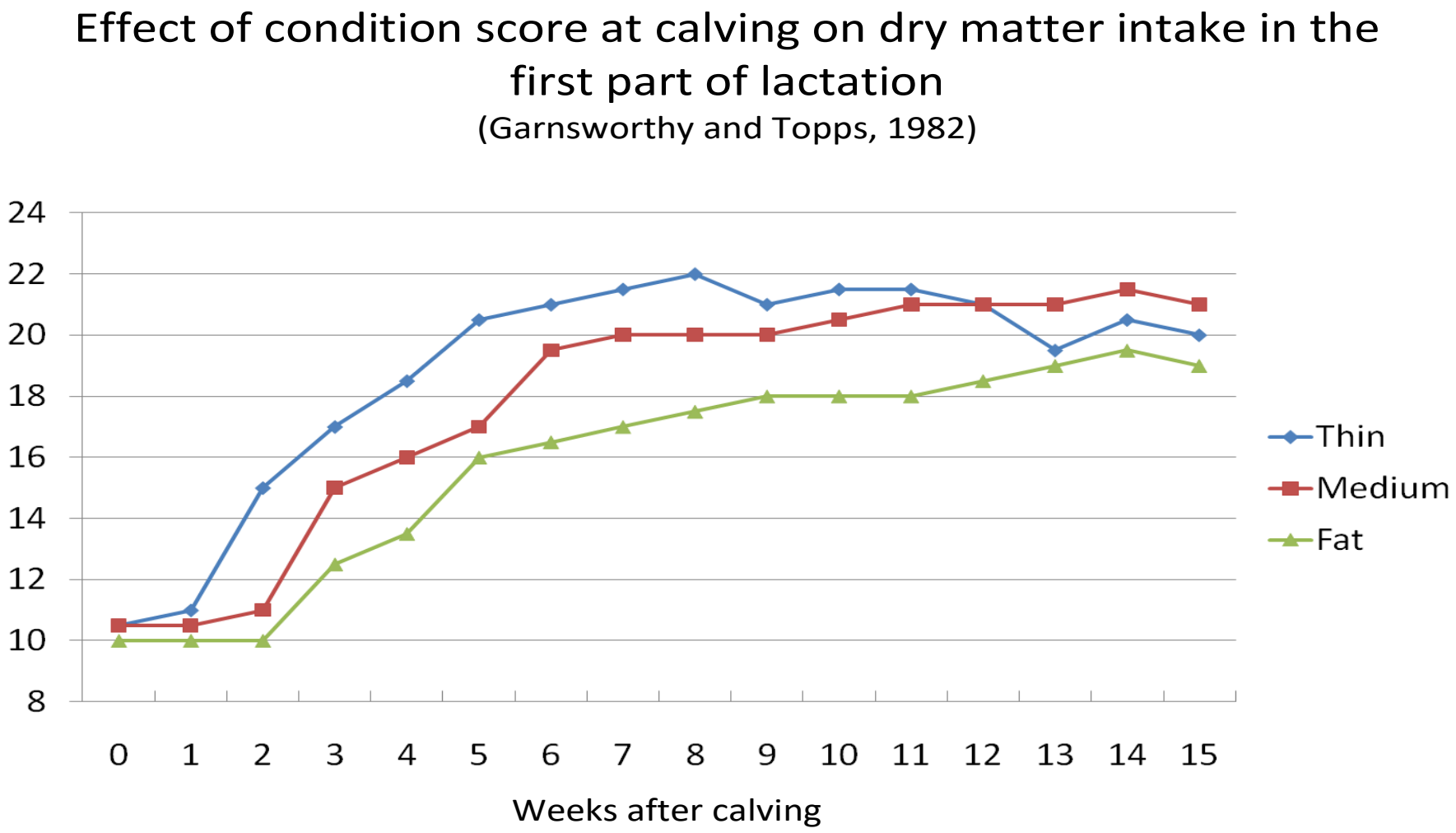


Broad impacts of XS NEFA flow and challenged liver lipid physiology

- low DMI (Hepatic oxidation of fat)
- Low milk yield (low DMI , low production of glucose
- Low gluconeogenisis and blood glucose
- Low ureagenosis (and hence high BUN levels)
- Low liver glycogen reserves
- ketosis
- Suppressed immune status (more later)
- Massive over inflammation status (more later)
- Poor fertility expressed in various ways
- Increased mastitis
- Increased lameness

What else can we do other then more DMI

Control BCS to limit the potential flow of fat to liver, limit oxidation and hold up DMI

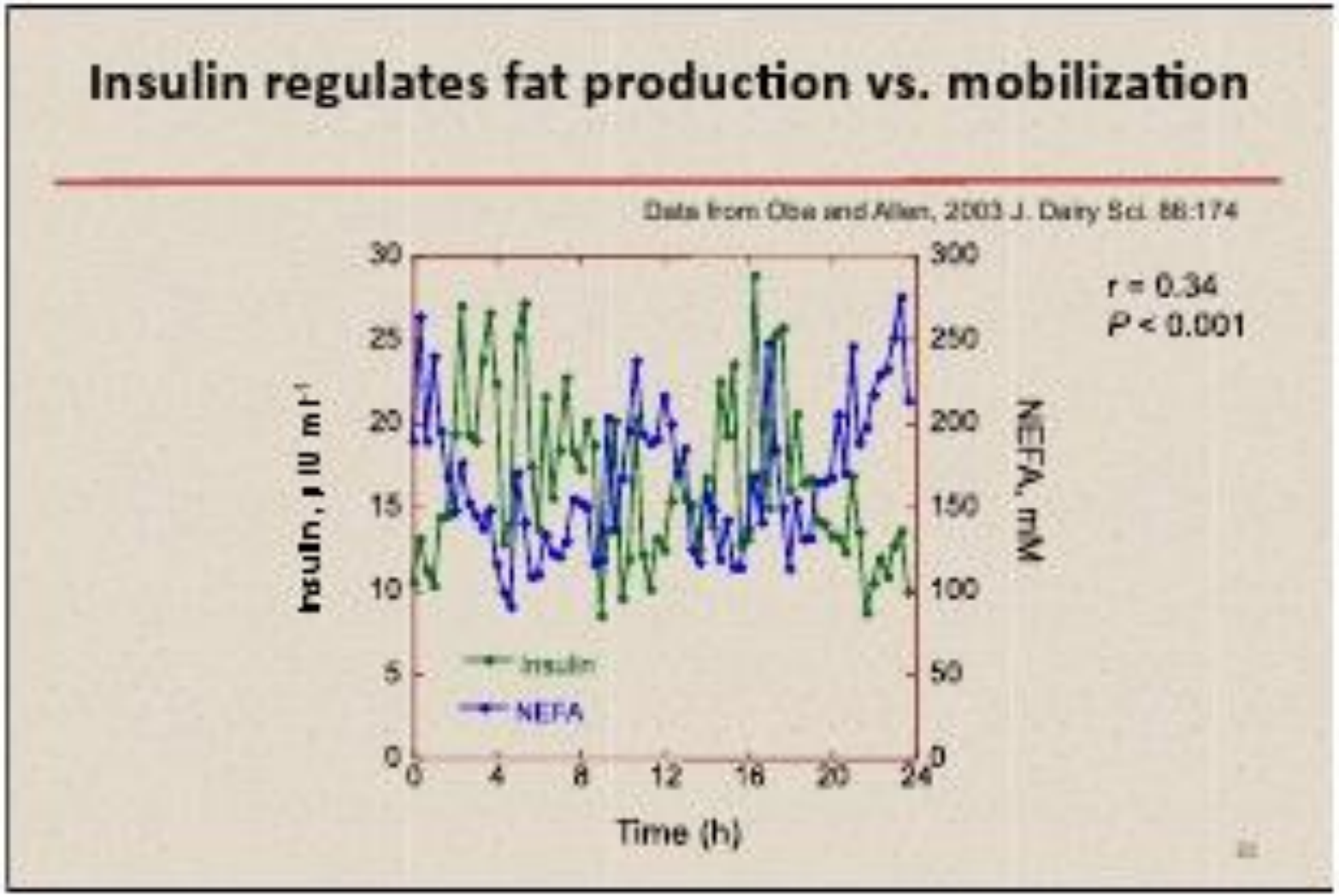


Some other things

- Slow starch…better DMI. Intestinal starch = more glucose
- Metabolisable protein is glucogenic too remember
- Propylene glycol. Liquid phase to intestine for glucose at day 1-3. 300-500ml per day
- Glycerol . Much as for propylene glycol
- Chromium think 7 mg daily
- Cobalt think 20 mg daily. Crucial for Vit b12 to get propionate to Glucose

- Methyl donors. Betaine. Choline. Methionine. Promotes VLDL export from liver. Liver function promotes gluconeogenesis
- Reduce stress overall

Insulin is your friend, so promote Glucose to promote insulin !

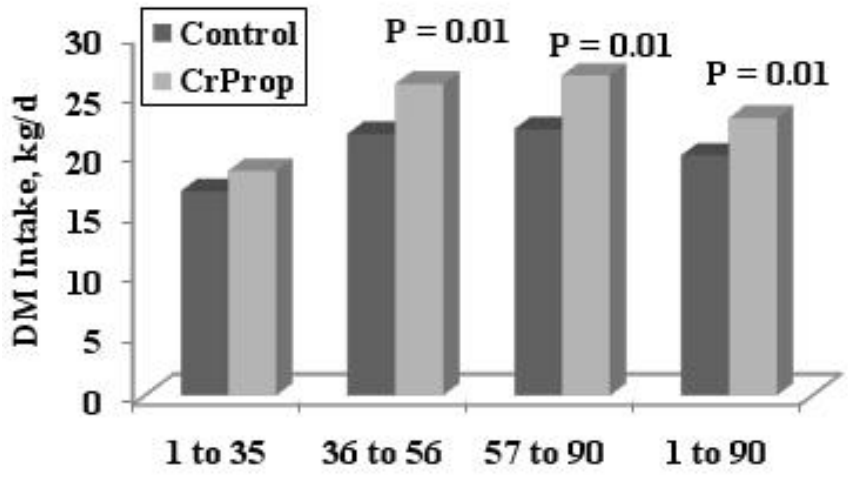


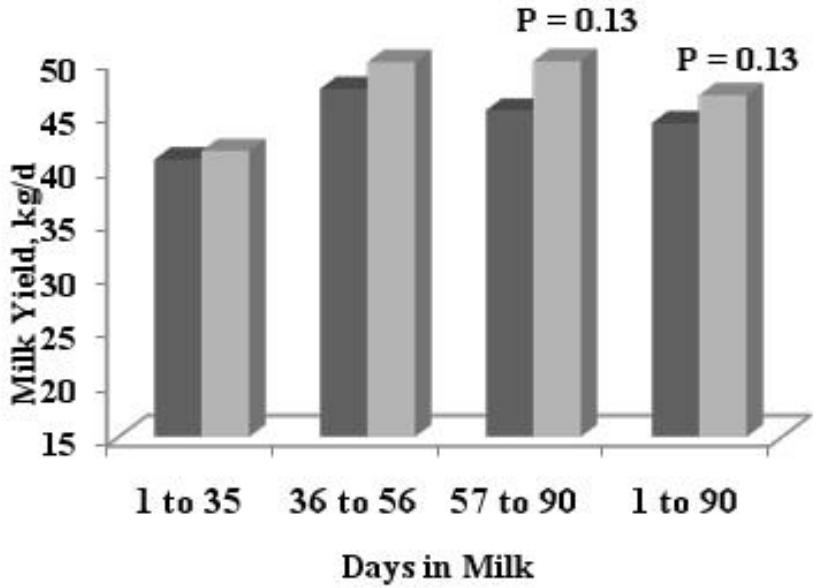
Glucose precursors => Insulin => lower NEFA levels in blood. Think Starch , prop Glycol etc. This is the Irish cows again

Table 1: Effect of propylene glycol supplementation on indices of negative energy balance in grazing cows at 15 days in milk. The BHB and NEFA concentrations observed for the control cows are indicative of excessive NEB

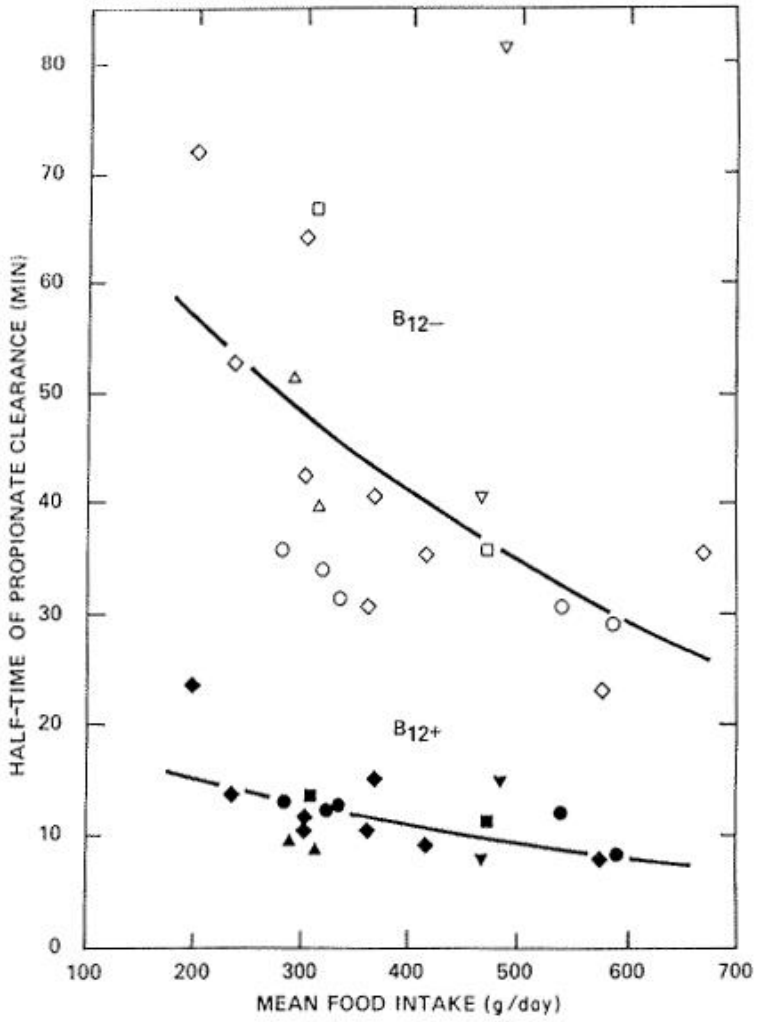
Plasma metabolite	Propylene glycol	Control
Glucose (mmol/l)	4.0	3.0
BHB (mmol/l)	0.5	1.5
NEFA (mmol/l)	0.55	0.95

Chromium increases insulin response





Optimise ruminal propionate to glucose with Cobalt/ Vit b12



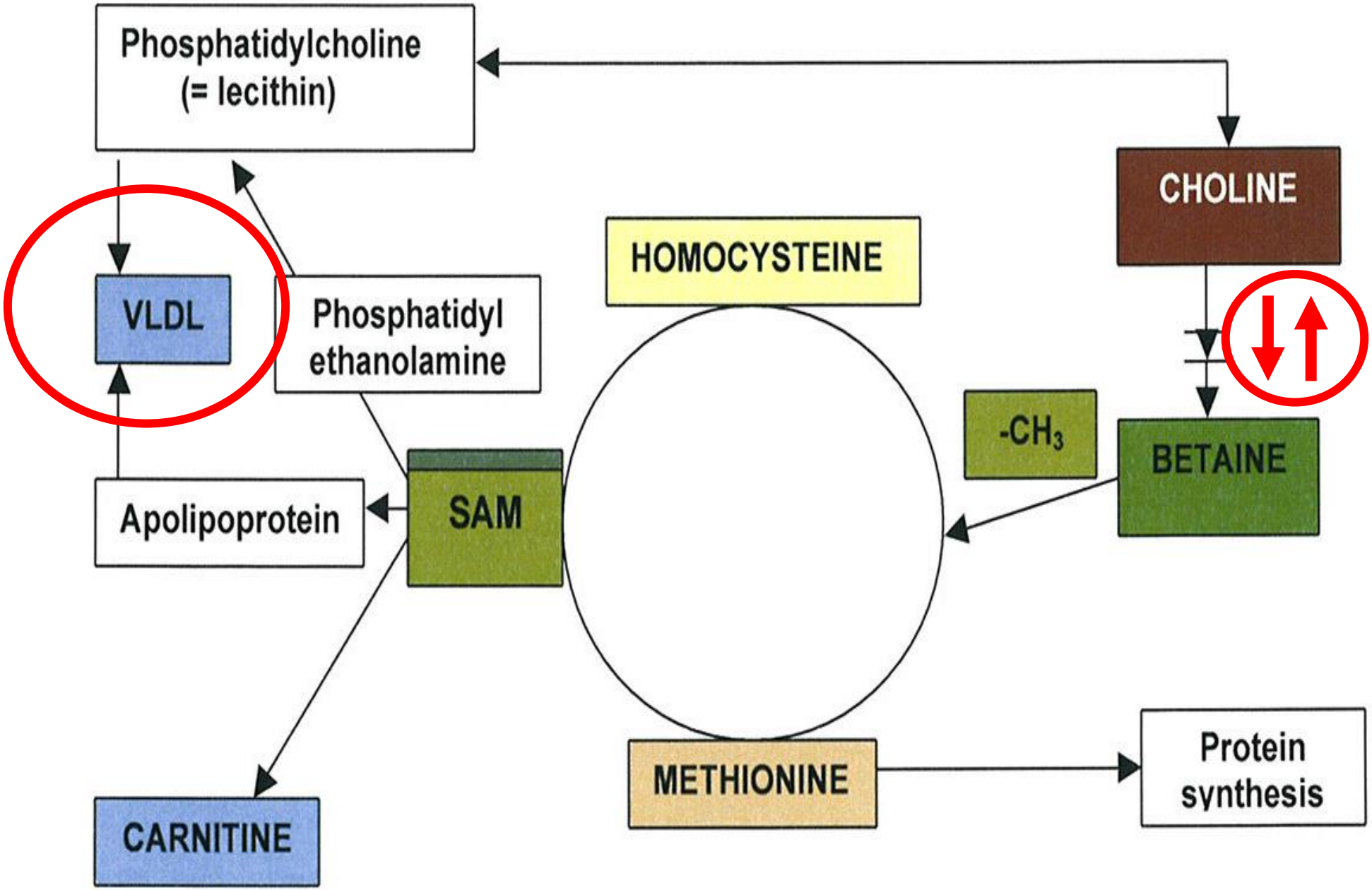
Propionate is of limited use unless it gets to Glucose within the liver…its not used systemically much at all (unlike acetate and butyrate that are used by body tissue)

My suggestion , run 20mg/head/day Cobalt as highly soluble forms eg sulphate + cobalt lactate or cobalt glucoheptonate

How to Get fat (NEFA) through the liver- VLDLS are the key.

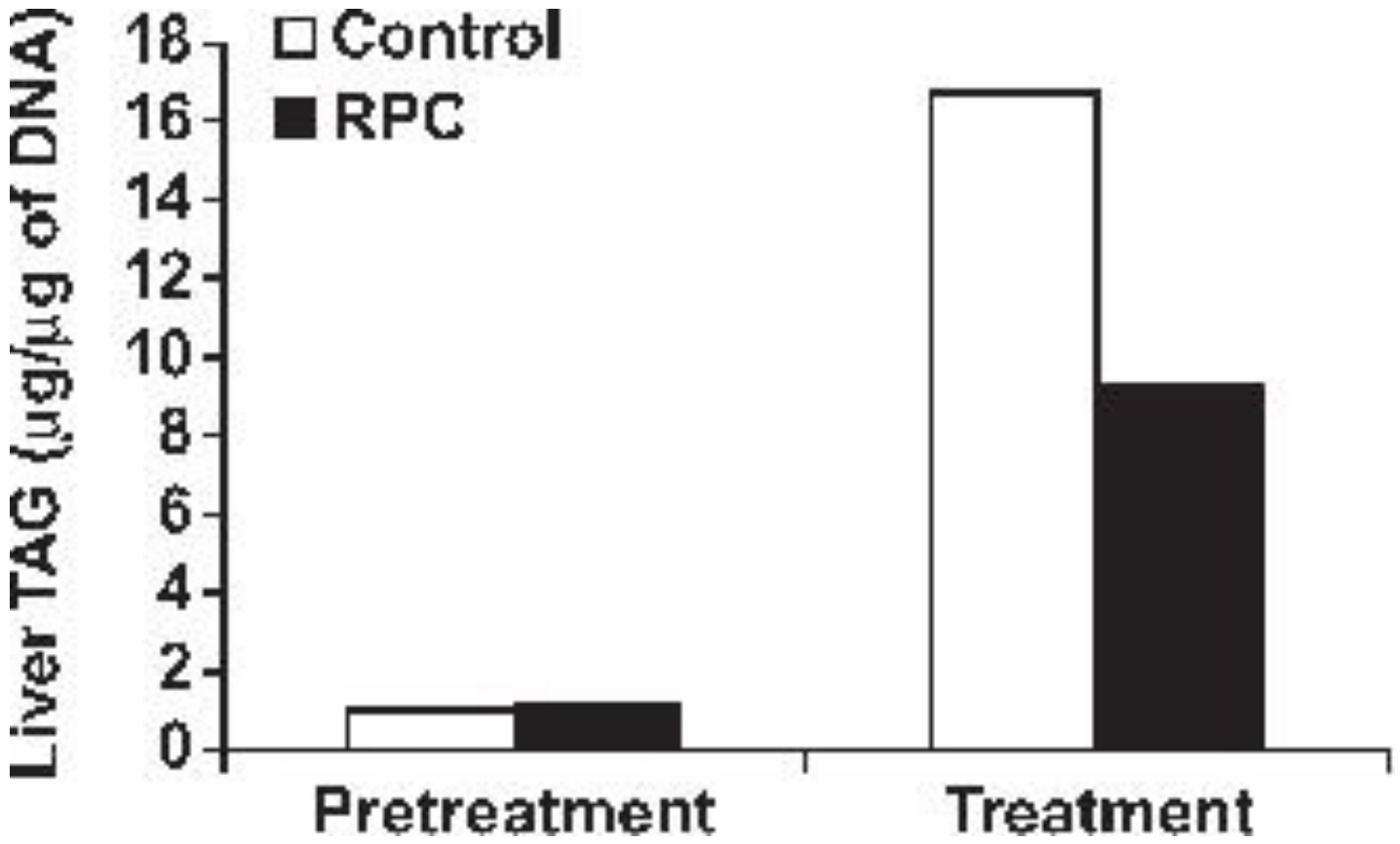
- Very low density lipo proteins. Small particle size fat bits that can move out of the liver and back into blood. Then into milk for fat yield.
- Methyl donors=protected choline or betaine or methionine
- NB betaine much cheaper then choline 10c vs 40c/day (Aus any way)

- Produce VLDLs , and address the shortfall in oxidative capacity of the liver by getting fat out of the liver and putting fat into milk
- Get better glucogenesis and ureagenesis action back into liver


Phosphatidylcholine
(= lecithin)
CHOLINE
VLDL
Phosphatidyl
ethanolamine
HOMOCYSTEINE
-CH3
BETAINE
Apolipoprotein
SAM
METHIONINE
Protein
synthesis
CARNITINE

Choline (methyl donor) slows fat build up in liver

(cooke et al 2007)



Choline (methyl donor) speeds up Fat leaving liver

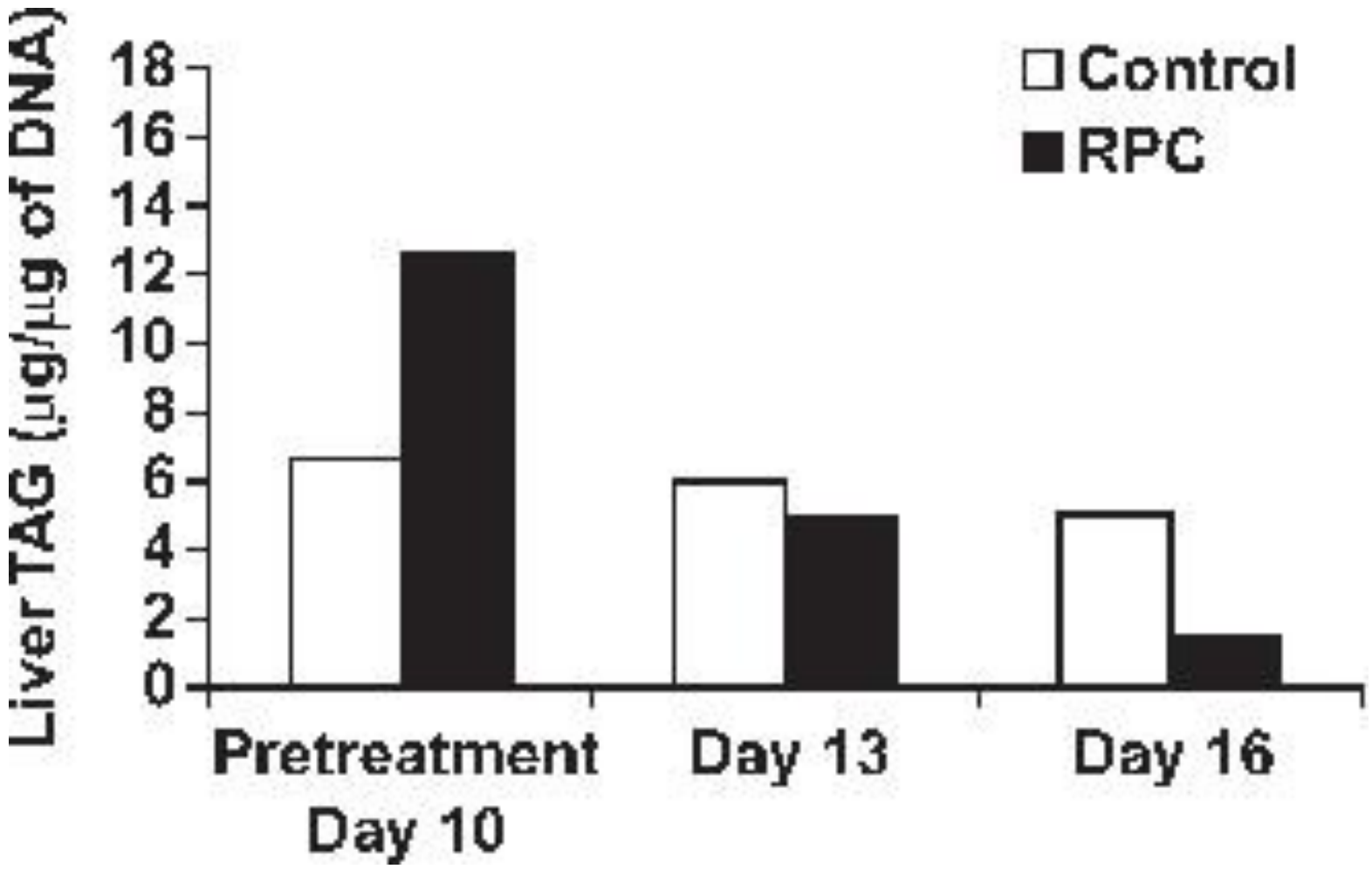


Table 1. Effect of rumen-protected choline (RPC) on plasma metabolites during feed restriction (experiment 1) [1]

Metabolite	Control	RPC	SEM	P-value
Plasma glucose, mg/dL	48.3	51.4	1.5	0.14
Plasma NEFA, μEq/L	703	562	40	0.004
Plasma BHBA, mg/dL	7.6	8.0	0.4	0.47

[1]Covariately adjusted least squares means.

25% reduction in blood NEFA levels

(cooke et all 2007)

Betaine (methyl donor) 90 DIM (Wang 2010)

	NDF %digest	ADF % digest	Total VFA	Glucose	NEFA	BHB	ECM L/day
Treat	50	45	133	3.2	228	717	26.5
Control	45	42	118	3.1	267	734	25.2
% Diff	+11% P=<0.05	+7% P=<0.05	+13% P=0.001	+3% NS	-15% P=0.013	-4% P=0.005	+5% P=0.03

So what causes Ketosis ?

- Is it the low dry matter intake if we don't feed them ?
- Is it the low dry matter intake from insulin issues and gestational diabetes?
- Is it the raised or XS NEFA flow from gestational diabetes?
- Is it the excess Body weight on some cows ?
- Is it limitations on liver function and high blood ammonia flows to urea flow ?
- Is it raised milk flows sucking up glucose ?
- Is it a lack of glucose precursors, even if I have OK DMI overall ?
- Is it compromised glucose metabolism
- YES. Best bet is to focus on more DMI.