Carbohydrates, ketones, and cancer

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Otto Warburg

THE METABOLISM OF TUMORS IN THE BODY.

By OTTO WARBURG, FRANZ WIND, and ERWIN NEGELEIN.

(From the Kaiser Wilhelm Institut für Biologie, Berlin-Dahlem, Germany.)

(Received for publication, April 29, 1926.)

In this contribution we discuss the question of whether tumor cells in living animals can be killed off through lack of energy, and the related question of how the tumors are supplied with oxygen and glucose in the body.

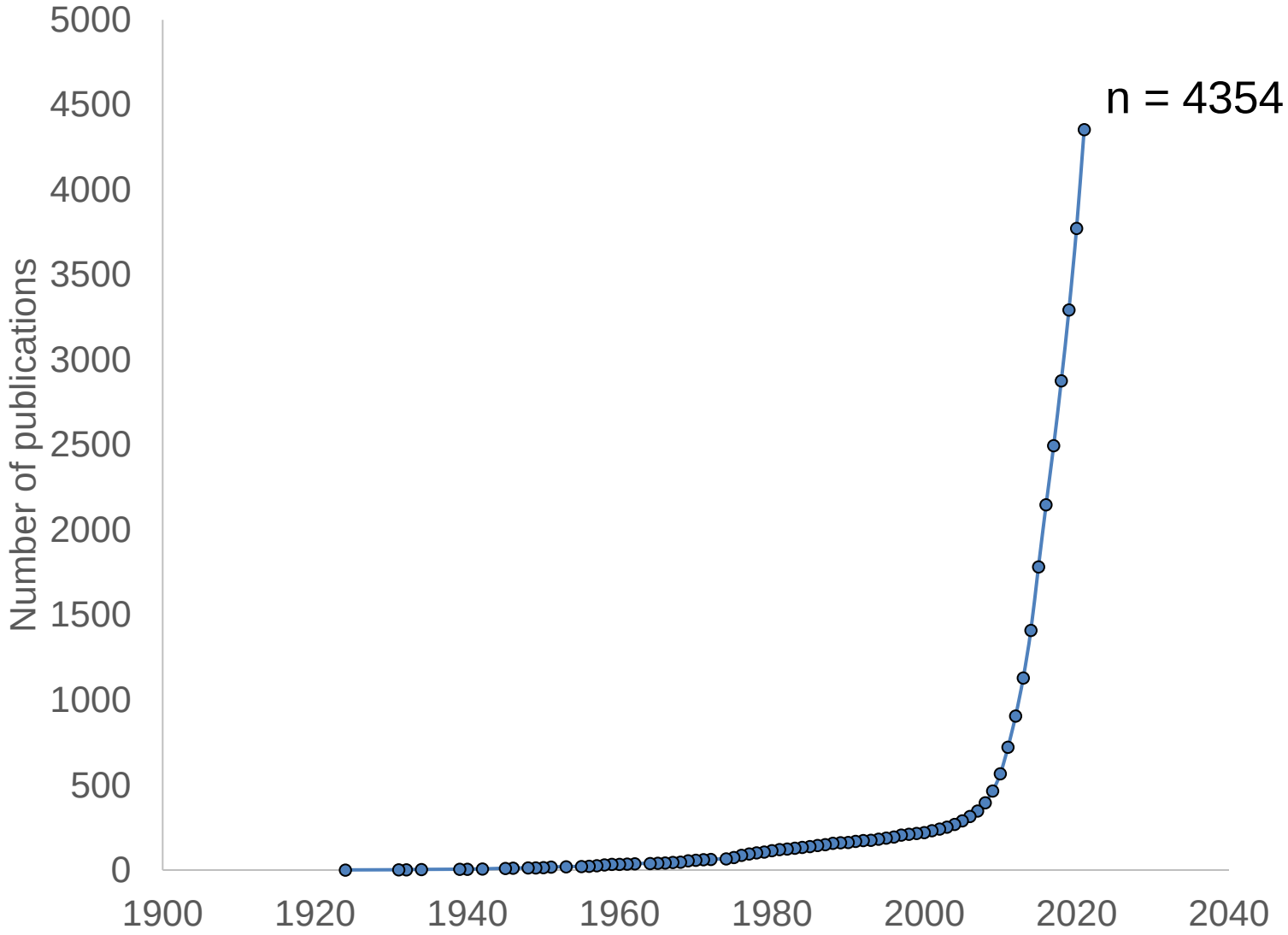
J.W. McGuire/U.S. National Library of Medicine

Warburg, O., Wind, F., & Negelein, E. (1927). The metabolism of tumours in the body. *The Journal of general physiology, 8*(6), 519-530. 10.1085/jgp.8.6.519

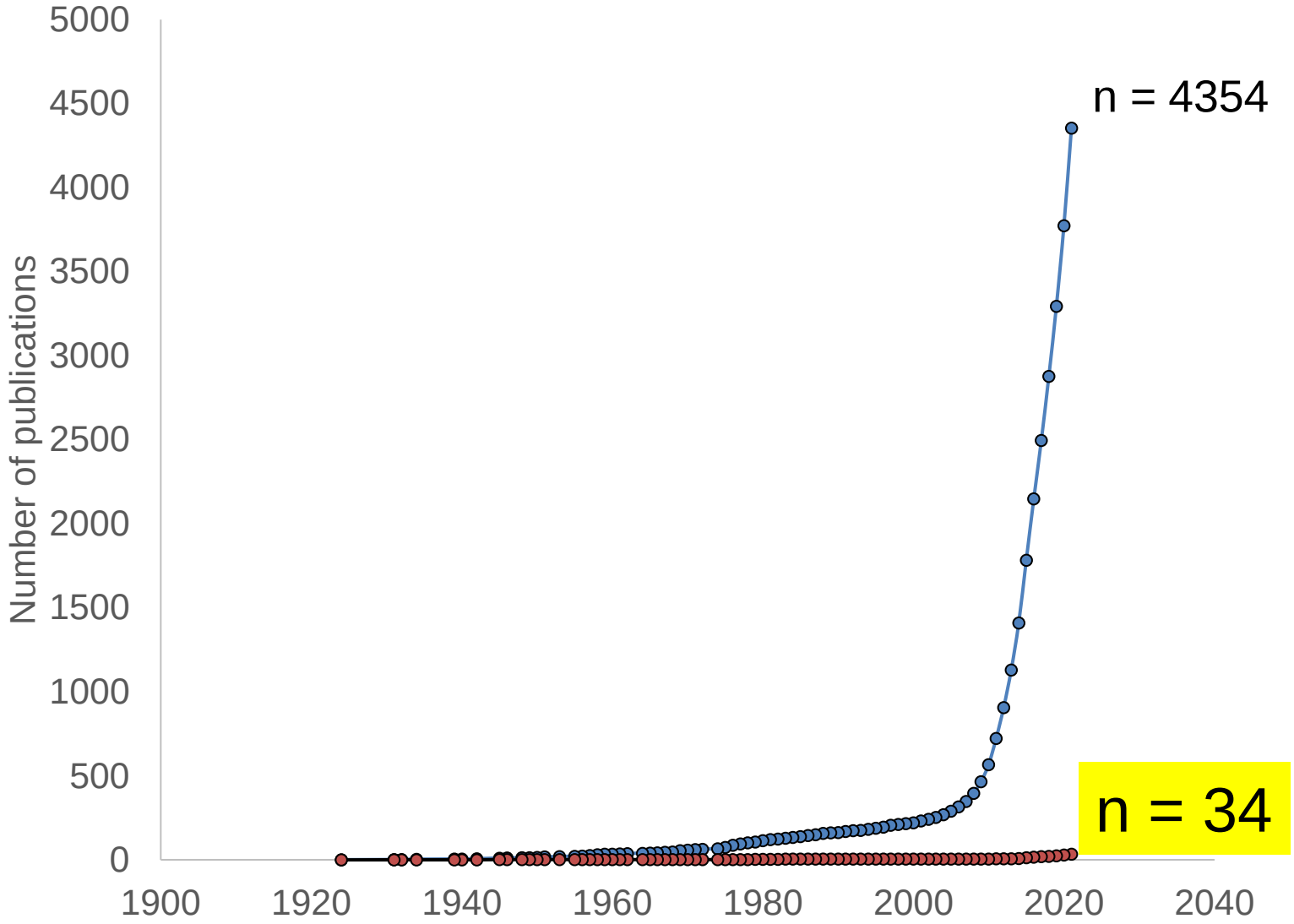
The *"Warburg effect"*

- Tumour cells produce ATP by anaerobic glycolysis even in the presence of adequate oxygen

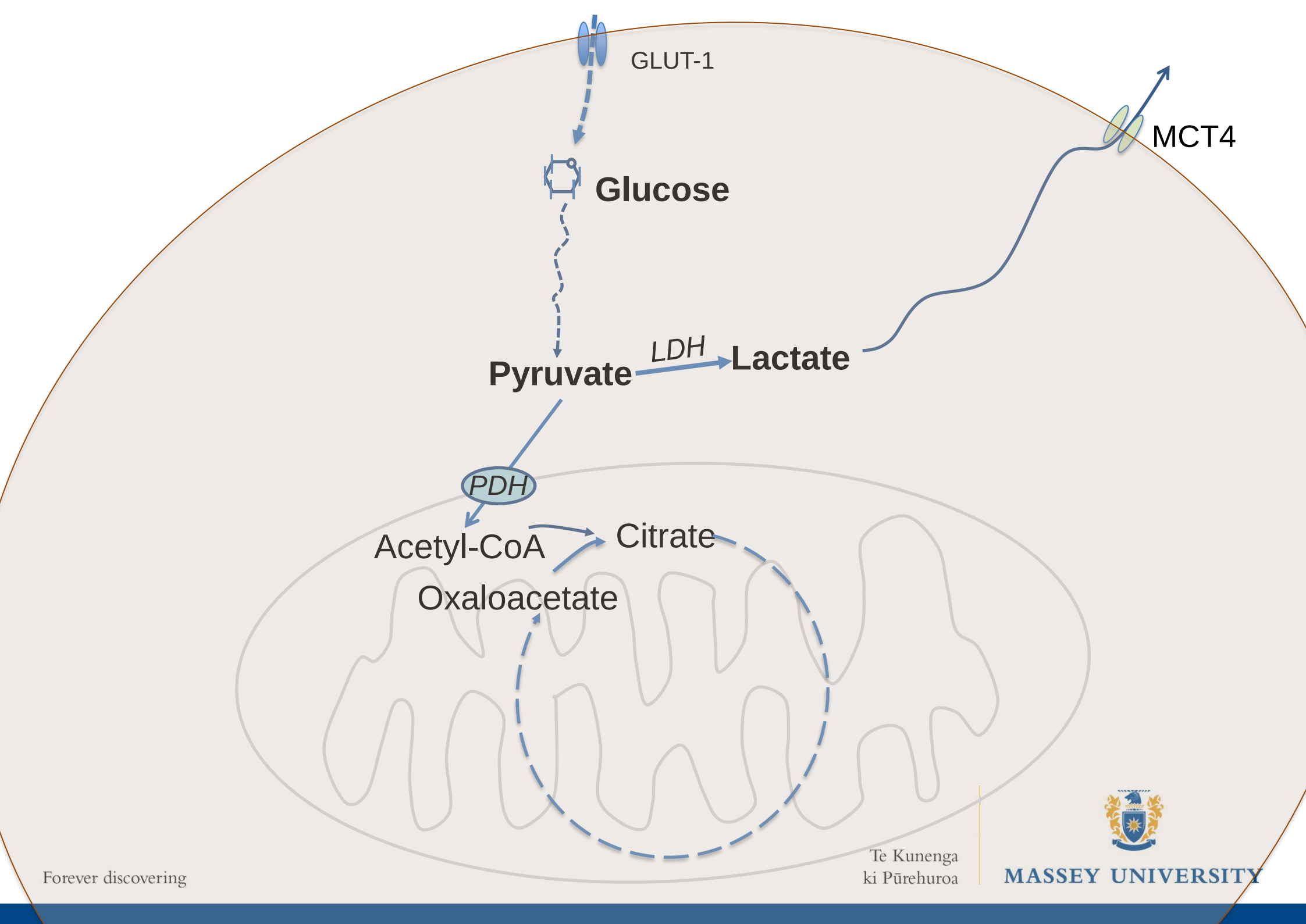
“Warburg effect” publications

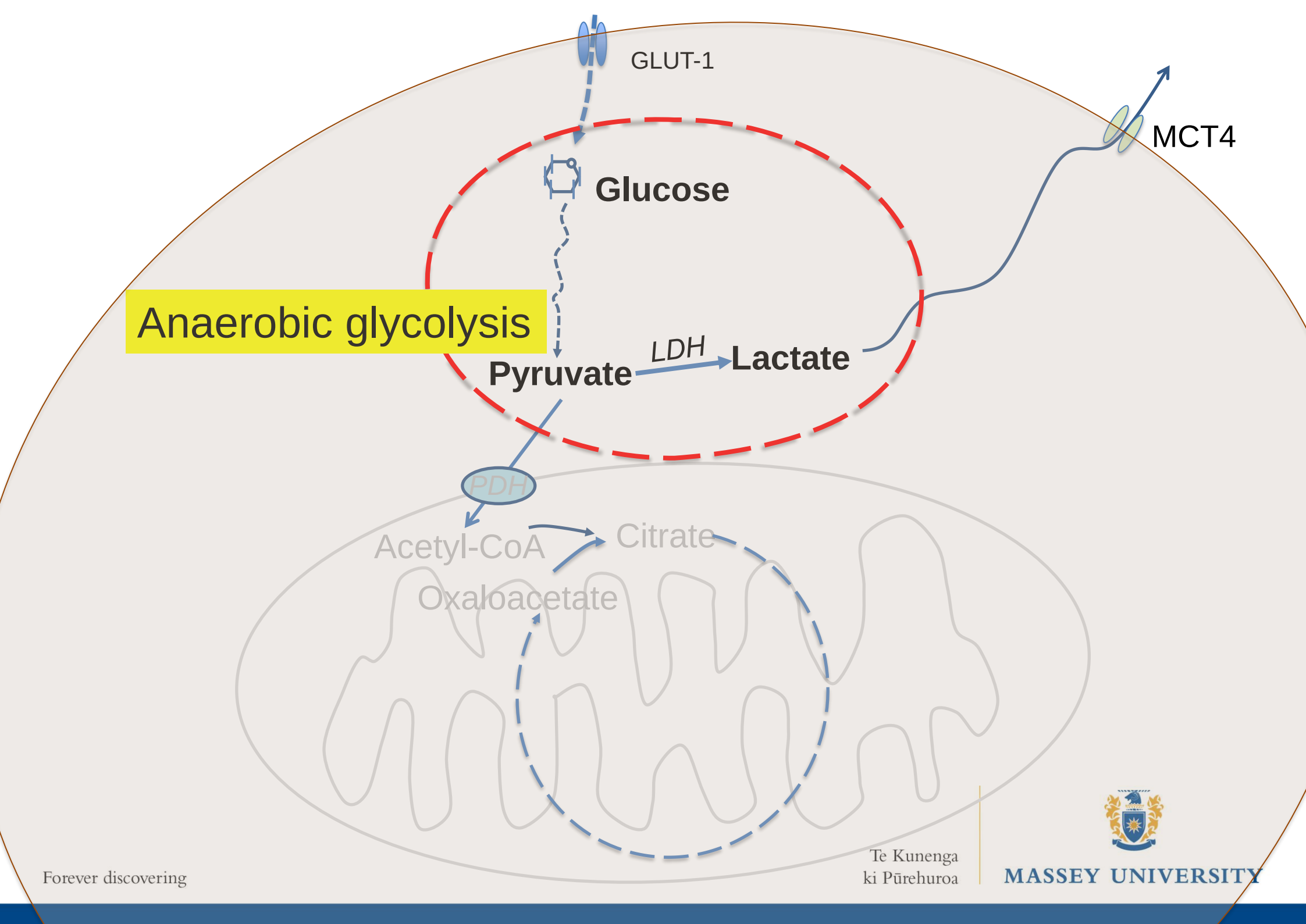


“Warburg effect” veterinary publications



Anaerobic glycolysis


GLUT-1
MCT4
Glucose
Pyruvate
LDH
Lactate
PDH
Acetyl-CoA
Citrate
Oxaloacetate


GLUT-1
MCT4
Glucose
Anaerobic glycolysis
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Pyruvate
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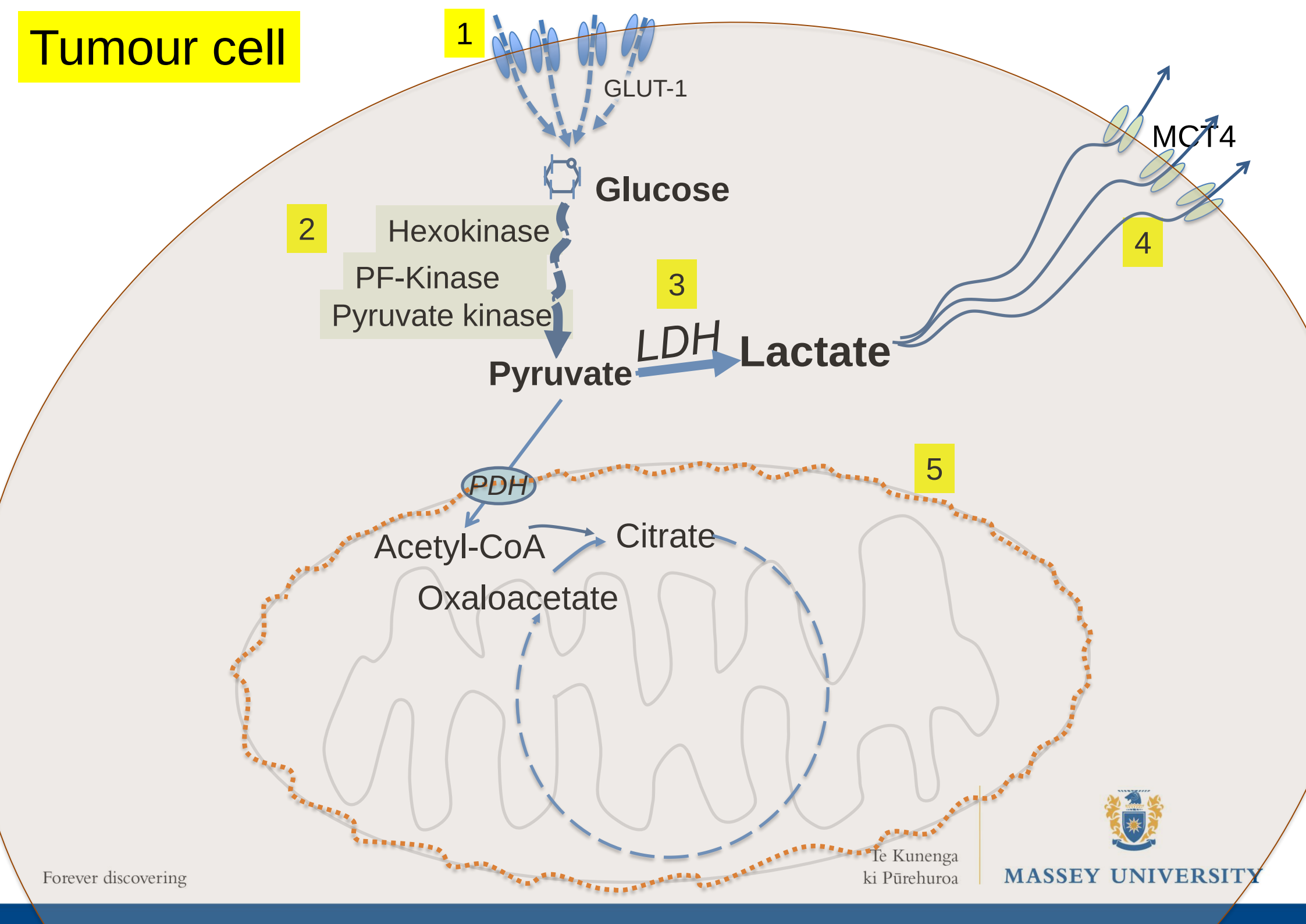
Citrate
Oxaloacetate

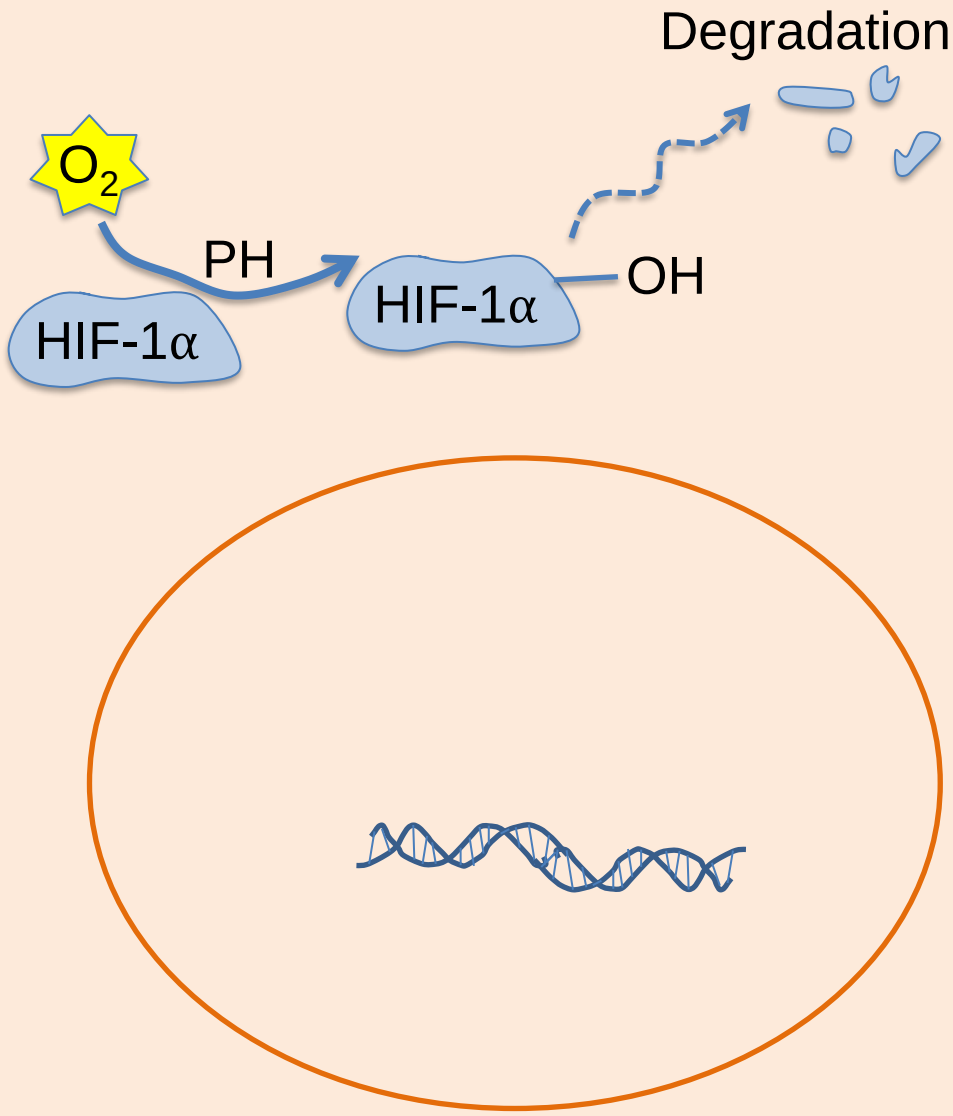
Warburg Effect Mechanisms

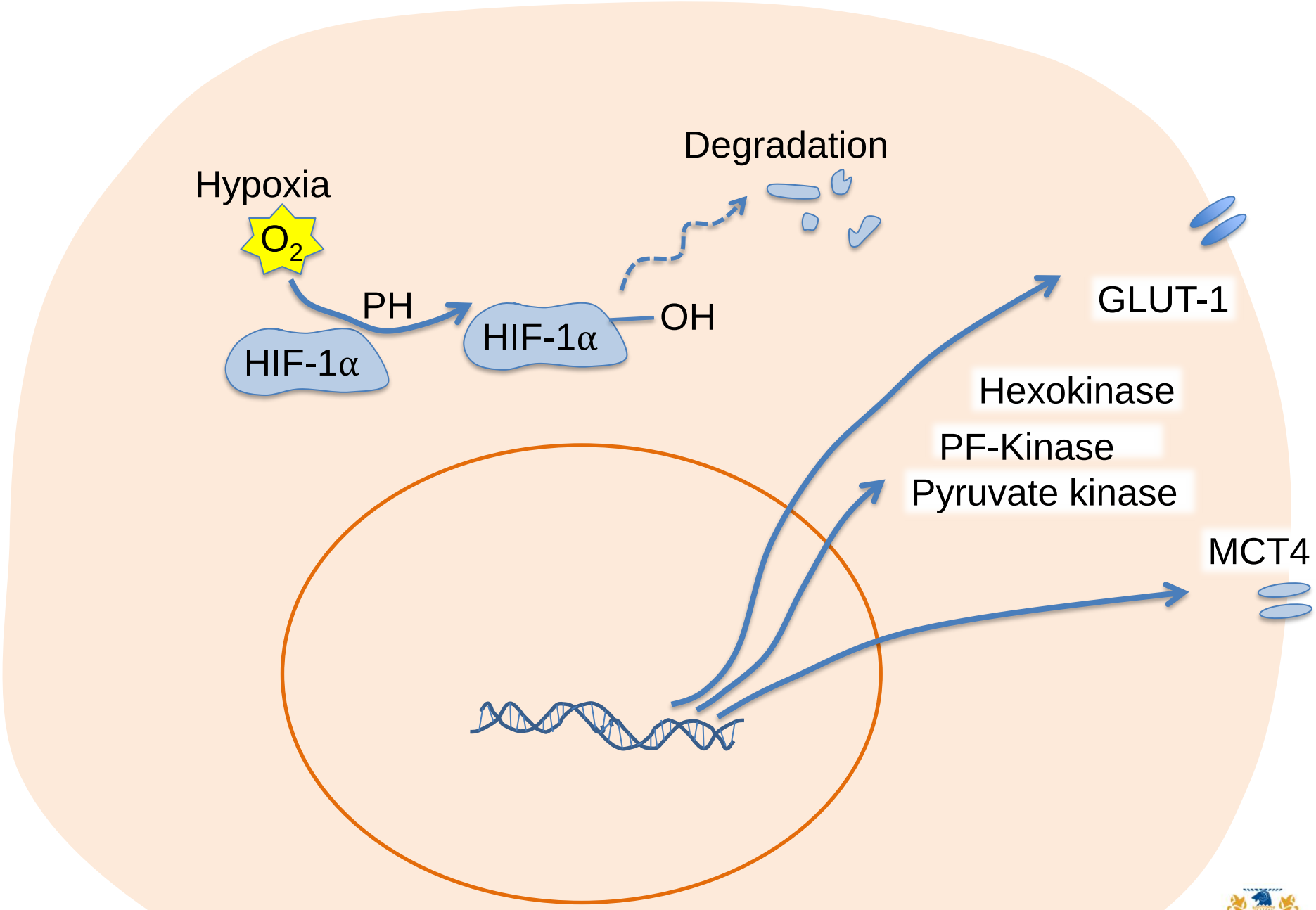

Tumour cell
1
GLUT-1
Glucose
2
Hexokinase
PF-Kinase
Pyruvate kinase
3
LDH
Lactate
Pyruvate
MCT4
4
5
PDH
Acetyl-CoA
Citrate
Oxaloacetate

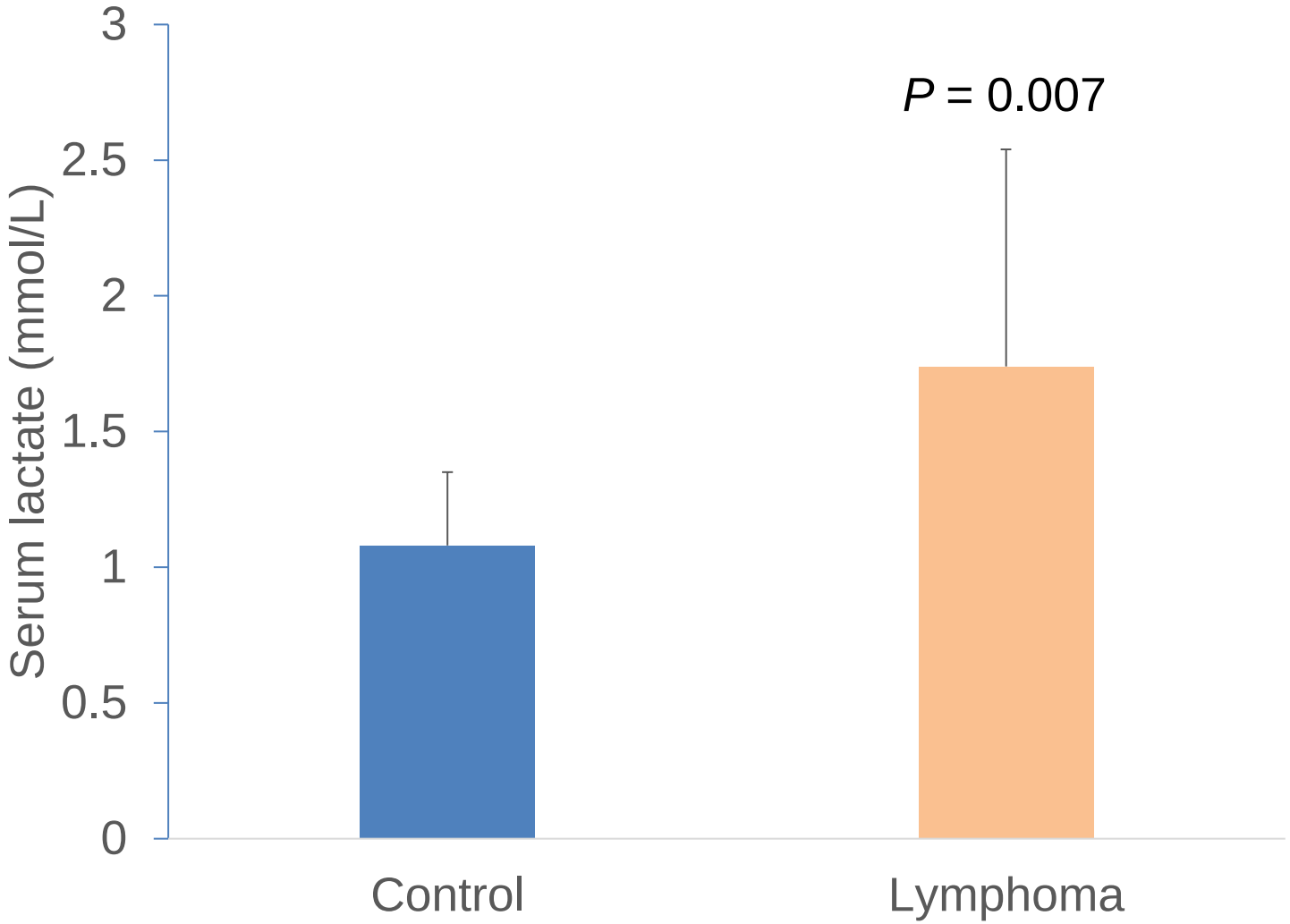
Regional hypoxia drives tumour adaptations

- Cells respond to hypoxia by activating hypoxia inducible factor (HIF-1α)
-

Hypoxia inducible factor (HIF-1α) regulates glycolysis in tumours




Degradation
Hypoxia
O_2
PH
HIF-1α
HIF-1α
OH
GLUT-1
Hexokinase
PF-Kinase
Pyruvate kinase
MCT4



McQuown, Bet al (2018). Preliminary investigation of blood concentrations of insulin-like growth factor, insulin, lactate and beta-hydroxybutyrate in dogs with lymphoma as compared with matched controls. *Vet Comp Oncol, 16*(2), 262-267

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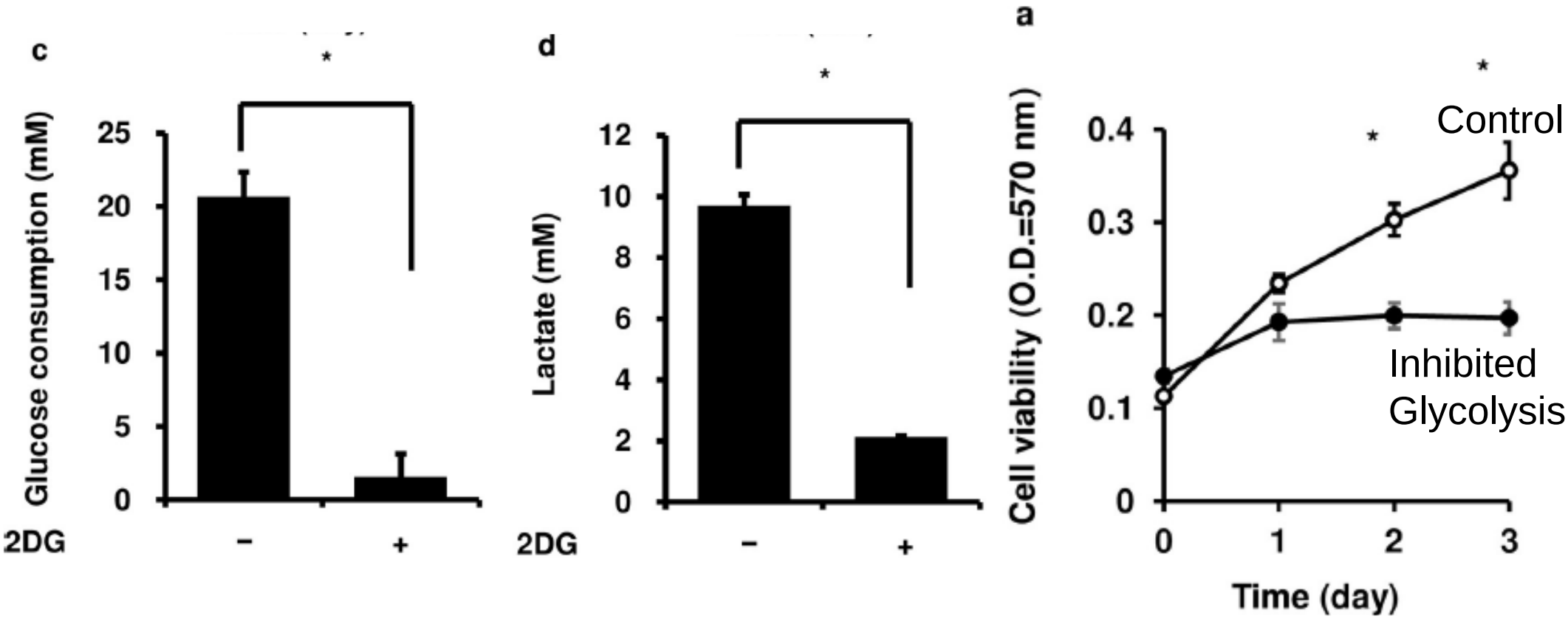
Preventing glycolysis inhibits canine melanoma cells



Suwabe, Y., et al (2021). Involvement of GLUT1 and GLUT3 in the growth of canine melanoma cells. *PLoS One, 16*(2)

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Hyperlactataemia in canine cancer is mild

- Mean lactate = c. 1.2 (0.98 – 2.5 mmol/L)
- Not all studies have found increased lactate with cancer in dogs

- Inference from small numbers with no control of diet
- Single concentration doesn't capture metabolism

McQuown, Bet al (2018). Preliminary investigation of blood concentrations of insulin-like growth factor, insulin, lactate and beta-hydroxybutyrate in dogs with lymphoma as compared with matched controls. *Vet Comp Oncol, 16*(2), 262-267

Touret, M., et al Prospective Evaluation of Clinically Relevant Type B Hyperlactatemia in Dogs with Cancer. *Journal of Veterinary Internal Medicine, 24*(6), 2010

Hyperlactataemia

- Mild hyperlactatemia may be found in dogs with lymphoma
- 90% of cases explained by mechanisms other than Warburg

Touret, M., et al Prospective Evaluation of Clinically Relevant Type B Hyperlactatemia in Dogs with Cancer. *Journal of Veterinary Internal Medicine, 24*(6), 2010

Serum lactate

$$[\text{Metabolite}] = \frac{\text{Rate of production}}{\text{Rate of elimination}}$$

Serum lactate

$$[\text{Metabolite}] = \frac{\text{Rate of production}}{\text{Rate of elimination}}$$

Serum lactate ≠ tumour metabolism

- Dogs with malignancies but without systemic complications have efficient clearance

- A single serum lactate concentration does not indicate tumour metabolism

Are all tumours the same?

- The Warburg phenotype is a metabolic signature of 70–80% of human cancers

- Probably similar in dogs and cats

Vaupel, P., & Multhoff, G. (2021). Revisiting the Warburg effect: historical dogma versus current understanding. *J Physiol, 599*(6), 1745-1757.

Low carbohydrate diets

- Neither dogs nor cats require CHO
- What effect does a low CHO diet have on interstitial glucose?

Low carbohydrate diets

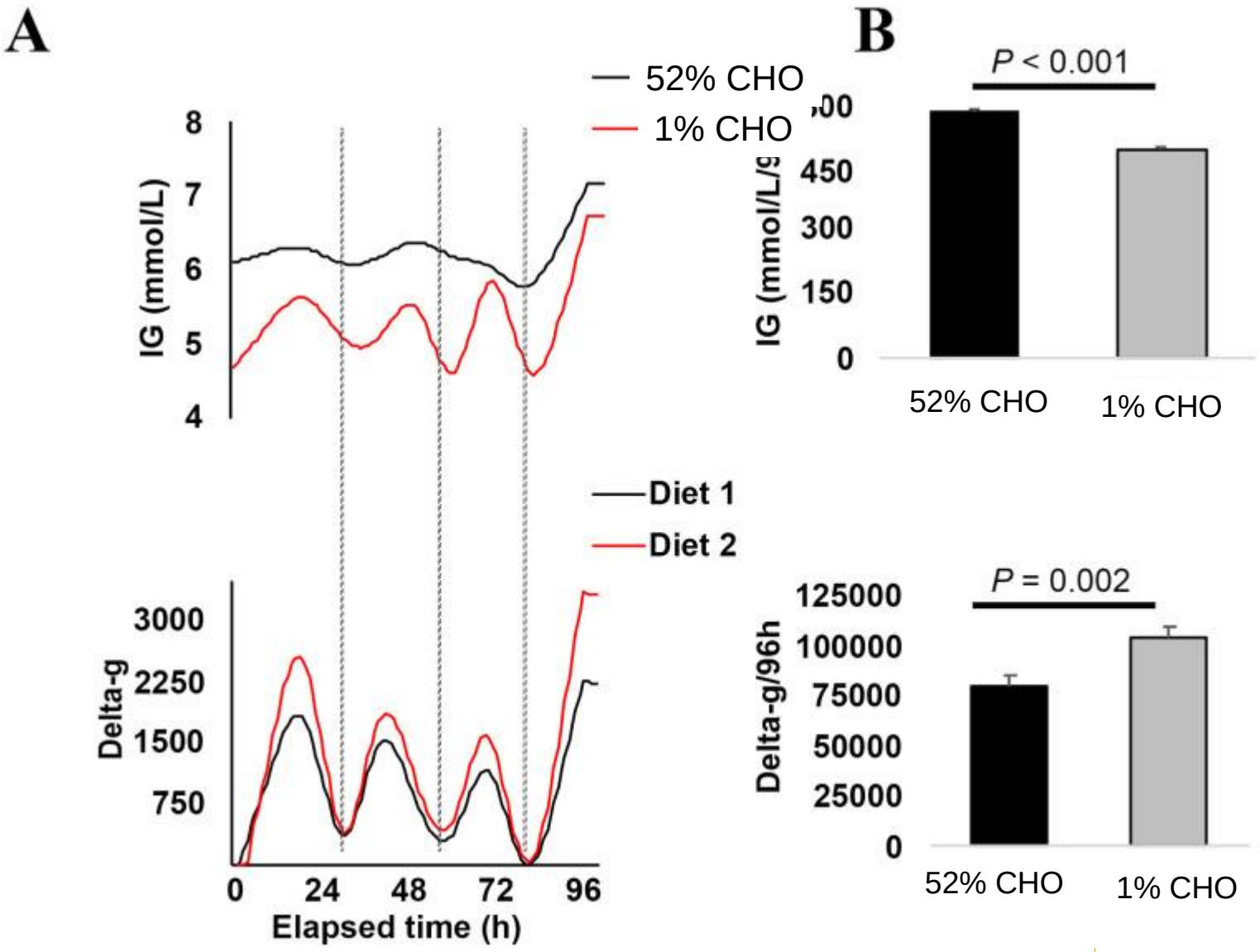
- Working farm dogs fed either:

A. 52% carbohydrate (%ME)

B. 1% carbohydrate

- What was the effect on glucose concentrations?
- What was the effect on exercise?

Continuous glucose monitoring in working dogs fed 52% or 1% carbohydrate



Gal, A., Cuttance, W., Cave, et al (2021). Less is more? Ultra-low carbohydrate diet and working dogs' performance. *PLoS One, 16*(12)

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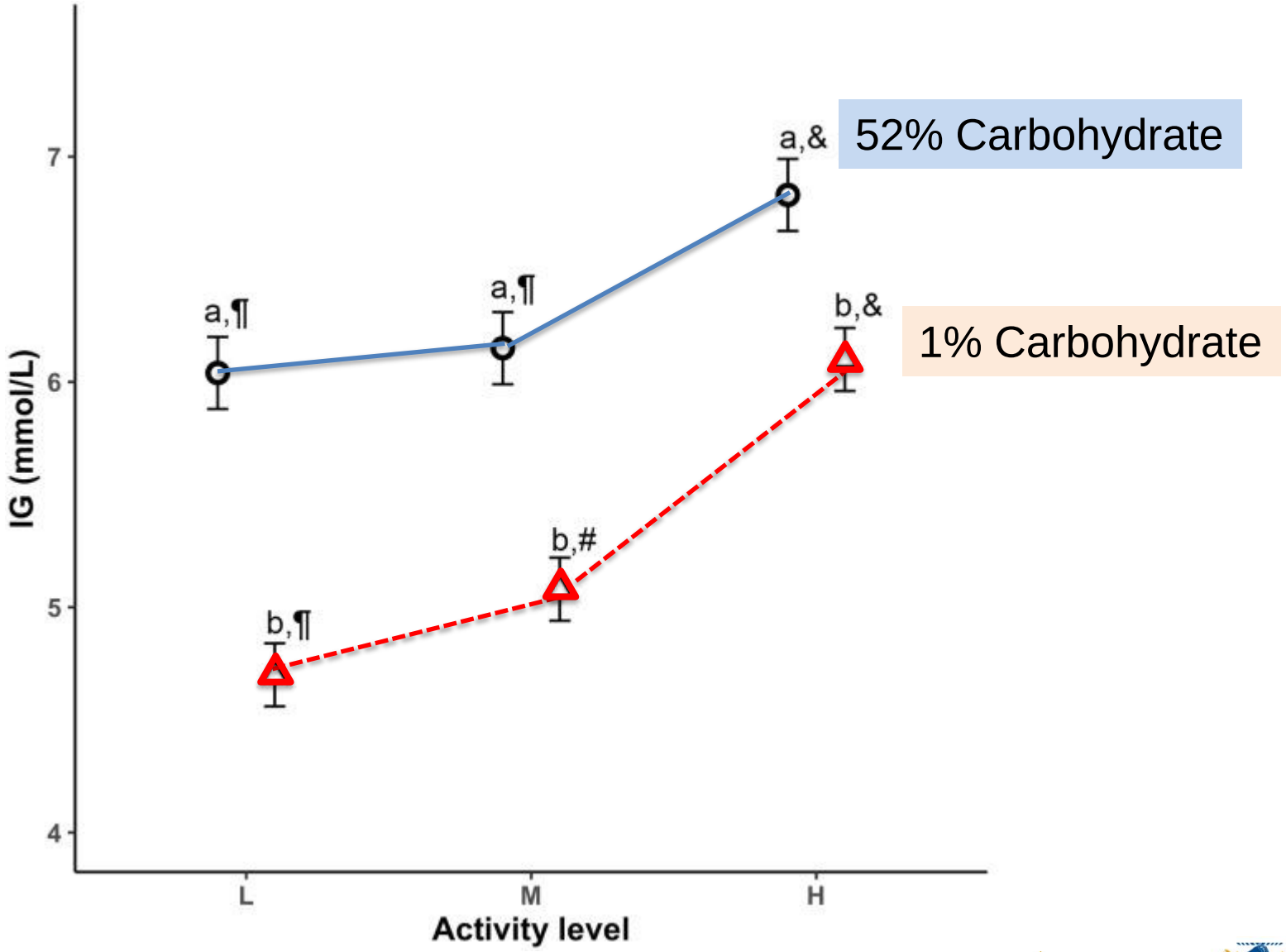

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Low carbohydrate diets increase ketones

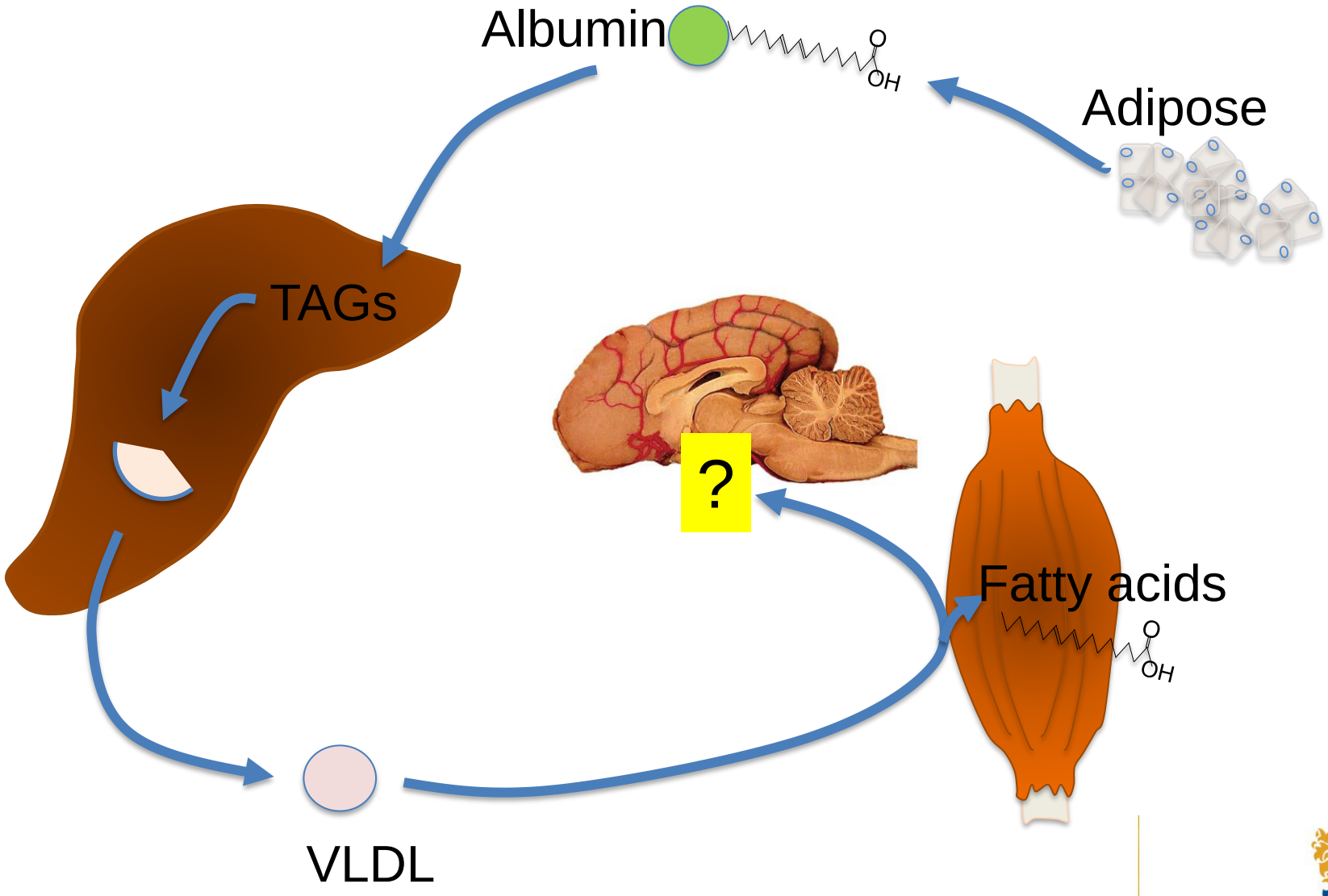
- What are ketones?

- β-Hydroxybutyrate
- Acetoacetate
- Acetone

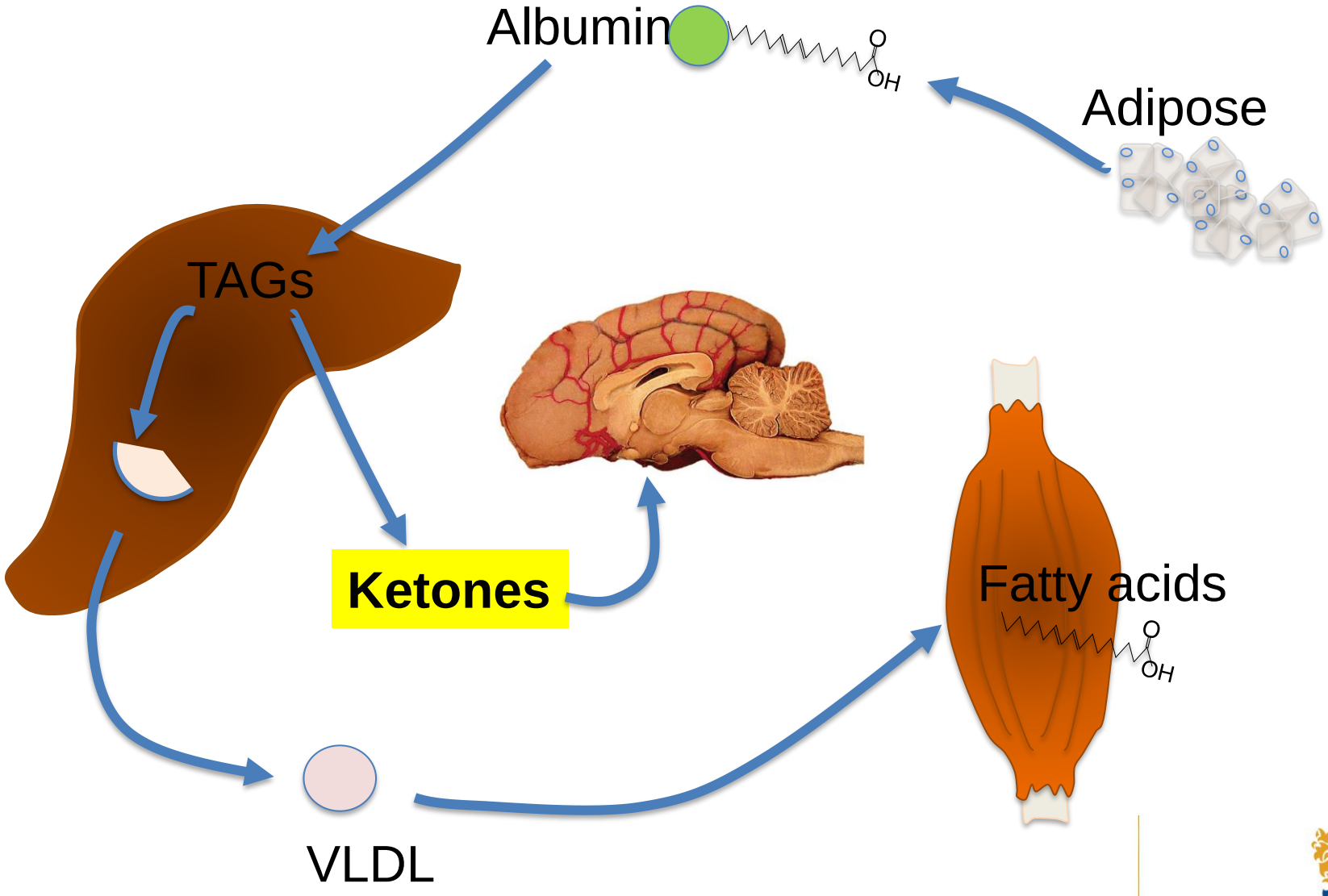
Ketones

- Ketogenesis evolved to create a fuel for the brain to utilise during starvation

Brain fuel during fasting

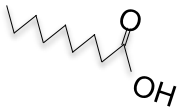


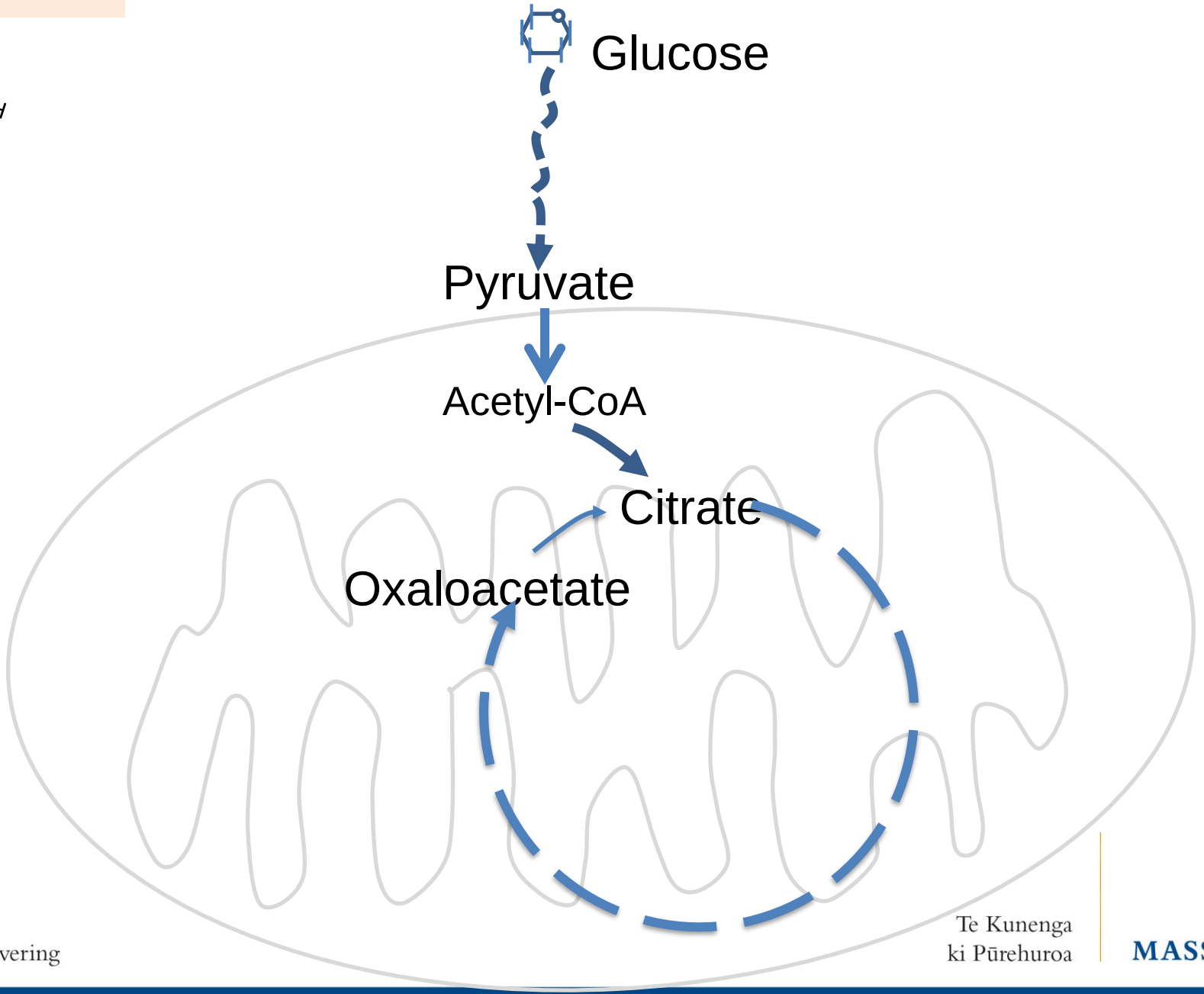
Brain fuel during fasting

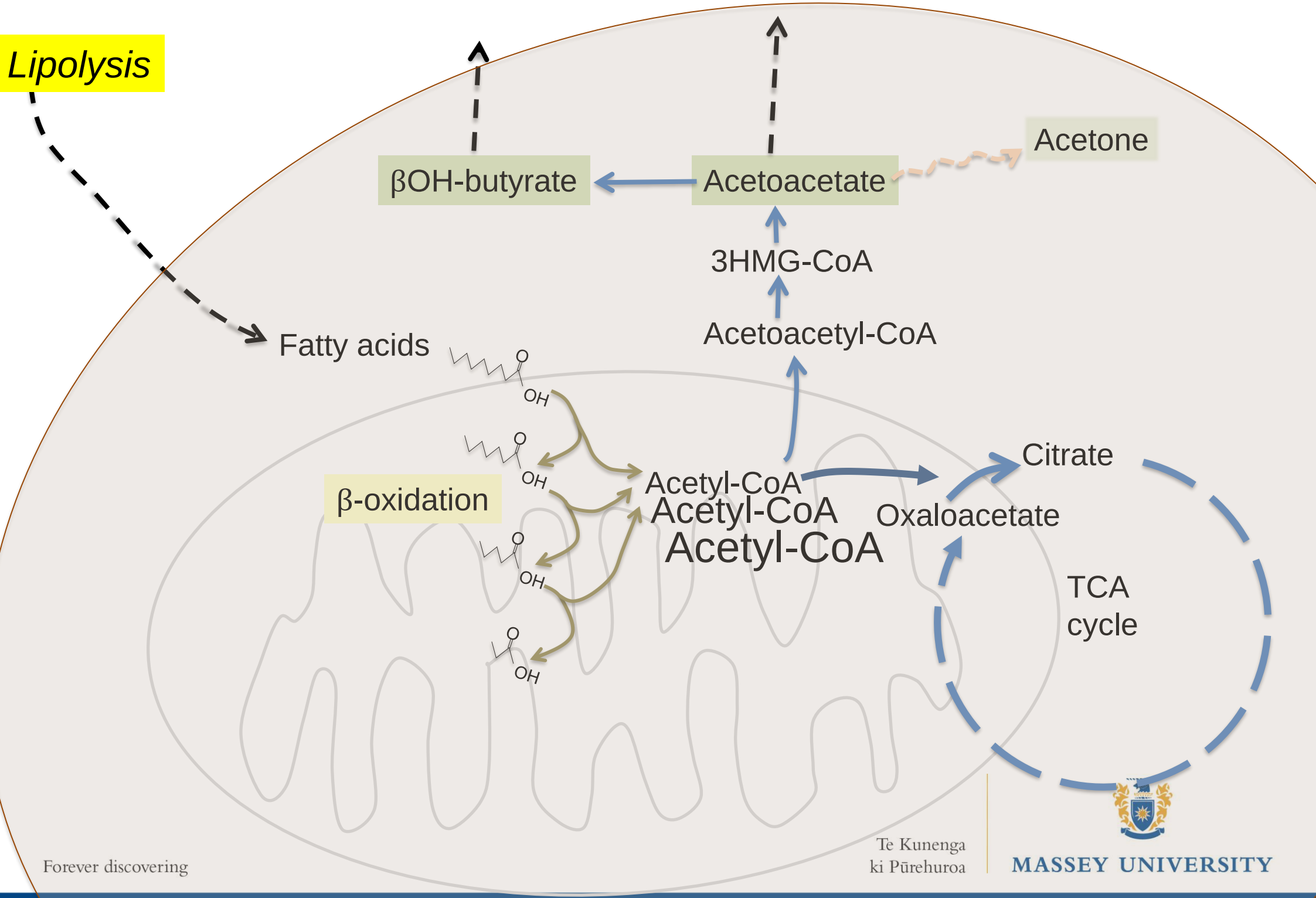


LIVER

Fatty acids

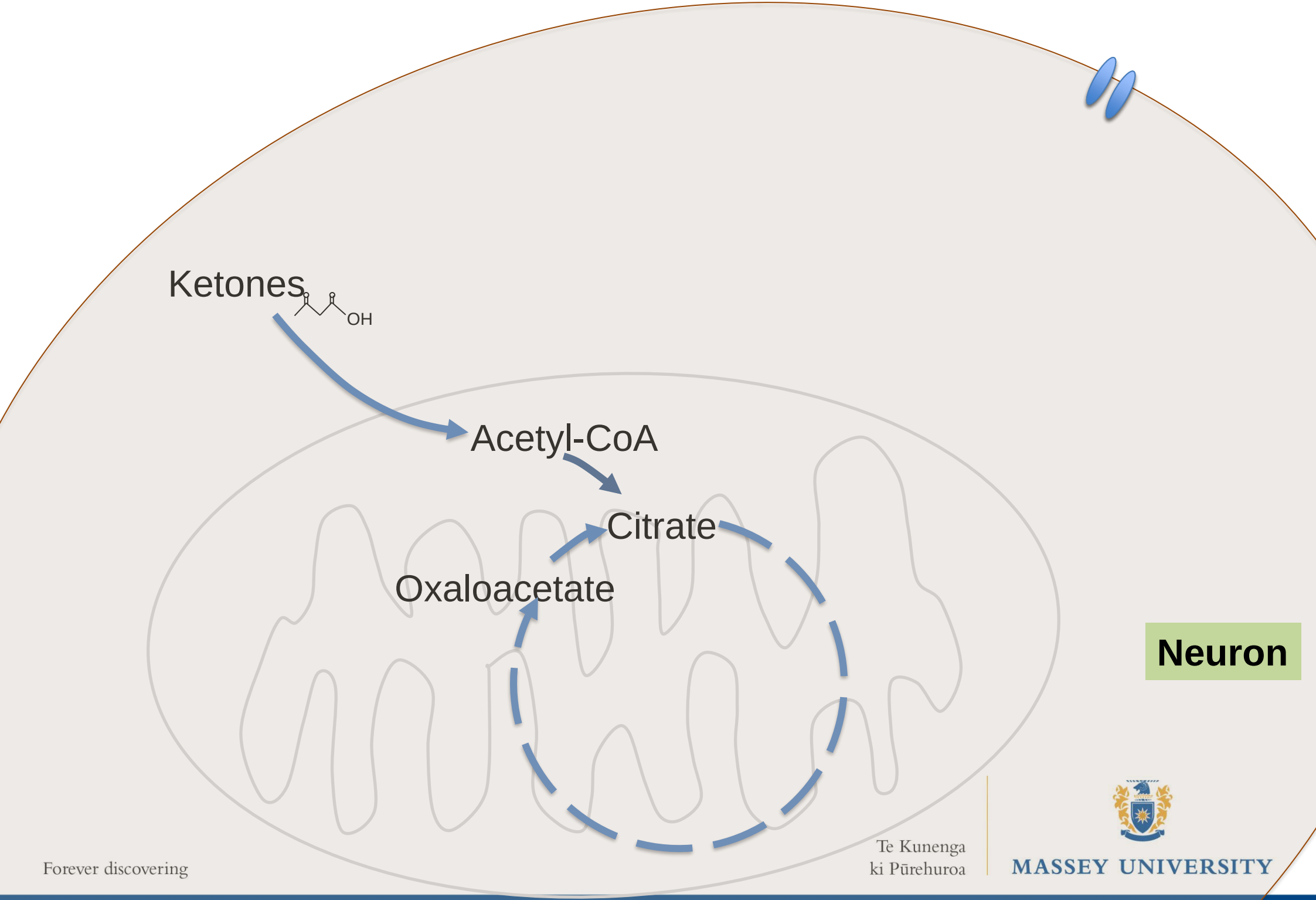





Lipolysis
βOH-butyrate
Acetoacetate
Acetone
3HMG-CoA
Acetoacetyl-CoA
Fatty acids
β-oxidation
Acetyl-CoA
Acetyl-CoA
Acetyl-CoA
Citrate
Oxaloacetate
TCA
cycle

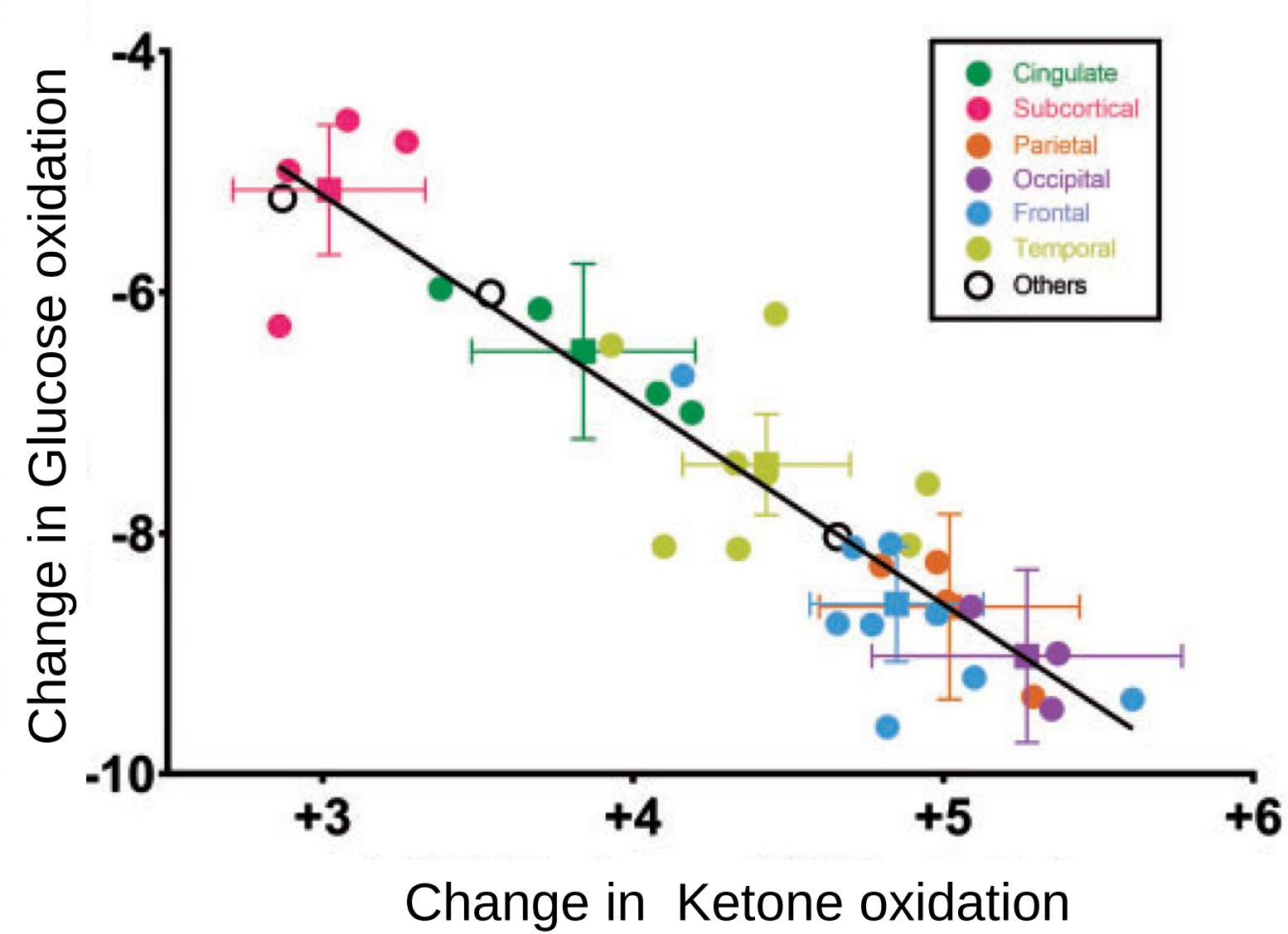
Ketone utilisation by the brain

- **Starvation**: up to 75% of ATP from ketones
- Increased MCT1 expression
- Decreased GLUT1/3
- **Neonates**: Brain = 11% BW, and 70% ATP
- Glucose supply insufficient ⇨ Ketones essential
- Preterm babies
  - Insufficient body fat to synthesise ketones
  - Susceptible to neurodevelopmental delay



Neuron

Change in substrate use on ketogenic diet



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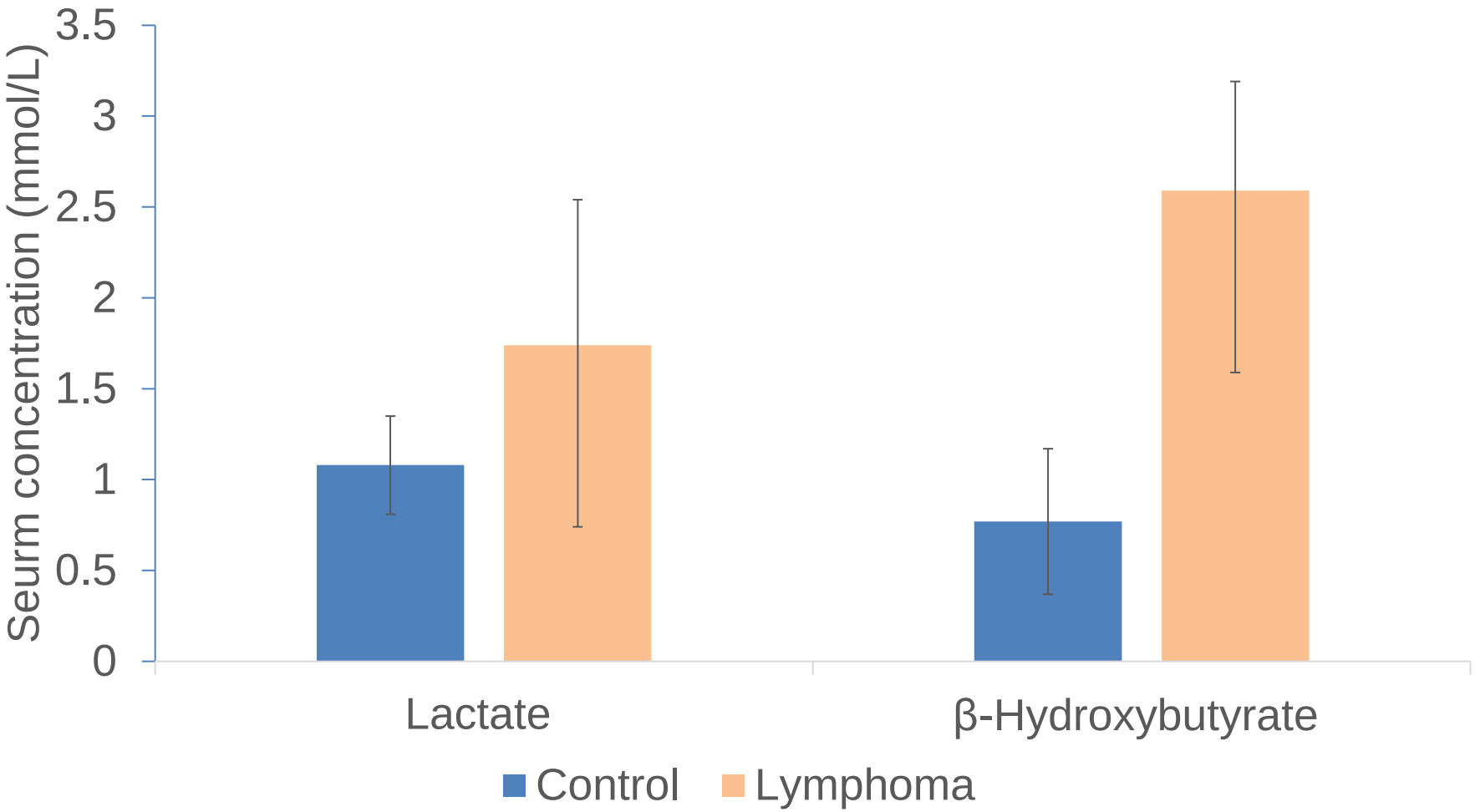
Ketone utilisation by tumours

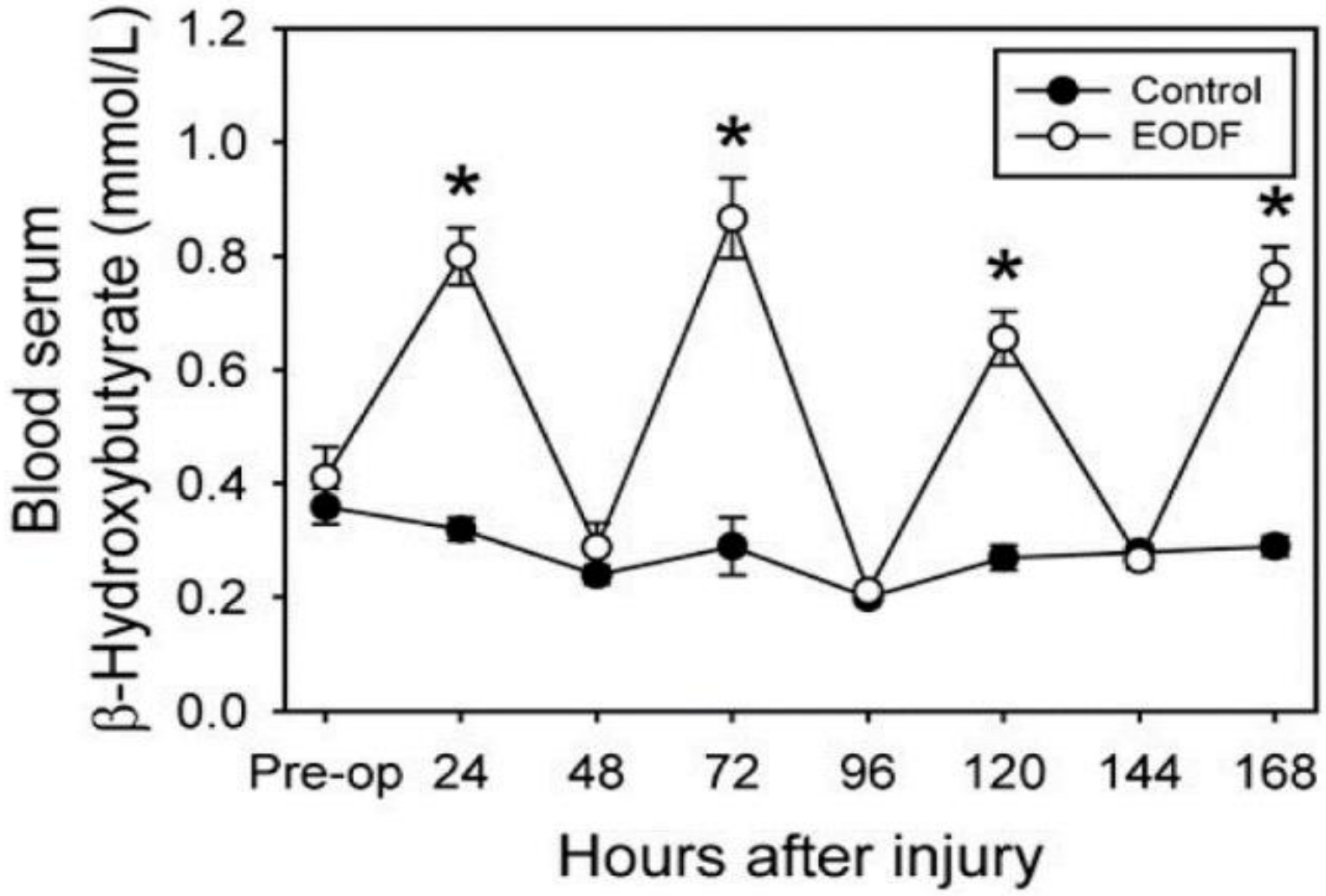
- Defective mitochondria in tumours impairs ketone utilisation



McQuown, B., Burgess, K. E., & Heinze, C. R. (2018). Preliminary investigation of blood concentrations of insulin-like growth factor, insulin, lactate and beta-hydroxybutyrate in dogs with lymphoma as compared with matched controls. *Vet Comp Oncol, 16*(2), 262-267.

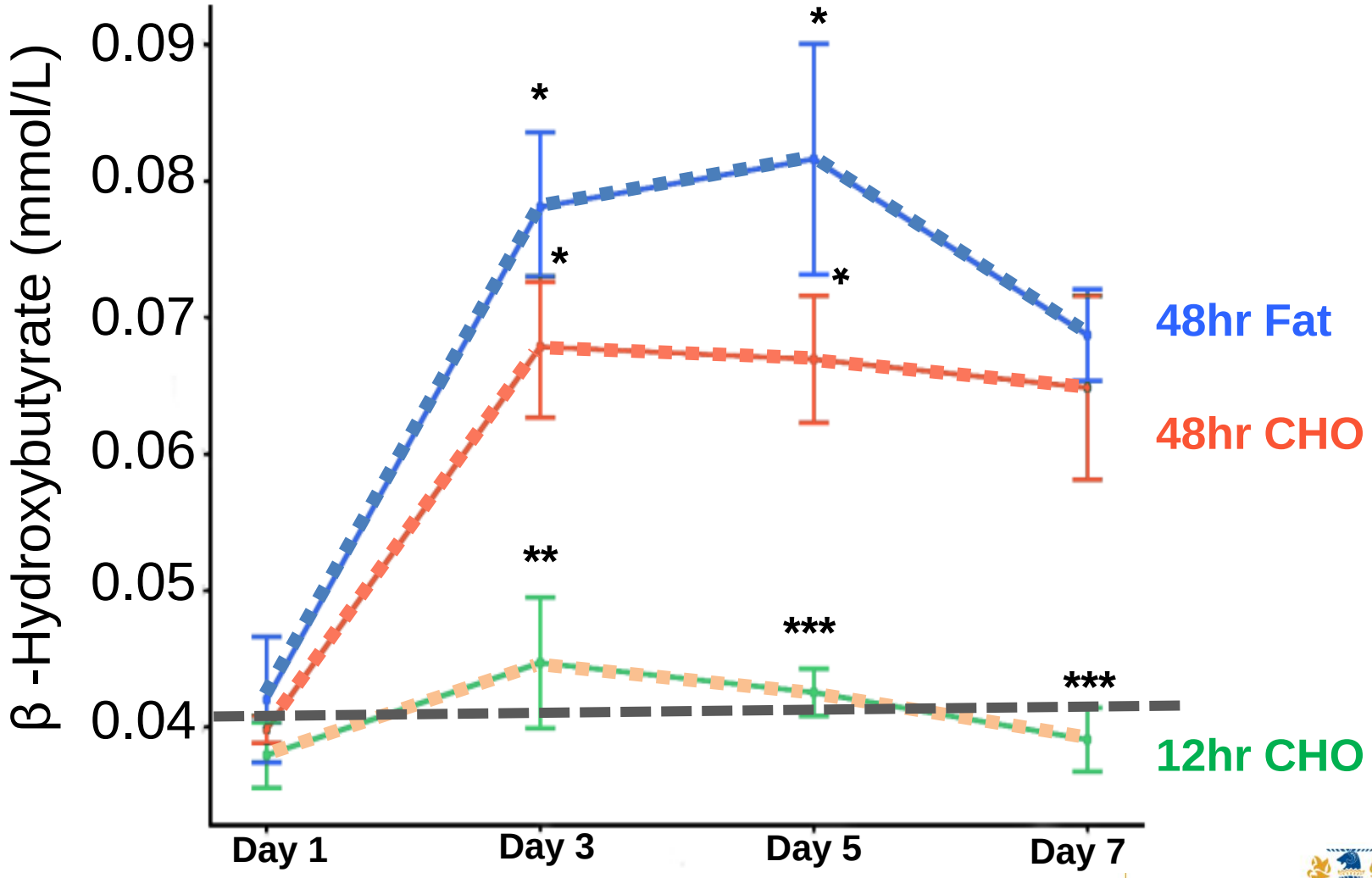
Intermittent fasting and ketones

Intermittent fasting in rats



Dietary restriction started after spinal cord injury improves functional recovery. Plunet WT, et al Exp Neurol. 2008 Sep;213(1):28-35.

β-Hydroxybutyrate in dogs fed high fat or CHO q 24 or 48hrs



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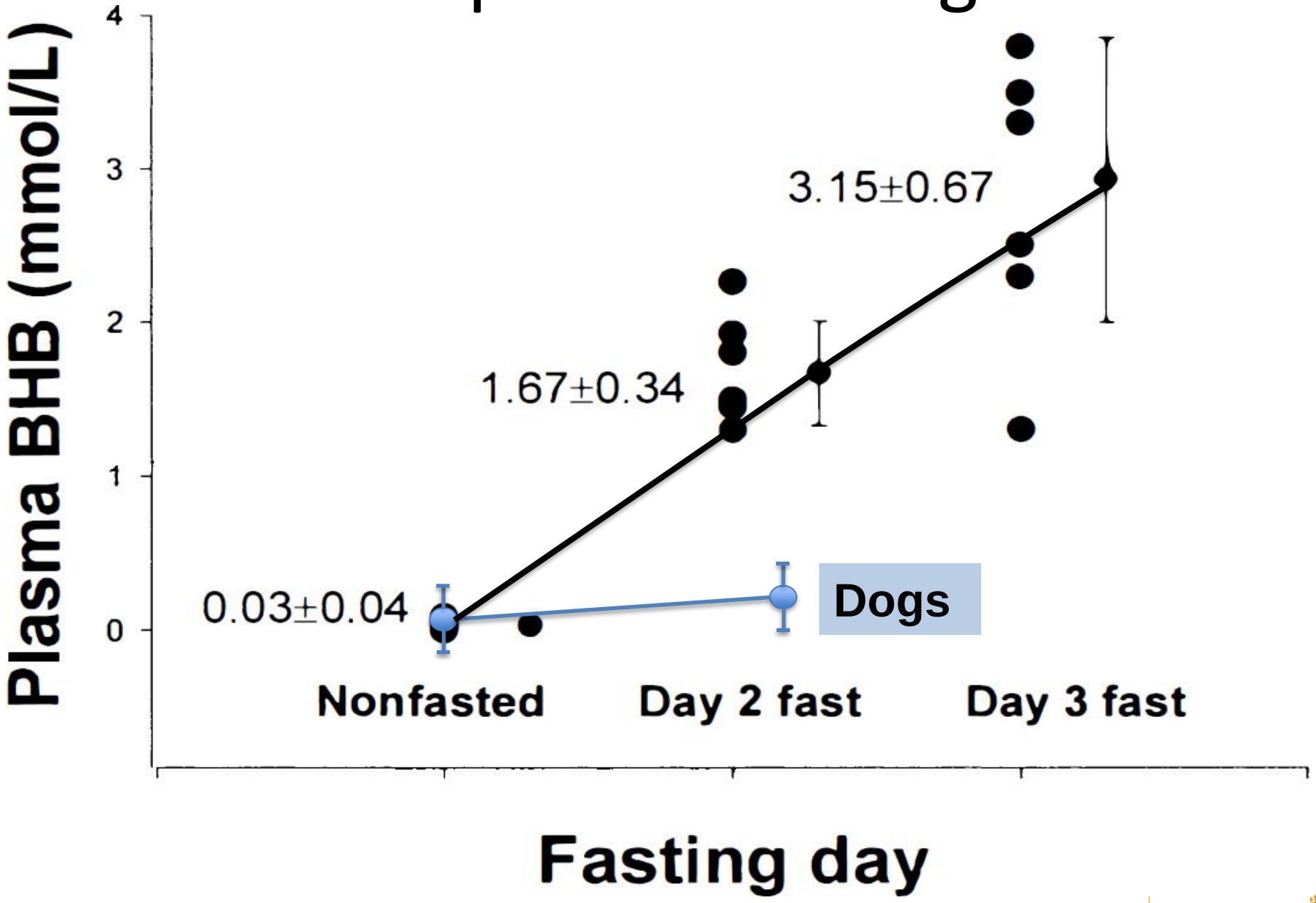
People and fasting

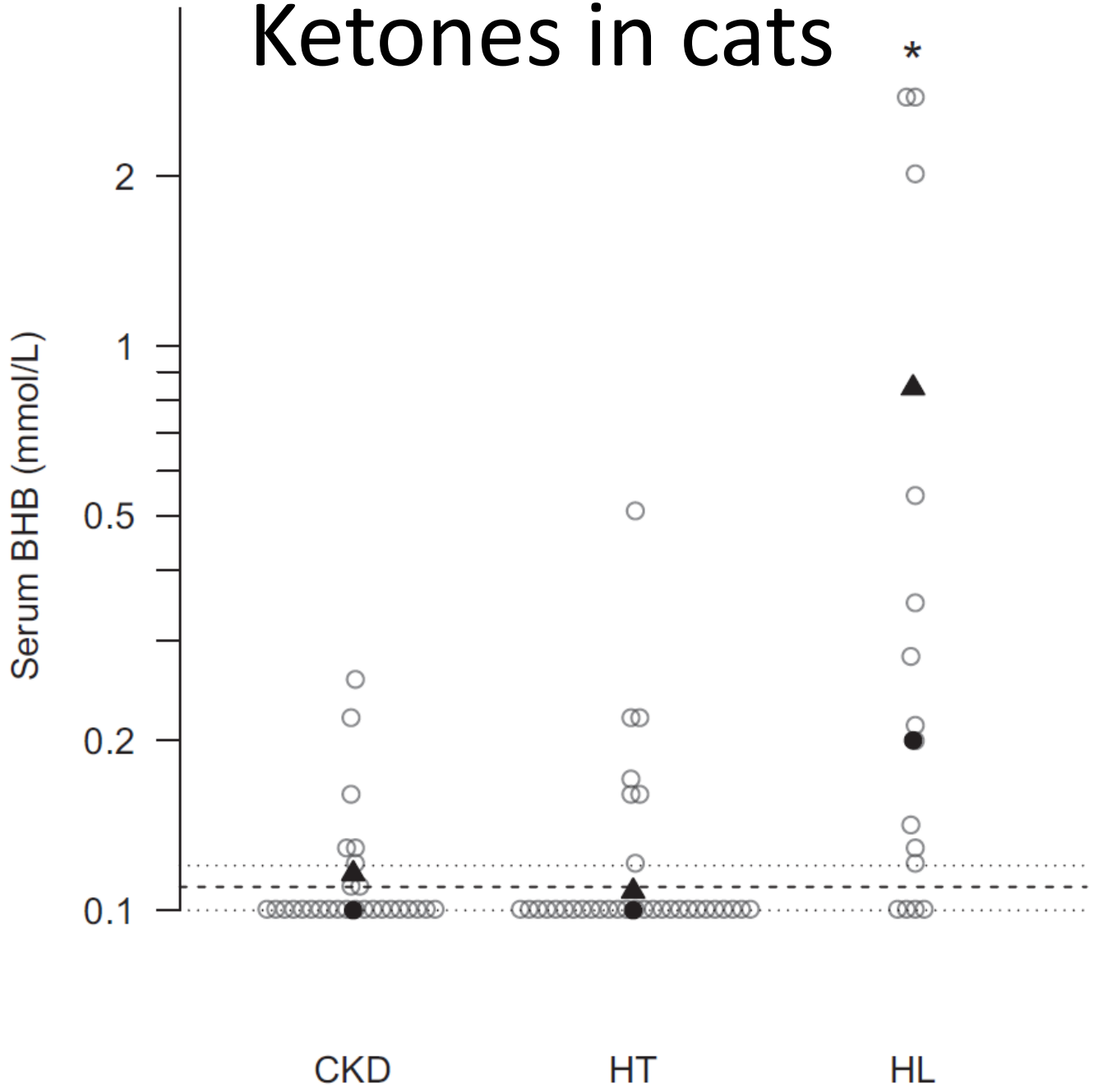


Pan, Jullie W., et al. "Human brain β-hydroxybutyrate and lactate increase in fasting-induced ketosis." Journal of Cerebral Blood Flow & Metabolism 20.10 (2000): 1502-1507.

Serum ketones

$$[\text{Metabolite}] = \frac{\text{Rate of production}}{\text{Rate of elimination}}$$

Ketones in cats



Gorman L, et al Serum Beta Hydroxybutyrate Concentrations in Cats with CKD, Hyperthyroidism, or Hepatic Lipidosis. J Vet Intern Med. 2016 ;30(2):611-

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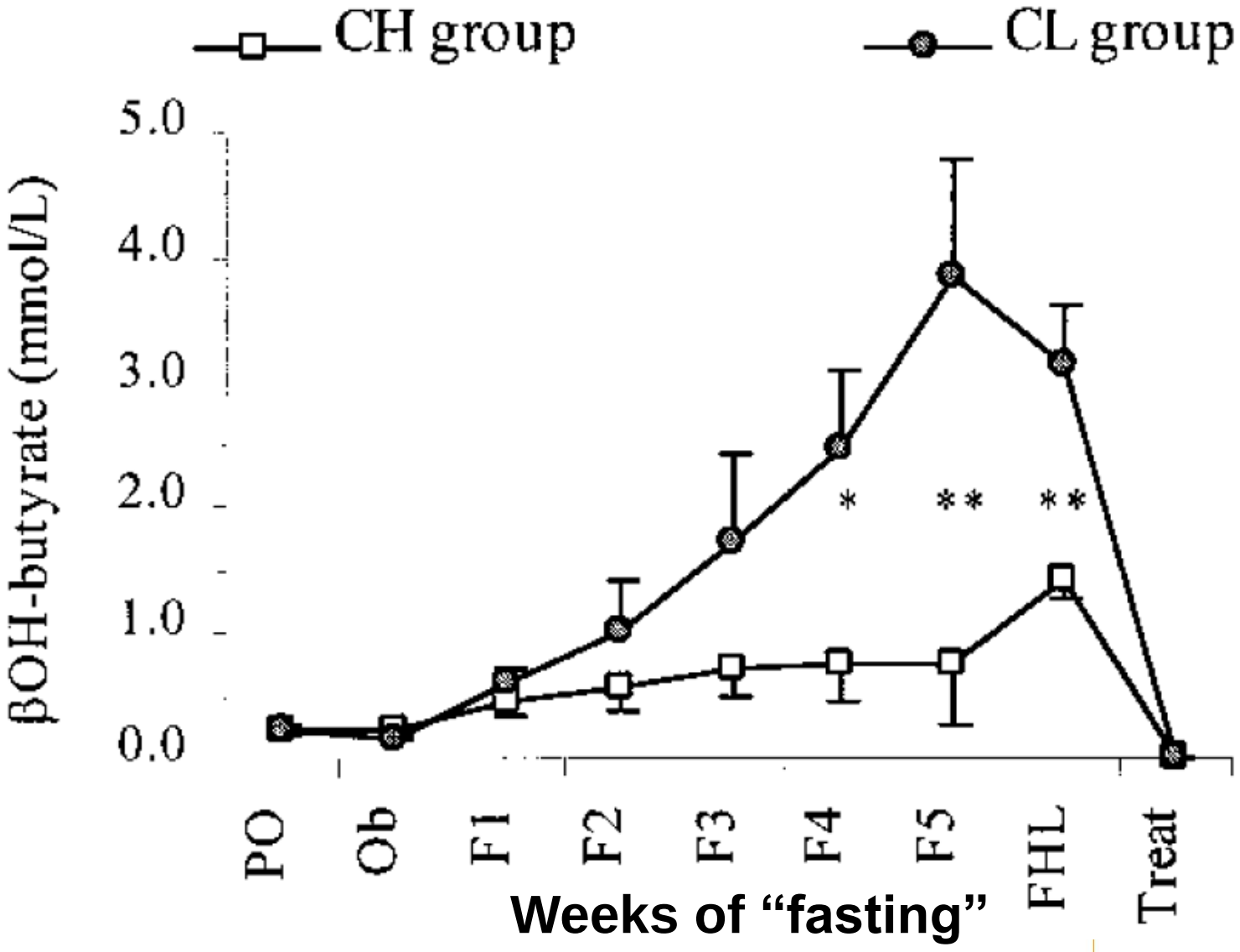
Ketones in cats



"Dietary L-carnitine supplementation in obese cats alters carnitine metabolism and decreases ketosis during fasting and induced hepatic lipidosis." Blanchard G, et al. J Nut 132.2 (2002): 204-210.

What is a ketogenic diet?

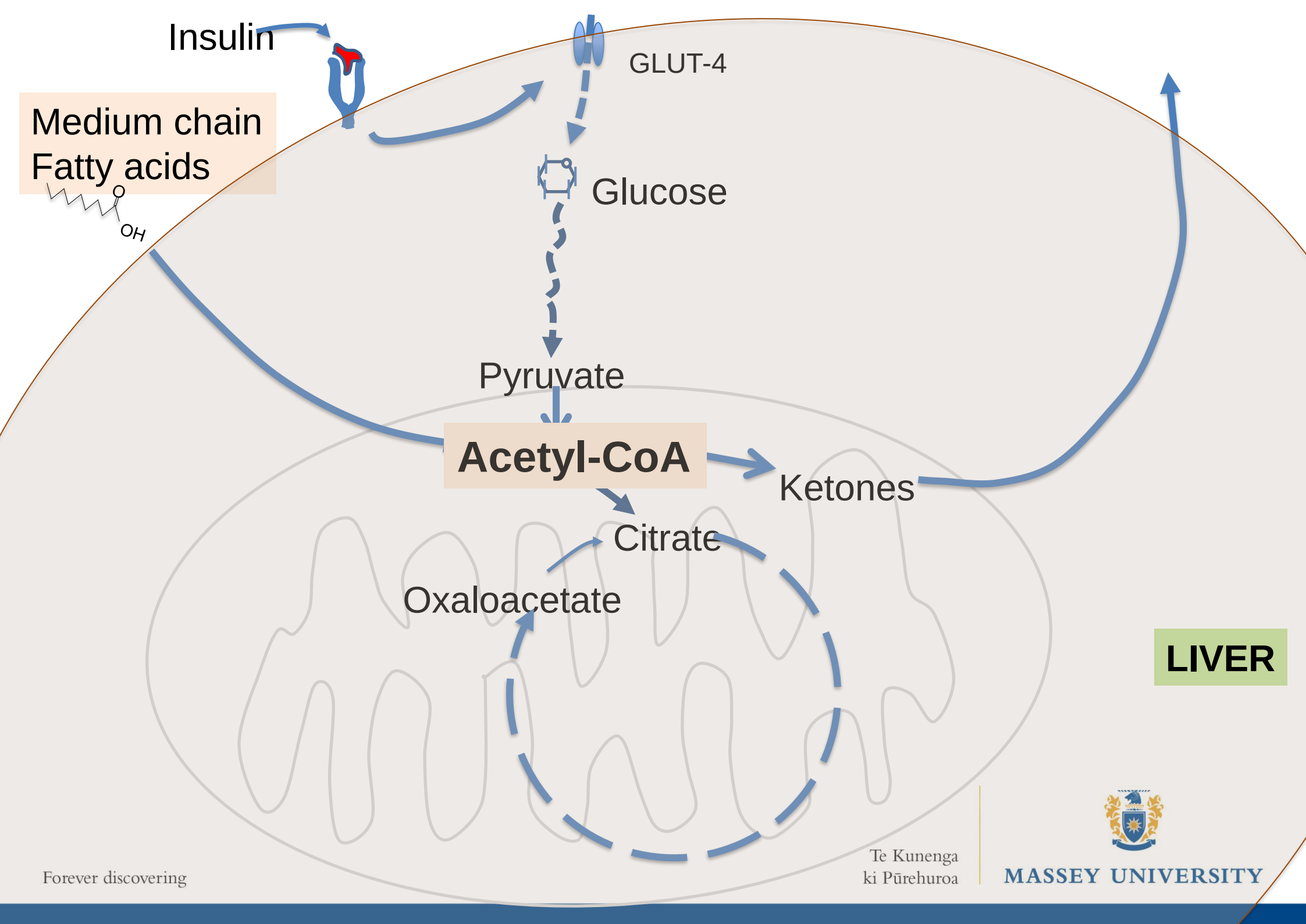
- Ideally
  - Little to no carbohydrate
  - High fat
  - Ketogenic fats
  - Fed intermittently

“Ketogenic fats”

Short to medium chain fatty acids

- C3 to C12
- Absorbed directly into portal blood and not lymphatics
- Very little incorporated into adipose
- Absorbed by the liver, and brain
- Enter hepatic mitochondria unregulated
- Generate excessive Acetyl-CoA and inhibit glycolysis

  ⇨ production of ketones


Insulin
GLUT-4
Medium chain
Fatty acids
O
OH
Glucose
Pyruvate
Acetyl-CoA
Ketones
Citrate
Oxaloacetate
LIVER

Ketogenic diets for dogs

Keto diet (Modified commercial)

Ingredient	Amount (grams)
Royal Canin® Recovery, canned	100
Rice, white, unenriched, cooked weight	20
Butter, no added salt	8
Coconut oil	6
Balance IT® Canine supplement	2

Keto diet (Home prepared)

Ingredient	Amount (grams)
Chicken, white and dark meat only, no skin, stewed	80
Rice, white, unenriched, cooked weight	48
Butter, no added salt	32
Coconut oil	10
Balance IT® Canine supplement	7

Diets - macronutrients

	Standard Hospital diet	Ketogenic diet commercial	Ketogenic diet home-made
Protein energy (%ME)	22	22	21
Fat energy (%ME)	23	66	70
Carbohydrate energy (% ME)	55	12	10
Energy (kcal/gram)	2.28^	1.85*	3.03*

Diets - macronutrients

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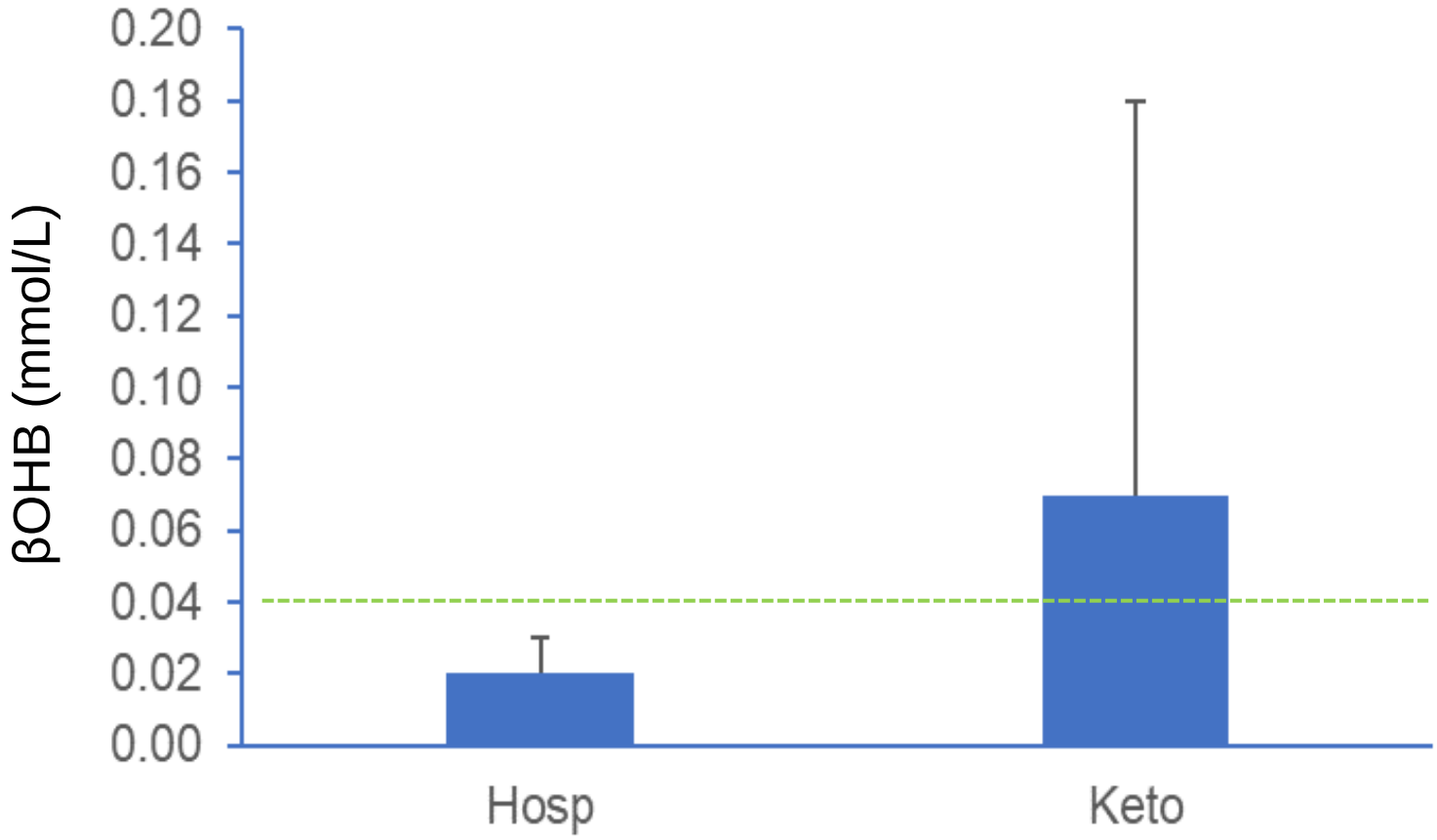
Energy (kcal/gram)	2.28^	1.85*	3.03*

Post prandial β-hydroxybutyrate



P=0.594

Using intermittent fasting and a ketogenic diet to improve nutritional and clinical outcomes in long-stay, hospitalised canine spinal patients. YM (Becca) Leung, PhD Thesis, 2021

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Rate of synthesis and utilisation

- Ketone kinetics study using infusions of stable isotopes

P=0.11

Using intermittent fasting and a ketogenic diet to improve nutritional and clinical outcomes in long-stay, hospitalised canine spinal patients. YM (Becca) Leung, PhD Thesis, 2021

Ketones vs. Carbs

- Which is more important for cancer patients?

a) Feed a low carbohydrate diet

b) Feed a ketogenic diet

⇒ We don't know

- However, we don't need to know, since we can do both

Ketogenic diets in cancer

- In most (26/49, 53%) rodent studies, a ketogenic diet shows a clear anti-tumour effect:
  - Slowed tumour growth
  - Prolonged survival
  - Delayed tumourigenesis
  - Reversed cachexia
  - Increased sensitization to chemotherapy
- Some showed no effect
- Some showed accelerated tumour growth

Kozal, K., Jozwiak, P., & Krzeslak, A. (2021). Contemporary Perspectives on the Warburg Effect Inhibition in Cancer Therapy. *Cancer Control, 28*

Practical feeding

- Don’t make strong recommendations in the absence of evidence
- All patients need to eat something
- If owner is interested:
  - I recommend low carbohydrate diet (1-5% ME carbohydrate)
  - Feed once daily as long as maintaining weight
- If owner is motivated:
  - Feed ketogenic diet + n-3 PUFA
- Ensure there is no contraindication for high dietary fat

Conclusion

- Theoretical basis for low CHO in some cancer patients – not all will benefit, but harm is unlikely
- Ketogenic fats may have added benefit
- *Practical* intermittent fasting is unlikely to help ketogenesis, but may help other aspects
- An error to assume that all tumours and all species behave the same
- We need clinical evidence

Thank you!

Questions?

Key references

1. Warburg, O., Wind, F., & Negelein, E. (1927). The metabolism of tumours in the body. *The Journal of general physiology, 8*(6), 519-530. 10.1085/jgp.8.6.519
2. Vaupel, P., & Multhoff, G. (2021). Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol, 599(6), 1745-1757. 10.1113/JP278810
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