# WHY DO CARDIOMYOCYTES (HEART MUSCLE CELLS) STORE GLYCOGEN?

by:

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## INTRODUCTION

Why do cardiomyocytes (heart muscle cells) store glycogen when their capacity for anaerobic energy production is extremely limited? A cardiomyocyte, deprived of its blood supply, cannot continue beating for more than a few minutes at the very most. The glycogen would therefore only be useful to survive a 40-60 second angina attack at the very most. Since ischaemic heart disease hardly ever occurs before the age of 50 years, and would have been an extreme rarity in past centuries, and during our long evolutionary history on the African savannah, it hardly seems likely that natural selection would have included a precautionary feature such as this into our physiologies from childhood.

This question is possibly related to other metabolic conundrums involving carbohydrate metabolism. Why, for instance, do we need a constant supply of glucose, when we could, supposedly, obtain all our energy from burning fats? Or, why does a glycogen depleted skeletal muscle become effectively paralysed (i.e. unable to exercise) when its blood supply is not compromised, and its supply of oxygen and fatty acids could still presumably support moderate exercise? Or, why produce glucose by means of gluconeogenesis, when the same process produces large quantities of ketone bodies that can be used instead of glucose?

It even impinges on the question why we store minimal quantities of carbohydrate (which can be depleted by 24 hours of starvation, or by a single marathon run), but store large quantities of fat, on which we can survive many weeks of total starvation. This being so, why is glucose so important? Its importance cannot be derived from its role as a potential fuel, otherwise we would store very much more of it than we do. In fact, under emergency circumstances (prolonged starvation or after an hour of exercise) all our glucose requirements can be met by gluconeogenesis.

## THE MITOCHODRION

To understand the probable answers to all these questions, it needs to be realised that the mitochondria are domesticated bacteria, which our cells nurture as domesticated livestock. The domestication process probably took place about 2000 million years ago when atmospheric oxygen first became a major problem on earth. The way it probably happened was that an anaerobe tried to phagocytose a newly evolved respiring bacterium (i.e. one that had mastered the utilisation of atmospheric oxygen to burn foodstuffs, without getting burnt itself).
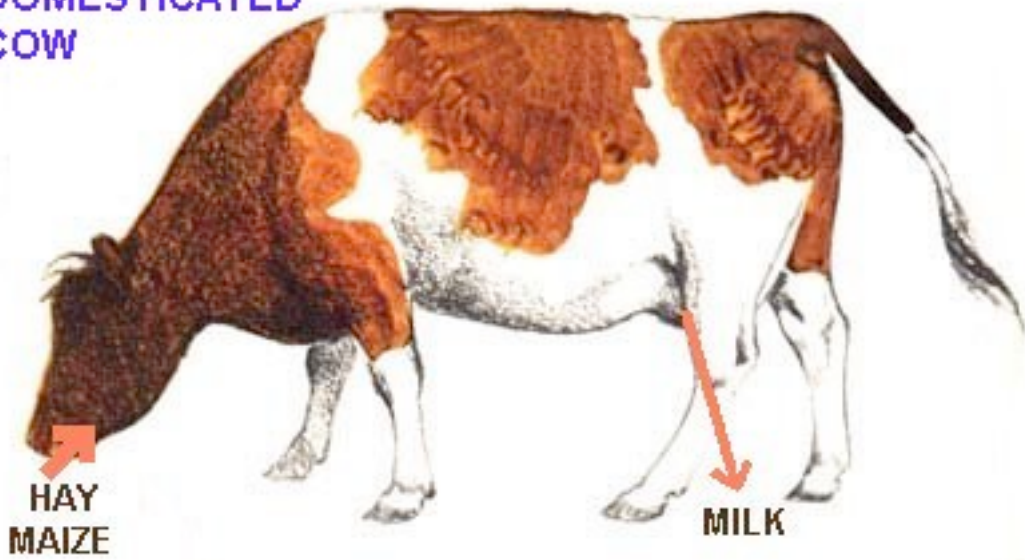
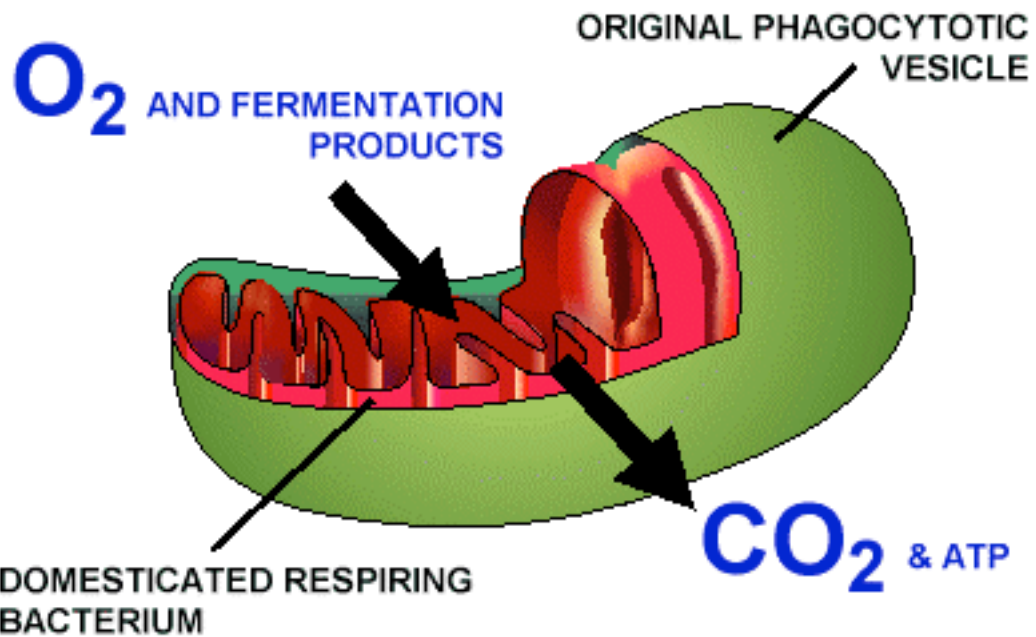# Chronic indigestion
## or, the domestication of the first pet
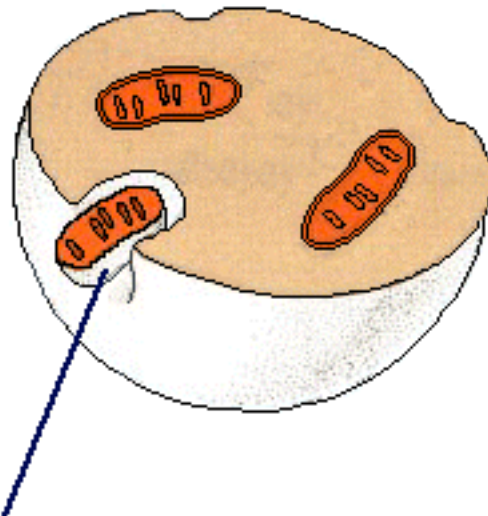


phagocytosis of
a respiring bacterium

The anaerobe (who could only ferment its food, and therefore not extract as much energy from it as the respiring bacterium could) somehow never managed to kill the ingested respiring bacterium, nor did the respiring bacterium manage to escape. In the end a metabolic truce was sealed and the respiring bacterium remained alive within the anaerobe in much the same way that tuberculosis bacteria (also oxygen loving organisms) live inside macrophages. The first domestication in the history of life had occurred.
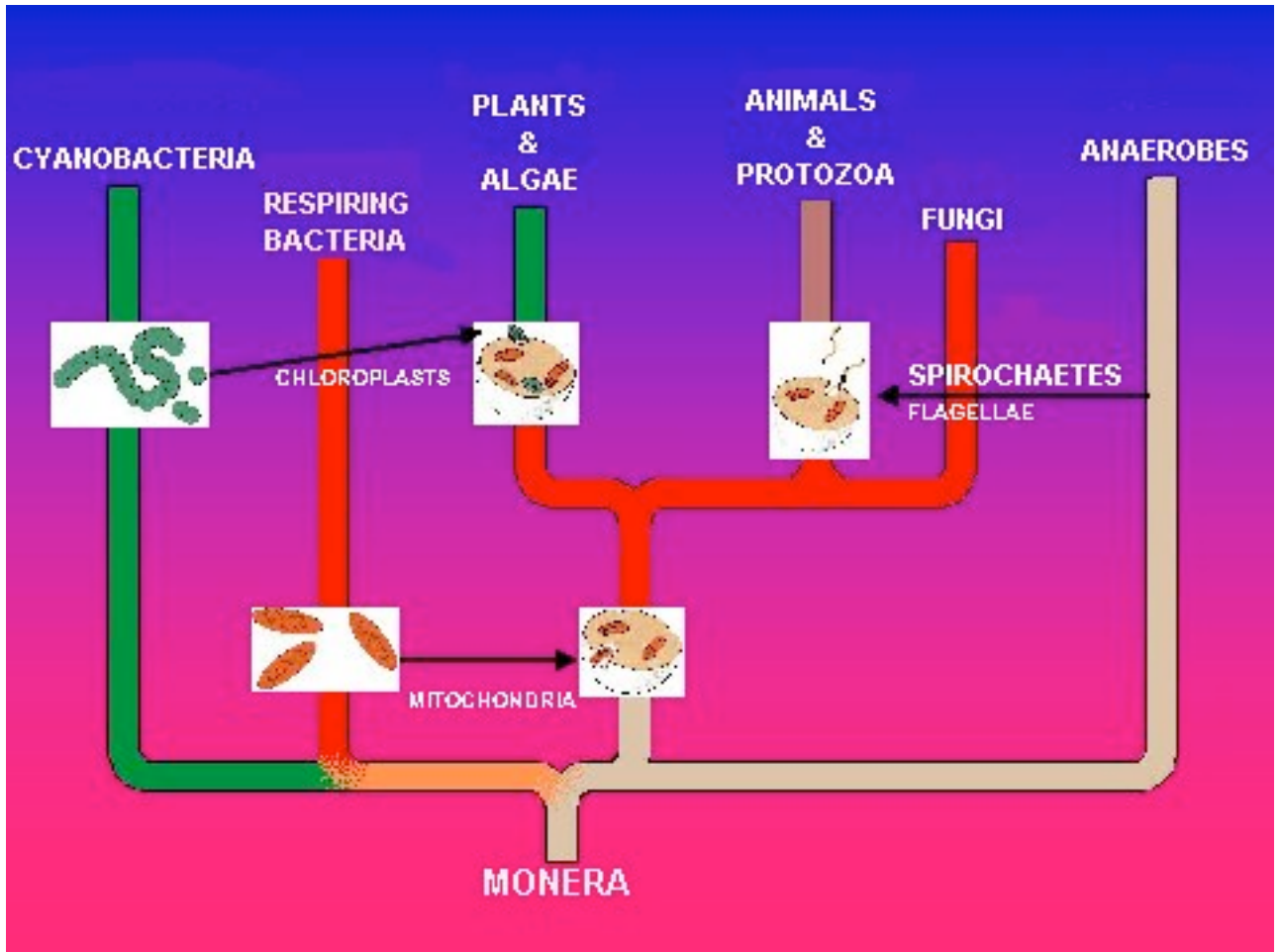
DOMESTICATED COW

HAY MAIZE

MILK



MITOCHONDRION

ORIGINAL PHAGOCYTOTIC VESICLE

$O_2$ AND FERMENTATION PRODUCTS

$CO_2$ & ATP

DOMESTICATED RESPIRING BACTERIUM

One of the anaerobes, with its tamed respiring bacterium inside it, eventually became the ancestor of all eukaryotes, from which originated, amongst others, all multicellular creatures.

The respiring bacterium became known as the mitochondrion: but it is an honest-to-goodness independent bacterium, with its own bacterial DNA, its own metabolism and its own reproduction. It reproduces, for instance, strictly asexually. (The anaerobic host is sexual.) Its DNA is in the form a circle, like that of other bacteria, and not arranged in chromosomes, as is its host's DNA. It still lives within a phagocytotic vesicle, the contents of which are acid.

The host cell (i.e. "our" cells) cannot, and dare not, use oxygen. The mitochondrion vacuum cleans our cells of oxygen and uses it to burn the fermentation products that we feed it, to carbon dioxide and water. The use of oxygen for metabolism is a very risky and dangerous business, which we leave entirely in the hands of our pet mitochondria.

The mitochondrion's favourite food, by far, is fats. Fats cannot be fermented, so "we" cannot use them except for structural purposes such as making cell walls. But the mitochondrion can burn fats, yielding large quantities of ATP per gram of fat burnt. The only foodstuffs that can be fermented are carbohydrates. So this is the only food "we" can use. The fermentation product is pyruvic acid, which we feed to our mitochondria either as food (in the form of acetate), or as a stimulant of its metabolism (in the form of oxaloacetate).

## CONTROLLING THE MITOCHONDRION'S METABOLIC RATE

Since the mitochondrion is an independent organism, a pet, it should be obvious that its production of ATP is not automatically geared to our need for ATP. A resting heart or skeletal muscle requires very little ATP, so its mitochondria need to be metabolically quiet. But when we exercise these muscles suddenly require vast amounts of ATP, which only the mitochondria can produce in sufficient quantities over a long period of time. How do we whip our mitochondria into metabolic activity?

The "Krebs' Cycle", otherwise known as the "Citric Acid Cycle", is a well-known metabolic pathway. It occurs only in the mitochondrion, and is a circular metabolic route that starts and ends with oxaloacetate. So, in fact, oxaloacetate is a catalyst: it takes part in the reaction, but is not consumed by the reaction. Essentially the amount of oxaloacetate in the mitochondria should always stay the same, if we (the anaerobic host) did not add or remove oxaloacetate from our mitochondria.

If acetate is added to the oxaloacetate, in a mitochondrion, citrate is formed. This sets the "Citric Acid Cycle" in motion. One turn of the cycle results in one molecule of oxaloacetate again, and the burning of the acetate to 2 molecules of carbon dioxide and two of water. It is the burning of the acetate that, of course, releases the energy for the production of ATP.

Most of the acetate comes from fatty acid breakdown inside the mitochondrion. Pyruvate can also be broken down to acetate, and thus also be burnt to provide ATP. But we use our pyruvate, in most cells, not to produce acetate, but to produce oxaloacetate! The reaction is known as "anaplerosis", because it tops up the mitochondrion's oxaloacetate supply.

The more catalyst (i.e. oxaloacetate) we push into the mitochondrion the faster will be that mitochondrion's rate of metabolism. Conversely if we remove catalyst (oxaloacetate) from the mitochondrion the slower will be its metabolism, and the slower will be its rate of ATP production.

This is therefore how heart muscle (or skeletal muscle) increases and decreases the rate of ATP production by its mitochondria. In resting muscles the oxaloacetate levels in their mitochondria are kept very low, but as soon as we start exercising we rapidly break the glycogen stored in those muscles down to pyruvate and then to oxaloacetate, which is fed to the mitochondria. The more oxaloacetate we give the mitochondria (i.e. the more glycogen we breakdown to make pyruvate) the faster they produce ATP.

At the end of exercise the oxaloacetate is removed from the mitochondrion via malate, and resynthesised into glycogen, or it can discharged into the circulation as lactate to be converted to glucose by the liver. The removal of the oxaloacetate from the mitochondrion slows down its rate of ATP production to resting levels.

## THE IMPORTANCE OF GLUCOSE

All cells need glucose. None can do without it. In red blood cells, which do not have mitochondria, the fermentation of glucose is the only source of ATP. Brain tissue has mitochondria, but a strange mechanism (which I do not understand) does not allow fatty acids into the brain. In brain tissue, therefore, the mitochondria are fed acetate

derived from pyruvate, and not from fats. So brain tissue is almost 100% dependent on glucose for its ATP production.

All other cells need pyruvate to top up the mitochondrial oxaloacetate, which keeps the "Citric Acid Cycle" running. If there is no glucose-derived pyruvate, mitochondrial metabolism will soon come to a halt, and the cell will die from a lack of ATP. (Oxaloacetate, though theoretically never used up by the mitochondrion, is gradually lost, because it is used for all sorts of other things apart from the Citric Acid Cycle.)

Ketone bodies can serve as a source of acetate in all tissues that have mitochondria, including brain, but all these tissue still require some glucose to form oxaloacetate which cannot be made from fats or ketone bodies.

The oxaloacetate that most tissues require to maintain the Citric Acid Cycles of their mitochondria is derived directly from glucose absorbed from the blood. Tissues, however, that need to be able to increase mitochondrial ATP production rates very suddenly and to very high levels, all store glycogen. It is only stored glycogen that can be mobilised fast enough to produce the sudden large quantities of oxaloacetate that enable these tissues' mitochondria to meet the energy demands of exercise. Finally, glucose is the substance from which we make very nearly all the chemicals that we can make ourselves. If the substance we need to manufacture contains nitrogen in its structure, then we also need to consume a source of nitrogen, usually in the form of amino acids, but the backbone of the substance remains glucose-derived. "Our" (anaerobic) metabolism is, therefore, carbohydrate driven. But that of our "pets" (the mitochondria) is primarily fatty acid driven. However, we control our pets' behaviour via carbohydrate driven anaplerosis.