CHELATION & THE KREBS CYCLE

KREBS CYCLE INTERMEDIATES AND NUTRIENT TRANSPORT

INTRODUCTION

Millions of people across the globe supplement their diets with macro and trace minerals. When the diet is lacking in these important nutrients, health issues ensue and is a very good idea to consume a non-food mineral source. There's only one catch… how do we know the minerals are going to end up where we want them to end up in our bodies. Just because you swallow a mineral doesn't necessarily mean its going to go where it's supposed to. This is one of the great dilemmas of human physiology and nutrition. Now if there were only a liaison, a chaperone if you will, that escorted the minerals to where they needed to go with much more efficiency than if left to themselves. Well, in fact our body's biochemistry does in fact make molecules that can take these minerals to where they need to go. Introducing the intermediates to the Krebs Cycle.

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The Krebs Cycle

Our bodies have the amazing ability to turn sugars, fats, and amino acids from the foods we eat into energy for later use. Back in 1937, Hans Adolf Krebs won the Nobel Prize for discovering an amazing feature that our bodies possess. All humans, as well as all other aerobic organisms, have the ability to break down macronutrients into a single common molecule (pyruvate) which gets rearranged and oxidized to yield all sorts of other valuable biomolecules that the body can use. This series of reactions is called the Krebs Cycle (aka. Citric Acid Cycle or Tricarboxylic Acid Cycle). Each turn of the Krebs Cycle, taking place within the mitochondria (the engine of each eukaryotic cell) and is largely regulated by calcium and other influencers 1,2, makes molecules of stored energy that the body can use

FACT…

Bioavailability is defined as the proportion of an ingredient or other substance that enters the circulation when introduced into the body and so is able to have an active effect. All substances that enter our mouths have a statistical probability of getting to where they need to go (or where we desire them to go) once they are swallowed. The likelihood of a given substance getting to its physiological destination depends widely on a myriad of biological variants.

(GDP, NADH, FADH). This series of chemical reactions also yields intermediates that provide a template for making a plethora of other molecules that are critical for normal physiology.

The Bioavailability Problem

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So, what are minerals and where do they come from? Minerology tells us that minerals are crystalline solids that are produced from non-biological processes and have one and only one unique composition3. Think of minerals as clusters of a single atom (usually multivalent cations) that exists as a solid chunk. Once dissolved or freed from the solid it's stuck to, the single positively charged atom is now naked and carries a charge. Because the atom wants to obey the octet rule, these naked atoms usually don't last very long being single – they immediately look for a mate to partner up with. When partnered up, this attraction is typically in the form of an ionic bond. This type of bond is very strong due to each partner staying extremely close to one another because they're both fighting over an electron.

Chelation

When a charged atom (i.e. mineral) partners up with a non-metallic molecule, a special type of bond is formed called a chelate. This becomes very important in the bioavailability of minerals. Now the questions becomes, what are the best natural substances to chelate minerals with? Minerals are usually chelated to inorganic or organic compounds. Inorganic compounds typically are oxides, phosphates, sulfates, etc. Organic compounds are pretty much every other compound found in nature that contains carbon. It turns out that a mineral actually has a better chance of getting to its target tissue when it is chelated to an organic compound rather than an inorganic one4,5. The problem lies when the mineral enters the duodenum from the stomach. Naked minerals do just fine in their soluble state when floating around in the stomach due to the low pH of the gastric juices. However, once the pH increases, as in the proximal and distal sections of the duodenum, these unbound, or loosely bound, minerals cluster together and precipitate. When this happens, they end up passing right along through the intestinal tract in which little to nothing actually makes it into the bloodstream. This is where a good chaperone comes into play. As stated earlier, intestinal uptake seems to be favored when the chaperone is an organic molecule (especially amino acids or intermediates of the citric acid cycle) as opposed to an inorganic molecule21,22. Inorganic molecules tend to drop off the mineral at the wrong spots along the intestinal tract and force the mineral to compete for absorption with other minerals, including themselves, at that absorption site6. Think of it as if you were dropped off at the wrong bus stop and still had to fight the crowd to get on the bus. Organic chaperones such as amino acids and Krebs Cycle intermediates have a way of carrying the mineral through the intestinal wall and into the bloodstream intact, only to then to release them to their assigned serum transport vesicles to be taken to their final destination7. Total serum mineral distributions typically range from a small portion still being bound to their organic chelate chaperone, a larger portion being bound to serum proteins, and a nominal amount as in its free ionic state8.

The Krebs Cycle Cast of Characters

When a molecule of pyruvate enters the mitochondrial matrix

and links up with a molecule of oxaloacetate to form citrate, an amazing series of stepwise reactions take place to rearrange citrate to make all sorts of fun intermediates as well as different energy-storing molecules. These Krebs Cycle intermediates have unique physiological features and functions outside of just being the result of citrate rearrangement. The stepwise bond breaking and bond forming of citrate yields: aconitate → isocitrate → alpha ketoglutarate → succinyl CoA → succinate → fumarate → malate → oxaloacetate. These are what are known as the Krebs Cycle intermediates.

What is so special about these intermediates?

Some of the intermediates to the Krebs Cycle have a unique ability to take certain amino acids and turn them into energy9, whereas some intermediates can simply turn themselves into energy via the gluconeogenic pathway. This can be especially helpful during times of increased stress, exercise, starvation, or disease. There are times however, during these situations, where the Krebs Cycle process slows down drastically. If and when this happens, a myriad of physiological problems can occur. Much research has been done to show how supplementation of these key players can improve such negative physiological conditions.

Alpha-ketoglutarate

A precursor to the amino acid glutamic acid, this intermediate plays a pivotal role in nitrogen metabolism. Alpha-ketoglutarate has been proven to decrease protein catabolism and increase protein synthesis to enhance bone tissue formation in skeletal muscle and can be used in clinical applications10. Further research also indicates that it has the potential to alleviate intestinal inflammatory responses and improve epithelial restitution and nutrient-sensing ability under stress injury11 (prevent intestinal epithelial damage).

Malate

The precursor to oxaloacetate, malate (in this case, malic acid) is the sour-tasting compound found in most fruits and is used as a food additive. Besides playing a vital role in putting more pyruvate back into the Krebs Cycle to produce more oxaloacetate, malate has been shown to have other benefits. Due to its ability to reduce inflammation and platelet aggregation, malate has been suggested to have pretty amazing cardioprotective effects12. Not to mention its role in β-oxidation of fatty acids (fat burning). This cannot happen without malate's involvement in the Krebs Cycle.

Citrate

Like malic acid, citric acid is the main culprit for the sour taste experienced when a citrus fruit is bitten into. But besides being just a sour molecule, citrate is the Krebs Cycle product of the condensation of oxaloacetate and acetyl-CoA, which then can be transported out of the mitochondria and then cleaved again to begin the fatty acid synthesis route (which may be a good or bad thing). Citrate also plays a role in hydroxyapatite formation13, a vital component of human bone. Further, if making healthy bones weren't enough, citrate also has been shown to aid in sustaining the health of other tissues by decreasing brain lipid peroxidation and inflammation as well as protecting against liver damage14.

Succinate

During the Krebs Cycle, alpha-ketoglutarate gets tweaked by 2 different enzymes to become succinate. This now 4-carbon intermediate has a couple of roles to play in the human body. Succinate plays a unique role as the gate keeper for a particular pathway that involves the Krebs Cycle in which GABA is synthesized and recycled15. Although there are many other roles that succinate plays in human biochemistry, the main factor in which succinate is the Krebs Cycle hero is the fact that the majority of the metabolism of carbohydrates, amino acids, fatty acids, cholesterol, and heme in the human body rely on the temporary formation of

succinate16. A pretty impressive role for one tiny molecule.

Fumarate

Fumarate is the intermediate between succinate and malate in the Krebs Cycle. As well as being a product of the urea cycle, it is used by cells in humans to produce energy – namely in the form of ATP. Since fumarate is produced in human skin cells much like vitamin D, when a deficiency is at hand, it is not abnormal for skin lesions and psoriasis to be present. This is probably one reason why fumaric acid and it's bi-products are responsible for its alleviation (17, 18. So, besides its use as a food additive to regulate acidity, fumarate seems to be a key player in skin health and energy production.

Krebs Cycle Intermediates & Chelation

As we leaned earlier when we talked about chelation, molecules that have the ability to chaperone minerals so as to protect them until they reach their destination are almost an invaluable asset to the mineral's bioavailability. The intermediates of the citric acid cycle are readily recognized by the cells of the small intestine and allow for the passage of these molecules into them and onto the bloodstream. The beauty of this feature is that they can also bring guests with them7 as mentioned above. Again, no stranger to any cell in the human body, these chaperones are recognized and taken up by passive or active transport – with or without their guests. Considering that the Krebs Cycle molecules carry and drop off minerals to target cells as well as serum proteins to transport, we can see exactly how the bioavailability of chelated minerals is dramatically increased. This can also be seen in the case of certain minerals when chelated to amino acids19, 20. Needless to say, there is a marked improvement in getting minerals to where they need to go in the body when strapped to the right chaperone as opposed to the wrong one… or nothing at all.

To Sum Up

Taking all of this into consideration, one might look upon the human body with both wonder and irritation. Wonder as to the complexity and intricate design, and irritation as to why a nutrient can't just get to where it needs to go once swallowed. Thankfully, we have science and technology to help alleviate us from this irritation. It is a wonder however, to understand all of the different mechanisms and routes that are involved in nutrient transport and delivery, and then to use science to our advantage – namely via the use of biomolecules. With the discovery and invention of chelation for the purpose of mineral bioavailability, a lot of the irritation and guesswork thankfully is quickly coming to an end due to the help of our new-found friends, the intermediates of the Krebs Cycle.

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on May 2nd, 2018

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