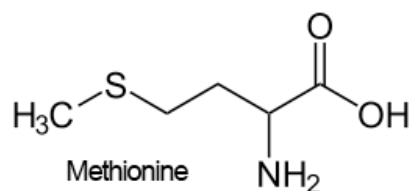




Omnivores unite

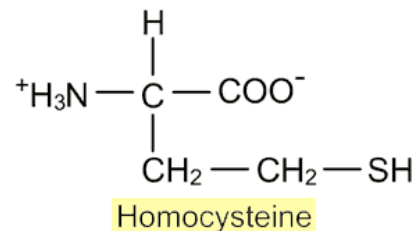
Life Itself Is The Proper Binge *Julia Child*

The other day while I was busy contemplating my navel I over heard a group of anesthesia providers discussing the ramifications of "homocysteine disease" This piqued by interest since I didn't know having homocysteine was a disease. In fact this amino acid is derived from the breakdown of methionine which as anyone with a PhD in biochemistry can tell you is a sulphur containing amino acid that is part of all

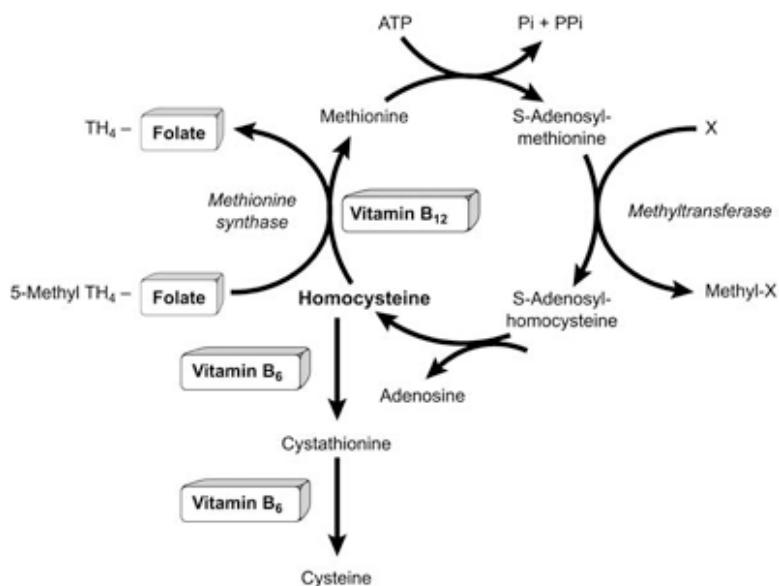


proteins that make eukaryotes*. In fact homocysteine looks a hell of a lot like methionine. The difference being that methionine has a methyl group (CH₃) on its terminal carbon and homocysteine does not. Since homocysteine is a derivative of methionine, I suppose it is safe to say that it appears in our bodies as a result of diet, since that's how methionine ends up in us. Yet too

much of this stuff can cause some serious problems such as osteoporosis, depression, Alzheimer's disease, erectile dysfunction, and problems with pregnancy which I'll discuss later. But why this amino acid becomes problematic requires that we take a look at some other players in its production namely the vitamins B6, B12 and folic acid.



When proteins are metabolized, they are broken down into individual amino acids, including the sulfur-containing amino acid methionine (see the diagram above). Methionine, in turn, is broken down further in several steps to produce homocysteine, which, once formed, can be removed from the body in only two ways. One, it can be remade into methionine through a process called remethylation. This requires both folic acid and vitamin B12, where B12 functions as an essential "cofactor" in the reaction. Secondly, homocysteine can be made into the amino acid cysteine through a process called transsulfuration, a process that requires two enzymes to work in concert with vitamin B6. Thus, if a person ingests lots of protein, and there is not enough folic acid, B6 and B12 available to help digest it, homocysteine levels can build up in the blood stream. As might be expected, the opposite is also true. Increased levels of these vitamins in the blood stream result in a reduction of homocysteine levels. And this is a good thing.



Our knowledge of homocysteine is not a new thing. In fact it was discovered back in 1932 but it wasn't until 1968 when its importance to human health first came to light when a Harvard researcher named Dr. Kilmer McCully (1) noticed that children with genetically elevated homocysteine levels experienced heart disease similar to the heart disease found in middle-aged patients. In fact, he wrote a paper describing several children with homocystinuria who had died of heart attacks. He noticed that they had blood vessels damaged by atherosclerotic plaques yet they lacked the typical fatty deposits in other organ systems seen in older populations. To him this suggested that maybe homocysteine had something to do with how these cholesterol deposits were formed inside the arteries. Unfortunately his idea was not shared by the medical community as a whole. Physicians and their patients were sold a bill of goods by the pharmaceutical and food industries that falsely claimed that cholesterol was the cause of cardiovascular disease despite evidence to the contrary (2-6). But that's a topic for another paper.

The fact that many heart attack victims actually have normal cholesterol levels has led researchers to again focus their attention on early observations by Dr. McCully. That's not to say that cholesterol has no culpability in the making of an atherosclerotic plaque. It has to share the spotlight, so to speak. It no longer has the starring role. Its old partner, homocysteine, now seems to be taking center stage. Studies show that homocysteine causes toxic superoxide radicals (7,8) to form in the blood, which in turn destroys the endothelial layer of certain susceptible blood vessels. What makes some vessels susceptible and others not, eludes me. But what is known is that once the endothelial layer is destroyed the collagen matrix of the vascular wall is exposed. And it is this exposure that allows platelets to become activated. And when activated they begin to release various substances. One such substance is serotonin.

This monoamine neurotransmitter is not only a potent vasoconstrictor but is an antagonist of antithrombin which blocks the fibrinogen to fibrin reaction. In other words it accelerates the conversion of fibrinogen to fibrin, the stuff that forms the basis of a blood clot. But wait there is more! Thromboxane A2 and ADP are also released. While ADP attracts more platelets to the injured area, thromboxane A2 promotes platelet aggregation, degranulation, and vasoconstriction. Thus ADP and thromboxane A2 promote more platelet adhesion and therefore more ADP and thromboxane. The positive feedback promotes the formation of a platelet plug and in the presence of circulating clotting factors, blood clots are formed (9-14).

As mentioned earlier, homocysteine plays an important role in pregnancy and in healthy fetal development. High maternal homocysteine levels have been implicated in causing mothers to miscarry, or develop serious complications such as pregnancy induced hypertension (PIH) and placental abruption. And although the jury is still out on the definitive causes of PIH, blood clot formation within the placental circulation is strongly associated with this maternal problem. Why, you may ask? Because the initiating event leading to PIH appears to be reduced uteroplacental perfusion and the development of placental ischemia. And although this reduced blood flow is usually a consequence of abnormal cytotrophoblast apoptosis[†] and invasion⁽¹⁵⁾ of spiral arterioles, it is not impossible to envision that blood clot formation within the uteroplacental unit can produce the same ischemic response. On the cellular level this response consists of an increase in the release of a variety of factors such as soluble fms-like tyrosine kinase-1^{**}, (holy crap! what is that!) and tumor necrosis factor- α ^{††} (give me a break!). These factors are ultimately responsible for formation of endothelin^{***} and thromboxane, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide and prostacyclin. And all these endothelial abnormalities, in turn, cause hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance (Why some women are prone to developing PIH and others do not remains a mystery but surprisingly (at least for me) diet seems to play a part (19). For example, studies have found that vegetarians who do not supplement their diet with vitamin B12 tend to have elevated homocysteine levels and in fact have a greater incidence of PIH (20,21). This is because Vitamin B12, an essential B vitamin, is not found in any significant amounts in plant foods; it is primarily found in those foods vegetarians tend to shun, namely eggs, meat, fish, poultry or dairy products...you know, the good tasting stuff. The British Medical Journal published an analysis of 12 studies on the effectiveness of reducing homocysteine levels with folic acid (aka folate) and vitamin B12 and/or B6 supplements for 3-12 weeks. They concluded that folic acid in the range of 500-5,000 μ g/day reduced homocysteine by 25%, and that B12 supplements (average intake of 500 μ g/day) reduced it a further 7%. Vitamin B6 supplements (average of 16.5 mg/day) did not reduce homocysteine further (24-28).

So here is the take home point. If you are strictly a beef eater and shun all vegetables, supplement your diet with folate; however if you are a grass eater and are repulsed at the thought of swallowing animal flesh then try to take in B12-fortified foods or supplements. That's all you need is about 100 µg per day. That should do the trick in keeping homocysteine levels at a minimum. (normal serum homocysteine levels are from 2.2 to 13.2 µmol/l)(22,23).

Footnotes:

*A eukaryote is an organism whose cells contain complex structures inside the membranes. The defining membrane-bound structure that sets eukaryotic cells apart from prokaryotic cells is the nucleus, or nuclear envelope, within which the genetic material is carried.

**Soluble fms-like tyrosine kinase-1 (sFlt-1) is an enzyme that disables proteins that cause blood vessel growth (angiogenesis), i.e. vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). sFlt-1 thereby blunts the beneficial effects of these proangiogenic factors on maternal endothelium, with consequent maternal hypertension and proteinuria. In normal pregnancy, the pro-angiogenic factor PlGF increases during the first two trimesters and decreases as pregnancy progresses to term. In contrast, levels of the anti-angiogenic factor sFlt-1 remain stable during the early and middle stages of gestation and increase steadily until term. In women who develop preeclampsia, sFlt-1 levels have been found to be higher and PlGF levels have been found to be lower than in normal pregnancy.

***Endothelins are proteins that constrict blood vessels and raise blood pressure. They are normally kept in balance by other mechanisms, but when they are over-expressed, they contribute to high blood pressure (hypertension) and heart disease. Comprised of 21-amino acid vasoconstricting peptides, it is produced primarily in the endothelium having a key role in vascular homeostasis and are among the strongest vasoconstrictors known.

† Apoptosis is the process of programmed cell death (PCD) that may occur in multicellular organisms. Programmed cell death involves a series of biochemical events leading to a characteristic cell morphology and death; in more specific terms, a series of biochemical events that lead to a variety of morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Defective apoptotic processes have been implicated in an extensive variety of diseases. Excessive apoptosis causes hypotrophy, such as in ischemic damage, whereas an insufficient amount results in uncontrolled cell proliferation, such as cancer.

†† Tumor necrosis factor is a cytokine involved in systemic inflammation and its primary role is to regulate the immune system and to induce cellular apoptosis (see above).

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