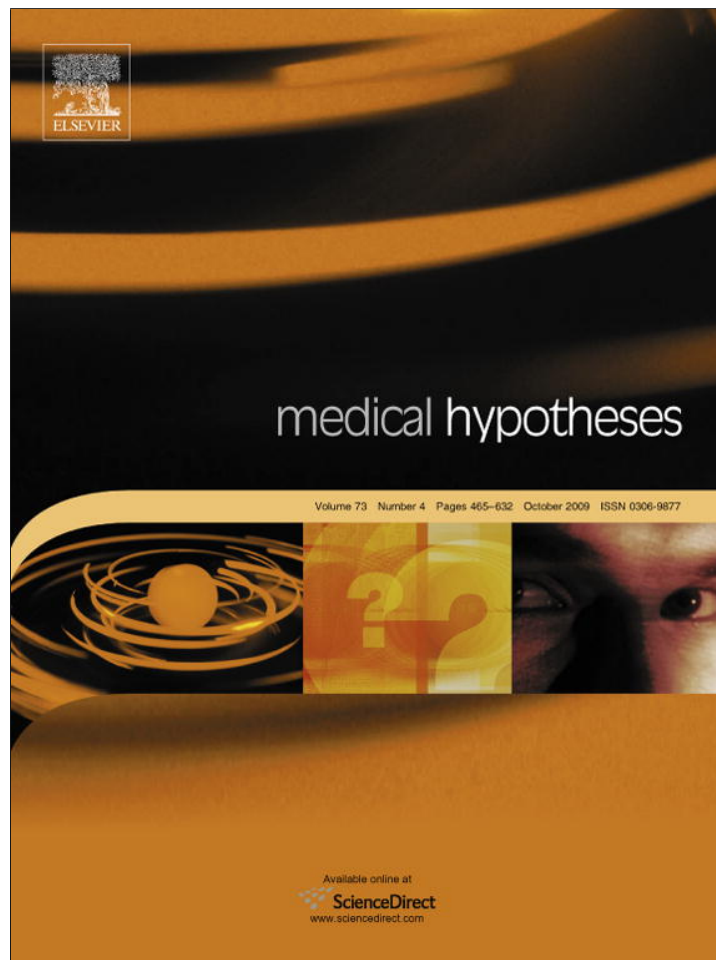


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Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Micronutrients and amino acids, main regulators of physiological processes

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ARTICLE INFO

Article history:

Received 1 June 2009

Accepted 6 June 2009

SUMMARY

Human physiology is supposed to be a complex interaction of regulating processes, in which hormones, genes, their proteins and apoptosis are thought to play a dominant role. We hypothesize that regulation of physiological processes is mainly influenced by amino acids and micronutrients with hormones, proteins, apoptosis and gene modifications being their derivatives. Furthermore, we suppose that the cells power plant, the mitochondrion, is in fact an intracellular bacterium, living in absolute symbiosis. Because of its intracellular existence it depends on the host's micronutrients completely. Within the host these micronutrients regulate their own formation, degradation, uptake and excretion. Known deficiencies, such as iodine and vitamin D, affect billions of people. Many micronutrients neither have been investigated, nor have they been studied in relation to each other and solid data are not available. Optimal levels of many micronutrients and all amino acids are not known. Amino acids, vitamins and minerals are capable of altering gene expression, inducing apoptosis and regulating chemical processes. It makes them highly attractive for creating better health, against low cost, as we have already proven in the case of rickets, cretinism and scurvy in severe deficiencies. By creating optimal living conditions and study mitochondria from a symbiotic point of view we suppose that diseases not only can be prevented, but the course of diseases can be altered as well.

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Introduction

In modern medicine the scientific interest in the role for micronutrients and amino acids is very limited, although most of our physiological processes are highly dependent on optimal availability of them. In most clinical studies only one single nutrient is studied although we are well aware of the fact that delicate balances between most nutrients exist. Correction for known deficiencies or changes in the balances between nutrients isn't performed. Nowadays micronutrients and amino acids are a nutrition topic instead of a medicine topic. It is known for a long time that micronutrient deficiencies in its extreme form can induces diseases, such as scurvy, cretinism or rickets. Our attempts to unravel the complex interactions between micronutrients and amino acids has been reduced by the introduction of medication and genetic driven research.

It is known that many deficiencies exist, such as 1 billion people with vitamin D deficiency and 2 billion with iodine deficiency [1,2]. Of other known deficiencies such as iron and vitamin B12 exact numbers fail. But for the majority of our micronutrients and amino acids solid data are not available or even worse, optimal concentra-

tion and/or nutrition levels fail. Nevertheless, we suppose that these deficiencies or missing data do not influence our research or development of diseases and death. As is shown in the article there is substantial evidence that micronutrients and amino acids greatly affect our physiological processes, both for the good and the bad.

Instead of putting our efforts in medicine research on medication and gene modification we should aim on optimizing our living conditions to start with the micronutrients and amino acids.

The hypothesis provides a change of perspective, where our most essential building blocks are the cause of diseases or syndromes but also provide the solution in the short and long term.

Hypothesis

We hypothesize that regulation of physiological processes is mainly influenced by amino acids and micronutrients with hormones, proteins, and apoptosis and gene modifications being derivatives of the latter. Disturbances in their balances will eventually lead to disease and death. We assume, based on the available scientific data, that it will be possible to optimize our physiological processes by altering micronutrients and amino acid content and thereby prevent the development of diseases and reduce the needs for medication and gene therapy dramatically. Furthermore, we assume that also curative possibilities will be present although the extent will depend on the severity of the alterations already

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present in tissues. The energy production for our physiological processes takes place in mitochondria which we assume to be intracellular living bacteria instead of cell organelles, living in perfect symbiosis. This will change our view on mitochondrial disease and apoptosis.

Support for the hypothesis

Hormonal regulation by micronutrients

To support the hypothesis of hormonal regulation by micronutrients we will focus on thyroid metabolism in which thyroid hormones thyroxine and triiodothyronine play a central role. Thyroid hormones consist of three or four iodine atoms and two tyrosine molecules. Regulation of T3 and T4 production is believed to be controlled by thyroid stimulating hormone (TSH) via thyrotropin-releasing hormone (TRH). We hypothesize that regulation is influenced by the amino acid tyrosine and products of tyrosine metabolism, especially dopamine. Tyrosine is produced out of phenylalanine, an essential amino acid. Tyrosine hydroxylase is the enzyme that in a rate limiting way converts tyrosine into dopamine. Tyrosine is considered to be the precursor of dopamine, (nor)adrenaline and melanin. Clinical effects of hyperthyroidism resemble the effects of (nor)adrenaline. Such resemblance cannot be fully explained from the produced effectors thyroxine and triiodothyronine. We suppose that overproduction of thyroxine, leads to a higher tyrosine release in the peripheral tissues which will increase the production of dopamine and noradrenalin. Increase of dopamine level suppresses TSH level, which might mean that in homeostasis dopamine plays a crucial role and not only T3/T4 [3,4].

As (nor)adrenaline is a rapidly acting hormone, it seems logical to assume that there is a storage pool of tyrosine. Tyrosine is present in proteins, but release from proteins would mean a considerable rate limiting step. Regulation on a post-translational level will ensure instant availability and rapid activation.

From that point of view, it seems logical that T4/T3 provide a directly accessible storage pool. This would mean that tyrosine directly affects thyroid metabolism via dopamine, which has indeed been shown in several studies. Earlier studies have shown the correlation between tyrosine levels and T3/T4 levels [5–9].

Other hormonal systems are greatly linked to amino acid metabolism as well, such as serotonin, acetylcholine and prolactin. The greatest challenge lies in studying these effects and interactions, making use of the immense literature that is already available on this topic from before 1960.

Enzyme regulation by micronutrients

Tyrosine hydroxylase activity is influenced by several factors including vitamin A and D [10–12]. Increase of vitamin D level eventually leads to increase of tyrosine hydroxylase. This might explain why vitamin D deficiency may resemble symptoms of hypothyroidism. Vitamin D deficiency means decrease of tyrosine hydroxylase activity with eventual decrease of dopamine and (nor)adrenaline production. In hypothyroidism tyrosine hydroxylase activity may still be intact, however, with decreased thyroxine production. We suspect that this decrease will lead to a decrease of tyrosine availability in the tissues and could be related to deficiencies such as for iodine, selenium or tyrosine. Eventually, this will lead to overlapping clinical symptoms. Not only vitamin A and D are capable of regulating enzyme activity. Also iodine is capable of influencing enzyme activity as is the case in lactate dehydrogenase [13,14].

Vitamin D production occurs under the influence of ultraviolet radiation, known for its irradiation effects. One of these effects is

the degradation of hyaluronate, inhibiting cell repair in the skin. In one study iodine protects for this degradation in the conjunctival fibroblast, but this hasn't been studied in the skin or related to clinical research in an iodine deficient subgroup [15]. It is also known that some amino acids are influenced by UV light as well. Recently, it has been shown that phenylalanine is converted into tyrosine under influence of UV light [16]. The phenomenon has also been described in human skin [17,18]. It is known that the shikimic acid pathway in plants, essential for the production of the aromatic amino acids, is stimulated by UVB radiation. Theoretically this could lead to higher phenylalanine and tyrosine levels in plants, which indeed has been shown in two studies but hasn't been investigated in relation to our food chain [19,20]. More toxic UVB levels by ozone depletion could on the other hand lead to lower levels of amino acids. Under normal UV levels these interactions theoretically could lead to higher tyrosine levels in our food during summer, with enhanced dopamine and adrenaline production possibilities. This, in turn, could lead to the lower TSH level known to exist in summer periods. Eventually, the increase of tyrosine will lead to a higher adrenalin production capability, in line with the energy demands during summer. Adrenalin will in turn stimulate energy production by the citric acid cycle [21].

Mitochondria

The citric acid cycle takes place in the mitochondria, in this way functioning as the most important energy production source. These structures are considered as cell organelles and have been connected to many mitochondrial diseases and apoptosis. In our opinion, mitochondria never evolved into cell organelles but remained (highly adapted) bacteria, living in perfect symbiosis with human beings. This hypothesis is based on the fact that mitochondria divide by binary fusion, similar as bacteria, that they rely on the availability of nutrients on the host cell, that they show a set of double membranes with a lipid composition not similar to eukaryotic cells and that they possess their own DNA which is circular, as is bacterial DNA [22]. We hypothesize that besides a role in basal tyrosine metabolism, the thyroid is involved in regulating energy demand by increase of T4 and T3 and thereby of adrenaline. In this way the thyroid guarantees a rapid adaptive and tissue targeted system upon a basal slow acting and non-specific system. The latter is formed by the proteins and, to a lesser extent, the free amino acid pool.

Gene expression, apoptosis and diseases

It is known that apoptosis is a complex programmed cell death in which mitochondria seem to play a crucial role. It can be mediated in several ways, not all being elucidated at this moment.

Apoptosis can be regulated by ornithine decarboxylase and this enzyme is upregulated in cancer cells [23,24]. Thereby it prevents the activation of cytochrome c and caspase induced apoptosis. To increase apoptosis in cancer cells, investigations have been made to inactivate or downregulate ornithine decarboxylase (ODC) [25–27]. However there are micronutrients that are already capable of influencing ODC activity. Research has shown that iodine is a micronutrient capable in decreasing ODC and thereby can induce apoptosis in goiter [28,29]. Iodine influence on ODC hasn't been investigated in cancer cells however. The active form of vitamin D3 is capable to inhibit ODC activity induced by tumor promoters [30]. Other micronutrients are known to exert an effect on ODC as well [31,32].

Other investigations have shown that, even in the presence of the apoptosis suppressor gene bcl-2, any single amino acid can induce apoptosis, with essential amino acids being more effective [33,34].

Finally, it is known that the pro-apoptotic bcl-2 associated X protein Bax induces apoptosis by disruption of the mitochondrial surface leading to the release of pro-apoptotic molecules from the intermembrane space such as cytochrome c [35–37]. The latter is produced by most bacteria as well. Furthermore, it is known that bacteria are highly sensitive to Bax and that even small concentrations lead to cell death of the bacteria [38,39]. It has been shown that delayed neutrophilic apoptosis is associated with lower levels of Bax [40], so that not only the apoptosis of neutrophils will be delayed but also the cell death of bacteria. Recently, it was shown that vitamin D supplementation could lead to increase of Bax expression [41] and thereby could enhance neutrophilic apoptosis and bacterial cell death.

It is also known that apoptosis can be induced in cancer cells by vitamin D in a caspase independent way but probably Bax dependent way [41]. On the other hand, the same vitamin D could increase Bcl-2 but also Bcl-x [42,43]. We assume that the alterations in Bcl-2 family by vitamin D are tissue specific and also depend on underlying disturbances of normal tissue.

Recent research shows that micronutrients can regulate the expression of genes in normal cells, but are also capable of altering gene expression in cancer cells. In that respect, it is remarkable to notice that iodine can alter gene expression in breast cancer cells and vitamin D regulates multiple sclerosis associated MHC class allele expression [44–46]. This could explain the geographically epidemiological changes in diseases, certainly if we take inhibitory factors (such as pollutants) and known micronutrient deficiency patterns into account.

Since apoptosis is tightly related to the well being of the mitochondria it could be assumed that micronutrients are essential for inducing or preventing apoptosis. Furthermore, micronutrients seem to be able to regulate gene expression as are single amino acids. Eventually, this could mean that evolution is an adaptation to the balance of deficient and excessive availability of micronutrients and amino acids in relation to interfering toxicological and environmental factors.

Supplying amino acids

Supply of a single amino acid eventually leads to a change in the free amino acid pool. To deal with varying amounts of amino acids in our food, it seems likely that the human body needs buffer capacity. Thus far, it has been assumed that this buffer is provided for by proteins. This is limited however by the rigid DNA sequence and the theory that one codon encodes for only one amino acid. This will be true for some codons but doesn't have to be for all, depending on their functional essential position. Recently, it was shown that one single codon is able to code for two amino acids [47]. It is known that not all parts of a protein are of functional importance. However, if we realize that one codon can bind more amino acids, this provides the possibility to buffer an excess of amino acids in the less essential parts of the protein. In that way the adaptation to variable amino acid concentrations is a very dynamic interplay in which genes are less rigid than has been assumed thus far. The codon's affinity for the amino acid could depend on the position, the configuration and the amino acid concentrations in the free amino acid storage pool.

Contributing to the non-rigid theory of genes are recent research results of revertant mosaicism [48,49]. The real question behind revertant mosaicism is what is influencing this phenomenon. It might be possible that micronutrients induce this mechanism. It is known that aneuploidy can be induced by environmental factors, such as colchicine by binding to tubulin [50,51]. However, it is also known that iodine is able to induce dissociation of the tubulin–colchicine complex [52]. This could mean that other micronutrients

and/or amino acids are responsible for gene-alterations or for protecting them by environmental factors.

Finally, it is known that the majority of the DNA is non-encoding. A great part of the non-encoding DNA belongs to the mobile genetic elements. These elements are thought to have a regulatory role in gene expression. Transposons or “jumping genes” are the major group. Recently it was shown that methylation of transposons and the adjacent promoter region of the gene can be influenced by micronutrients [53]. This could mean that transposon regions could be influenced by nutrition and thereby influence the adjacent promoter region of the DNA. On the other hand, it could be hypothesized that also the movement of these mobile genetic elements is influenced by micronutrients.

Regulatory mechanisms of micronutrients

It has been shown that taste receptors can be activated by amino acids [54,55]. Moreover, amino acids are responsible for the taste of our food. Well known examples are glutamate and aspartate. It has also been shown that appetite is regulated at a hypothalamic level and can be influenced by amino acids [56–60]. It seems logic to suppose that the need for essential micronutrients by associated chemical processes is regulated by micronutrients and amino acids themselves. Thereby, a learning system in close association with a basically innate system is hypothesized to exist. The innate system ensures the knowledge which taste contributes the most to the needed amino acids and/or micronutrients. From the taste and positive feed-back from the innate system one is learning which food contributes most to the amino acid need of that moment. The stronger the taste stimulus will be, the more likely it will contain the right amino acids. That innate concept has been frustrated considerably in the last 100 years. By adding salt and sugars or engineered alternatives to our food this regulation can easily be distracted. Seeking for sweet, but sugar rich instead of amino acid rich, food by example, will diminish our need for sweet, but because of shortage of the needed and expected amino acids this effect is only temporarily.

But not only amino acids are regulated, also other micronutrients regulate their own needs as well. We assume that iodine plays a crucial role in binding two tyrosine molecules and offering this to the peripheral tissues as thyroxine. Recently, it was shown that the iodine receptor is widely spread throughout the body [61]. Remarkably, the receptor has been found in the kidney and iodine uptake has been shown to be dependent of sodium concentration. Possibly, a very low salt diet reduces re-uptake in the kidney with enhanced urine iodine excretion, however, with low iodine concentration in the peripheral tissues. As a consequence, binding possibility of tyrosine in the thyroid is reduced. The same phenomenon could occur by blockade of the iodine receptor by thiocyanate (cigarettes), bromide and possibly polychlorinated biphenyls [62,63]. Thus, not only micronutrients are capable of influencing each other, also environmental factors are of great influence in the homeostatic possibilities of micronutrients.

Testing the hypothesis

1. Storage of amino acids in proteins as a buffer for too low or too high concentrations of amino acids, assuming one codon encodes for more than one amino acid. In experimental studies groups of animals could be given a single amino acid or micronutrient besides their regular food, after which comparison of body proteins could possibly point to a difference in amino acid sequence although the same codon sequence is investigated.

2. Tyrosine as a regulator of chemical processes. First it could be studied whether it is possible to induce hypo- or hyperthyroidism in animals by tyrosine depletion or supply. Optimal nutritional environment will be necessary to induce this.
3. To study the influence of salt intake on iodine excretion in urine animals could be given various amounts of sodium under standard iodine intake. The same could be done for pollutants such as thiocyanate. Furthermore it is of interest to find the triggers for increased iodine uptake by the kidney. Several factors could be investigated for instance iodine itself, tyrosine or dopamine.
4. Amino acids as regulators of chemical processes. It seems logic to study the effect of single amino acid supply on biochemical balances, such as tyrosine and TSH, tryptophan and serotonin.
5. It would be interesting to study whether apoptosis can be induced by changing the amino acid content of food. Moreover, it is worthwhile to study the effect of nutrients on the number and activity of mitochondria.
6. In clinical practice it seems logic to see in ADHD populations whether the benefit of artificial increase of dopamine levels by methylphenidate, could be reached by supplementation of the above mentioned factors that contribute towards an optimal dopamine metabolism. Special attention should be given to iodine, vitamin D and tyrosine.
7. In case of obesities it is known that inhibition of tyrosine hydroxylase leads to hyperleptinaemia [64]. In that respect it seems of importance to study micronutrients known to play a crucial role in the thyroid-tyrosine metabolism on leptin levels, such as vitamin D, tyrosine and iodine [65].
8. In case of skin cancer the effects of iodine protection on the radiating effects of UV light on the skin could be studied. Given the large numbers of iodine deficiency, with increasing numbers in countries with an increase of incidence of skin cancer such as Australia and Europe, this increased incidence could be related to a less protective effect of iodine on hyaluronate degradation by UVB. Iodine deficiency could even be related to the vitamin D deficiency, given the fact that the skin could be less productive because of a higher damage rate by irradiation and less possibilities to withstand the oxidative stress.
9. To study the influence of micronutrients on the mobility of the mobile genetic elements it would be of interest to study the changes in the non-encoding DNA related to different micronutrient levels.
10. Above mentioned ideas are only some of the many possibilities for further investigation. Eventually, further studies should lead to insight in optimal nutrition balance for human cells, the intracellular living bacteria and for our environment as well. Only in that way an optimal human adaptive physiological system will exist.

Consequences of the hypothesis

The consequences of our hypothesis could lead to changing views on metabolism and mechanisms of disease. If it is true that amino acids are the most important elements in metabolism and directly influence it, it means that they are evenly able to cause and/or modify diseases. Given the fact that shortages in amino acids can cause several diseases, it seems logic to suppose that disbalances in amino acids are able to do this as well. From this point of view, as shortage of tyrosine can lead to hypothyroidism, too much tyrosine could in a similar way lead to hyperthyroidism.

Inducing hyperthyroidism will only be possible in optimal conditions, for example optimum ferro for TPO formation, sufficient vitamin D for tyrosine hydroxylase and sufficient selenium for deiodinase activity. Instead of focusing on one single micronutrient or amino acid, research should focus on the interactions between them. Than it offers real possibilities to determine the facts that contribute to optimal health. In modern food industry huge changes take place. Animal food is enriched with amino acids (e.g. L-lysine) or depleted for other amino acids. Eventually, this affects protein content of food and in that way food intake of human beings.

Assuming mitochondria to be bacteria, living in complete symbiosis with the human cell, we will have to look upon mitochondria as a solitary living organism from a symbiotic point of view. Mitochondrial diseases may be caused by insufficient nutrition. To ameliorate the cell circumstances, by providing optimal nutrition, fitting the mitochondrial and host cells needs, eventually human life is positively affected. In that respect, negatively contributing environmental circumstances have to be taken in account as well, such as pollutants.

The most important consequence of the hypothesis lies in the fact that it is essential to study intake of our (semi)-essential nutrients before drawing all our attention to medicines or manipulating genetics. It might be possible that congenital diseases are the consequence of suboptimal food intake, such as is the case in cretinism and iodine deficiency. It is essential that we do our research as part of the whole puzzle, never leave the whole picture out of sight and fit the results into it. If the hypothesis is true it could create a paradigm shift, with huge possibilities for metabolic and preventive medicine.

We first have to study how to nurture nature before we change nature itself.

Conflict of interest statement

There is no conflict of interest statement.

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