

Vitamins and endocrine disruptors: The exohormone system

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Abstract

In our present knowledge the human endocrine system is composed of endocrine glands, hormones (signals) which are produced by them and hormone receptors which recognize and bind the hormone and forwards the signal. However there are molecules outside the body which also have hormonal characters however, not having the name: hormone. These are some vitamins (A and D, possibly E and K), and natural or man-made endocrine disruptors. In contrast to their names they are real hormones in character and impacts and belong to the endocrine system (exohormones) as after entering into the human body, participate in the inside regulation. These molecules will have important role in the future evolution of the human endocrine system and can be internalized as it was in the case of vitamin A. Their classification into the real category is very important, because of doctor's and laymen's motivation, and avoidance of faulty treatments.

There are such molecules in the medical vocabulary which are classified by medicative effects in case of diseases, or effects on physiological processes however they are in a faulty place [1,2]. Although decades after their faulty categorization when the real place in medical taxonomy is known, they remain unmoved, constituting false image. These also can be found among vitamins and endocrine disruptors.

What is a vitamin?

Vitamins are different molecules (in our modern life mostly in the category of food supplements) with life-important functions, which are needed in micro doses for sustaining life (they are absolutely needed) however they could be medicaments in mega doses. Vitamins are named by numbers which were given in the order of their recognition independent of their structure and function. In normal, natural conditions the overdosing is improbable, however, it is possible in artificial conditions [3], which shows that their classification is dose-dependent.

The name "vitamin" represents a dustbin into which many newly discovered molecule are fitting in, independent of their origin and function, the only basic demand is the effect in small (minimal) amounts. They are indeed in connection of life ("vita"), however they are mostly not amines. Most of the vitamins have been discovered in the time, when their effects could not be cleared and this was not necessary, as the accent was set on the effect, because of the disease, in connection with the vitamin, must be treated. So got ascorbic acid (vitamin C, water-soluble) and cholecalciferol (vitamin D, lipid soluble) in the same category, as "vitamins". With the development of chemistry and its instruments the possibilities are given to refine the system, but it seems to be difficult to change. Not only the name proved to be conservative, but the effect and the dosage, for example vitamin C is booked as the drug against scurvy and its dose is believed the amount, which sufficient for avoiding scurvy. Only today came the time, when mega doses of vitamin C (vitamin D and others) begins to be accepted as needs for our present-day health.

Two vitamins which are exohormones

Vitamin D

In the 18th and 19th centuries with the increased industrialization and its consequences (smoke and smog) in England (London) a very peculiar disease (rickets) was proliferated which had been recovered by the consumption of cod liver oil. The agent contained by this latter had been named vitamin D as the fourth in the line of dietary supplements (vitamins) after vitamin A, B and C [4]. In that time it was believed that the only function of this vitamin is the influence of bone formation however later many (possibly more important) functions of the vitamin has been cleared and this process is continuing permanently [4-6].

Vitamin D is produced by the skin, which is the largest endocrine organ of the human organism [7-9], however induction by the sunshine (uv B, 280-320 nm) [10-12] is needed for its vitamin D production. The high-energy uv photons after penetrating the epidermis photolyze provitamin D3 to pre vitamin D3 which is followed by thermally induced isomerization to vitamin D3 (calcitriol), which is the effective form of the series [13]. Sunshine was at the disposal of African men however after migrating to north less and less sunshine diminished the vitamin D synthesis in the skin, so outside help has been needed, as vitamin D was indispensable for human life. This was found in fatty meats, milk and eggs, nevertheless this was not sufficient for complementing the loss of sun-induced amount, especially in the case of paupers. This explains the need for cod-liver oil treatment, in which

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sufficient amount of vitamin D and its precursors were present, for preventing the rise of rickets [14].

“Pandemy” of rickets has been eradicated however other very important physiological functions of vitamin D has been cleared. It seemed to be very important for the regulation of calcium and bone metabolism [15] and for the function of the immune system [16]. Vitamin D receptors are present in many cells, with otherwise regulated functions and in these cases calcitriol has a side-regulator role [17,18].

The classification of „vitamin” D is faulty, as it is a hormone, with regular receptor in the steroid (nuclear) receptor superfamily in which used to be overlaps between the receptors, considering the hormones and binding specificity of receptors [19,20].

Vitamin A (retinoids)

It is the first in the series of vitamins. It is a group of molecules, with similar functions: retinol, retinal, retinoic acid and provitamin A., vitamin A It is needed for vision (colour vision and vision in dim light) in its deficiency night-blindness appears, however it has many other functions [21,22].

While one receptor is sufficient to one hormone in general, retinoids have two types of receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Vitamin A as polyunsaturated fatty acid can be found in trans and cis formations, depending on the conformation of the double-bonds [23]. The ligand recognized and bound by RARs is all-trans-retinoic acid, and for RXR receptor is 9-cis retinoic acid. The retinoid receptors belong to the nuclear superfamily of receptors, which family has a lot of different hormone receptors with many overlapping in case of hormone binding.

In addition to the service of vision retinoids are needed for the care of immunity, mucous membranes and skin, growth and development. This vitamin is not produced by the human organism at all, it is entering to the human body from outside, in the form of foods (milk, plant foods etc). This means that retinoids (vitamin A) are the most classic (vitamin-named) exohormones partly by the above mentioned properties, partly as -likely- they are the most ancient and most comprehensive in impact.

Vitamin D is a transient hormone between the exclusively endocrine gland-produced hormones and exohormones, as it was present before the appearance of exohormone-demand and after that it is also able to synthesize cholecalciferol in the skin. Vitamin A is a clear exohormone, which does not synthesized inside the organism and import is needed for sustaining its functions. However there are two other „vitamins” in this lipid-soluble group: vitamin E and K. There is not any creditable evidence on their hormone-being however, this is not disclose that will not be in the near or far future, as traces of actions through receptors can be found [24-26]. Hormone-like functions by water-soluble vitamins (e.g. vitamin C) also can be found [27,28].

What is a hormone?

In the mammalian (human) organism the nervous system is the main guider however, the main executor is the endocrine system, which using its chemical materials (hormones) is able to arrange quickly the wills of brain or can react spontaneously to the inside and outside events. For the fulfilment of the function of hormones receptors are needed, without them the message transported by the hormone cannot be recognized and forwarded to the executing mechanism of the target cell. The hormones are evolutionarily supported and developed molecules, members of the system forming a network which reacts together or by the response of a single hormone. The hormones are

produced by specific endocrine glands (e.g. thyroid and adrenal gland) or such tissues which have also other functions (e.g. testis or ovary). In addition there are hormones which are produced by isolated cells inside organs or tissues (e.g. renin). Nevertheless, there are such hormones which do not fit in any categories mentioned, as they are not produced by the organism, but they enter to the organism from outside or outside provocator is needed for their production inside the organism (e.g. sunshine). This means that there are members of the human endocrine system, which are produced inside the body (endohormones) and which are produced outside the body (exohormones), which are entering into the human organism from the environment, however absolutely needed in minimal amounts for the normal functions of human life. These latter usually do not have the name, hormone, at the same time their function is hormonal. It seems to be basic that the „hormone” contain a message and have receptors which recognize and bind it, without these criteria there is not possibility to list a molecule as hormone and fulfilling these criteria it can be listed as hormone, independent of its origin.

A hormone is a molecule, which contains information for doing something or forbid something and the information can be deciphered by a cell, which executes the task. However it does not prescribed the origin of the information. This means that the information can arrive from the neighbouring cells, from cells far from the executor in the same organism and also from outside, (e.g. in form of a medicament or in form of a supplement). For the normal function of a hormone receptor is needed, which recognize the hormone in the tide of different molecules transported by the blood circulation or other transporters (lymph or peritoneal fluid etc), and select it for binding. Although the hormone and the receptor seem to be equally important, the decisive factor is the receptor without which the hormone is a meaningless molecule. This means that hormone-like molecules can activate the receptor binding by it, while there are not receptor-like structures with hormone recognizing and binding capacity. Originally hormones belonged to the organism which was able to produce the commander molecule (hormone) as well as the receptor, without which the hormone could be invaluable, however from the beginning of human evolution must be present independent hormones as products of non-human organisms (steroid-like molecules of vulcanic eruptions, products of combustions, plant hormones (steroids), as phytoestrogens, mycoestrogens etc. These molecules could be named exohormones and entering into the human organism expose hormonal functions. It is not known what was the qualitative or quantitative impacts of these molecules during the millenaries of human evolution, nevertheless it cannot be neglected as formatting pover of the endocrine system. However, there is a drastic quantitative and qualitative change in the last decades, when man-made chemicals flooded the human environment and entering into the human organism and exceeds the amount of physiological presence of real hormones, disturbing the normal process of hormonal regulation (endocrine disruption). It seems to be very difficult to declare, that e.g. phytoestrogens are beneficial and bisphenol A is harmful, as the decision is dependent on the aspects and so many new molecules appeared as exohormone, that almost impossible at present to decide, what will be evolutionarily useful without acute destroying effect, or acutely useful with evolutionarily harmful effects [29]. The fact is: in contrast to the earlier times, exohormones must be considered and from this aspect the so-called vitamins and so-called endocrine disruptors are in the same category.

Endocrine disruptors

The molecules named endocrine disruptors used to be categorized as man-made materials however, this is not obligate. Before man,

as a result of conveyed evolution, reached the grade in which it was able to produce such molecules which work as endocrine disruptors, these latter were present already in the ancient human environment [30] and their effect has been heritable [31]. Chemicals, as e.g. dioxin or benzpyrene have been produced by volcanic eruptions and forest burning, and have been respired, phytoestrogens, as e.g. genistein and daidzein, as well as mycotoxins have been consumed as nutrients millenaries ago and formed the endocrine system and organs influenced by them. These molecules are really hormones, exohormones which could have similar functions as vitamin A or D however, the mechanism by which they act or the target to which they act is unknown at present. Only the mass-production of hormone-like materials by man called the attention to them, and time will be needed to the complete cognition of them.

At the same time, the entrance of Chinese kitchen to European one called the attention on the possible effects of phytoestrogens as endocrine disruptors, nevertheless, it is not decided their harmful or beneficial effect to human beings up to now [32].

The above mentioned molecules can be classified as exohormones and in this qualification they do not differ from e.g. vitamin A however time is needed for clearing their (and the metabolites [33-35] physiological functions. It seems to be strange to classify the presently dangerous-labelled bisphenol-A as a hormone, however the classification is only time, investigation and motivation-dependent. It is not known up to now, why e.g. vitamin (?) A is responsible for many life-important physiological processes, a molecule, which is purchased for the mammalian organism from outside (and does not synthesized in human body at all) exposed to loss, which could cause fatal consequences. So, it is not surprizing if we do not know the future of bisphenol and other endocrine disruptors (?) in a long run.

The global production of bisphenol A in 2007 was 4.36 million tons and the growth is about 10%/year. and there is an extreme growth of production of other „endocrine disruptors” [36,37]. This means that the attack by endocrine disruptors will be continuous and the „boarding” is full. This warrants the continuous stimulus for the endocrine system and the possibility of setting to the stimuli, consequently the comprehension of disruptor-presence as physiological which requests the planting of bisphenol into the endocrine system. However, it seems to be more plausible at first the planting of phytoestrogens [38-42] as it happened in the case of „vitamins” A and D.

Internalization of exohormones

Vitamin A and Vitamin D are the exohormones which have been internalized however it is not known in what time and why? Vitamin D which is a transient hormone between endo- and exohormones had a complete machinery when it was a real hormone of the skin and this machinery could have been used also for the exohormone however, vitamin A likely never was produced in human beings, so the complete machinery had to be established. If we hypothesize that present-day exohormones (endocrine disruptors, or some of them) will also be internalized, vitamin A would be the best model however the manner of vitamin A internalization is also unidentified. In any case it justifies that there is a possibility of such process, which may be occurred in any time. Endogeneous (endo-) hormones act at very low concentrations (part per billion or trillion). If endocrine disruptors have the same effectivity [43,44], this could help their internalization.

“Internalization” in the present case does not mean, that the human organism will produce the molecule given actuating the mechanism

of production, but it means the continuous utilization and demand, similar to the case of retinoids.

Faulty hormonal imprinting

In contrast to the endogenous hormones, exohormones could provoke faulty hormonal imprinting in very low dose and special developmental periods of life (perinatally, pubertally or in any periods of life in differentiating cells). This means that in the presence of low doses of the molecule a special memory is induced which could cause alterations in the function of endocrine or endocrine-influenced cells (organs) which is manifested after months or years [45-48] as disease, on which the DOHaD theory (developmental origin of health and disease) is based, and trans generationally inherited. This is done by vitamins (A and D), and endocrine disruptors alike (provoking the event during gestation) and causing the sequelae in adult age (in sexual behavior, bone development, immunity etc).

Conclusions

There are names which categorize molecules to classes which introduces them one-sidedly and by this way hide their important properties, sheltering very important characters. It is not only a taxonomical problem, but influences the aspect and appreciation. It is believed that a vitamin seems absolutely harmless (independent of its dose) while a hormone could be dangerous basically influencing in minimal doses forms and function alike, while they are identical molecules considering their taxonomical category. Vitamins can be purchased from the shelves of a grocery, while hormones can be bought by prescription in pharmacies. Not only the laymen are influenced by the names (categories) but also the medical brain, which also influences the prescription. This means that vitamins are categorized in the brain as food supplements, while hormones as dangerous tools, which can transform function and behavior of the patients. The translocation of vitamins to hormone category is more than a semantic alteration, it changes the weight and direction of the name and defends the patient. The name: exohormone gives good standing to the molecule, whilst helps to arrange its place in the brains of doctors. However, in case of prompt acceptance of the changes written in this paper by textbook-writers (which cannot be expected), time is needed for the penetration into the common knowledge.

The above-mentioned facts justifies that there are exohormones (named „vitamins” at present) and candidates for hormone-being (named „endocrine disruptors” presently), which are waiting impatiently the change of category. This must be considered when regulating systems are discussed.

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