Review

Endocrinological Aspects of Dietary Habits

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Abstract

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Dietary habits reflect both the recent economic possibilities and the cultural history of individual human populations. They may influence endocrine systems and thus affect the health of the respective populations in several manners: (1) People consuming exclusively local products may lack certain micronutrients. This is important especially in areas with low levels of iodine and/or selenium in the environment. Thyroid gland insufficiency resulting from the iodine deficiency was widespread in many areas of Central Europe until the introduction of iodine supplementation in the second half of 20th century. Iodine deficiency is still a serious problem in many areas of Africa and Asia. (2) Numerous cultural plants contain compounds able to influence important metabolic pathways. Iodine deficiency is usually worsened by thyroidal peroxidase inhibitors, so-called goitrogens. Phenolic and terpenoid compounds may interfere in the metabolism of steroid hormones. Glycyrrhetinic acid from licorice is a potent inhibitor of 11-β-hydroxysteroid dehydrogenase. Isoflavonoids from legumes (e.g. genistein and daidzein) and their metabolites (e.g. equol) were found to inhibit the following enzymes: aromatase, 5α-reductase, 7α-hydroxylase, 3β-hydroxysteroid and 17β-hydroxysteroid dehydrogenases, etc. Isoflavonoid sulphates influence local availability of steroids by inhibiting sterol sulphatases. (3) Plant-derived compounds are able to interact with nuclear receptors and act either as hormone agonists or as antagonists. Recently, the attention has been paid namely to the phenolic substances interacting with oestrogen receptors so-called phyto-oestrogens.

Keywords: dietary habits; thyroid gland; endemic thyreopathie; goitrogen; steroid; mineralcorticoid; phyto-oestrogen; inhibitor; enzym; receptor

Unlike the other animals, humans are spread on all continents and climatic zones and are able to get nutrition from numerous different sources. At the beginning of the 21st century, people living in advanced countries may afford food enough to cover all their basic needs. Thanks to the developed market, they can choose from a wide scale of food products, often coming from distant areas. However, the situation is dramatically different in developing countries where large groups of people depend on limited local sources.

Dietary habits are formed by multiple factors. Together with recent economic possibilities the historical and cultural experience plays an important role. Moreover, inherited differences exist in the perception of tastes, which influences the choice of certain groups of food (Kaminski *et al*. 2000). There is no doubt that nutrition impacts on human

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health in many ways. The adequacy of macronutrient intake, i.e. the quantity and balance of proteins, fat and carbohydrates, is only one part of the topic. Very often, micronutrients and non-nutrients are the crucial components. In this contribution, a few examples will be mentioned how the dietary habits impact upon the endocrine system.

The following dietary factors influence the endocrine system, often in their indivisible combinations: availability of micronutrients, modulators of hormonogenic enzymes and hormonally active compounds.

Cabbage, millet, cassava and iodine deficiency

Thyroid hormones control many functions necessary for both mental and bodily development. Iodine is an inevitable component of thyroid hormones, and its daily need is about 150–200 μg. Iodine intake below 70 μg/day may cause serious health problems including disturbances of energetic metabolism, slow bodily development, late sexual maturation and low fertility, low educability, etc. Iodine deficiency during pregnancy may cause cretinism (Zamrazil 1999). An indispensable part of the thyroid hormone signalling network is the system of deiodinases – the selenium-containing enzymes responsible for the interconversion of thyroid hormones. While the thyroid gland secretes mainly thyroxin (3,5,3′,5′-tetraiodothyronine), hormonally more potent metabolites (i.e. 3,5,3′triiodothyronine and 3,5-diiodothyronine) are generated by its partial deiodination in tissues. Dietary selenium requirement is 40–200 μg/day, the intake lower than 17 μg/day causes numerous health disorders, on the other hand, the intake over 800–1000 μg/day may be toxic (Yang & Xia 1995).

Iodine or/and selenium content in the environment is rather low in many areas, often in mountains and plateaus (White & Zaoski 1999). The iodine uptake efficiency may be decisive for the quality of life or even a limiting factor in populations living in such areas.

Iodine is incorporated into thyreoglobulin – the thyroid hormone precursor – by a heme-containing enzyme, thyroidal peroxidase (TPO). Enzymes of this class are prone to inhibition by compounds that complex iron (e.g. cyanide, thiocyanate, carbonyl oxide, azide, etc.); however, the sensitivity of individual enzymes may differ. The most important TPO inhibitors of dietary origin are thiocyanates and flavonoids, their main sources being cruciferous plants in Europe and cassava and millet in the subtropics and tropics.

Cruciferous plants (*Brassicaceae*) include vegetables that are very important sources of vitamins, minerals, protein, oils and sugars – e.g. cabbage, kale, kohlrabi, cauliflower, broccoli, rape and mustard. They may contain up to 1% dry weight of glucosinolates (Figure 1). After plant tissues were damaged, glucose is cleaved and aglycones are liberated by the action of the myrosinase enzyme (Fahey *et al*. 2001; Chen & Andreasson 2001). Glucosinolates protect the plant from pathogens and pests; on the other hand, some insects use them as an oviposition signal (Moyes & Raybould 2001). Amongst the others, these compounds are responsible for typical spicy tastes and aromas of cruciferous plants. Degradation products of glucosinolates include thiocyanates, isothiocyanates, cyanides and several other TPO inhibitors. The cyanides are converted to thiocyanates again by the action of the sulphur-transferase enzyme (Jones 1998).

Toxicity of cruciferous plants to the thyroid gland was recognised already in the first quarter of the 20th century (Fahey *et al*. 2001). The risk of adverse effects is high in individuals with a low iodine intake and a high consumption of the brassica veg-

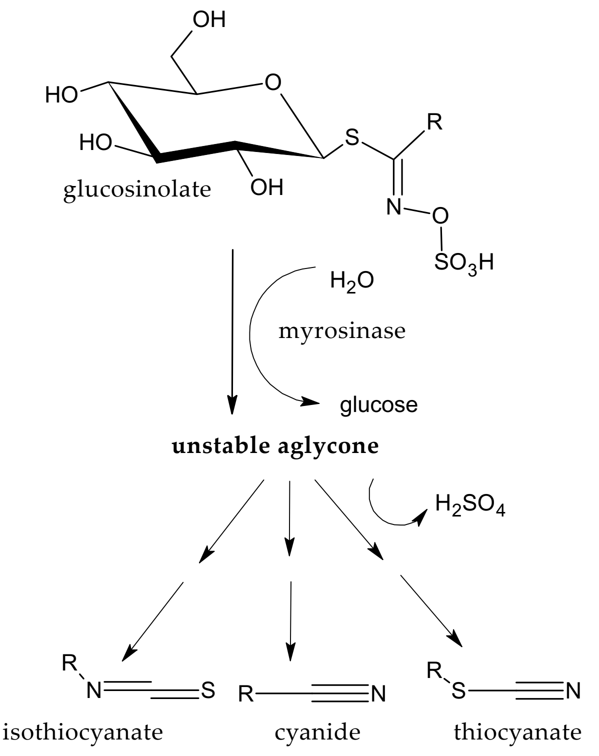


Figure 1. Dietary inhibitors of TPO: glucosinolates

etables. A striking evidence of this phenomenon comes from the veterinary field when sheep and cattle feed exclusively on the cruciferous plants (Taljaard 1993). In Europe, the iodine deficient area includes namely the Alps and the Carpathian mountains, making thus an arc from Switzerland and Austria through the Czech Republic and Slovakia to Ukraine, Moldavia and Romania (Delange 1995). For centuries, cabbage and kale have been a very important part of traditional cuisine in the Carpathian area, due to their ease to grow and to be stored either fresh or fermented. Namely the lower social groups often suffered from poor and monotonous nutrition, lacking adequate amounts of basic nutrients (Pelc 1894; Vomela 1953; Štika 1980). Resulting lower educability and working ability of these people formed a self-perpetuating circle of poverty (Figures 2 and 3). Industrial development improved the social situation of large segments of the population in Europe during the second half of the 19th and the first half of the 20th centuries; iodine supplementation was introduced during the 20th century (Vomela 1953). Nowadays, glucosinolates are recognised to display a scale of quite beneficial effects when their intake is moderate. They were found e.g. anti-carcinogenic, chemoprotective and anthelminthic (Fahey *et al*. 2001). Nevertheless, the consumption of cabbage and kale is still a risk factor for prevalence of thyroid goiter in some European areas (Obradovic 2000).

Millet (*Pennisetum* sp.) is a traditional cereal in large semi-arid regions of Africa and Asia. Flavonoids from millet have been proven to inhibit TPO. The effect of vitexin, the most potent of them, was comparable to that of methimazole – a strong synthetic TPO inhibitor used in medicine (Gaitan *et al*. 1989).

The consumption of millet is believed, together with malnutrition and vitamin A deficiency, to cause the high prevalence of goiter in the Blue Nile area of Sudan, despite iodine sufficiency (El-nour *et al*. 2000). Millet is considered to worsen the situation in iodine deficient districts of India (Brahmbhatt *et al*. 2001). These undesired effects of millet on the thyroid gland bring additional arguments for the idea to replace partly this traditional cereal by some economically more effective plants.

Cassava (*Manihot esculenta*) is an important dietary staple for more than 500 million people

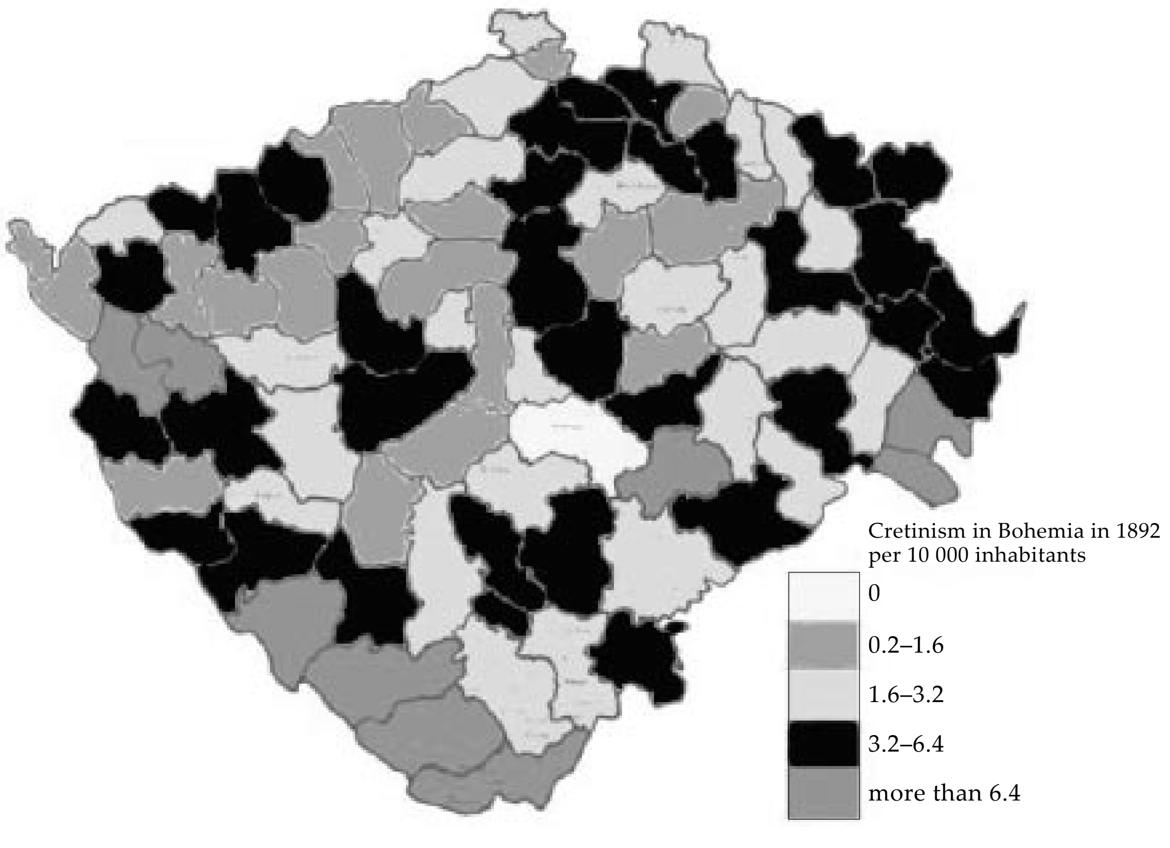


Figure 2. Prevalence of cretinism in Bohemia in 1892 (data from Pelc 1894)

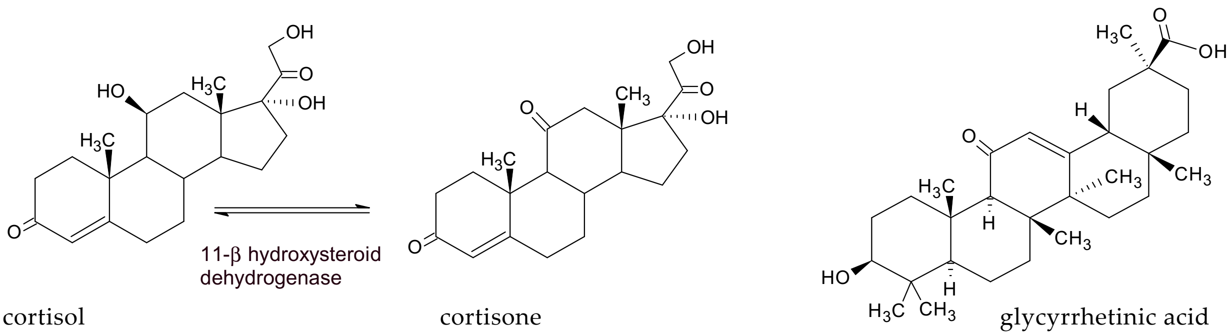
Figure 3. Goiter in the Carpathian area, 1920-ties (from Vomela 1953)

in developing countries. People eat 60% of the cassava produced and one third of the harvest feeds animals. All cassava cultivars contain the cyanogenic glucoside, linamarin, but in different concentrations. The roots of those cultivars with high cyanogenic content are processed to reduce the level of linamarin, because linamarin is hydrolysed in the intestinal tract of both men and animals by microbial flora and HCN is released (Kamalu 1995). The technology includes peeling, grinding, fermentation and drying. The care given to this laborious procedure is decisive for the influence of cassava on human health in individual cultures (Padmaja 1995; Dillon *et al*. 1999). The recommended WHO limit of the cyanide content in cassava flour is 10 mg/kg. Legislation of individual states usually accepts several times higher levels; e.g. in Indonesia, the permitted value is 40 mg/kg. However, the real concentration of cyanide in cassava products often exceeds any acceptable levels, causing thus chronic poisoning to the consumers (Jones 1998; Djazuli & Bradbury 1999). As mentioned above, cyanide is detoxified to thiocyanate, which is a TPO inhibitor (Jones 1998). Especially in conditions near to insufficient iodine intake, the consumption of cassava may be the crucial epidemiogenetic factor. The Bororos, a nomadic tribe in Central Africa, whose diet is based rather on milk products, have considerably low goiter prevalence when compared to local rurals, whose nutrition is based on cassava (17% vs. 76%, respectively) (Biassoni *et al*. 1998).

Licorice – not just a candy

The mineralocorticoid signalling system is responsible for the electrolyte balance of the organism. In addition to its cognate ligand, aldosterone, the mineralocorticoid receptor has a slight affinity to cortisol, a corticosteroid. As the plasmatic concentration of cortisol may exceed that of aldosterone by two orders of magnitude, a metabolic protection has developed. In mineralocorticoid sensitive tissues, cortisol is converted to hormonally ineffective cortisone by the action of the 11-β-hydroxysteroid dehydrogenase enzyme (Stewart & Edwards 1991).

Licorice, the root of *Glycyrrhiza* spp. (*Fabaceae*), has been used in the Mediterranean area over two thousand years and in China only a few centuries less. In addition to its use in traditional medicine, an extract of licorice is widely used in many countries as a flavour and sweetener in pastry, candies, herb teas and other drinks including pastis, chewing gums, breath fresheners and even in chewing tobacco (Shibata 2000). Licorice contains glycyrrhetinic acid, a potent inhibitor of 11-β-hydroxysteroid dehydrogenase (Figure 4). Inhibition of this enzyme causes the syndrome of acquired apparent mineralocorticoid excess, characterised by sodium and water retention, losses of potassium,



cortisol cortisone glycyrrhetinic acid

Figure 4. The cortisol-cortisone shuttle and glycyrrhetinic acid

oedema, high blood pressure, alkalosis, increased risk of left ventricular hypertrophy and coronary artery disease. In healthy individuals the licorice causes a shift in the mineral balance that can be observed by laboratory methods, but its clinical demonstrations are not frequent (Bernardi *et al*. 1994; Sigurjónsdóttir *et al*. 2001). However, the symptoms may be more pronounced and even lead to fatal consequences in predisposed subjects, e.g. in people suffering from hypertension, renal or liver failure and in people treated with diuretics or oral contraceptives. Hypertension episodes accompanied by other serious complications (hypokalemia, oedema, headache, etc.) were caused by regular intake of licorice tea, candies and even by "non-negligible amounts" of licorice flavoured chewing gum (Michaux *et al*. 1993; Brouwers & van der Meulen 2001; Heldal & Midtvedt 2002). A fatal intoxication was recorded after drinking a glycyrrhetinic acid-rich liquor (Bedock *et al*. 1985).

Glycyrrhetinic acid was also reported to inhibit 17,20-lyase, which catalyses the conversion of 17-hydroxyprogesterone to androstenedione. Ingestion may result in decreased levels of serum testosterone and increased levels of 17-hydroxyprogesterone. This may result in decreased libido or sexual dysfunction. Unlike the clearly evident mineralocorticoid action of GA there is not a consensus regarding the practical importance of this effect (Armanini *et al*. 1999; Josephs *et al.* 2001).

Tasty oestrogens

Oestrogens were originally discovered as regulators of female fertility and the reproduction-related behaviour. Later, many other functions of oestrogens were recognised that are important equivocally for both sexes, e.g. in bone development and homeostasis, lipid metabolism, cardiovascular system, cognitive functions etc. The oestrogen signalling system is rather complex. The main oestrogen-secreting gland is ovary in females; however, considerable amounts of oestrogens are produced in testes in males, and in extra-gonadal places in both sexes, including breast, bone, adipose tissue, vascular smooth muscles and brain (Simpson 2002). There exist two types of oestrogen receptors, with different tissue distribution and functions in gene regulation (Kupier *et al*. 1996; Barkhem *et al*. 1998). Circulating oestrogen levels depend on age, sex and the physiological status of the individual. They are relatively low and stable in males, while in females during the fertile period of life oestrogen levels are considerably higher and depend on the menstrual cycle. After menopause, oestrogen levels drop down dramatically, which is accompanied by menopause related symptoms, e.g. osteoporosis, hot flushes, changes in vaginal histology, increased risk of cardiovascular diseases. In order to prevent menopause related complications, a considerable part of women uses oestrogen substitutes as a hormone-replacing therapy (HRT). Nevertheless, HRT appears double-edged, as it increases the risk of breast cancer (Anonymus 1997; La Vecchia *et al*. 2002). Noticeable efforts have been developed to overcome this inconvenient feature of HRT or to find some non-risky alternatives. For the last two decades, many expectations have been connected with non-steroidal oestrogenic mimics of plant origin – the phyto-oestrogens.

Bennets *et al*. (1946) postulated the oestrogenic activity of plant origin in order to explain specific fertility problems of sheep grazing on subterranean clover. His hypothesis was later verified. Formononetin, an isoflavonoid abundant in clover was found weakly oestrogenic itself and recognised as a precursor of the potent oestrogen equol. The common term "phyto-oestrogens" was coined for oestrogenically active compounds of plant origin including their active metabolites (Adlercreutz 1998).

Now we know several groups of phyto-oestrogens of different structure and taxonomic origin. Unlike the authentic oestrogens, phyto-oestrogens are not steroids (Figure 5). Their common feature is the flatness of molecule and the presence of phenol moieties with appropriate distance of hydroxyl groups (Mazur & Adlercreutz 2000). Major phyto-oestrogen groups represent individual branches of phenyl-propanoid metabolism in plants, i.e. isoflavonoids, coumestans, chalcones, lignans, flavonoids, and stilbenes (Adlercreutz 1995; Mueller 2002). Main dietary sources of phyto-oestrogens for humans are as follows: soy and other legumes for the isoflavonoids, alfalfa and clover sprouts for coumestrol (a coumestan), oilseeds and nuts for the lignans, grapes and some vegetables for a stilbene resveratrol; an oestrogenic flavonoid 8-prenyl narringenin was recently found in hops (Milligan *et al*. 1999; Wu *et al*. 2001).

Soy (*Glycine max*.) is probably the most important dietary source of isoflavonoids, containing from 50 up to 300 mg of isoflavonoids per 100 g of beans. Main soy isoflavones are daidzein and

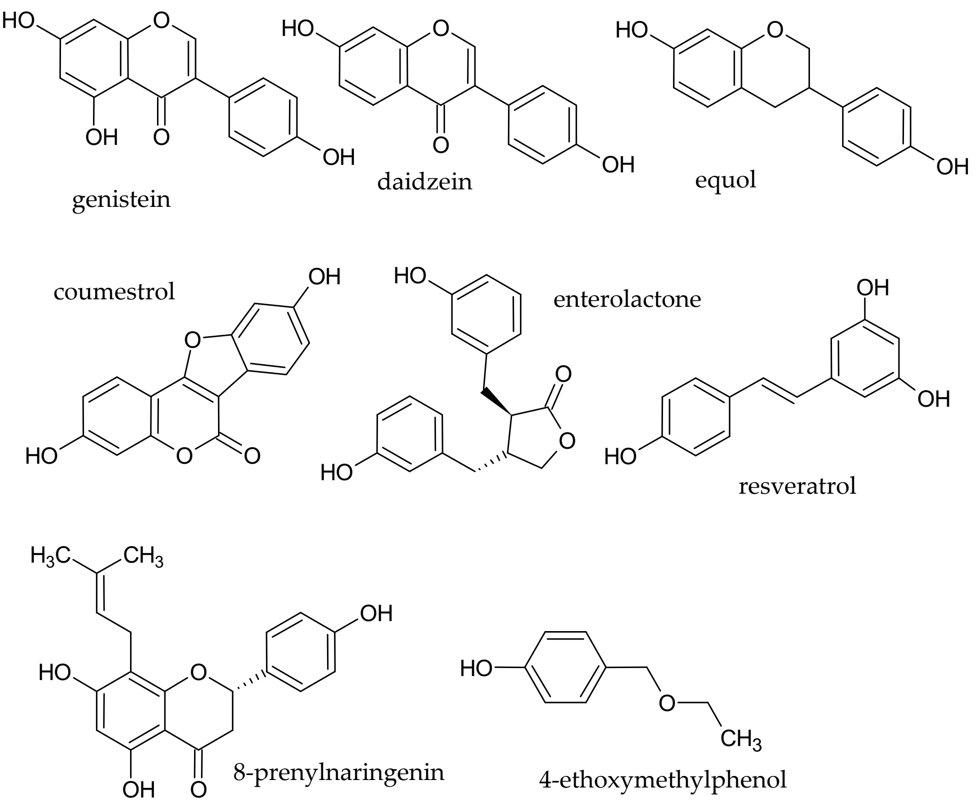


Figure 5. Main phyto-oestrogen structures

genistein and their glycosides. The glycosides are cleaved during cooking and in the gastrointestinal tract and the aglycones are liberated. Moreover, daidzein is partly metabolised to a more potent oestrogen, equol. Considerable amounts of isoflavonoids are also found in mung beans (*Vigna* sp.), chickpea (*Cicer* sp.), alfalfa (*Medicago sativa*) and clover (*Trifolium* sp.) (Franke *et al*. 1995; Mazur & Adlercreutz 1998). Humans consume the last two items as sprouts almost exclusively, and there is an observation that the isoflavonoid content increases during sprouting (Lapčík *et al*. 1999).

The *in vitro* and *in vivo* laboratory experiments show a promising beneficial influence of isoflavonoids on bone metabolism, parameters of lipid and cholesterol metabolism, vaginal histology and other oestrogen related parameters. At the same time, these compounds do not stimulate oestrogen dependent cancer cells. Especially genistein was reported many times to inhibit the growth of both oestrogen dependent and oestrogen independent cancer derived cell lines, influencing also other signalling systems in the cell (Zava & Duve 1997; Rappaport *et al*. 1997). Dietary intake of soybeans has been associated with lower incidence of several hormone dependent cancers, e.g. the breast and uterine cancer, prostate and colon cancer, and with lower risk of cardiovascular diseases (Adlercreutz 1995; Setchell 1998).

Seeds and nuts are rich in lignans, of which secoisolariciresinol and matairesinol are precursors of enterolactone, a weakly oestrogenic lignan found in mammalian body fluids (Mazur *et al*. 1996). The effect of enterolactone on oestrogen dependent tissues is biphasic. While the concentrations 0.5–2μM slightly stimulate the growth of oestrogen dependent cell lines in the absence of other oestrogenic substances, the concentrations above 10μM are growth inhibiting. At concentrations about 1μM, enterolactone is able to decrease the effect of oestradiol on MCF-7 breast cancer cells, supposedly by competition for oestrogen receptors (Wang 2002). Adlercreutz found that the risk of breast and uterine cancers was lower in Scandinavian women with high dietary intake of enterolactone than in those with low intake (Adlercreutz *et al*. 1982).

Resveratrol is a stilbene derivative found in some vegetables (e.g. cabbage, broccoli, onion) and in vine grapes (Šmidrkal *et al*. 2001; Wu *et al*. 2001). It became popular during the last decade in connection with so-called "French paradox" – i.e. the statistically lower incidence of cardiovascular diseases in France when compared to other Western countries. An explanation of this phenomenon has been attributed to the French life style, namely to their regular consumption of wine and the vegetables rich cuisine (Halliwell 1994; Wu *et al*. 2001; Sun *et al*. 2002). Despite the structural similarity to the strong synthetic oestrogen stilbestrol, resveratrol is a very weak ligand of the oestrogen receptor. Molecular modelling revealed that different amino acid residues are engaged in the interactions of the receptor with diethylstilbestrol and with resveratrol, respectively (Abou-Zeid & El-Mowafy 2002).

Beer has been mentioned as breast protecting and stimulating in the Central European tradition. A few glasses of beer per day used to be recommended to breast-feeding women in order to support lactation (Mennella & Beauchamp 1993; Koletzko & Lehner 2000). Disputations have been held for a long time whether the frequent tendency to an apparent feminisation in strong beer drinkers (the "beer makes pretty bodies" effect) may be attributed to some hormonally active compounds or is caused solely by the oestrogenic potential of the adipose tissue (Couwenbergs 1988; Gavaler *et al*. 1995). We have found phyto-oestrogen isoflavonoids in beer, namely daidzein, genistein, formononetin and biochanin A, but their concentrations did not reach 0.1μM, being by several orders of magnitude lower than in legumes (Lapcik *et al*. 1998). Recently, a flavonoid from hops, the 8-prenylnaringenin, was recognised as a potent phyto-oestrogen (Milligan *et al*. 1999).

The comprehensive reviews of epidemiological and clinical data regarding the phyto-oestrogen action have been published recently (Setchell 1998; Vincent & Fitzpatrick 2000; Kurzer 2002). Though the expectations that were originally connected with the phyto-oestrogens seem to be overestimated, evidence of their expediency and safety has been repeatedly demonstrated. Dietary phyto-oestrogens are neither panacea nor efficient enough to be a widely applicable alternative to HRT (Vincent & Fitzpatrick 2000; Moravcová & Kleinová 2002). However, they may positively influence the quality of life by protective effects on the cardiovascular system and lipid metabolism, by reducing the frequency of menopausal symptoms ant thus decreasing the need for medication.

Conclusions

The intake of potentially endocrine-active substances is an indivisible aspect of nutrition.

Dietary factors may influence the endocrine system on several levels, including hormone synthesis and secretion, hormone transport and its reception in the target tissues.

Health impacts of these interactions may be beneficial, adverse or negligible, depending on particular conditions, i.e. the respective substance and its dietary load, synergy/antagonism with other factors and physiological status of the respective individual.

Malnutrition and illness makes humans susceptible to harmful effects.

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Souhrn

Lapčík O. (2004): **Endokrinologické aspekty stravovacích zvyklostí**. Czech J. Food Sci., **22**: 29–38.

Stravovací zvyklosti jsou ovlivněny jak současnými ekonomickými možnostmi, tak historií dané společnosti. Řada potravin obsahuje látky, které významně zasahují do endokrinního systému, a jejich konzumace může ovlivnit zdravotní stav celých populací. Stravování založené na výhradně lokální produkci v řadě oblastí vede k nedostatku mikronutrientů. Z endokrinologického hlediska je významný zvláště nedostatek jodu a selenu v endemických oblastech. Ve střední Evropě byl tento problém do značné míry vyřešen ve druhé polovině 20. století suplementací jodu, mnohé oblasti Asie a Afriky však na obdobné akce dosud čekají. Kulturní plodiny obsahují látky, které ovlivňují významné metabolické dráhy: 1. Jodový deficit bývá často prohlubován přítomností inhibitorů thyroidální peroxidasy (tzv. goitrogenů) v důležitých plodinách. Nejvýznamnějšími goitrogeny ve výživě Evropanů jsou glukosinoláty z brukvovitých rostlin (zelí, kapusta, květák aj.). Epidemiologie strumy v Africe a Asii je spojena s konzumací prosa, které obsahuje goitrogenní flavonoid vitexin, a manioku bohatého na kyanogenní glykosid linamarin. 2. Četné fenolické a terpenoidní sloučeniny jsou schopny inhibovat enzymy steroidogenese, a tím ovlivňovat rovnováhu mezi jednotlivými metabolity. Jedná se například o isoflavony z luštěnin (genistein, daidzein) a jejich metabolity (equol), které ovlivňují aktivitu 5-α-reduktasy, 7-α-hydroxylasy, dehydrogenasy 3β-hydroxysteroidů a 17β-hydroxysteroidů; naringenin a další flavonoidy z grapefruitů (inhibice cytochromu P450 1A2) nebo kyselinu glycyrhizovou z lékořice (inhibice dehydrogenasy 11-β-hydroxy-steroidů). 3. Látky rostlinného původu interagují s jadernými receptory a působí jako agonisté nebo antagonisté hormonů. Zájem humánní i veterinární medicíny upoutaly zejména fenolické látky působící prostřednictvím estrogenních receptorů – tzv. fytoestrogeny. Jde o chemicky i taxonomicky heterogenní skupinu látek. Významnými fytoestrogeny jsou zejména isoflavonoidy z luštěnin, dále lignany obsažené v řadě zrnin a oříšků, 8-prenylnaringenin z chmele, resveratrol z vína a další.

Klíčová slova: dietní návyky; štítná žláza; endemická thyreopatie; goitrogen; steroid; mineralokortikoid; fytoestrogen; inhibitor; enzym; receptor

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