THE EXTRAGENITAL EFFECTS OF HORMONES IN WOMEN AND IN MEN – A COMPARISON

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It is a great misconception to believe that the gynecologist – in competition with the urologist – plans to take over the male patients by studying the male endocrine system. There are other reasons why the intensive study of the male endocrine system is supported by gynecology.

The opinion that ovarian steroids serve not only for reproduction but also have numerous extragenital functions, which are very important for the diagnosis and therapy of disorders that do not have anything to do with gynecology, has long prevailed in gynecology. Just as certain disorders in women can only be identified and interpreted properly, if the extragenital dimensions of the sexual steroids are taken into account, various complaints and even clear clinical symptoms can be found in men that are not initially associated with testicular function, but which nonetheless are physiologically connected. For gynecologists who have been studying the hormonal situation of men more intensively in recent years, it is not so much a case competing with the urologists and to treat every man with DHEA or testosterone replacement therapy, but rather an issue of widening the understanding for a development which has clearly improved the pathological understanding of the female body in gynecology. In the English-speaking world, gender specificity is a concept that is taken into account in the presentation of many disorders. In the German-speaking literature, it is still not really taken into consideration.

Three examples will serve to explain the differences and the parallels in the physiological and pathophysiological processes that are gender specific and which play a role in the lipid metabolism, bone metabolism and hormone-related tumors. These three examples should illustrate *pars pro toto* the fundamental gender-specific processes in our body, and how they are partly controlled by the sexual steroids.

LIPID METABOLISM

The lipids ingested with food are – put simply – transported by chylomicrons and LDL fractions in the blood stream, and supplied to various parts of the body as an energy source. To this aim, the triglycerides must be broken down into monoglyceride and free fatty acids, however; the latter enter the cell, where they are subject to oxidative decarboxylation. The triglycerides are broken down into monoglyceride and fatty acids that can penetrate the cells by lipoprotein lipase, an enzyme in the endothelium that splits off the fatty acids for ATP production mainly in the muscle tissue and exploits them in the mitochondria. Therefore, lipoprotein lipase activity is present to a particularly high degree in the muscle cells.

Fatty acids can be used not only as an energy supply for the muscles; they can also be transported back to the fat cells – especially if there is not a sufficient energy demand –, where they are used together with monoglyceride for renewed triglyceride synthesis. Thereby, the fat circulating in the blood stream is used for fat storage rather than as a source of energy. That is why the lipoprotein lipase activity is also present and active in the fat cells – rather like in the muscle tissue.

In contrast to the male organism, lipoprotein lipase activity in women is particularly marked at one – tissue-specific – site, namely in the *gluteo-femoral area*. It is the progesterone and the estradiol which effect an increased lipoprotein lipase activity in this region of the body, and thus results in the enhanced incorporation of fat in the adipose cells. This is also the reason why the typical "female" shape is developed during puberty, and why weight problems may occur in this region in cases of estrogen and progesterone excess – as may occur within the scope of hormone replacement therapy.

Pregnancy and three months of lactation require about 140,000 calories, which have to be stored prior to the beginning of reproduction. This happens in the *gluteo-femoral region*, and it is one aspect of the highly interesting clinical "cooperation contract" between the metabolic processes and reproduction.

There is no such estrogen- and progesterone-induced lipoprotein lipase activity in the **male organism**. Instead, the hormone-related lipase that mobilizes the triglycerides stored in the adipose cells is controlled gender-specifically by the androgens. The fatty acids in the adipose cells are accessed – when required – via beta-3-adrenergic agonists that break down the triglycerides in the adipose cells and provide the necessary fat to the various regions of the body for **lipolysis**. Since the triglycerides within the adipose cells are broken down mainly at the command of representatives of the beta-3-adrenergic ligands, this enzyme is also referred to as "hormone-related lipase". The male hormones reinforce the activity of this metabolic enzyme by increasing the receptors for beta-3-adrenergic hormones and expressing them on the surface of the adipose cells. As a result, androgens lead to an increased release of triglycerides into the blood. If fatty acids are not converted directly into adenosine triphosphate, they circulate in the peripheral blood stream for some time and the LDL fraction increases. This is one aspect that explains why the androgens have an unfavorable modulation effect on the peripheral lipid status. On the other hand, male hormones are necessary in order to be able to mobilize fatty acids during physical exercise, during sports activities and also after fasting. Rather like with estradiol, progesterone and lipoprotein lipase, there is a tissue-specificity of the androgenic effect on hormone-dependent lipase: the fat cells of the subcutis in the abdominal region react sensitively to testosterone and increase the beta-3-adrenergic receptors with tissue-specificity due to the influence of androgens: a requirement for the mobilization of triglycerides.

The effect is similar but less marked in the **female body**. However, some women do complain of weight problems in the abdominal region, especially when an androgen deficiency occurs. This problem can often be solved with a cautious percutaneous androgen replacement therapy.

Whilst the male hormones – not least due to the above mechanism – increase

the triglycerides and LDL fraction, estradiol has a protective effect in the female body. From the perspective of pregnancy, this is understandable: During pregnancy, both the fetal and the maternal organism require cholesterol, especially for membrane synthesis. Therefore, 17-beta-estrdiol enhances the transport of peripheral cholesterol to the cell during pregnancy. As a result, the peripheral cholesterol level drops, but this mechanism is designed exclusively under the aspect of reproduction. 17-beta-estradiol has a cholesterol-lowering effect not only during pregnancy: It stimulates the expression of the LDL receptors, as a result of which the influx of cholesterol into the cell is enhanced. This is one of the aspects that explain the cardioprotective effect of 17-beta-estradiol, although it only becomes understandable when regarded in the context of pregnancy.

Male hormones can also have a partial beneficial effect on the blood lipids: The partly genetically disposed lipoprotein-a is a high cardiovascular risk factor. Because of its similarity to plasminogen, it inhibits intravasal lipolysis when present in too high concentrations, thus increasing the thrombosis risk. Despite the genetic determination, male hormones can modulate the serum concentration of lipoprotein-a and thus lower the total lipoprotein-a level. This offers a mechanism of protection against thrombosis from which mainly the male organism benefits.

Gender-specificity of the Cardiovascular Situation

The differing cardiovascular mortality of men and women before the age of 50 is most likely explained by the influence of 17-beta-estradiol on the endothelium. This female sexual steroid stimulates endothelial NO-synthase, which splits off nitrogen monoxide from arginine and triggers a biochemical cascade via the cyclical guanosine monophosphate, which ultimately leads to dilatation of the actinomyosin filaments and thus to muscular relaxation. The importance of this physiological reaction once again lies in reproduction. During pregnancy, NO protects the uterus from contractions that would result in premature delivery. During delivery, this situation changes fundamentally: The expression of uterine NO-synthase is reduced, whilst in the cervix nitrogen monoxide is synthesized in masses by the same mechanism. This leads on the one hand to contractions of the uterine muscles, and on the other hand to relaxation of the cervix, preparing vaginal delivery.

The same mechanism leads to relaxation of the vascular muscles: Under the influence of estradiol, the endothelial NO-synthase produces nitrogen monoxide, which diffuses into the vascular muscle layer and causes relaxation and vasodilatation. This explains the cardioprotective effect of estrogens, which is not present in male blood vessels.

However, recently a similar effect of testosterone in **men** was described. Following a bolus injection of testosterone, there was a strong dilatation of central blood vessels similar to that observed after the administration of intravenous estrogen. The effect appears to be dose-dependent: The higher the testosterone dose, the stronger the dilatation of coronary vessels. This vascular effect is underlined by another observation: Whilst acetylcholine causes vascular dilatation both in alpha and in the socially lower omega females, this

is only the case in the dominant alpha male among the male primates. In the omega male, acetylcholine causes vasoconstriction. Alpha and omega males have different testosterone concentrations, which leads to the conclusion that an increased male hormone level also improves the cardiac performance.

This may well occur via an endothelial aromatization of the androgens: Rather like in the adipose cells, testosterone can be converted into estradiol in the endothelial cells, which could have a similar vasodilatory effect in the male as in the female.

It was recently shown that the heart can also release the p450 enzyme in different ways. This would mean that – like the ovary – the heart produces sexual steroids in order to protect itself.

Bone and Sexual Steroids

Osteoporosis presents itself differently in men and women. During puberty, the bone of the female organism is protected. Once the ovarian function ceases, some women have a very rapid inclination towards softening of the bone, however. Osteoporosis is less common in men, but once it does occur, it is associated with a mortality that is twice as high as in women.

The osteoprotective mechanism of 17-beta estradiol appears to act preferentially via the cytokine interleukin-6, which has a docking site for estradiol in the promoter section, so that its expression and activity are reduced. If the estrogen level drops, the interleukin-6 level rises and frequently acts as a catabolist. This mechanism is also seen in reproduction. Immediately before ovulation, as well as before menstruation and prior to the commencement of contractions, the sexual steroid levels drop and the interleukin-6 level rises, thus effecting the destructive biological processes that are associated with follicular rupture, with casting off the endometrium, and with the onset of contractions. The mutual balance between estrogen and interleukin-6 is therefore also important for reproduction.

In the event of an estrogen deficiency in the postmenopause, the interleukin-6 level also rises and leads to activation of the osteoclasts, thus shifting the permanent balance between bone formation and bone destruction towards the latter. Blocking interleukin-6 activity can prevent osteoporosis, but the physiological interleukin-6 suppressor is estradiol.

In the **male**, a different mechanism appears to be responsible for bone protection. Testosterone is an activator of progenitor cells and stimulates pre-osteoblast mitosis, thus maintaining the bone balance in favor of bone formation during sufficient androgen production.

The influence of androgens on the stem cells – as with the pre-osteoblasts – is also illustrated by the erythroblasts: Testosterone has the same effect as erythropoietin; it withdraws the erythrocytes from the progenitor cells and is thus partly responsible for the red blood cell count. In our own patients, we were able to show that a low androgen level correlates with an insufficient red blood cell count, which is expressed by symptoms such as fatigue, lack of concentration, and chronic susceptibility for infections. This aspect will probably be very important within the scope of hormone replacement therapy for men.

Hormone-dependent Tumours

The "cross-talk" between urologists and gynecologists should be intensified by the fact that two carcinomas for which they care have numerous features in common. The incidence of both breast cancer and cancer of the prostate is increasing continuously, even though men do not receive estrogen replacement therapy, which can thus be excluded as the aetiological factor. It is possible that environmental factors may be responsible. This is also underlined by the fact that the regional incidence of both hormones is closely correlated. The incidence of both carcinomas is low in Asia, and increases rapidly in the Anglo-American countries and the EC. Since immigrants from Asia are subject to the same incidence in these countries, a hereditary factor can be excluded.

The risk of heredity in mammary carcinoma and cancer of the prostate overlaps: Families with an increased incidence of breast cancer also have a predisposition for cancer of the prostate in male members of the family.

A number of biochemical parameters are also identical in breast cancer and in cancer of the prostate. Apart from similar mutations on the estrogen and androgen receptor, mammary carcinoma expresses the prostate-specific antigen in the same way as cancer of the prostate. An understanding of these connections between the two types of carcinoma will be very important for the dialogue between urologists and gynecologists in the future.

From our own experience we can report that there was controversy and it took a long time before the extragenital effects of the female sexual steroids were accepted and became clinically relevant. The same is currently happening with the interpretation of the male sexual hormones. If endocrine gynecology can be of help here, we will be happy to do so.

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