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The information encoded by the sex steroid hormones testosterone and estrogen: A hypothesis

Amotz Zahavi *, Marina Perel

Dept. of Zoology, Tel-Aviv University, Tel-Aviv, Israel

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ABSTRACT

It is suggested that the sex steroid hormones testosterone and estrogen (SSH) provide receptor cells with reliable information on protein synthesis and on the level of oxidative metabolism in the cells of the gonads. The SSH are derived from the oxidation of cholesterol. This oxidation is a side reaction of the oxidative processes in the mitochondria that generate most of the energy to the organism. The amount of SSH that is synthesized is correlated to the partial pressure of oxygen at the synthesizing cells. The amount of free SSH that a cell can hold is checked by the damage that free steroids may cause. This damage is prevented by proteins that bind with SSH. As a result, SSH levels are correlated also with the ability of the SSH synthesizing cell to produce proteins that bind with them. A cell can only synthesize SSH in relation to the oxidative processes within it and to its ability to produce the binding proteins necessary to prevent the damage caused by SSH. As a result, the information conveyed by SSH is reliable. We examine the specific damage caused by testosterone and estrogen, and suggest why each of them is best suited for its function. Although both SSH can provide similar information on the metabolism in the cells that synthesize them, there are secondary reasons why testosterone and estrogen were selected to serve particular functions. Testosterone improves the efficiency of the proton pump at the mitochondria in producing ATP, but increases oxidative damage. Estrogen on the other hand decreases oxygen damage but also decreases the efficiency of the proton pump. These differences between the two SSH may explain why females use estrogen to inform the body about the activity of the cells in their gonads while males do it by testosterone. The increased oxidative damage may also explain why in males the testosterone that reaches the brain is turned into estrogen. We also suggest why fish use 11-keto testosterone and why insects do not use these two steroids.

1. Introduction

There is a vast amount of experimental data about the steroid sex hormones testosterone and estrogen (SSH): their synthesis, their secretion, the structure of the receptors that react to them, the binding of the receptors to DNA, and their effects on various organs and behaviors. However, as far as we know, no one has attempted to suggest why these particular steroids have been targeted by natural selection to serve their functions, rather than other steroids, or other molecules altogether. SSH serve these functions in all vertebrates and are found in some other classes of organisms e.g. mollusks, (Baker, 2002) and even among corals (Tarrant et al., 2003; Twan et al., 2003, 2006).

Karlson (1983) reviewed the evolution and the use of steroids as hormones and described the advantages steroids possess to function as signals in general. However, he did not address the question why a particular steroid is best adapted to serve a particular function. In the following we suggest how the chemical properties of testosterone and estrogen adapted them to serve as signals and discuss the reliable information they provide.

In 1975 Zahavi suggested the theory of the "handicap principle" that explains how signals evolve to provide reliable information (Zahavi, 1975). According to the handicap principle, signalers invest to ensure the reliability of signals. This investment is differential—it benefits honest signalers but it is costly for cheaters (i.e., the investment decreases the fitness of cheaters). The theory of the handicap principle also suggests that the pattern of a signal is selected to be the optimal pattern to convey reliably a particular message (Zahavi and Zahavi, 1997). To give an example: a rich person can waste money to display wealth, but wasting money may be prohibitive for the poor; courage, (the readiness to fight), can be displayed by the risk an individual is ready to take. An experienced fighter can take a risk more easily than a less experienced fighter. However, taking risks, when threatening an opponent, cannot display wealth and wasting money cannot display courage.

* Corresponding author. Tel.: +97236408008; fax: +97236409304.
E-mail address: Zahavi@post.tau.ac.il (A. Zahavi).

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Grafen (1990) published a formal model that supports the theory of the handicap principle. However, he suggests that there are signals which are not loaded with handicaps, and also that among individuals which do not conflict in their interests, e.g., among kin, signals should not require handicaps. Maynard-Smith (1991) and Hasson (1991) also pointed to a set of signals which they termed indices, that need not require handicaps. However, Zahavi and Zahavi (1997) pointed out the handicaps involved even in these cases and claimed that handicaps are inherent components in all signals.

As predicted by the handicap principle, many of the chemical signals used among organism are noxious chemicals, such as alkaloids and various fatty metabolites used by insects as pheromones (Morgan, 2004), or DIF used by slime molds when forming their fruiting bodies (Atzmony et al., 1997).

Chemical signals within the multicellular organism are often very noxious as well, like NO (Snyder and Bredt, 1992; Warrell et al., 2005) and other neurotransmitters that are noxious even in small concentrations. Snyder and Bredt described their astonishment at the fact that natural selection selected NO, a highly noxious molecule, rather than some non-toxic ones, to serve as signals within important organs of the body.

However, Zahavi (2003, 2008) and Zahavi and Zahavi (1997) suggested that within the organism signals with handicaps serve to prevent mistakes that may arise from signaling by cell phenotypes that are not supposed to signal, and to limit signaling cells from signaling at levels higher than their phenotypic quality permits. It is therefore reasonable to assume that, like the investment in signaling between organisms, signals within the organism are also selected to require a pattern of investment that tests the reliability of the particular message encoded in them. These messages are expected to provide reliable information, to other cells in the organism, on the level of the phenotypic activity of the signaling cells.

It is also reasonable to assume that under ordinary conditions signaling cells have already evolved to signal at a level that does not damage them. Therefore it is not easy to demonstrate the difficulties that the production of the signal causes to the signaling cells. Sometimes the difficulty lays in the investments needed to produce chemicals that protect the producing cells from the damage caused by the signaling molecules.

Krakauer and Pagel (1996) developed a formal model to show that signals loaded with handicaps within an organism can help an organism to select, among its cells, cells of a higher quality to serve a particular function and consequently increase the fitness of the organism. They illustrate their model by the way neural axons are selected to innervate muscle cells. They suggest that the amount of the neurotransmitter, acetyl choline, is the cost by which neurons display their quality to the muscle cells. However they did not discuss the chemical properties of acetyl choline that adapted it to serve its function.

In the followings, we attempt to understand from the chemical properties of estrogen and testosterone, what ensures the reliability of the information encoded by them, and suggest why they are best adapted to provide that information. We also discuss the special harm testosterone and estrogen cause, since according to the handicap principle it is the special harm that signals impose that tests the reliability of the information in the particular signal. The chemical properties of the signal should therefore be related to the information provided by the signal.

2. The information encoded in the sex steroids

It is well-established that the levels of sex steroid hormones are correlated to the activity of the gonads, and that the levels of SSH provide that information to the hypophysis and other organs in the body (Hillier and Tetsuka, 1997). We suggest that SSH provide information about the levels of the ongoing oxidative processes in the cells of the gonads. The SSH are produced from cholesterol by oxidative reactions, mainly in the cells of the gonads that nourish the gametes. The oxidation of cholesterol, the reaction that cleaves off the side chain of cholesterol, starts in the mitochondria as a side reaction of the oxidative cycle. This side reaction uses energy that otherwise would have produced ATP, and hence is correlated to changes in the production of ATP in the mitochondria. In vitro studies found that the amount of SSH synthesized is correlated to the partial pressure of oxygen (Basini et al., 2004; Defaye et al., 1994). It is thus reasonable to assume that the level of SSH is correlated to the level of oxygen brought by the blood to the cells of the gonads (Nishimura et al., 2006; Chabre et al., 1993), and consequently that it is also correlated to the level of all other nutrients that are brought by blood to the cells of the gonads. In other words, the level of SSH provides reliable information about the level of ongoing metabolism in the signaling cells within the gonads.

3. The harm caused by free SSH and the special investment required to overcome the damage

Once SSH is used as a signal to show the level of metabolism in the cells in the gonads, can the cells in the gonads overproduce SSH and create a false signal? That is, can the cells in the gonads divert more energy from the respiratory cycle to the synthesis of SSH and thus provide false information? According to the handicap principle, there should be some specific limiting factor (a "handicap") that would prevent signaling cells from manufacturing higher levels of SSH than the amount correlated to their metabolism. And indeed, when one starts looking, it is possible to suggest such factors.

Hendry et al. (1986, 2007) suggest that SSH can intercalate into unwound DNA, between two base pairs, binding the two strands. They suggest that when the steroid receptor proteins bring the SSH to the specific sites on the DNA (the recognition elements) the SSH intercalate into the unwound DNA. Assuming that their computer model is valid, we speculate that some free steroids can intercalate into the DNA in non-specific sites, between the same two base pairs, without the help of the steroid receptors and can interfere with DNA functioning, since the combination of these two base pairs is very common in the genome. It is likely that SSH-binding proteins and non-specific steroid-binding proteins prevent such damage by reducing the amount of free steroids.

According to Mahesh (personal communication), only steroids with a double bond between carbon atoms 4–5 can intercalate into unwound DNA—and it is precisely steroids with such a bond that function as steroid hormones, out of all the various steroids that are produced by the oxidation of cholesterol. Steroids such as pregnenolene and DHEA, which are produced along the same series of oxidative reactions, that lead to the production of SSH from cholesterol but do not have a double bond between carbon atoms 4–5, do not function as hormones.

Testosterone and estrogen also damage gap junctions in sertoli cells, unlike steroids with 21 carbon atoms, which do not damage gap junctions (Herve et al., 1996) the functioning of gap junctions is critical for the gonads, since metabolites brought by blood have to cross several layers of cells in order to reach the germ cells, and they have to pass through gap junctions. Herve used high doses of steroids to shut down completely the transfer of vital dyes through gap junctions. However, we suggest that if this is the effect of very high doses, the much lower levels of SSH that occur

in the cell can reduce somewhat the functioning of gap junctions, and natural selection counteracted this interference by evolving binding proteins that prevent it. It is quite possible that free SSH also cause other harmful effects of which we are unaware as of yet. We suggest therefore that the special investment required to counter the potential damage of free SSH steroids ensures the reliability of the message provided by SSH about the ongoing activity at the cells in the gonads.

In the ovary, cells in the large follicles that have good access to metabolites are able to produce high amounts of SSH and counter the noxious effects of the SSH they produce, while cells in small follicles that have less access to metabolites are unable to produce enough binding proteins to counter the effects of the high level of SSH that reach them from the more developed follicles. This may be the origin of the evolutionary mechanism by which dominant follicles in the ovary dominate smaller follicles (Dierschke et al., 1983; Hutz et al., 1990; Hillier and Tetsuka, 1997; Billig et al., 1993). Cells in small follicles are unable to cheat by producing high level of SSH, that is, signal that they are more developed than they really are, because these cells cannot produce enough binding proteins to counter the damage caused by free SSH. It is interesting to note that in the mammalian ovary a special retrograde transfer of SSH occurs, causing the levels of SSH in the ovary to be higher than that in the blood system of the rest of the body (Stefanczyk-Krzymowaska et al., 2002; Einer-Jensen and Hunter, 2005). It is reasonable to suggest that this special anatomy of the ovary was developed in order to inhibit the development of the smaller follicles without burdening the entire body with high levels of SSH. Small follicles which attempt to develop in the presence of a large follicle are destroyed by the high levels of SSH.

4. Why is it necessary to have more than one SSH?

If both testosterone and estrogen provide information about the metabolic activity at the gonads, what is the evolutionary advantage of having two sex hormones? Testosterone improves the efficiency of ATP production in the mitochondria (Starkov et al., 1997; Starkov, 1997), but it also increases oxidative damage (ROS). Estrogen on the other hand reduces ROS damage (Moosmann and Behl, 1999; Miyaguchi et al., 2004; Green et al., 1997), but at the same time it decreases the efficiency of ATP production. A 10% decrease in the efficiency of ATP production decreases ROS damage by up to 50%. Males compete by strength against other males, and thus it makes sense that they signal with testosterone that improves the efficiency of ATP production, in spite of the ROS damage it causes. Females, who are not competing as much by strength, provide the same information with estrogen that decreases ROS damage. The danger of increased ROS damage is probably the reason why in males testosterone is changed into estrogen when it enters the brain (Roselli, 2007; Garcia-Segura et al., 2003). Cells in the brain are not usually replaced by new cells if they are damaged. Hence the information about ongoing activity at the gonads had better enter the brain as estrogen, the level of which is correlated to the levels of testosterone that reaches the blood brain barrier and consequently presents the same information

In both sexes the cells that produce testosterone – the theca cells in the female and the leidig cells in the male – are adjacent to blood capillaries but are not in direct contact with the developing gametes. On the other hand, the cells that produce estrogen, the sertoli cells in males and the granulosa cells in females, are in direct contact with the gametes, away from blood capillaries and from the cells that synthesize testosterone. It is also interesting to note that although the granulosa cells can produce progesterone from its precursors, they do not oxidize the progesterone into testosterone but transfer it to be oxidized by the theca cells (Magoffin, 2005). Later that testosterone is sent back to the granulosa cells to be oxidized into estrogen. This indirect way suggests that somehow the synthesis of testosterone or its presence may damage the ova more than the synthesis of estrogen from testosterone.

5. Puzzles that may be explained by our hypotheses

1. Although SSH are present in all vertebrates and also in corals and mollusks, insects do not use them. If SSH hormones are optimal molecules to indicate oxidative processes in the mitochondria, why are insects not using them? The answer may be that in insects, cells receive their oxygen directly through a system of trachea, not through the hemolymph. Thus, the supply of oxygen is independent of the way by which insects receive their essential metabolites. Hence, the synthesis of the oxidative products of cholesterol may not represent in insects the variation in the current arrival of nutrients to the gonads, as they do in other taxa. Ecdysone, the steroid hormone in insects, is not a product of the oxidative mechanism that breaks the side chain of cholesterol that leads to the formation of the SSH (Karlson, 1983). We have not studied the special handicap that ecdysone, with its intact side chain, imposes on insects.
2. The testosterone of all fish is different from the testosterone of all other vertebrates (Yaron and Sivan, 2006) by having a keto group attached to carbon atom 11-forming the 11 keto hormone of fish that serves the same function in fish as testosterone in other vertebrate taxa (Leal et al., 2009). Fish transfer testosterone from the cytoplasm, where testosterone is synthesized, back to the mitochondria where it is further oxidized into 11 keto testosterone. The oxidation at C 11 forming the 11-keto hormone is more sensitive to changes in oxygen levels than the oxidation leading to the synthesis of testosterone (Thomas et al., 2007). Hence the oxidation to the 11 keto provides fish with more precise and immediate information on the current arrival of oxygen to the mitochondria than the levels of testosterone. Fish receive their oxygen from water. When the temperature rises, fish are more active and require more oxygen, but oxygen levels in the water is lowered with the rise of temperature. The amount of oxygen also changes with the turbulence of the water. Fish that are exposed to anoxia can counter the anoxia by moving to water richer in oxygen. Land vertebrates cannot increase the amount of oxygen that reaches the gonads by moving to environments richer in oxygen, since oxygen concentrations in the air hardly varies. We suggest that this special extra investment in passing testosterone for oxidation to the mitochondria evolved to provide fish with this more precise information that can benefit fish but is of no use to terrestrial vertebrates that breathe by lungs.
   A similar reason is probably responsible for the fact that the final step in the oxidation of the adrenal steroids, the steroids that serve to provide information on changes in the composition of the blood, is also provided by the added oxidation at the C 11 because these hormones, the gluco-corticoids and the mineralo-corticoids, are expected to provide current information to which the organism is expected to respond quickly (Zahavi and Weiss in prep.).
3. The importance of countering the damage of steroids, by the production of proteins that bind with them, may be the reason why a mutation that reduces the efficiency of protein synthesis in the brain (Schiffman and Elroy-Stein, 2006) also harms the cells in the gonads (Labauge et al., 2007).

To conclude: We provide a hypothesis, based on the handicap principle, that suggest how the chemical properties of estrogen and testosterone fit their function as signals that display in a reliable

way the ongoing oxidative metabolism within the secretor cells and the ability of the gonads to produce proteins that counter the harmful effect of the steroids on the secretor cells.

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