The biological basis and clinical significance of hormonal imprinting, an epigenetic process

György Csaba

Abstract The biological phenomenon, hormonal imprinting, was named and defined by us (Biol Rev, 1980, 55, 47-63) 30 years ago, after many experimental works and observations. Later, similar phenomena were also named to epigenetic imprinting or metabolic imprinting. In the case of hormonal imprinting, the first encounter between a hormone and its developing target cell receptor—usually at the perinatal period—determines the normal receptor-hormone connection for life. However, in this period, molecules similar to the target hormone (members of the same hormone family, synthetic drugs, environmental pollutants, etc), which are also able to bind to the receptor, provoke faulty imprinting also with lifelong—receptorial, behavioral, etc.—consequences. Faulty hormonal imprinting could also be provoked later in life in continuously dividing cells and in the brain. Faulty hormonal imprinting is a disturbance of gene methylation pattern, which is epigenetically inherited to the further generations (trans-generational imprinting). The absence of the normal or the presence of false hormonal imprinting predispose to or manifested in different diseases (e.g., malignant tumors, metabolic syndrome) long after the time of imprinting or in the progenies.

Introduction

Hormonal imprinting is a basic biological phenomenon which was first observed, named, and defined by us more than 30 years ago. Today, it develops thousands of web-pages in Google Scholar and hundred thousands of web-pages in Google. The phenomenon means that in the developmentally critical periods, animals or their cells memorize normally or pathologically the first encounter with a given hormone or related structures, and this determines the receptors' later binding capacity as well as the reaction of the imprinted cell to the hormone for life (Csaba 1980, 1981, 1984, 2000, 2008). This memory is transmitted to the progeny generations of the imprinted cell. Imprinting with the normal (physiological) hormone is needed for the normal maturation of the receptor (Csaba and Nagy 1985); however, the faulty imprinting as well as the absence of the imprinting can be manifested in diseases or inclination to diseases.

The phylogenetic basis of hormonal imprinting

The unicellular Tetrahymena has binding sites (receptors) for hormones of higher vertebrates (Csaba and Lantos 1973). This observation called our attention to the hormonal system at unicellular level and led to many experiments demonstrating mammalian hormones in Tetrahymena and to the successful study of their receptors and transduction pathways (Christopher and Sundermann 1995; Christensen et al. 2003; LeRoith et al. 1980, 1982; Lenard 1992; Köhidai et al. 2001, 2003; Csaba 2008). These latter were very similar to that of the mammalian ones (Köhidai et al. 1992; Kovács and Csaba 1997).

Tetrahymena memorizes the first encounter with the hormone, and a different (in general more intensive) reaction can be observed in case of the second (and further) encounters. We named the phenomenon to hormonal imprinting (Csaba 1980). The individual life of Tetrahymena is very short (few hours only); however, the memory is
inherited to the progenies and can be observed after hundreds of generations (Csaba 1985, 2008). Imprinting can be provoked not only by hormones but by other molecules which are able to act at receptorial level (Csaba 2008). This seems to be very important for the unicellular population as the cells are able to recognize better and earlier molecules which are dangerous for them and can escape in time. In addition, they are able to recognize more easily useful molecules (e.g., food) far from their sites and can approach them for engulfing. Nevertheless, the phenomenon is important also from evolutionary aspect, as it helps to select molecules suitable for being hormones in the further steps of evolution (Csaba 2008).

### The perinatal hormonal imprinting

Evolution erases the unnecessary mechanisms, while keeping those which are useful and suitable. This suggested the idea that hormonal imprinting, observed in *Tetrahymena* must be present in higher-ranked animals, and the phenomenon must be accomplished in the critical stage of development (Csaba 1984). When—in the first experiment, 34 years ago—newborn rats were treated with high dose of thyrotropic (TSH) or gonadotropic (GTH) hormone, their thyroxine content in the blood of adults was 40–70% less then that of the controls, as a result of faulty imprinting (Csaba and Nagy 1976). Since then, many experiments were done by us and other researchers justifying the need of normal imprinting and the deteriorating effect of faulty imprinting caused by related molecules which are able to bind to the hormone receptors, provoke imprinting in the normal development and function of the receptor (Csaba and Nagy 1976).

Not only polypeptide (as were TSH and GTH and related molecules) or amino acid type hormones acting on cell membrane receptors can provoke faulty imprinting but hormones and hormone-like molecules acting on intracellular (nuclear) receptors as well. These are mainly steroids and the hormones of thyroid gland, T3 and T4. There are many variations in the steroid structure which can bind to the members of the steroid receptor superfamily (Neubert 2002), and our environment is full of synthetic steroids (in the exhaust gas of diesel motors and cigarette smoke, as well as refuse burners) decrease the number of glucocorticoid receptors and increase the activity of liver enzymes in adult rats (Csaba and Inczefi-Gonda 1984; Csaba et al. 1991a). Numerous plant-protecting chemicals can bind to the steroid receptors, as vinclozolin, having androgene character and bisphenol, having estrogenic character (Ho et al. 2006; Newbold et al. 2007). Nonsteroidal components present in the soy bean (which has a very important role in our nutrition, especially in the artificial feeding of infants [baby foods]), such as genisten, bind steroid receptors (Martin et al. 1978; Miksicek 1995), and also imprints (Csaba and Inczefi-Gonda 2002; Csaba and Karabélyos 2002). Imprinting with these steroids decrease the binding capacity of steroid receptors and influence the immune system in adult age as well as the sexual activity of male and female rats (Csabanova et al. 1999; Csaba and Karabélyos 2002; Delclos et al. 2001; Guo et al. 2002). These induce several response to estrogen in various target organs including the uterus (Gaete et al. 2010). In addition, numerous other receptor-level-acting molecules cause faulty imprinting (Tchernitchin et al. 1999).

Without the completeness of these data, it can be established that the hormones or molecules which can bind to the hormone receptors, provoke imprinting in the perinatal period, which resulted in alterations of many physiological processes. Imprinting is needed for the normal development and function of the receptor.
The late imprinting

The perinatal imprinting is physiological and obligate. It is taking place with hormones which are present in this critical period. There is a possibility of imprinting also in earlier time, in the developing fetus, caused by foreign molecules; however, characteristic is the perinatal imprinting, just after birth, as in this time maternal hormones do not disturb the process and the mother does not protect the infant. In rat experiments, the first 24 h are the most critical from this point of view, which gradually decreases with time. While this obligate general imprintability diminishes, a facultative imprintability appears. This means that continuously dividing cells, which are in a developmental phase, can be imprinted in any time of life, as e.g., the cells of bone marrow, lymph nodes, etc. This type of imprinting is also durable (valid for life). Though this imprinting does not enforce the perinatal imprinting, it results in faulty imprinting with life-long consequences. The imprinters can be hormones or synthetic molecules with hormonal character, drugs acting at receptor level (Cicero et al. 1991), and environmental pollutants similar to the perinatal imprinters. These materials change not only the receptors of their own, but related receptors, too. A single, minimal dose endorphin treatment at weaning life-long influences the endorphin and serotonin content of immune cells, cells of some brain regions, the binding capacity of uterine estrogen receptors, and sexual activity (Csaba et al. 2004a, b, c). Treatment with the tricyclic antidepressant mianserin (Csaba et al. 2003c) as well as H1 receptor blocker terfenadine (Csaba et al. 2003b) durably influence the histamine content of white blood cells. Single treatment with vitamin D3 or dexamethasone at puberty significantly influenced the glucocorticoid receptors' binding capacity in the thymus (Csaba and Inczéfi-Gonda 1999a). The most drastic and extensive effect was produced by the aromatic hydrocarbon, benzpyrene, which provokes imprinting very strongly at different ages (Pap and Csaba 1994; Csaba and Karabélyos 1995; Csaba and Inczéfi-Gonda 1999b; Csaba et al. 2004b). The cells are imprinted also during regeneration (Csaba et al. 1989) and not only hormone binding could be influenced, but the microsomal enzyme system (Csaba et al. 1987), similarly to the perinatal treatment (Ishizuka and Yonemoto 2003).

The results demonstrate that the perinatal imprinting is the obligate; however, faulty imprinting can develop at any phase of life in the actually developing cells. This is justified in case of continuously dividing cells. It can be surmised that it is also taking place in such organs or their cells, which are believed stationary.

Hormonal imprinting of the central nervous system

For a long time, it was believed that the structural development of the central nervous system is finished at birth. However, recent investigations show that stem cells are present in the brain, which are able to build new structures (Mehler 2008). Any conception is accepted; the fact is that the central nervous system is hormonally imprintable (Csaba and Tekes 2005).

Konrad Lorenz was the first who proposed the “imprint- ing” name for the phenomenon of behavior of neonatal birds, as a reaction to the first object with whom they meet after birth, independent on being their mother or a spotted ball, and this imprinting has a life-long effect (Lorenz 1957). We used the name hormonal imprinting also to a “first encounter” to the meeting of the receptor and its hormone, generalizing the phenomenon of imprinting to all of the developing organs and cells, and we concretized it to molecules acting at receptor level and to developing receptors (Csaba 1980). The imprinting, proposed by Lorenz is the imprinting of the brain, as it is the setting of the sex when estrogens (transformed from androgens) transform the basic female sex to male sexual behavior (Gorski 2002). This process could be distorted by molecules similar to the sexual target hormones, provoking faulty imprinting. This leads to pathological states. The question is, whether—in addition to this basic phenomenon—other hormones or chemicals can provoke faulty imprinting perinatally or later stages of life.

Beta-endorphin is an endogeneous opioid produced by the code of proopiomelanocortin gene in the brain or other (e.g., immune) cells (Blalock 1998; Csaba et al. 2002). Perinatal endorphin imprinting decreases the serotonin content of striatum, and this stimulates the aggressivity of male and sexual activity of female rats and influences the binding capacity of estrogen receptors (Csaba and Tekes 2005; Csaba et al. 2003a) in adults. At the same time, it increases with magnitudes the concentration of another pain killer, nocistatin, in the cerebrospinal fluid (CSF) (Tekes et al. 2004). Considering that during parturition, the intensity of pain and duration of delivery is individual, the variable endorphin production could influence the aggressivity of adults. Imprinting with the pain-stimulating nociceptin or pain killer nocistatin influences the brain biogenic amine levels in adults, region specifically (Tekes et al. 2009c).
In addition, the effects at weaning also could be settled on the perinatal imprinting. As a consequence of the mother’s alcohol consumption, the nocistatin level of CSF and blood increases (Tekes et al. 2007a). Other molecules (benzpyrene, vitamins A and D) also can imprint the brain, is manifested in the change of biogenic amine levels of the brain and CSF (Tekes et al. 2007a, b, 2009a, b, c). Perinatal stress—which disturbs the whole endocrine system—also life-long influences the brain biogenic amine and CSF nociceptin level (Tekes et al. 2010).

The data show that the cells of the brain can be imprinted, similar to the dividing cells. The imprinters could be the brain’s own products (in a surplus amount or exogeneously given) as well as other molecules able to bind to receptors. It is very difficult to tell whether their effect is manifested through stem cells or through the receptors of matured brain cells, although this latter seems to be likely. (Wu et al. 2004), and this is done by estradiol and bisphenol (Prins et al. 2008) as well as by ethanol (Haycock 2009). In animal and human experiments, the change of the perinatal methylation pattern in depression alters the hypothalamic-pituitary-adrenal axis (Oberlander et al. 2008). Early adversity also influences the methylation patterns (Champagne et al. 2006; Champagne 2010) by drastically disturbing the whole endocrine system in the period of imprinting.

Though our knowledge is sketchy, the effect of imprinters through the change of methylation pattern seems to be likely. This change fixes the information of imprinting and transmit it across generations. This means that hormonal imprinting is an epigenetic imprinting which life-long influences the manifestation of genes without change of the genes themselves. It determines the manifestation of the genes for life or changes and inherits it.

**The mechanism of the imprinting**

In the time of recognition of hormonal imprinting, its mechanism was unknown. As the materials provoking imprinting were not known as mutagens, the mechanism was very hardly explainable. Later, genomic imprinting became known and after it, the mechanism of epigenetic processes were studied. This was the time of the recognition of epigenetic imprinting and later the metabolic imprinting, which were hormonal imprinting-like phenomena, and this helped to clear also the mechanism of hormonal imprinting.

The molecules mentioned in the previous paragraphs do not cause changes (mutations) in the genes. However, it is known that the manifestation of genes is regulated by epigenetic factors, and there is a bidirectional relationship between the environment and the epigenome (Mohammad and Baylin 2010; Satterlee et al. 2010). These modifications could be done by DNA methylation, histone modification, or nucleosome positioning (Portela and Esteller 2010). Nevertheless, DNA methylation seems to be the most likely as such a factor during imprinting, which is able to influence durably the manifestation of a gene, as just in the critical phase of ontogeny, this pattern is rebuilding and fixes in the developing cells and their progenies. We believe that our experiment, done 20 years ago, was the first which called attention to this possibility, when methylation of cytosine was inhibited by azacytidine, and this heavily influenced the imprinting in *Tetrahymena* (Csaba and Kovács 1990). Since this time, many experiments were done also in mammals, and these supported the methylation theory of imprinting. Neonatal imprinting with DES provokes a hypomethylation (Li et al. 2003a and b), and dioxin (TCDD) also influences the methylation pattern.

**The transgenerational imprinting**

If hormonal imprinting takes place neonatally and its effect is measured when adult, this means that it is transmitted from cell to cell not only in *Tetrahymena* but in mammals as well. This is experimentally justified, indeed (Csaba et al. 1991b). However, the effect of perinatal hormonal imprinting is also manifested in the progeny generations. If neonatal rats are treated with a single dose of insulin and are mated when matured, the insulin binding capacity of the F1 progenies’ liver changes: increases in females and decreases in males (Csaba et al. 1984). Similar effect was observed when only one parent was treated. However, in the F1 generation, there is a direct contact between the neonatally treated mother and its progeny. In case of neonatal benzpyrene treatment, F2 generation was studied, and here, the binding capacity of glucocorticoid receptors changed (Csaba and Inczéfi-Gonda 1998) and also the libido of the females (Csaba and Karabélyos 1997) decreased. Fertility was reduced in the F2 generation not only by the decrease of libido, but by the decrease of sperm count and motility (Mohamed et al. 2010). This means that the effect of grandparental imprinting was manifested in the grandchildren. In the F1 generation of DES-imprinted mothers, the frequency of tumors increased (Newbold et al. 2000). Imprinting with receptor level acting vitamins A and D influenced the brain biogenic amine levels of F1 progenies (Tekes et al. 2009a, b, c) as well as the hormone production of immune cells (Csaba et al. 2007). Morphine exposure at puberty caused the increase of anxiety and sensitivity to morphine (Byrnes 2005) in the offspring. These transgenerational effects are characteristic to the aromatic hydrocarbons, to drugs, as cocaine, to phytoestrogens, as the components of soy bean, to the mykocide.
and pesticide chemicals, as vinclozolin and bisphenol. The methylation affecting effect of vinclozolin is experimentally justified (Stouder and Paolini-Giacobino 2010). Some nutritional factors, as the folates also have transgenerational effects (Campbell and Perkins 1988; Skinner 2010) and neonatal overfeeding caused glucose intolerance in adult mice, which was transmitted transgenerationally (Pentinat et al. 2010).

The results of animal experiments justify the transmission of hormonal imprinting to the progeny generations and similar or different symptoms are manifested in them. The key factors are the alteration of methylation pattern and epigenetic inheritance (Skinner 2008, 2010; Ho and Burggren 2010; Daxinger and Whitelaw 2010).

### Imprinting and transgenerational imprinting in man

Epidemiological studies demonstrated the presence and effects of hormonal (epigenetic, metabolic) imprinting in man. In the perinatal period of life, the mother prenatally directly or postnatally (through the mothermilk) can transmit imprinters, or this is done also by baby foods. These factors life-long influence the functions of cells and organs (Csaba 2008; Skinner 2007, 2010; Skinner et al. 2010; Grün and Blumberg 2009) as cardiovascular diseases, second type diabetes (Ling and Groop 2009), obesity (metabolic syndrome), certain tumorous diseases, asthma, and obstructive pulmonary disease (Schwartz 2010) can be deduced to the faulty imprinting. Toxic effects, which were believed to be caused by mutations, also can be caused by epigenetic influences (Trosko 2010). The alteration of methylation pattern of genes in the critical developmental phases has a role in the faulty imprinting, and methyl donors (methionin and cholin) and co-factors (folic acid, vitamin B12 and piridoxal phosphate) are needed for the process. In the early period of life, the quality and quantity of nutrition can let or succeed the normal program, or it is reprogrammed. In this latter case, the methylation pattern irreversibly changes, and second type diabetes and pathological glucose tolerance (Holmang 2001; Miles et al. 2005; Signorello and Trichopoulos 1998) appears. In addition to the nutrition factors, estrogens, androgens, progestagens, or similar receptor level acting molecules, as endocrine disruptors (plant protecting chemicals, aromatic hydrocarbons), certain medicaments and hormones, as insulin and leptin can provoke faulty imprinting, as it was shown in case of animal experiments. More observations support the interrelation of adult obesity with perinatal encounter of receptors with the above-mentioned materials (Newbold et al. 2009), as imprinting details mechanisms which are in connection to weight control (Grün and Blumberg 2009).

The DES catastrophe justified that years or decades after maternal treatment with an estrogen receptor binding synthetic molecule provokes benign or malignant tumors (leiomyoma or adenocarcinoma) in the offspring. The disturbance of methylation pattern can be shown as well as in the case of (not DES provoked) prostate, colon, thyroid, gaster, uterine, and cervical carcinoma (Li et al. 2003b). Similar diseases are caused by perinatal exposure to endocrine disruptors.

A special case is represented by oxytocin which is used worldwide for provoking delivery. In the United States, about 80% of parturitions are done by the help of oxytocin. The oxytocin imprinting—similar to the endorphin imprinting in animal experiments—influences the central nervous system (Plothe 2010). The effect of this imprinting is manifested in infant age in the loosening of infant–mother connections and in the screaming children symptom, when the infant calms only in the arms of an adult. Later, hypotonia or hypertonia could appear as well as absence in the control of head movement. At puberty or in adult age aggression, disturbance in twitting and phobies can appear.

Transgenerational imprinting was observed in human beings mainly in case of nutritional factors (Kaati et al. 2002; Pembrey 2002; Pembrey et al. 2006). Epidemiological statistics justified that the starvation of grandfather in the slow growth phase, just before puberty, when the methylation imprinting of the germ cells happens, increased the lifespan of the grandchildren with years. At the same time, the cardiovascular mortality decreased. In contrast, the overeating of grandfather in the same time decreased the granchildren's life span with years and four times increased their diabetes mortality. Starvation of the father in similar life period also decreased the cardiovascular mortality of children and the overeating of father protected them from diabetes. These effects were more expressed in grandfather–grandson relation than grandmother–granddaughter relation. Considering this, the sex-specificity is not disclosed (Handel and Ramagopalan 2009), what calls attention to the importance of sex chromosomal genes' methylation. Not only the transgenerational effect of nutrition was observed, but it also was found in case of smoking (Pembrey et al. 2006) and in the case of DES mothers, where hypospadias is more frequent in the progenies (Brouwers et al. 2006).

The study of human imprinting is more difficult than it is in animal experiments. This means that—although the above-mentioned data support the presence and importance of hormonal imprinting and transgenerational imprinting in man—new and thorough investigations are needed for mapping it. The mechanism of the most studied nutritional imprinting also is not cleared: there is a possibility of direct effect to the methylation through methyl donors and co-factors; however, it can be done indirectly by hormones or...
by starvation stress, which disturbs the whole hormonal system.

**Conclusions**

Considering the above-mentioned data and facts, it is obvious that molecules acting at receptor level provokes imprinting in critical phases of ontogenetic development. The most critical period is the perinatal one; however, in any time of life, imprinting can develop in organs and cells which are in a developing state (bone marrow, brain etc). In the developing embryo, the teratogenic effects are gradually decreasing, and in the fetal period, the imprintability is gradually increasing, reaching the top perinatally, when the physiological imprinting is taking place and the possibility of faulty imprinting by exogenous substances appears.

The physiological imprinting, coded by the genetic program is needed for the normal function of cells (receptors), its absence could be as harmful, as the faulty imprinting. However, faulty imprinting durably alters the function of cells, provoking a state, different from the normal one. It is not sure that this state is wrong or harmful, as there is a chance to improve cell function by stimulating it; however, it differs from the function prescribed in the original program. Nevertheless, more likely that the faulty imprinting spoils the original program, as the partial original program is the suitable, which adapts to the whole program of the organism, and this serves the health of the person. The faulty imprinting can develop in the critical periods (of organ or cell) because the developing receptor is not able to differentiate between the self (target) and related foreign molecules, and these later change the methylation pattern. The functional difference provoked by the faulty imprinting finds room in the physiological variants approaching extreme variants; however, it is not able to tolerate loading. Till now, the role of the amount of imprinter, the time of the intervention, or other accompanied factors are not known.

Hormonal imprinting has a role in the rise of some diseases (Waterland and Garza 1999; Csaba 2008; Plagemann 2006)). This could mean the initiation to or induction of the disease. This means that not only genes can be responsible (not considering outer factors) for the rising of or a resistance to a disease, but also epigenetical endowments (faulty imprinting). As the DES treatment of the mother was responsible for the the vaginal cancer of daughters (and other pathological states also in boys), so as the perinatal soy imprinting could be responsible for the relative resistance to mammary and prostate cancers of the Asian population.

Considering the presence of transgenerational imprinting, we have to suppose that the imprinters alter the methylation pattern not only on the genes of the target cells, but they are able to do it on the germ cells. Theoretically, only these cells would be able to transmit the epigenetic information to the offspring. However, there is a possibility of transmission by the maternal milieu (intrauterine or by mother milk). If the germ cells are the transmitters, this is a regular epigenetic inheritance. If the maternal role is likely, this means a special mechanism characteristic to the imprinting.

Hormonal imprinting is a basic biological mechanism, which sets the receptorial system to the natural environment present in the infant already not protected by the maternal organism. However, this mechanism is not prepared to the mass of imprinters which appear in our present chemically contaminated environment. Proportionally to the increasing number of car increases, the amount of aromatic hydrocarbons (benzpyrene, TCDD) and steroids are increasing in our drinking water; as a consequence of oral anticonception and plant protection, hormone-like molecules are increasing in our foods; as a consequence of plant protection, agriculture, soy bean, and these materials cause faulty imprinting already perinatally. To this ground, the medical intervention is added, with medicaments acting at receptorial level. The physician does not treat untouched people, but (faulty) imprinted ones, and influence them further. In the early phase of development, the medical intervention also artificially imprints the receptors and not only molecules with DES strength, but by such molecules as perinatal vitamin A and D treatment (McGrath 2001), by surfactants as cortisol, by oxytocin and antihistamines. However, longer is the list of imprinter molecules which were not mentioned, as it is not allowed by the volume of the article, or their imprinter effect was not tested till now, although it would be important, as they are in connection with the endocrine system and/or they act at receptor level (Igaz et al. 2000). This flood of imprinting influences the life of people who were the direct victims of imprinting or transgenerationally inherited it (Jirtle and Skinner 2007).

This means that with interventions acting at receptor level in the critical phases of life, we influence not only the life of our own, but the life of the progeny generations (Ho and Burggren 2010), epigenetically intervening to the human evolution (Csaba 2007; Anway et al. 2005; Kaiser 2005; Ubeda and Wilkins 2008; Turner 2009).

Imprinting-like interventions in the critical phases of life must be seriously considered, especially if these are done en masse (as it was in case of DES and its successors, the oral contraceptive agents, or oxytocin). These interventions have to be considered as the factors of the anamnesis as basic factors of therapy and as influencing factors of the
human evolution. As our cells develop in a flood of imprints, we have to know that receptor level-acting medicaments used in the last decades can have other effects and can provoke other reactions than it was observed earlier, and modern medical care professionals should consider these effects and adapt therapeutical procedures to them.

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