

## REVIEW ARTICLE

# Hormonal Imprinting: The First Cellular-level Evidence of Epigenetic Inheritance and its Present State

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**Abstract:** Hormonal imprinting takes place perinatally at the first encounter between the developing hormone receptor and its target hormone. This process is needed for the normal function of the receptor-hormone pair and its effect is life-long. However, in this critical period, when the developmental window is open, related molecules (members of the same hormone family, synthetic hormones and hormone-like molecules, endocrine disruptors) also can be bound by the receptor, causing life-long faulty imprinting. In this case, the receptors' binding capacity changes and alterations are caused at adult age in the sexual and behavioral sphere, in the brain and bones, inclination to diseases and manifestation of diseases, *etc.* Hereby, faulty hormonal imprinting is the basis of metabolic and immunological imprinting as well as the developmental origin of health and disease (DOHaD). Although the perinatal period is the most critical for faulty imprinting, there are other critical periods as weaning and adolescence, when the original imprinting can be modified or new imprints develop. Hormonal imprinting is an epigenetic process, without changing the base sequence of DNA, it is inherited in the cell line of the imprinted cells and also transgenerationally (up to 1000 generations in unicellulars and up to the 3<sup>rd</sup> generation in mammals are justified). Considering the enormously growing number and amount of faulty imprinters (endocrine disruptors) and the hereditary character of faulty imprinting, this latter is threatening the whole human endocrine system.

**ARTICLE HISTORY**

Received: February 06, 2019  
 Revised: September 24, 2019  
 Accepted: October 21, 2019

DOI:  
 10.2174/1389202920666191116113524

**Keywords:** Hormonal imprinting, epigenetic inheritance, developmental window, endocrine disruptors, faulty imprinting, heredity.

**1. INTRODUCTION**

Hormonal imprinting is a physiological process in which the developing hormone receptor meets the target hormone for the first time and as a consequence, its binding capacity changes (usually increases) for life. The effect of hormonal imprinting is transmitted to the progenies of the imprinted cells (to the members of the cell line) durably influencing the binding capacity of the receptor and the response to the given hormone by the cell. Hormonal imprinting does not change the nucleotide sequence of the genes, its effect is epigenetic, nevertheless life-long and inherited to the progenies of the individual.

Epigenetic inheritance, which was hypothesised by Lamarck and systematically studied by Waddington, was rediscovered about three decades ago, so before that time the first observations on hormonal imprinting were called receptor memory [1-3]. This was also needed because of the dominance of Michurinism and Lysenkoism in the Soviet Union and its satellite countries in which the inheritance of acquired traits was not a supplement to classical genetics, but a substitution of it [4, 5]. From the acceptance of the notion, epigenetics, hormonal imprinting was classified in this

category. In our laboratory, hormonal imprinting was extensively studied at a unicellular (*Tetrahymena*) and mammalian (rat) level. The name hormonal imprinting was used first in 1980, in a review published in *Biological Reviews of Cambridge Philosophical Society* [6].

**2. FACTS****2.1. Hormonal Imprinting at a Unicellular Level**

The unicellular eukaryote, ciliated *Tetrahymena pyriformis*, synthesizes hormones, characteristic to vertebrates and also have receptors for binding them. The hormones synthesized by the Protozoan have a broad scale, which means that amino-acid type and polypeptide type hormones are produced by them; however, steroid hormones are not present in the repertoire. These amino acid and polypeptide hormones are structurally and functionally similar to the mammalian hormones and they participate in the communication of *Tetrahymena* as well, as in helping their survival and different life functions [7-11]. They are also bound by *Tetrahymena* and the message of the hormone is transmitted into the cell, deciphered and the command given by the hormone is executed. The production of hormones and the presence of the receptors are not continuous, hormones appear under the pressure of different substances and receptors are build up by the evocation of different molecules. According to Koch's theory, there is a continuous change in the plasma

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membrane pattern of unicellulars and in the presence of certain molecules (imprinters), these are stabilized and become receptors [12-18], permanent components of the cell line after that. The mammalian hormone, insulin has binding sites (receptors) in the plasma membrane of *Tetrahymena* [19], which is insulin-like, and this protein can be observed also intracellularly, which is different in insulin imprinted and non-imprinted cells [20]. Insulin and insulin receptor of *Tetrahymena* is structurally similar to that of mammalian ones [21-23]. The effect of imprinting is durable: it can be observed after 1000 generations [24, 25], studied either by the hormone synthesis or functional parameters [26-29]. The strength and durability of imprinting are dependent on the type of hormone-composing amino acids, the length of the peptide chain [30], the age of the cell culture, the hormonal environment [31], and the phases of the cell cycle in which the exposure started [32-34].

As it was mentioned, steroid hormones were not found in *Tetrahymena*. However, they synthesized if induced by the presence (imprinting) of the steroid hormones. At first, hydrocortisone and estradiol synthesis were provoked by mostly imprinting, and testosterone in a lesser amount [35]. This shows that *Tetrahymena* has the enzymatic machinery for producing steroid hormones; however, these are not produced in normal conditions. Imprinting also evokes receptors for steroid hormones [36]. This means that in lower eukaryotes, the basis of the higher level endocrine system can be found [37] and hormonal imprinting has an important role in their further evolution.

5-azacytidine is incorporated into DNA and inhibits DNA methylation, consequently evoking the action of specific genes [38, 39]. Treatment of *Tetrahymena* by it [19] inhibits insulin binding by the receptors and the insulin imprinting induced formation of binding sites but enhances insulin binding in the daughter cell generations. This demonstrates the epigenetic character of the hormonal imprinting at least at a unicellular level [19, 40].

Hormone receptors are present not only in the plasma membrane but also in the nuclear envelope. These receptors are similar to the receptors of the plasma membrane and seems to be likely that there is a continuous circulation between them [41].

### 3. HORMONAL IMPRINTING IN MAMMALS

#### 3.1. The Perinatal Hormonal Imprinting

The hormonal control of embryonic development is done by maternal hormones. These are able to pass across the placenta and reach the embryo to influence their cells and organs. In addition, placental hormones also participate in the modulation of embryonal endocrinology [42]. The embryonal and fetal development of the brain is dependent on the presence of thyroid hormones [43] as well as in the effect of triiodothyronine and its releasing hormone (hypothalamic-pituitary-thyroid axis) [44]. Maternal thyroxine can be observed in the embryo at the 4<sup>th</sup> week after implantation and is absolutely needed for the normal early fetal neurogenesis. Presence and action of thyrotropin and thyroxine are needed for normal implantation and early development [45]. Sex steroid hormones are also present and needed as early as the

time of implantation [46]. However, at the end of fetal development, the fetus' own hormones appear and begin to take over the function of maternal hormones, and their function becomes exclusive after birth. This process requires the encounter between the developing hormone receptors and their target hormones, which provokes the hormonal imprinting, with lifelong consequences. The receptors and their target hormones form a suitable pair, always recognizing themselves. However, in this critical period of endocrine development, the specificity (selectivity) of receptors is not complete, which means that molecules, similar to the target hormone (related hormones of the same hormone family, synthetic molecules, hormone analogues, endocrine disruptors) are also able to be bound by the receptors, causing faulty hormonal imprinting, also with lifelong consequences. This can be manifested in altered binding capacity of the receptor, with the disturbed transmission of the message (contained by the hormone-like molecule) and the disturbed response of the receptor-bearing cell. The time of manifestation can be far from the time of imprinting, so the unraveling of the interrelations is not easy in each case. However, this mechanism could be responsible for the developmental origin of health and disease (DOHaD) and other adult age-manifested diseases and inclinations to diseases (immunological imprinting, metabolic imprinting, *etc.*).

The necessity of normal hormonal imprinting, as well as the consequences of faulty imprinting, are justified in animal experiments, as described below.

#### 3.1.1. Receptor and Hormone-Level Effects

Neonatal suppression of TSH production (six-day treatment with triiodothyronine or thyroxine= neonatal hyperthyroidism) decreases the thyroxine production in adult age, as a response to TSH, which means that the presence of the hormone (and imprinting by it) is needed for normal adult-age function [47]. A single treatment of newborn rats with serotonin increases the serotonin content of white blood cells and peritoneal cells in adults [48]. Single neonatal endorphin treatment caused a decrease of endorphin and serotonin content of adult rat white blood cells and mast cells [49]. Neonatal nociceptin or nocistatin treatment decreased the dopamine, noradrenalin, and 5-hydroxyindoleacetic acid in the hypothalamus, brainstem, and striatum in the adult rats [50]. Thymic glucocorticoid receptor density was increased by neonatal treatment with single imprinting by vitamin D3 [51], which has receptors in the same receptor-family. Triiodothyronine content of lymphoid cells and monocytes/granulocytes were decreased after single neonatal vitamin A treatment [52]. Retinoid imprinting (receptors belong to the same family) influenced glucocorticoid and estrogen receptor density of adults through breastmilk transmission [53]. Isotretinoin imprinting decreased glucocorticoid receptor affinity and increased serum level [54]. The steroid-like benzpyrene seriously influenced the density of adult steroid receptors after perinatal imprinting [55-57].

#### 3.1.2. The Sexual Sphere

Neonatal imprinting with a small dose of vitamin D3 completely inhibited ejaculation of male rats, without influencing the sexual desire. Large dose imprinting influenced desire and ejaculation alike [58]. The sexual activity of fe-

males was depressed by both doses. The perinatal sex steroid imprinting causes permanent modifications in the structure and function of the prostate [59]. Human libido was strongly influenced by perinatal imprinting with sexual steroids [60]. Neonatal exposure to diethylstilbestrol or estradiol benzoate caused epithelial and stromal hyperplasia of adults' prostate [61].

Imprinting by endocrine disruptors, like bisphenol A, benzpyrene, vinclozolin, *etc.*, have serious effects on the male and female reproductive systems, causing functional reproductive disorders [62, 63]. Sperm quality and count are influenced by bisphenol A faulty imprinting [64, 65].

The timing of puberty is influenced by hormonal imprinting caused by endocrine disruptors [66, 67], and this is demonstrated both in animal and human experiments [68-70]. An outstanding representative of these disruptors is bisphenol A, which can produce precocious puberty or isolated premature breast development in 2 months to 4 years old infants [71], and alterations were observed in boys and girls alike [72, 73]. Sexual differentiation of rats is strongly influenced by exposure of low dose bisphenol A in the fetal and suckling periods [74]. In some cases, the addition of peripubertal exposure exacerbated adverse effects [75]. The perinatal imprinting reduced testosterone levels in adult male rats [76]. Lactational exposure altered adult mice behavior [77], and especially social behavior [78]. In men, prenatal exposure to bisphenol A causes problems in school-age boys [79].

Oxítocin imprinting (single treatment) neonatally, strongly influenced the biogenic amine level of the adult brain, (hypothalamus, medulla oblongata, and striatum were affected) [80, 81]. The later endocrine functions are especially disturbed by treatments with estrogen, androgen, or thyroid hormones [82]. Vitamin A and Vitamin D hormonal imprinting influenced the biogenic amine contents of the adult brain: vitamin A imprinting provoked a reduced level, while vitamin A imprinting caused increased tissue levels [83].

### 3.1.3. The Behavioral Sphere

Prenatal bisphenol A exposure provokes externalizing behavior in animals and humans in early childhood (2 years old and especially in girls) [78]. Higher bisphenol A level (three-times related to the control) was found in the urine of children with autism spectrum disorder [84]. Memory, cognition, and social behavior are affected first of all [85]. Aggressive behavior, attention deficit hyperactivity disorder, depression, and anxiety impairments are provoked in adolescent girls [86]. Bisphenol A and phthalate prenatal exposures are in connection with neurobehavioral disorders [87]. Autism spectrum disorder is also listed in potential associations with endocrine disruptors [88].

### 3.1.4. Immunity

The maternally mediated immunological imprinting is disturbed by the different effects of endocrine disruptors [89-92]. Bisphenol A seriously alters the immune system: T cell subsets, B cell functions, dendritic cell, and macrophage biology are especially affected. Immune cells synthesize, contain, and transport hormones and these processes are deeply influenced by hormonal imprinting [93, 94].

Lifespan, in connection with the state of the immune system, is also influenced by hormonal imprinting [95].

### 3.1.5. Effects on Bones

Neonatal glucocorticoid treatment (imprinting) of rats reduced bone mineral density and content in male rats parallel with the decrease of body weight [96], similarly to allylestenol or diethylstilbetrol, or vitamin D3 treatment [97-99].

## 4. THE LATE HORMONAL IMPRINTINGS

Although the perinatal imprinting seems to have a decisive role in the later function of the receptor-target hormone pair, there are further critical periods when the developmental windows are open, giving the possibility for modifying the perinatal effects or developing new ones.

Endorphin exposure at weaning caused the decrease of endorphin and serotonin in adult mast cells and white blood cells [100]. Similar treatment decreased brain serotonin levels, while sexual activity increased [101]. Histamine, benzpyrene, and vitamin D3 enhanced liver glucocorticoid receptors binding capacity [102]. Single serotonin treatment of female rats at adolescent age caused a reduction of serotonin content in mast cells and white blood cells in adult rats [103]. Estrus frequency doubled in rats, which were stressed at weaning by food and water deprivation for two days.

The immune cells, which are continuously differentiating and retain their proliferative capacity are the best examples for demonstrating the adult age imprinting [104, 105].

### 4.1. Age-related Diseases

Type 2 diabetes and cardiovascular diseases are in close correlation with perinatal epigenetic dysregulation [106].

## 5. DISCUSSION

There are hundreds of experiments and observations in the scientific literature on the effects of faulty imprinters, the above-mentioned data were selected only for exemplifying these effects. However, it is not accidental that most of the above-mentioned data originated from the sexual sphere: the endocrine disruptors are steroid-like molecules, which are bound by sexual-steroid receptors. There are many overlaps in the binding of receptors and in the effects caused by them. It can be said that the smallest disruption in the correctly programmed, sexual-steroid regulated endocrine system can cause major changes in the function of any parts of the human organism. This is why endocrine disruptors seem to be so dangerous and this is poked by the effect in the early (perinatal) period when faulty hormonal imprinting is able to provoke lifelong events. In addition, the trouble, which in the first time seems to be manifested only at a receptor level, is inclined to be dispersed and will be associated with other disturbances.

Faulty imprinting is executed in different periods of organ- or system development. This means that its effect is not only time-dependent, but it depends on the developmental state of the target. From this aspect, the faulty imprinting of the developing immune system is obvious, as it influences the protection of the organism in case of inner and outer attacks as well, as in cancerous alterations and longevity. It

seems to be likely that in the case of autoimmunity and allergy (in adults), faulty hormonal imprinting has a role [107].

The sexual sphere is also rather sensitive to alterations caused by endocrine disruptors and the alterations are easily observed however, this does not mean that other spheres are not affected in a similar manner. In addition, sexual steroid receptors belong to the nuclear receptor superfamily and overlappings between the binding of receptors are very frequent. In this family, the aromatic hydrocarbon receptor (Ah-receptor) can be found as well, as the peroxisome proliferator receptor which broadens the effectiveness of the disruptor and difficult to clear what was the origin of the faulty process.

The change of base sequences easily leads to the death of the cell but the change in the methylation pattern is not necessarily and directly lethal, its effect is manifested in the function of the cell, which will be altered without cell death; however, the consequence of it could lead to death of other (function-dependent) cells or disturbed function of the organism, which could be lethal, while the direct correlation can not be demonstrated. It could be told that adult's diabetes or cardiovascular disease can be deduced to a perinatal disturbance [108]; however, a lot of time passes between the endocrine disruptor exposure and the manifestation of the disease, consequently strongly dubious the direct correlation between them. Only animal experiments are decisive and they are at our disposal in a sufficient amount. This was the reason for listing the selected animal experiments and results which support the relation between the faulty hormonal imprinting and their consequences. There is not the slightest doubt that faulty hormonal imprinting is a functional teratogen [89], which must take into consideration in case of diseases manifested in adult age. This is an alteration in epigenetics, which is inherited during the life in the cell line, and also inherited by the progenies of the individual. This also means that in the further generations, the alterations caused by new imprinters are manifested in the changed epigenome, which makes the recognition of the direct correlations more difficult. The supposition of the connections is easier in the case of receptor density than *e.g.* in the case of sexual behavior; however, the targeted experiments lead to accurate results. The hormonal imprinting was named according to the observation of Konrad Lorenz, which was behavioral imprinting, nevertheless, up to now, there were no experiments justifying that epigenetic changes appear in the case of Lorenz's behavioral imprinting. However, it is very likely that some epigenetic changes take place, as this imprinting is also durable (lifelong) and there is no other acceptable explanation [109]. The epigenetic evidence of hormonal imprinting is more acceptable. In this case, an epigenetic reprogramming is supposed which is manifested in the target cells as well, as in the germ cells of the individual, which transmits the new information in the cell line (this establishes the life-long effect) and in the germline (which establishes the transgenerational transmission) [110, 111]. The details of the process are unknown at present. However, many experiments were done to explain the phenomenon (up to the use of stem cells) [112]. It was shown that only germ-line dependent epigenetic modifications can be truly transgenerational [113], this means that the faulty hormonal (hormone-like) effect has to affect the germ cells (or their progenitors),

which have receptors for them. At present, the effect of transgenerational transmission (in case of diethylstilbestrol, in men) was observed in the third generation [113] but it seems likely that this will be continued. There is no exception: each organ, including the brain, can be influenced and the result could change the definition of evolution [114].

The transformation of the lifestyle of present-day mankind by the use of enormous applications of new tools can be observed, and the change of sexuality has an outstanding role. However, it is not known what is the role of endocrine disruptors in them and what is the role of computerization, mass communication, *etc.* And from our aspect: what is the role of faulty hormonal imprinting? In addition: considering the epigenetic heritability of faulty hormonal imprinting, will this destroy the earlier stable human endocrine system, or only transform it, which could also be a useful process, and accommodation to the modern world? It seems to be likely that in the past, there had also been changes in the endocrine regulation (this is shown by the internalization of exohormones: vitamin A and D). There were not tools before for the exact observation of these changes, so we believe that the present changes, provoked by the modern endocrine disruptors are the first, which cause such events, but heavy volcanic eruptions and phytoestrogens could also provoke such alterations in the past, and these also had been inherited epigenetically, participating in the evolution [115].

Alcohol, tobacco, and illicit drugs can impact standing into the construction determined prenatally [110] and give a new basis for subsequent interactions [111]. There is a crucial phase of synaptic maturation which can shape normal behavioral patterns [112]. In addition to the industrial, communal, nutritional, and medical exposures, which seem to be unavoidable, there is a voluntary exposure, which is growing in our modern age, this is the drug-dependence. The perinatal exposure to cannabinoids and opioids influence gene expression in the brain, manifesting in sex-dependent behavioral alterations by binding to steroid hormone receptors of the hypothalamic-pituitary system [116-120]. Cannabinoids can pass across the placenta and also easily pass into mother-milk, consequently acting across breastfeeding, which is the most recommended nourishing form of the infants. The perinatal faulty imprinting effects of the drugs are manifested in the adult age of progenies. However, there is also late imprinting by cannabinoids at adolescent age [121], which is settled on the perinatally sensitized brain (receptors), or provoke independent imprinting. The behavior of an adult person is introduced considering these basic changes. The most frequent changes are observed in motor activity, drug-seeking behavior, nociception, and other processes as well, as in sexual orientation, neurobehavioral, and neuropsychiatric disorders [122-126]. About 70 % of women in the United States believe that there is "slight or no risk of harm" in using cannabis during pregnancy [127-131], and the percentage value is higher if we consider the rather touched early postnatal (perinatal) period. Pathological manifestations (diseases) are considered first of all; however, the general behavioral alterations which is believed normal at present are more important. Showing a general medical example: the normal blood tension in the XIX century was 120/80; in the XX<sup>th</sup> century 140/90 and now again 120/80, as this value is measured in most cases. Aggressivity is a less

measurable index; however, its acceptability is also dependent on the tolerance of people living in the community. If endocrine disruptors change the human aggressivity by faulty perinatal hormonal imprinting massively, this will be the norm and pathological cases will be compared to it. This means that faulty perinatal hormonal imprinting cooperating with the growing amount of endocrine disruptors and the epigenetic heritability of the effects can change the normal (official) human physiology and pathophysiology (behavior included).

As the amount and variety of endocrine disruptors are growing, the importance of hormonal imprinting increases. It is not known the direction (useful or dangerous) of the effects of faulty imprintings at present and much rather in the future, as we do not know how the endocrine system developed to its present form during the human evolution; however, we must recognize that such attack by outer factors - likely- had never been considered before and this can not be without consequences. Though the significance of epigenetic effects to human evolution was recognized recently, these have not been without previous influences and will be most important in the future. In the manifestation of these effects, the perinatal faulty hormonal imprinting has the most important role which seriously influences the life of the target persons and their progenies. Further experiments and observations are needed for recognizing the mechanisms working in it and time for knowing the number of generations touched by it. In the unicellular *Tetrahymena*, the traces of a single treatment (hormonal imprinting) are present after 1000 generations; however, in man, there is no possibility to follow the events for such a long time. Nevertheless, considering the similarities between the unicellular imprinting and mammalian perinatal hormonal imprinting, the durability of human imprinting is likely.

Some observations show that the epigenetic changes are erased in germ cells before fertilization. However, there are such changes which are durable. This means that we see those which remain and can be studied. These are environmentally induced changes, which are transmitted to further generations.

Endocrine disruptors and mainly bisphenol A are the most widely produced chemicals in the world today [132, 133]. In 2015, the global bisphenol A production exceeded 5 million tonnes and this amount is gradually growing. The expressed value of this was US dollar 16.6 billion, and 16.4 billion in 2016. This value is forecasted in US dollar 22.5 billion by 2022. Bisphenol A which is the main representative of dangerous endocrine disruptors is an estrogenic substance, having all of the deleterious effects of endocrine disruptors. Bisphenol A is used in the plastic industry. However, also growing are the amount of agricultural, medical, food disruptors. Most people have a measurable amount in urine and blood serum. Considering these data, the future seems to be hopeless. Nevertheless, it is not sure that the mass-effect of endocrine disruptors will cause negative consequences. It is also possible that it will provoke the change of the endocrine system in a positive direction as this likely happened in the case of the lipid-soluble vitamins (A and D) which became exohormones (having receptors in the nuclear receptor superfamily, as it is in the case of endocrine disruptors). It is possible that the rear-

angement of the whole endocrine system is a basic need to the fitting for the modern age and this is executed by the co-operation of endocrine disruptors and faulty hormonal imprinting.

## CONCLUSION

The theory of hormonal imprinting was published in 1980, almost 40 years ago. Since this, new imprinting-like theories have been published, as immunological imprinting, considering the immune state after perinatal exposures by endocrine disruptors, metabolic imprinting, perinatal exposures by imprints or after starvation or overfeeding (obesity, metabolic syndromes) [134-137], and at least the developmental origin of health and disease (DOHaD) [138], without mentioning the first observation of cellular level imprinting, the hormonal imprinting and its faulty variations. However, these new theories and observations strengthen the theory and evidence of hormonal imprinting [139, 140].

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

Declared none.

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