Annals of Thyroid Research

Open Access

Austin Publishing Group

Special Article - Thyroid Hormones

Receptorial and Functional Overlapping between Thyrotropin (TSH) and Gonadotropins (FSH, LH): Phylogenetic, Ontogenetic and Clinical Application Aspects

Csaba G[1]* and Shahin MA[2]

[1]Department of Genetics, Cell and Immunobiology, Semmelweis University, Hungary

[2]Department of Biological Sciences, Ain Shams University, Egypt

***Corresponding author:** Csaba G, Department of Genetics, Cell and Immunobiology, Semmelweis University, Budapest, Hungary

Received: October 18, 2018; **Accepted:** October 26, 2018; **Published:** November 02, 2018

Abstract

There are overlapping in the receptorial hormone binding, as well as the physiological and pathological functions of glycoprotein hormones from the unicellular level (Tetrahymena) to mammals (human beings). The overlapping can be explained by the analogous structure of receptors and similarities of hormones; however, the specificity-in contrast, to the hormonal similarities-is not understandable. The overlap is more expressed during the ontogenetic development however; it is present in matured (adult) age, sometimes causing characteristic alterations and diseases in humans. Overlapped (nonspecific) hormones' effect can be stronger, than that of the original (specific) ones. In the fetal, perinatal and early postnatal development the overlapping could cause faulty hormonal imprinting with late consequences in sexual or thyroid regulated functions. Imprinting can be executed also in tissue cultures with similar consequences. Overlapping in adults are manifested in alteration of sexuality (menstrual disturbances and infertility included) and bone loss (osteoporosis) as well, like other diseases.

Keywords: Thyroid-stimulating hormone; Luteinizing hormone; Gonadotropins; Ontogenetic

Introduction

During the evolution developed hormone and receptor families caused by genetic changes, creating similar or almost identical structures. One of these families is present among the pituitary hormones, named glycoprotein hormones. The members of the family are the Luteinizing Hormone (LH), the Follicle Stimulating Hormone (FSH) and Thyroid-Stimulating Hormone (TSH). The 4th member of the family is not produced by the anterior pituitary gland, but by the placenta (syncytiotrophoblasts) during pregnancy, having the name: Chorionic Gonad tropic hormone (CG, in human case: hCG). Receptors for the glycoprotein hormones belong to the group of the G protein-coupled receptors with a specific N-terminal extracellular domain for binding the hormone (hormone specificity) and the seven membrane-spanning segments in the C-terminal intracellular end [1]. Eleven amino acids (Lys-201-Lys 211) and the corresponding region of the LH/CG receptor (Thr-202-Ile 212) are responsible for specific TSH and hCG binding [2]. However, TSH receptor gene is related to FSH and LH receptors [2]. The α subunit of TSH displays homology with LH, FSH and hCG [3].

There is a co-evolution of hormones and receptors, the system can work only in this case. This means that in addition to the hormone family there is also a receptor family, which contains LHR, FSHR, CGR, and TSHR. These are plasma membrane receptors and the end-product of receptor activation is the liberation of the cyclic AMP (cAMP) which evokes the response of the receptor-bearing cell. The hormones, as well as their receptors, are rather similar to each other. Each hormone has α and β subunits; β subunits for recognizing and binding of the target hormone, and α subunit for activating the receptor and -consequently- the cell [4,5]. According to these functions, α subunits of the four hormones are identical and β subunits are different, with a very close similarity. This causes that there are overlapping (in binding) between the members of the hormone families without regards to their origin (anterior pituitary, or placenta, in human).

Phylogeny and phylogenetic overlap between TSH and gonadotropins

There were studies on sea lamprey for elucidating the similarities of glycoprotein hormones and hormone receptor system to the vertebrate systems and it was found that there is a strong similarity between the structure of hormones and receptors. Sea lamprey (Petromyzon marinus) is a jawless vertebrate, which represents the oldest lineage of vertebrates (jawless fishes) [6]. In the sea lamprey instead of the three classical pituitary glycoprotein hormones (characteristic of jawed vertebrates), it has only two, lamprey glycoprotein hormone (IGpH) and thyrostimulin as well as two receptors (IGpH-R1 and R2). Consequently, there is a primitive overlapping, yet functional hypothalamo-pituitary gonadal and thyroidal systems [7]. This would be the basis of overlapping also in mammals [8]. In sea lamprey, a 781 amino acid long residue protein was prepared from the glycoprotein hormone receptor and 43% of this protein was identical with mammalian TSH or FSH receptors [7]. This suggests the existence of a primitive functional overlapping of

Citation: Csaba G and Shahin MA. Receptorial and Functional Overlapping between Thyrotropin (TSH) and Gonadotropins (FSH, LH): Phylogenetic, Ontogenetic and Clinical Application Aspects. Annals Thyroid Res. 2018; 4(3): 158-163.

FSH and TSH at this low phylogenetic level. When TSH, LH, and FSH were purified from ovine, bovine, ostrich, sea turtle, and bullfrog and were tested by stimulation of thyroid in four species of amphibians, it was found that all animals tested responded specifically to mammalian TSH in stimulating thyroid [9]. In addition, bullfrog LH was more potent in its effect on the thyroid gland, than bullfrog TSH. In an experiment using Japanese toad (Bufo japonicus), gonadotropin β subunit was more similar to tetrapod TSH β subunit than to fish TSH β subunit [10]. Very scarce data are at our disposal on experiments with other animals, but in bony fish, TSH receptors which composed of 779 amino acids showed higher homology (57-59%) to mammalian TSH receptors, than to mammalian LH (47-49%) receptors [11]. It must be considered that vertebrate glycoprotein receptors evolved by gene duplication and subsequent functional divergence during the split of gnathostomes (jawed vertebrates) from their ancestors [12].

In the male frog chorionic gonadotrophin induces ejaculation. This observation is used in the Galli-Mainini reaction when woman's urine is injected into adult male frogs and the subsequent sperm production (ejaculation) reports the pregnancy. In this case, the injection of thyrotrophic also causes ejaculation by overlapping on the CG receptors [13,14].

There are studies also in the lowest phylogenetic level, in unicellular. Unicellular (Tetrahymena pyriformis as a model organism) have receptors for hormones of higher vertebrates, even synthesize these hormones which influence their physiological functions [15]. Thyrotropin, as well as gonadotropins (FSH, CG) influence RNA synthesis in Tetrahymena [16]. Considering the effect of TSH, this seems to be specific, as triiodothyronine production by the unicellular animal is justified [16]. However, gonadotropin is able to mimic the effect of thyrotropin, regulating triiodothyronine production. Nevertheless, in contrast to other hormones (insulin, epinephrine, melatonin) [15,17], the role (function) of triiodothyronine is dubious at the unicellular level.

Overlapping effect of pituitary glycoprotein hormones on the developing organs

In the newly hatched male and female chickens, TSH and gonadotropins (FSH, LH) increased the number of spermatogonia or Sertoli cells in the seminiferous cords and the number of granulosa cells in the ovarian follicles [18,19]. However, they do not change each other's effect, if they were administered one after the other. Considering the ultra structure of the testes by the electron microscope, in the Sertoli cells, the amount of SER and RER increased with enhanced surface activity [20,21]. After TSH treatment the activity of the Golgi system was outstandingly increased. In newly hatched chickens FSH overlapped the effect of TSH, increasing the follicular diameter and height of epithelial cells in the thyroid gland [22]. In case of treatment chick embryos with gonadotropins at the 8th day of incubation an increase in the seminiferous cord diameter, as well as a marked increase in the number of Sertoli cells and germ cells (plus the increase of testicular weight) was observed in 20-day old male embryos. However, the same treatment in female embryos produced an increase of ovarian weight plus ovarian width and cortical thickness, as well as in the number of oocytes [23]. This indicates that only gonadotropin preparations caused a significant increase in gonadal (testis and left ovary) development. On the other hand, TSH caused opposite results in both sexes in organotypic culture experiments. 12 and 15-day old chick embryo testes and ovaries exposed in vitro to the tested hormones showed a good response (enhancing the growth and migration of cells) to both gonadotrophic and thyrotropic stimulation [24]. In 20 days old chick embryo, treatment with TSH on the 15th day of incubation provoked a response similar to that of gonadotropin, increasing the diameter of seminiferous tubules, testicular weight and gonocyte counts [25]. A single treatment with TSH or GTH similarly increased the thyroxine and testosterone levels in newly hatched cockerels [26]. Although gonadotropins have similar actions on the gonads of the developing chickens, they influence primarily the parenchyma of the gonads, inducing an increase in the diameter of seminiferous tubules and in the thickness of the ovarian cortex, while TSH acts primarily on the interstitial tissue and its effect is more pronounced in the testis than in the ovary. Gonadotropins enhanced the effect of TSH on the interstitial cells. FSH and TSH binding to medullary cord cells of the developing chicken ovary is justified and the binding of the two hormones was similar [27]. When the hypothalamo-pituitary-thyroid axis begins to develop (12th day of embryonic development) there is no distinction between the recognition of these hormones [28]. The fine structure of the thyroid gland of the chick embryo has been studied following the administration of Gonadotropins (FSH+LH) and Thyrotropin (TSH) on the 8th or 15th day of embryonic life [29]. Ultra structural observations showed considerable stimulation of the thyroidal follicles in TSH as well gonadotropin treated embryos on the 15th day of incubation. Moreover, TSH treatment on the 8th day did not show remarkable developmental changes in the gland. On the other hand, the thyroids of gonadotropin treated embryos showed different response i.e. the exposure on the 8th day caused atrophy whereas on the 15th day it exhibited an enhancement in the development of the thyroidal cells of 20-days old chick embryos.

Hormonal imprinting by glycoprotein hormones

The developing mammalian embryo and fetus are under the hormonal control of the mother. Their developing hormone receptors are influenced by maternal hormones, however, at the end of this developmental period, the receptors must be suited to their own hormones and this happens in the prenatal period, during birth and postnatal [30]. The first encounter between the developing receptor and their target hormones provokes the hormonal imprinting, which is absolutely needed for the later normal function of the receptor-hormone complex and this is a life-long effect. However, hormone-like molecules (related hormones of the hormone families, synthetic hormones, endocrine disruptors) can disturb the physiological imprinting, provoking faulty hormonal imprinting also with life-long consequences (alterations in receptors' binding capacity, pathological (sexual) behavior, disturbed bone development etc) [31].

Newly hatched male chickens treated with TSH or FSH at hatching and on the 5th week showed that posthatching exposure influenced the impact of re-exposure at 5 weeks [32]. The treatment facilitated the hormonal effects at the 5th week, amplifying the effect of FSH slightly more, than that of TSH. TSH and FSH similarly influenced testosterone secretion, however, though thyroxin level was influenced by both hormones, it was more pronounced in case of TSH. The treatments at hatching with any of the tropic hormones caused a diminution of the T4 level augmenting of FSH or TSH administered

at the age of five weeks [33]. In male rats, a single treatment with TSH or gonadotropin at the neonatal period (imprinting) considerably increased the weight of the testis and the diameter of the seminiferous tubules measured at the age of six weeks. Repeated treatment by any of the tested hormones at the age of six weeks decreased the testis weight and the diameter of seminiferous tubules [34]. Furthermore, a single gonadotropin (FSH+LH) treatment of neonatal male rats resulted in depression of sexual activity in adult rats [35]. TSH treatment caused similar, but less pronounced effect. In vitro cultured testicular and ovarian cells of newborn rats illustrated an increase in their hormone-binding capacity after the first treatment (imprinting) with gonadotropin or TSH [36]; the effect was most pronounced in testicular than in ovarian cells.

Human relations (clinical aspects)

On the plasma membrane of thyroid cells, there are TSH receptors, which can bind TSH, FSH, LH, and hCG. However, there are various human organs (testis, ovary, adrenal gland, and liver) which possess TSH-cellular receptors [37]; the capacities of high-affinity sites were similar. Moreover, other investigations reported that the capacity of binding TSH extended to cellular components of the anterior pituitary, hypothalamus, skin, kidney, the immune system, bone marrow, and adipose tissue, and bone. This latter has an outstanding clinical importance, as was unknown before the last decade of research [38]. It was demonstrated that dysregulation of the pituitary-bone axis leads to the bone-loss of osteoporosis [39]. Clinical observations and studies on TSH receptor knock-out mice suggested that TSH has a direct role in skeletal homeostasis [40]. In the process of bone resorption and remodeling TSH as well, as FSH have an outstanding role [41]. In the case of hyperthyroidism, many disturbances of menstruation have been observed, whereas hypothyroidism led to polymenorrhea and an ovulation [42]. Hypothyroidism in girls can cause precocious puberty [43]. Both hyper and hypothyroidism can cause infertility and spontaneous abortions [44]. HCG induced hyperthyroidism represents a rare paraneoplastic syndrome of hCG secreting testicular cancer [45]. TSH has a modulatory influence on the sexual and spermatogenic function of males [46]. In thyrotoxicosis (Graves' disease) loss of libido and decreased potency were observed, with a reduction of sperm count (less than 40 million) [47]. Considering high statistics, 70% of hyperthyroid and 60% of hypothyroid men had decreased libido [48]. Hyperthyroidism affects the responsiveness of the hypothalamo-pituitary axis to steroid sexual hormones [49]. In Graves' disease, the sperm motility was decreased [50]. Additionally, asthenospermia (85.7%), hypospermia (61.9%), oligospermia (42.9%), necrospermia (42.9%), and teratospermia (19.0%) were reported in men with Graves' disease [51]. A correlation between hypo and/or hyperthyroidism and inhibition of the development of Graafian follicles was postulated by Fedail et al. [52]. In a similar trend, Liu et al. [53] observed interruption of FSH and LH levels in rats suffering hypo or hyperthyroidism. Enlargement and cystic changes in ovaries of patients with hypothyroidism have been observed in numerous case reports [54,55]. A case study of a young female patient with severe hypothyroidism due to autoimmune thyroiditis and multiple ovarian cysts is reported by Panico et al. [56]. The latter authors added that it is necessary to identify the relation between the severe increase in TSH levels and multiple ovarian cysts in young girls suffer from autoimmune thyroiditis. This obviously indicated that thyroid hormones affected gonadal function, which correlated with dysregulation between the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-gonadal axis [57]. There is a positive correlation between LH and TSH in Polycystic Ovarian Syndrome (PCOS) patients [58]. It appears from these data that dysregulation of thyroid function can be associated with gonadal disorders which may impaired fertility. This multifunctional correlation could pave the way for investigating the pathological impacts of these hormones [59].

Discussion

The observations and results show that there is indeed overlapping between TSH and gonadotropins at the level of the receptor as well as at the hormonal effects, in case of unicellular and human beings, alike. The most interesting overlap is at the level of unicellular, where Tetrahymena reacts to thyrotropin (in this particular case, mammalian hypophyseal TSH) synthesizing triiodothyronine, a vertebrate hormone. The reaction means that a TSH receptor is present, which transmits the hormonal information and this transmission has resulted in the hormonal product. In addition, this effect is done also by the related hormone, human chorionic gonadotropin. There are two possibilities, which can explain this strange phenomenon. The first possibility is, that in the Tetrahymena genome there are such genes which are similar to mammalian genes, and in a fraction of Tetrahymena genes this has experimental support in case of other genes. A fraction containing 207 base pairs of Histidine Decarboxylase (HDC) gene was compared to HDC cDNA (exon) sequences and it was found that the HDC-cDNA of Tetrahymena pyriformis similar to mammalian cDNA [60]. In addition, 52% of Tetrahymena genes showed significant identity to genes of other organisms, represented in the GenBank, of which 92% matched human proteins [61]. Although there are concrete data in the case of glycopeptide hormones, the validity of the mentioned similarities could be imagined.

A further possibility is based on the theory of Koch et al. [62]. According to this theory, there are not preformed receptors in unicellular, but there is a continuous traffic between the new molecules produced by the cells and others, presented in the plasma membrane and these are building into the plasma membranes forming membrane patterns which can recognize and bind environmental molecules, including hormones. This transitional „receptors" can bind the hormones which are recognized also by similarity and can be fixed after founding the partners [63].

There is an easier situation for explaining overlappings in case of vertebrates. The members of the glycoprotein hormone family have common producer organs (as in the case of TSH, FSH, LH, and HCG). In this case, the problem is, how is the response to the given hormone is specific (in general), if many related hormone molecules are present in the blood circulation. This question is not answered [64,65], and the mentioned human cases show the problems of overlapping, causing abnormal states or diseases. This requests further research for eliminating the causes of diseases, as the problem seems to be universal. For example, in the case of nuclear receptors, as sexual hormone receptors, glucocorticoid receptors, etc. also there is receptorial and hormonal overlapping, however, it is accepted, not

knowing what causes the specificity in the everyday practice.

Faulty perinatal hormonal imprinting with overlapping glycoprotein hormones could cause abnormal receptor-hormone contact and influences alterations in case of a second encounter [66,67]. This could be the cause of different diseases. However, though the determining period of receptor-hormone contact is perinatal, there is a possibility also later, during adolescence, or in the continuously dividing cells, during the whole life [68]. This is well demonstrated when seven weeks old (adult) rats were treated with gonadotropin and showed a decrease in thyroid response to TSH later. TSH treatment was not able to restore the normal thyroxine level [69].

It is also interesting that TSH amplified FSH receptors in a greater degree for Chinese hamster ovary (CHO) cells (in tissue culture) than FSH itself [70] and for imprinting very low concentration of hormones (10-13 mol) was needed for a short time [70,71]. The effect of the overlapping hormone was stronger than the real, physiological (specific) hormone, causing disturbances in hormone regulating systems, or causing diseases. This also means that the hormonal overlappings of glycoprotein hormones have to take more seriously and further research is needed to clear the problems caused by it. This is more important in the present era of enormous spreading of endocrine disruptors, which are able to disturb the whole endocrine system [72,73]. These exogenous chemicals can mimic the effects of natural hormones by binding to their receptors. This latter is more likely considering the broad expression of extra thyroidal TSH receptors [74]. Polychlorinated Biphenyls (PCBs) influence gonadotropin as well as TSH levels in rats [75] and maternal exposure to diethylstilbestrol influences thyroid function and testicular function [76], consequently the development of the brain [77,78]. Bisphenol A (BPA) exposure caused alterations in the gonadotropin levels of adult female workers [79] and in male smokers [80]. There was an association between urinary BPA and serum TSH levels, consequently thyroid function [81].

Considering the perinatal hormonal imprinting, human maternal exposure to BPA resulted in advancing puberty in females [82], variations in sperm count and motility in males and alterations in the estrus cycle in female rats [84]. Although there is no direct glycoprotein hormone overlapping observations, our knowledge on these processes calls attention to the expected and potentially serious problems which will be caused in the future by the endocrine disruptors' provoked overlapping imprinting. Considering also the epigenetic inheritance of hormonal imprinting and the enormous proliferation of endocrine disruptors, it is the time to keep seriously the overlapping between hormones and especially between the glycoprotein hormones [85-87].

References

1. Nwabuobi C, Arlier S, Schatz F, Guzeloglu-Kaysli O, Lockwood CJ, Kayisli UA. hCG: biological functions and clinical applications. Int J Mol Sci. 2017; 18.

2. Nagayama Y, Russo D, Wadsworth HL, Chazenbalk GD, Rapoport B. Eleven amino acids (Lys 201 to Lys 211) and 9 amino acids (Gly-222 to Leu-230) in the human thyrotropin receptor are involved in ligand binding. J Biol Chem. 1991; 266: 14926-14930.

3. Griswold MD, Heckert L, Linder C. The molecular biology of the FSH receptor. J Steroid Biochem Mol Biol. 1995; 53: 215-218.

4. Nunez Miguel R, Senders J, Chirgadze DY, Blundell TL, Furmaniak J, Rees Smith B. FSH and TSH binding to their respective receptors: similarities, differences, and implication for glycoprotein hormone specificity. J Mol Endocrinol. 2008; 41: 145-164.

5. Xuliang J, Dias JA, Xiaolin He. Structural biology of glycoprotein hormones and their receptors: insights to signaling. Mol Cell Endocrinol. 2014; 382: 424-451.

6. Sower SA. Landmark discoveries in elucidating the origins of the hypothalamic-pituitary system from the perspective of a basal vertebrate, sea lamprey. Gen Comp Endocrinol. 2018; 264: 3-15.

7. Freamat M, Sower SA. A sea lamprey glycoprotein hormone receptor similar with gnathostome thyrotropin hormone receptor. J Mol Endocrinol. 2008; 41: 219-228.

8. Sower SA, Freamat M, Kavanaugh SI. The origins of the vertebrate Hypothalamic-Pituitary-Gonadal (HPG) and Hypothalamic-Pituitary-Thyroid (HPT) endocrine systems: new insights from lampreys. Gen Comp Endocrinol. 2009; 161: 20-29.

9. McKenzie DS, Licht P. Studies on the specificity of thyroid responses to pituitary glycoprotein hormones. Gen Comp Endocrinol. 1984; 56: 156-166.

10. Komoike Y, Ishii S. Cloning of cDNAs encoding the three pituitary glycoprotein hormone beta subunit precursor molecules in the Japanese toad, Bufo japonicus. Gen Comp Endocrinol. 2003; 132: 333-347.

11. Kumar RS, Jjiri S, Kight K, Swanson P, Dittman A, Alok D, et al. Cloning and functional expression of a thyrotropőin receptor from the gonads of a vertebrate (bony fish): potential thyroid-independent role for thyrotropin in reproduction. Mol Cell Endocrinol. 2000; 167: 1-9.

12. Freamat M, Sower SA. Glycoprotein hormone receptors in the sea lamprey Petromyzon marinus. Zoolog Sci. 2008; 25: 1037-1044.

13. Csaba G, Dobozy O, Deak BM. HCG-TSH overlap and induction of Galli-Mainini reaction with TSH in adult male frogs. Horm Metab Res. 1982; 14: 617-618.

14. Csaba G, Dobozy O, Deák BM. Interaction of Thyrotropin (TSH) and gonadotropins in the function of genital organs I. Investigations in the frog. Acta Physiol Hung. 1983; 61: 137-140.

15. Csaba G. The hormonal system of the unicellular Tetrahymena: a review with evolutionary aspects. Acta Microbiol Immunol Hung. 2012; 59: 131-156.

16. Csaba G, Ubornyák L. Effect of polypeptide hormones (insulin, thyrotropin, gonadotropin, adrenocorticotropin) on RNA synthesis in ítetrahymena, as assessed from incorporation of 3H-uridine. Acta Biol Acad Sci Hung. 1982; 33: 381-384.

17. Kőhidai L, Vakkuri O, Keresztesi M, Leppaluoto J, Csaba G. Melatonin in the unicellular Tetrahymena pyriformis: effects of different lighting conditions. Cell Biochem Funct. 2002; 20: 269-272.

18. Dobozy O, Csaba G, Shahin MA, Lazáry G. Histological analysis of the overlapping effect of hypophyseal hormones on the cockerel' testes. Acta Morphol Acad Si Hung. 1980; 28: 11-20.

19. Shahin MA, Csaba G, Dobozy O. Effect of gonadotropins and thyrotropin on the testes and ovaries the newly hatched chicken. Acta Morphol Acad Sci Hung. 1980; 28: 317-335.

20. Shahin MA, Sudár F, Dobozy O. Electron microscopic study of the overlapping effect of thyrotropin and gonadotropins on the Sertoli cells of chick embryo. Z Miksosk Anat Forsch. 1982; 96: 1044-1068.

21. Dobozy O, Sudár F, Shahin MA, Csaba G. Overlapping effect of Follicle Stimulating Hormone (FSH) and Thyrotropin (TSH) on the ultrastructure of immature chicken testes. Acta Morphol Acad Sci Hung. 1982; 30: 11-26.

22. Dobozy O, Balkányi L, Csaba G. Overlapping effect of thyroid stimulating hormone and follicle stimulating hormone on the thyroid gland in baby chickens. Acta Physiol Acad Sci Hung. 1981; 57: 171-175.

23. Shahin MA, Csaba G, Dobozy O. Effects of mammalian hypophyseal hormones: gonadotropins, thyrotropin and adrenocorticotropin, on the embryonic development of 8 days chick embryo gonads. Arch Anat Histol

Embryol. 1981; 64: 111-119.

24. Shahin MA, Török O, Csaba G. The overlapping effects of thyrotropin and gonadotropins on chick embryo gonads *in vitro*. Acta Morphol Acad Sci Hung. 1982; 30: 109-125.

25. Csaba G, Shahin MA, Dobozy O. The overlapping effect of gonadotropins and TSH on embryonic chicken gonads. Arch Anat Histol Embryol. 1980; 63: 31-38.

26. Dobozy O, Nagy SU, Fehér T, Hetényi G, Csaba G. Selective and/or overlapping effect of pituitary hormones (thyrotropin, gonadotropin) on serum thyroxin and testosterone levels in newly hatched cockerels. Acta Physiol Hung. 1985; 66: 177-181.

27. Woods JE, Daamianides-Keenan M, Thommes RC. FSH- and TSH of the developőing chick embryo-binding cells in the ovary of the developing chick embryo. Gen Comp Endocrinol. 1991; 82: 487-494.

28. Shahin MA, Csaba G, Dobozy O. Effect of gonadotropins, thyrotropin, and adrenocorticotropin on the development of 12 day chick embryonic gonads. Roux Arch Dev Biol. 1981; 190: 58-59.

29. Shahin MA, Madarasz B, Dobozy O, Csaba G. Electron microscopic study of the gonadotropin-thyrotropin overlap on the chick embryo thyroid. Z Mikrosk Anat Forsch. 1984; 98: 926-938.

30. Csaba G. Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. Biol Rev Camb Philos Soc. 1980; 55: 47-63.

31. Csaba G. The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics. 2011; 2: 187-196.

32. Dobozy O, Shahin MA, Csaba G. Permanent amplifying effect on the cockerel gonad of hypophysis hormones (FSH, TSH) administered at hatching. Acta Moephol Acad Sci Hung. 1981; 29: 19-25.

33. Dobozy O, Csaba G, Nagy SU, Fehér T, Shahin MA, Hetényi G. Influence of hormonal imprinting on hormone level. Permanent receptor damaging effect of pituitary hormones administered to newly-hatched cockerels. Acta Physiol Hung. 1987; 70: 69-73.

34. Dobozy O, Csaba G, Hetényi G, Shahin MA. Investigation of gonadotropin-thyrotropin overlapping and hormonal imprinting in the rat testis. Acta Physiol Hung. 1985; 66: 169-175.

35. Csaba G, Dobozy O, Shahin MA, Dalló J. Impact of a single gonadotropin (FSH + LH) or thyrotropin (TSH) treatment on the sexual behavior of the adult male rat. Med Biol. 1984; 62: 64-66.

36. Csaba G, Török O, Kovács P. Overlapping imprinting of Thyrotropic (TSH) and Gonadotropic (FSH, LH) hormones in cultures of newborn rat testicles and ovaries. Acta Morphol Hung. 1986; 34: 171-176.

37. Trokoudes KM, Sugenova A, Hazani E, Row VV, Volpé R. Thyroid Stimulating Hormone (TSH) binding to extra thyroidal human tissues: TSH binding to extra thyroidal human tissues: TSH and thyroid-stimulating immunoglobulin effects on adenosine 3', 5'-monophosphate in testicular and adrenal tissues. J Clin Endocrinol Metab. 1979; 48: 919-923.

38. Zaidi M, New MI, Blair HC, Zallone A, Baliram R, Davies TF et al. Actions of pituitary hormones beyond traditional targets. J Endocrinol. 2018; 237: R83-R98.

39. Agrawal M, Zhu G, Sun L, Zaidi M, Igbal J. The role of FSH and TSH in bone loss and its clinical relevance. Curr Osteoporos Rep. 2010; 8: 205-211.

40. Sendak RA, Sampath TK, McPherson JM. Newly reported roles of thyroid-stimulating hormone and fol 2013 licle-stimulating hormone in bone remodeling. Int Orthop. 2007; 31: 753-757.

41. Takeuchi Y. Possible involvement of pituitary hormones in bone metabolism. Clin Calcium. 2013; 23: 195-202.

42. Koutras DA. Disturbances of menstruation in thyroid disease. Ann NY Acad Sci. 1997; 816: 280-284.

43. Doufas AG, Mastorakos G. The hypothalamic-pituitary-thyroid axis and the female reproductive system. Ann NY Acad Sci. 2000; 900: 65-76.

44. Veeresh T, Moulali D, Sarma HS. A study on serum FSH, LH and prolactin levels in women with thyroid disorders. Int J Si Res Publ. 2015; 5: 2250-3153.

45. Voigt W, Maher G, Wolf HH, Schmoll HJ. Human chorion gonadotropin-induced hyperthyroidism in germ cell cancer-a case presentation and review of the literature. Onkologie. 2007; 30: 330-334.

46. Kumar A, Shekhar S, Dhole B. Thyroid and male reproduction. Indian J Endocrinol Metab. 2014; 18: 23-31.

47. Kidd GS, Glass AR, Vigersky RA. The hypothalamic-pituitary-testicular AXIS in thyreotoxicosis. J Clin Endocrinol Metab. 1979; 48: 798-802.

48. Velázquez EM, Bellabarba Arata G. Effects of thyroid status on pituitary gonadotropin and testicular reserve in men. Arch Androl. 1997; 38: 85-92.

49. Földes J, Bános C, Fehér T, Bodrogi L, Szalay F, Borvendég J, et al. Functional relationships of the hypothalamic-pituitary-testicular system in Graves' disease. Acta Med Acad Sci Hung. 1982; 39: 109-116.

50. Hudson RW, Edwards AL. Testicular function in hyperthyroidism. J Androl. 1992; 13: 117-124.

51. Abalovich M, Levalle O, Hermes R, Scaglia H, Aranda C, Zilbersztein C et al. Hypopthalamic-pituitary-testicular axis and seminal parameters in hyperthyroid males. Thyroid. 1999; 9: 857-863.

52. Fedail JS, Zheng K, Wei Q, Kong L, Shi F. Roles of thyroid hormones in follicular development in the ovary of neonatal and immature rats. Endocrine. 2014; 46: 594-604.

53. Liu J, Guo M, Hu X, Weng X, Tian Y, Xu K, et al. Effects of thyroid dysfunction on reproductive hormones in female rats. Chin J Physiol. 2018; 61: 152-162.

54. Shu J, Xing L, Zhang L, Fang S, Huang H. Ignored adult primary hypothyroidism presenting chiefly with persistent ovarian cysts: a need for increased awareness. Reprod Biol Endocrinol. 2011; 9: 119.

55. Sharma Y, Bajpai A, Mittal S, Kabra M, Menon PS. Ovarian cysts in young girls with hypothyroidism: follow-up and effect of treatment. J Pediatr Endocrinol Metab. 2006; 19: 895-900.

56. Panico A, Lupoli GA, Fonderico F, Colarusso S, Marciello F, Poggiano MR, et al. Multiple ovarian cysts in a Young girl with severe hypothyroidism. Thyroid. 2007; 17: 1289-1293.

57. Dittrich R, Beckmann MW, Oppelt PG, Hoffmann I, Lotz L, Kuwert T, et al. Thyroid hormone receptors and reproduction. J Reprod Immunol. 2011; 90: 58-66.

58. Rrupulli A, Vrushi L, Gishto B. Correlation of LH and FSH with serum TSH levels in polycystic ovarian syndrome. Endocrine Abstracts. 2018; 56.

59. Gracia-Campayo V, Kumar TR, Boime I. Thyrotropin, Follitropin, and Chorionic Gonadotropin expressed as a single multifunctional unit reveal remarkable permissiveness in receptor-ligand interactions. Endocrinology. 2002; 143: 3773-3778.

60. Hegyesi H, Szalai C, Falus A, Csaba G. The Histidine Decarboxylase (HDC) gene of Tetrahymena pyriformis is similar to the mammalian one. A study of HDC expression. Biosci Rep. 1999; 19: 73-79.

61. Fillingham JS, Chilcoat ND, Turkewitz AP, Orias E, Reith M, Pearlman RE. Analysis of expressed sequence tags (ESTs) in the ciliated protozoan Tetrahymena thermophila. J Eucariot Microbiol. 2002; 49: 99-107.

62. Koch AS, Nienhaus R, Lautsch M, Lukovits I. An advanced version of the dynamic receptor pattern generation model: the flux model. Biol Cybernet. 1981; 39: 105-109.

63. Csaba G. Phylogeny and ontogeny of chemical signaling: origin and development of hormone receptors. Int Rev Cytol. 1994; 155: 1-48.

64. Ryan RJ, Charlesworth MC, McCormick DJ, Milius RP, Keutman HT. The glycoprotein hormones: recent studies of structure-function relationships. Faseb J. 1988; 11: 2661-2669.

65. Salesse R, Remy JJ, Levin JM, Jallal B, Garnier J. Towards understanding the glycoprotein hormone receptors. Biochimie. 1991; 73:109-120.

66. Dobozy O, Csaba G, Deák BM. Interaction of Thyrotropin (TSH) and

gonadotropins in the function of genital organs. Effect of TSH and gonadotropin pretreatment (hormonal imprinting) of newborn rats on hormonal overlap in adult animals. Acta Physiol Hung. 1983; 61: 205-211.

67. Dobozy O, Csaba G, Hetényi G, Shahin M. Investigation of gonadotropin-thyrotropin overlapping and hormonal imprinting in the rat testis. Acta Physiol Hung. 1985; 66: 169-175.

68. Csaba G. The non-perinatal faulty hormonal imprinting: a review. Integr Pediatr Child Care (in press). 2018.

69. Csaba G, Nagy SU. Effect of gonadotropin (FSH-LH) and Thyrotropin (TSH) treatment in adolescence on TSH-sensitivity in adult rats. Acta Physiol Hung. 1990; 75: 101-105.

70. Csaba G, Török O, Kovács P. Hormonal imprinting in cell culture II. Evidence of hormonal imprinting and Thyrotropin (TSH) -gonadotropin (FSH) overlapping in Chinese Hamster Ovary (CHO) cell line. Acta Physiol Hung. 1984; 64: 135-138.

71. Csaba G, Török O, Kovács P. Influence of hormone concentration and time factor on TSH-FSH imprinting and overlap in CHO cells. Acta Biol Hung. 1983; 34: 425-431.

72. Sher ES, Xu XM, Adams PM, Craft CM, Stein SA. The effects of thyroid hormone level and action in developing brain: are these targets for the action of polychlorinated biphenyls and dioxins? Toxicol Ind Health 1998; 14: 121-158.

73. Schell LM, Gallo MV. Relationships of putative endocrine disruptors to human sexual maturation and thyroid activity in youth. Physiol Behav. 2010; 99: 246-253.

74. Williams GR. Extrathyroidal expression of TSH receptor. Ann Endocrinol (Paris). 2011; 72: 68-73.

75. Desaulniers D, Leingartner K, Wade M, Fintelman E, Yagminas A, Foster WG. Effects of acute exposure to PCBs 126 and 153 on anterior pituitary and thyroid hormones and FSH isoforms in adult Sprague Dawley male rats. Toxicol Sci. 1999; 47: 158-169.

76. Yamamoto M, Shirai M, Sugita K, Nagai N, Miura Y, Mogi R. Effects of maternal exposure to diethylstilbestrol on the development of the reproductive system and thyroid function in male and female rat offspring. J Toxicol Sci. 2003; 28: 385-394.

77. Boas M, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. Eur J Endocrinol. 2006; 154: 599-561.

78. Meeker JD, Calafat AM, Hauser R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Technol. 2010; 44: 1458-1463.

79. Miao M, Yuan W, Yang F, Liang H, Zhou Z, Li R, et al. Associations between íbisphenol A exposure and reproductive hormones among female workers. Int J Environ Res Public Health. 2015; 12: 13240-13250.

80. Liang H, Xu W, Chen J, Shi H, Zhu J, Liu X. The association between exposure to environmental bisphenol A and gonadotropic hormone levels among men. PLoS One. 2017; 12: e0169217.

81. Andrianou XD, Gangler S, Piciu A, Charisiadis P, Zira C, Ariatidou K, et al. HF and chlorinated bisphenol A derivatives and thyroid function. Plowman exposures to bisphenol A derivatives and thyroid function. PLoS One. 2016; 11: e0155237.

82. Xu G, Han A, Xu N, Su P. Effects of maternal exposure to bisphenol A during pregnancy on puberty in advance and hypothalamo-pituitary-gonadal axis hormones level in female offspring. Wei Sheng Yan Jiu. 2018; 47: 425-431.

83. Hart RJ, Doherty DA, Keelan Ja, Minaee NS, Thorstensen EB, Dickinson JE, et al. The impact of antenatal Bisphenol A exposure on male reproductive function at 20-22 years of age. Reprod Biomed Online. 2018; 36: 340-347.

84. Fernandez MO, Bourguignon NS, Arocena P, Rosa M, Libertun C, Lux-Lantos V. Neonatal exposure to bisphenol A alters the hypothalamic-pituitary-thyroid axis in female rats. Toxicol Lett. 2018; 285: 81-86.

85. Csaba G. The present and future of human sexuality: impact of faulty perinatal hormonal imprinting. Sex Med Rev. 2017; 5: 163-169.

86. Csaba G. Hormonal imprinting: phylogeny ontogeny, diseases and possible role in present-day human evolution. Cell Biochem Funct. 2008; 26: 1-10.

87. Csaba G. The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics. 2011; 2: 187-196.

Citation: Csaba G and Shahin MA. Receptorial and Functional Overlapping between Thyrotropin (TSH) and Gonadotropins (FSH, LH): Phylogenetic, Ontogenetic and Clinical Application Aspects. Annals Thyroid Res. 2018; 4(3): 158-163.