Neuroendocrinology Letters Volume 41 No. 3 2020
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

REVIEW ARTICLE

Possible role of gonadotropin excess in age–related diseases – return to the old hypothesis in the light of current data

Marek Pawlikowski[1], Katarzyna Winczyk[2]

1 Department of Immunoendocrinology, Medical University of Lodz, Poland.
2 Department of Neuroendocrinology, Medical University of Lodz, Poland.

Correspondence to: Prof. Katarzyna Winczyk MD, PhD
Department of Neuroendocrinology, Medical University of Lodz 251/A1
Pomorska Str., 92-213 Lodz, Poland
tel.: +48 42 201 42 99; e-mail: katarzyna.winczyk@umed.lodz.pl

Submitted: 2020-06-22 Accepted: 2020-08-02 Published online: 2020-08-12

Key words: **FSH; LH; Alzheimer's disease; osteoporosis; cardiovascular diseases; cancer; aging**

Neuroendocrinol Lett 2020; **41**(3):118–122 **PMID:** 33201648 NEL410320R01

Abstract

The paper presents the evaluation of a hypothesis assuming that the elevated levels of gonadotropins which occur physiologically in older persons are involved by their direct extra-gonadal action in the pathogenesis of age–related disorders. The data on the possibilities of the direct action of follicle–stimulating hormone (FSH) and luteinizing hormone (LH) and their possible deleterious effects in the brain, bone, cardiovascular system and cancer in older persons are reviewed. A proposal of a new approach to the hormonal prevention treatment of age–related disorders (suppression of gonadotropins by means of gonadotropin releasing hormone analogs) is discussed.

INTRODUCTION

Human aging is characterized by deep alterations of hormone secretion. Among others, the gonadal steroid hormones undergo a sharp decrease, especially in women. The gonadal hormone deficiency, although less pronounced, is also present in men. This decrease is generally thought to contribute to the progression of aging. On the other hand, the enhanced secretion of gonadotropins in older subjects, resulting from the drop of gonadal steroids connected with the well–known feedback mechanism, has been considered for a long time as not meaningful. One of authors of the present paper proposed several years ago a hypothesis, claiming that the gonadotropin excess in the elderly may contribute to the aging process and the pathogenesis of age–related diseases (Pawlikowski, 1994). The hypothesis is based on the available data showing the possibility of the direct extra–gonadal action of both – follicle stimulating hormone (FSH) and luteinizing hormone (LH) and the observations demonstrating that the experimental procedures leading to the anti–aging effects, like caloric restriction (Campbell *et al.* 1977, Pierpaoli 1977) or melatonin treatment (Pierpaoli *et al.* 1990) also diminish the gonadotropin secretions. The early studies supporting the possibility of the direct extra–gonadal action of gonadotropins showed the morphological effects of FSH and LH administration on sympathetic ganglionic cells (Pawlikowski 1962) and adrenal cortex (Roels 1963; Mikolajczyk & Pawlikowski 1965; Mikolajczyk 1967) in gonadectomized–hypophysectomized rats. Because of numerous newer data on the direct extra–gonadal actions of gonadotropins and their possible involvement in the pathogenesis of age–related disease we re–evaluate our hypothesis.

EVIDENCE OF DIRECT EXTRA–GONADAL ACTION OF FSH

The presence of FSH receptors (FSHR) was revealed by means of molecular biology techniques, in the following cells beyond the reproductive system: monocytes (Robinson *et al.* 2010) and osteoclasts (Sun *et al.* 2006; Robinson *et al.* 2010), chondrocytes (Kong *et al.* 2018), yellow and brown fat cells (Liu *et al.* 2015). The above receptors were shown to be active by additional experiments. The follicle–stimulating hormone increases in vitro expression of the genes involved in osteoclasts function (Rank, Trap, Mmp–9, cathepsin K) (Wang *et al.* 2018). This pituitary hormone was also shown to accelerate lipid droplet formation, to increase the leptin and to lower adiponectin secretion from the human adipocytes in culture (Liu *et al.* 2015). Moreover, FSH stimulates the release of interferon gamma (Yousefi *et al.* 1993), interleukin–6 (Komorowski & Stepien 1994) and tumour necrosis factor – α (Musabak *et al.* 2003) from monocytes in vitro. Besides, follicle–stimulating hormone receptors (FSHR) were also demonstrated by immunohistochemistry in the endothelia of peri–tumoral and intra–tumoral blood vessels in several human cancers, in contrast the endothelia of vessels situated in non–malignant tissues do not express FSHR (Radu *et al.* 2010, for review see: Ghinea 2018). Since FSH is known to stimulate the neo–angiogenesis in its "canonical" targets, i.e. the reproductive organs (Reisinger *et al.* 2007) it seems reasonable to suppose that FSHR–positive blood vessels represent the vasculature formed through tumoral neo–angiogenesis. Although the FSHR immunopositivity was revealed also in cells of several malignant tumours of endocrine origin (for review see: Pawlikowski 2018) the specificity of the used antibodies was considered as doubtful (Chrusciel *et al.* 2019).

EVIDENCE OF DIRECT EXTRA–GONADAL ACTION OF LH

Common receptors for LH and chorionic gonadotropin (LH/CGR) were revealed in the adrenal cortex by means of molecular biology techniques (Pabon *et al.* 1996, Feelders *et al.* 2003; Nicolini *et al.* 2014) or by immunohistochemistry (Lasley *et al.* 2016; Korol *et al.* 2019). The functionality of adrenocortical LH/CGR was documented by in vitro effects of the chorionic gonadotropin on cortisol (Feelders *et al.* 2003) and aldosterone (Nicolini *et al.* 2014) secretion. LH/CGR mRNA and protein were found in the rat brain (Lei *et al.*1993; Al-Hader *et al.* 1997a; Apaja *et al.* 2004) and in the rat glial cells and hypothalamic neurons GT–1 cultured in vitro (Lei *et al.* 1994; Al-Hader 1997b). Although there are no data on the expression of LH/CGR in monocytes, LH like FSH, stimulates the IL–6 secretion from these cells (Komorowski & Stepien 1994). LH/CGR are also shown to be expressed in the breast cancer cells (Ziecik *et al.* 2005; Sanchez *et al.* 2016) and the toxic ligand of this receptor, Hecate peptide – chorionic gonadotropin beta subunit conjugate, destroys the mammary cancer cells in culture (Bodek *et al.* 2003).

INVOLVEMENT OF GONADOTROPINS IN THE AGE–RELATED DISEASES

Mental disabilities including Alzheimer's disease

It is well known that the advancing age is connected with more or less pronounced regression of the cognitive functions, including the increased risk of the Alzheimer's disease. The negative effects of excessive LH on cognitive functions in older people were reported in many studies (for review see Webber *et al.* 2007; Batha *et al.* 2018). A direct deleterious action of LH on neuronal brain structures via brain LH/CGR was suggested. Higher LH levels were found in the patients suffering from Alzheimer's disease in comparison to non–Alzheimer controls (Short *et al.* 2001). Moreover, LH was shown to enhance the production of beta–amyloid, pathological protein characteristic for Alzheimer's disease (Verdile *et al.* 2015). In rats chorionic gonadotropin was shown to decrease spatial memory and to increase beta–amyloid levels (Verdile *et al.* 2008). In mice the genetic ablation of LH/CGR results in diminution of beta–amyloid accumulation in the brain (Lin *et al.* 2012). Although the link between elevated LH and cognitive disorders is now generally accepted in the literature, there are also negative observations (Hogervorst *et al.* 2003; Hu *et al.* 2017). It seems probable that the deleterious effect of LH in the brain depends on age and/or LH/FSH ratio. Rodrigues *et al.* (2008) observed that in non–demented older women high LH levels were associated with a lower cognitive score, but disproportionally well-preserved cognitive functioning was found for the oldest women who had very high levels of FSH. In our study, no significant relations were found between LH or FSH levels and mental ability scores of older (over 75 yrs old) patients, but a negative correlation was observed between LH/FSH ratio and clock drawing test (CDT) results in women (Pawlikowski *et al.* 2020).

Osteoporosis

Another great health problem associated with older age, mostly in women, is osteoporosis. Although osteoporosis is considered mostly as a result of oestrogen deficiency, the role of elevated FSH acting via FSHR expressed on osteoclasts should be also considered (Sun *et al.* 2006; Robinson *et al.* 2010). FSH serum concentrations in postmenopausal women with osteoporosis are increased in comparison to the respective controls (Chin 2018).

Age–related obesity and weight loss

The body weight gain is a common phenomenon in women in early postmenopausal age. The same

is observed also in middle–aged men. Liu *et al.* (2015) assumed that this body mass change is a result of a direct action of elevated FSH on the fat tissue. The quoted authors showed the positive correlation on the body mass index (BMI) in women in the early postmenopausal age (51–59 yrs.) as well as in men aged 61–69 yrs. In contrast, in a very advanced age a body weight loss is rather observed. Although this phenomenon may have many different causes, like loss of the appetite or impaired intestinal absorption, the role of elevated gonadotropins cannot be neglected. In our study we found a negative correlation of both FSH and LH levels with body mass index in older (> 75 years old) women (Pawlikowski *et al.* 2019). It is possible that the action of gonadotropin receptors in the fat cells is shifted from lipogenesis to lipolysis with advancing age, but this presumption needs further investigation.

Cardiovascular diseases

There are many papers showing that high FSH levels increase the risk of cardiovascular diseases including atherosclerosis in women (for review see: Lizneva *et al.* 2019). In the men treated for the prostate cancer with androgen deprivation therapy (ADT), FSH has been suggested to increase the risk of atherosclerosis, insulin resistance and metabolic syndrome (Crawford *et al.* 2017). It was suggested that these effects of FSH result from the activation of monocytes which infiltrate the atherosclerotic plaques. Activated monocytes enhance, in turn, the activation of osteoclasts, which resorb calcified areas and provoke the atherosclerotic plaque instability (Crawford *et al.* 2017). On the other hand, the over–secretion of LH may contribute to the development of arterial hypertension. As it was described above, all adrenocortical layers express the LH/CGR. Thus, the elevated levels of LH may overstimulate the above – mentioned receptors. Because the age–related atrophy concerns zona reticularis, but neither aldosterone–secreting zona glomerulosa nor cortisol–secreting zona fasciculata (Pawlikowski 2005), the overstimulation of LH/CGR leads exclusively to aldosterone and cortisol hypersecretion (Saxena and Seely 2012). Both above mentioned hormones are known to be involved in the pathogenesis in arterial hypertension. LH may also stimulate the aldosterone secretion from the Conn's adrenocortical adenomas (aldosteronomas), because these tumours also contain the active LH/CGR (Nicolini *et al.* 2014).

Cancer

The aging is also connected with the increased risk of cancer. Although there are no studies on the relationship of gonadotropin excess with the cancer incidence in older people, FSH is suggested to increase the tumour neovascularization and in consequence, to accelerate the tumorigenesis (Papadimitrou *et al.* 2016; Ghinea 2018). Inhibition of FSHR as a novel therapeutic procedure in oncology is suggested (Papadimitrou *et al.* 2016; Ghinea 2018; Pawlikowski 2018). Because of the expression of LH/CGR in the breast cancer cells (Ziecik *et al.* 2005; Sanchez *et al.* 2016), it can be presumed that the LH excess may also enhance the cancer incidence in postmenopausal women.

CONCLUDING REMARKS AND PERSPECTIVES OF THERAPEUTIC APPLICATIONS

Summing up, there is a bulk of the data indicating the involvement of the elevated gonadotropin levels in pathogenesis of age–related diseases in humans. Although the further studies of this problem are urgently needed, a novel approach of therapeutic interventions in the aging should be considered, namely the suppression of the elevated gonadotropin levels. So far, the most known therapeutic interventions in aging–related disorders is the replacement with the gonadal hormones, mostly of oestrogens in women. It is worth to recall that their beneficial effects might, at least partially, depend on gonadotropin suppression. Such replacement procedures, for instance the administration of oestrogens in postmenopausal women, have important limitations. On the first place the increased risk of the breast cancer and cardiovascular complications connected with enhanced blood coagulation can be indicated. The compounds which suppress the elevated gonadotropin levels and at the same time decrease a risk of cardiovascular pathology and neoplasia may be optimal in the prevention and treatment of age–related disorders. The GnRH analogues seem to be the best candidates for the clinical attempts in this respect. These compounds have been used for many years in the human therapy, mostly in the treatment of the prostatic cancer (for review see: Salciccia *et al.* 2016). Their effectiveness in suppressing of gonadotropins and their safety is well known. The treatment with GnRH analogues is already suggested but limited so far to the Alzheimer's disease (Casadesus *et al.* 2006). The preclinical studies on the animal models of Alzheimer's disease were performed using the GnRH antagonist Cetrorelix with promising effects (Telegdy *et al.* 2009; 2010). Moderate encouraging effects were observed in a preliminary clinical study using another GnRH analogue leuprolide acetate in women suffering from the Alzheimer's disease (Bowen *et al.* 2015).

We presume that the suppression of elevated gonadotropins possibly will be more effective in the prevention than in the treatment of age–related diseases. However, such presumption needs further intensive studies to be approved in the clinical practice.

DECLARATION OF CONFLICTING INTEREST

The authors declare that there are no conflicts of interest.

FUNDING

This work was supported by the Medical University of Lodz.

REFERENCES

1 Al-Hader AA, Lei ZM, Rao CV (1997a). Neurons from fetal rat brains contain functional luteinizing hormone / chorionic gonadotropin receptors. Biol Reprod. **56**: 1071–1076.
2 Al-Hader AA, Lei ZM, Rao CV (1997b). Novel expression of functional luteinizing hormone/chorionic gonadotropin receptors in cultured glial cells from neonatal ret brains. Biol Reprod. **56**: 501–507.
3 Apaja PM Hariu KT, Aatysinki JT, Petaja-Repo UE et al. (2004). Identification and structural characterization of the neuronal luteinizing hormone receptor associated with sensory systems. J Biol Chem. **273**: 1899–1906.
4 Batha S, Blair JA, Casadesus G (2018). Luteinizing hormone involvement in aging female cognition: not all is estrogen loss. Front Endocrinol. **9**: 544 doi:10.3389/fendo.201800544.
5 Berry A, Tomidokoro Y, Ghiso J, Thornton J (2008). Human chorionic gonadotropin (a luteinizing hormone homologue) decreases spatial memory and increases brain amyloid – beta levels in female rats. Horm Behav. **54**: 142–154.
6 Bodek G, Rahman NA, Zalewska M Sollymani R et al. (2003). A novel approach of targeted ablation of mammary carcinoma cells through luteinizing hormone receptors using Hecate-CGbeta conjugate. Breast Cancer Res Treat. **79**: 1–10.
7 Bowen RL, Perry G, Xionng C, Smith MA et al. (2015). A clinical study of lupron depot in the treatment of women with Alzheimer's disease: preservation of cognitive function in patients taking an acetylcholinesterase inhibitor and treated with high dose lupron over 48 weeks. J Alzheimer's Dis. **44**: 549–560.
8 Casadesus G, Garrett MR, Webber KM, Hartzler AW et al. (2006). The estrogen myth: potential use of gonadotropin releasing hormone agonists for the treatment of Alzheimer's disease. Drugs RD **7**: 187–193. doi:10.2165/00126839-200607030-00004.
9 Campbell GA, Kurcz M, Marshall S, Meites J (1977). Effect of starvation in rats on serum levels of follicle stimulating hormone, luteinizing hormone and prolactin in response to LH-releasing hormone. Endocrinology. **100**: 580–585.
10 Chin K-Y (2018). The relationship between follicle–stimulating hormone and bone health: alternative explanation for bone loss beyond oestrogen? Int J Med Sci. **15**: 1373–1383.
11 Crawford ED, Schally AV, Pinthus JH, Block NL et al. (2017). The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy. Urol Oncol **35**: 183–191
12 Chrusciel M, Ponikwicka-Tyszko D, Wolczynski S, Huhtaniemi I et al. (2019). Extragonadal FSHR expression and function-is it real? Front Endocrinol. 10.32 doi10.3389/fendo.2019.00032
13 Feelders LA Lamberts SW, Hofland LJ, van Koetsfeld PM et al. (2003). Luteinizing hormone (LH)-responsive Cushing's syndrome: the demonstration of LH receptor messenger ribonucleic acid in hyperplastic adrenal cells which respond the chorionic gonadotropin and serotonin agonists in vitro. J Clin Endocrinol Metab. **88**: 230–237.
14 Ghinea N (2018). Vascular endothelial FSH receptor, a target of interest for cancer therapy. Endocrinology. **159**: 3268–3274.
15 Hogervorst E, Combrinck M, Smith AD (2003). Testosterone and gonadotropin levels in men with dementia. Neuro Endocrinol Lett. **24**: 203–208.
16 Hu J, Chu K, Song Y, Chatooah ND et al. (2017). Higher level of circulating estradiol is associated with lower frequency of cognitive impairment in Southeast China. Gynecol Endocrinol. **33**: 840–844.
17 Komorowski J, Stepien H (1994). FSH and LH induce interleukin-6 (IL-6) release from human peripheral blood monocytes cultured in vitro. A dose–response study. Horm Metab Res. **26**: 438–439.
18 Kong D, Guan Q, Li G, Xin W et al. (2018). Expression of FSHR in chondrocytes and the effect of FSH on chondrocyte. Biochem Biophys Res Commun. **495**: 587–693.
19 Korol P, Jaranowska M, Pawlikowski M (2019). Immunohistochemical demonstration of LH/CG receptors in non-neoplastic human adrenal cortex and adrenocortical tumors. Folia Histochem Cytobiol. **57**: 23–27.
20 Lasley B, Conley A, Morrison J, Rao CV (2016). Identification of immunoreactive luteinizing hormone receptors in the adrenal cortex of the female rhesus macaque. Reprod Sci. **23**: 524–530.
21 Lei ZM, Rao CV, Kornyei JL et al. (1993). Novel expression of human chorionic/ gonadotropin / luteinizing hormone receptor gene in brain. Endocrinology. **132**: 2262–2270.
22 Lei ZM, Rao CV (1994). Novel presence of luteinizing hormone / human chorionic gonadotropin (hCG) receptors and the down regulating action hCG on gonadotropin releasing hormone gene expression in immortalized hypothalamic GT 1-7 neurons. Mol Endocrinol. **8**: 111–121.
23 Lin J, Li X, Yuan F, Lin L et al. (2010). Genetic ablation of luteinizing hormone receptor improves the amyloid pathology in a mouse model of Alzheimer disease. J Neuropathol Exp Neurol. **69**: 253–261.
24 Liu XM, Chan HC, Ding GL, Cai J et al. (2015). FSH regulates fat accumulation and redistribution in aging through the Gαi/ Ca(2+) / CREB/ pathway. Aging Cell. **14**: 409–420.
25 Lizneva D, Rahimova A, Kim SM, Atabiekov I et al. (2019). FSH Beyond Fertility. Front Endocrinol. (Lausanne). **10**: 136. doi: 10.3389/fendo.2019.00136. eCollection 2019.
26 Mikolajczyk H, Pawlikowski T (1965). Histologic changes in the adrenal cortex of hypophysectomized-gonadectomized rats treated with gonadotrophins and adrenocorticotropin. Endokrynol Pol. **16**: 359–369.
27 Mikolajczyk H (1967). Possible synergic influence of ACTH and FSH on the adrenal cortex in hypophysectomized–gonadectomized rats. Nature. **213**: 806–807.
28 Musabak U, Bolu E, Ozata M, Oktenli C et al. (2003). Gonadotropin treatment restores in vitro interleukin 1β and tumour necrosis factor – α production by stimulated peripheral blood mononuclear cells from patients with idiopathic hypogonadotropic hypogonadism. Clin Exp Immunol. **132**: 265–270.
29 Nicolini G, Balzan S, Morelli L Iacconi P et al. (2014). LH, progesterone and TSH can stimulate aldosterone in vitro: a study on normal adrenal cortex and aldosterone producing adenoma. Horm Metab Res. **46**: 318–321.
30 Pabon JE, Li X, Lei ZM, Sanfilippo JS et al. (1996). Novel presence of luteinizing hormone/chorionic gonadotropin receptors in human adrenal glands. J Clin Endocrinol Metab. **81**: 2397–2400.
31 Papadimitriou K, Kouniourakis P, Kottorou AE, Antonacopoulou AC et al. (2016). Follicle stimulating hormone receptor (FSHR): a promising tool in oncology? Mol Diagn Ther. **20**: 523–530.
32 Pawlikowski M (1962). The effect of gonadal and gonadotropic hormones in the prostatic ganglion and superior cervical ganglion in the male white rats. Acta Medica Polona. **31**: 71–183.
33 Pawlikowski M (1994). Is gonadotropin excess involved in the process of aging? A hypothesis. Folia Medica Lodzensia. **21**: 137–145.
34 Pawlikowski M (2005). Adrenal cortex-the next biological clock? Neuroendocrinol Lett. **26**: 193–195.
35 Pawlikowski M (2018). Expression of follicle stimulating hormone receptors (FSHR) in intra-tumoral vasculature and in tumoral cells – the involvement in tumour progression and the perspectives of application in cancer diagnosis and therapy. Endokrynol Pol. **69**: 192–195.
36 Pawlikowski M, Kostka T, Pisarek H, Guligowska A et al. (2019). Gonadotropin and steroid hormones in older people: their mutual connections and relations to body mass indices. Endokrynol Pol. **70**: 484–488.
37 Pawlikowski M, Kostka T, Pisarek H, Pigłowska M, et al. (2020). Are physical and mental abilities of older people related to gonadotropin and steroid hormone levels? Neuroendocrinol Lett. **41**: 101–106.
38 Pierpaoli W (1977). Changes of hormonal status in young mice by restricted caloric diet Relation to lifespan extension. Experientia. **33**: 1612–1613.

39 Pierpaoli W, Dell Ara A, Pedrinis E, Regelson W (1990). The pineal control of aging. Ann NY Acad Sci. **719**: 291–313.
40 Radu A, Pichon C, Camparo P, Antoine M et al. (2010). Expression of follicle stimulating hormone receptor in tumor blood vessels. N Engl J Med. **363**: 1621–1630.
41 Reisinger K, Baal N, McKinnen T, Munstedt K et al. (2007). The gonadotropins: tissue specific angiogenic factors? Mol Cell Endocrinol. **269**: 65–80.
42 Robinson LJ, Tourkova J, Wang Y, Sharrow AC et al. (2010). FSH-receptor isoforms and FSH-dependent genes transcription in human monocytes and osteoclasts. Biochem Biophys Res Commun. **394**: 12–17.
43 Rodrigues MA, Verdile G, Foster JK, Hogervordt E et al. (2008). Gonadotropins and cognition in older women. J Alzheimers Dis. **13**: 267–274.
44 Roels H (1963). The effect of some pituitary hormones on volume and DNA content of cell nuclei of the adrenal cortex in hypophysctomized-castrated rats. Exp Cell Res. **31**: 407–415.
45 Salciccia S, Gentilucci A, Cattarino S, Sciarra A (2016). GnRH – agonist or antagonist in the treatment of prostate cancer: a comparison based on oncological results. Urologia. **83**: 173–178.
46 Sanchez AM, Flamini MI, Russo E, Casarosa E et al. (2016). LH and FSH promote migration and invasion properties of a breast cancer line through regulatory actions on the actin cytoskeleton. Mol Cell Endocrinol. **437**: 22–34.
47 Saxena AR, Seely EW (2012). Luteinizing hormone correlates with adrenal function in postmenopausal women. Menopause. **19**: 1280–1283.
48 Sun L, Peng Y, Sharrow AC, Iqbal J et al. (2006). FSH directly regulates bone mass. Cell. **126**: 247–260.
49 Short RA, Bowen RL, O'Brien PC, Graff–Radford NR (2001). Elevated gonadotropin levels in patients with Alzheimer disease. Mayo Clin Proc. **76**: 906–909.
50 Telegdy G, Tanaka M, Schally AV (2009). Effects of the LHRH antagonist Cetrorelix on the brain function in mice. Neuropeptides. **43**: 229–234.
51 Telegdy G, Adamik A Tanaka M, Schally AV (2010). Effects of the LHRH antagonist Cetrorelix on affective and cognitive functions in rats. Reg Pept. **59**: 142–147.
52 Wang J, Zhang W, Yu C, Zhang X et al. (2015). Follicle stimulating hormone increases the risk of post menopausal osteoporosis by stimulating osteoclast differentiation. PLOSOne. **10**: e0134986, doi: 10.1371/journal.pone.013498637.
53 Webber KM, Casadesus G, Bowen RL, Perry G et al. (2007). Evidence for the role of luteinizing hormone in Alzheimer disease. Endocr Metab Immune Disord Drug Targets. **7**: 300–303.
54 Verdile G, Yeap BB, Clarnette RM, Dhaliwal S et al. (2008). Luteinizing hormone levels are positively correlated with plasma amyloid-beta protein levels in elderly men J Alzheimer Dis. **14**: 201–206.
55 Verdile G, Asih PR, Barron AM, Wahjoepramono EJ, et al. (2015). The impact of luteinizing hormone and testosterone on beta-amyloid (Aβ) accumulation: animal and human clinical studies. Horm Behav. **76**: 81–90.
56 Yousefi S, Karamiou K, Vaziri N, Carandang G et al. (1993). The effect of gonadotropins on the production of human interferon-gamma by mononuclear cells. J Interferon Res. **132**: 213–220.
57 Ziecik AJ, Bodek G, Blitek A, Kaczmarek M, et al. (2005). Nongonadal LH receptors, their involvement in female reproductive function and a new applicable approach. Vet J. **169**: 75–84.