

Commentary

Could Luteinizing Hormone be Involved in the Maladies of Elderly Women?

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Women are living longer in industrialized societies due to better health care, diet, healthy life style choices, regular exercise, etc. As a result, a greater number of women are surviving into their 80s, 90s and beyond. These increases are coming with higher incidences of several life threatening and non-life threatening illnesses. However, these illnesses are not a part of normal aging. Conventional wisdom suggests that estrogens are involved in endometrial carcinoma development and their deficiency was responsible for Alzheimer's disease and others like, hot flashes, vaginal dryness/dyspareunia, mood changes, depression, anxiety, memory and cognitive losses. This wisdom now requires upending due to scientific advances, which suggests that luteinizing hormone (LH), could be potentially involved in these illnesses.

As women age, their ovarian activity progressively declines. This decline is reflected by a fall in the circulating estrogen (estradiol and estrone) levels. The fall relieves the negative feedback inhibition that estrogens exert on the release of LH and follicle stimulating hormone (FSH) from the anterior pituitary gland. As a result, the levels of both these hormones increase. LH is structurally and functionally similar to human chorionic gonadotropin (hCG) and they bind to the same cell surface G-protein coupled receptors [1,2]. These receptors have now been found to be widely distributed in the body [3]. Some of the non-gonadal tissues that contain them include endometrium, cervix, brain, skin, adrenal glands, fat, pancreas, vasculature in the target tissues, etc [3-7]. Like LH and hCG, FSH is a glycoprotein hormone, but it is not structurally and functionally related to them [1]. FSH bind to distinct cell surface G-protein coupled receptors, which are also present in non gonadal tissues [8]. But they have not been as extensively investigated as the LH/hCG receptors.

Type 2 endometrial carcinomas are primarily seen in elderly women, who have low circulating estrogen and high LH levels [9,10]. The LH levels are further elevated in women who develop endometrial carcinomas as compared with those who do not develop the disease [11,12]. LH/hCG receptors are over expressed in endometrial carcinomas as compared with pre and post-menopausal endometrial [13]. The receptor activation in primary and immortalized endometrial

carcinoma cells results in an increased cell proliferation, invasion, activation of β_1 integrin receptors and increased metalloproteinase-9 secretion in an active form [14,15]. Treatment with gonadotropin releasing hormone agonist (GnRHa) results in growth inhibition, which is independent of GnRH receptors [16].

Estrogens cannot be mitogens in type 2 endometrial carcinomas, as they do not contain estrogen receptors [9, 10]. Yet they can still play an important role in the disease development by further enhancing the LH release from anterior pituitary gland [17]. The estrogens come from aromatization of androgens in fat and endometrial carcinoma tissues [17]. LH actions in ovaries and adrenals increase the secretion of androgens, the actions in fat and endometrial carcinoma increases the aromatization and the actions on pancreas increases the secretion of insulin [17]. Insulin on its own can also increase ovarian secretion of androgens and aromatization in fat and endometrial carcinoma tissues [17]. Recently, type 2 endometrial carcinomas have been reclassified as LH dependent disease and type 1 as LH independent disease [18].

Estrogens are neuroprotective and their deficiency in elderly women has been suspected to play a role in Alzheimer's disease development [19]. This led to the use of estrogen replacement therapy (ERT) for women with Alzheimer's disease. But the results were inconclusive [19]. The Women's Health Research Initiative Memory Study (WHIMS) with 4894 women, revealed that hormone replacement therapy (HRT, consisting of estrogen plus progestin), did not prevent the cognitive decline [20,21]. In fact, it exacerbated the dementia in some women [20,21]. The failure appears to be the timing of therapy. Thus, while HRT could have worked if it is administered shortly after the onset of menopause, it fails if there is a time delay. In fact, HRT was administered years after the menopause onset in many women in WHIMS trials [20,21]. The failure suggested to be due to neurological damage, which increases with an advancing age in Alzheimer's disease patients.

The above results led to the realization that Alzheimer disease development could be related to chronic elevation of LH levels. In support of this possibility, the elderly women who develop Alzheimer's disease have an increased LH levels as compared with the cohorts who do not develop the disease [22,23]. Epidemiological studies have also confirmed that an increased Alzheimer's disease risk in women parallels higher LH levels [22,23]. Hippocampus, the region most affected in Alzheimer's disease, contains the highest LH/hCG receptor density [4]. An activation of these receptors by LH/hCG treatment results in hallmark changes that are characteristic of Alzheimer's disease [24-32]. These are, increase in amyloidogenic precursor protein metabolism towards an amyloidogenic pathway, increase in β secretase activity, increase in amyloid β protein levels and their deposition in brain [24,26,30]. Increasing LH levels by ovariectomy induces similar biochemical changes as well as

impairment of the memory and cognition [27,33]. Decreasing the elevated LH levels by treatment with GnRH results in their reversal [29, 33]. Studies on transgenic Alzheimer's disease animal model further reaffirmed the causative role of LH in the disease [26].

The prevalence of hot flashes, vaginal dryness/dyspareunia, mood changes, depression, anxiety cognitive and memory losses, increase from premenopausal transition period and can persist for as long as 10 or more years [34]. The relief of symptoms provided by ERT (hysterectomized patients) or HRT (patients with uterus) supports the theory that estrogen deficiency was responsible for these illnesses [34]. But the theory now requires revisiting, because falling estrogens are accompanied by an increase in LH levels and ERT/HRT can bring down these levels. The tissues that are affected in these illnesses (skin and blood vessels in hot flashes and brain in mood, memory, depression and anxiety) are LH/hCG receptor positive and potentially elevated LH levels can activate these receptors [4-6].

We do not know whether vaginal tissue contains LH/hCG receptors. But it is not farfetched idea that it does, as uterus and cervix, which are its anatomical continuations, contain these receptors [3, 7].

There is good evidence that LH is involved in the development of Cushing's syndrome in elderly women [35]. These women also have an increased cardiovascular disease and metabolic syndrome [36]. These were thought to be related to functional changes in adrenals due to elevated LH levels [36]. The levels are positively correlated with urinary free cortisol and negatively with aldosterone secretion [36]. Nothing beyond is known at this time.

It is important to determine whether LH is involved in the maladies of elderly women for the following reasons:

- a. GnRH therapy, instead of ERT and HRT, which have side effects, should be used in LH dependent illnesses.
- b. The realization of LH involvement should stimulate further research and discovery path for finding new therapeutic targets in the diseases.
- c. It can also help in coming up a combination therapy with ERT/HRT and GnRH for women, who are in perimenopausal period (1 year before and 2 years after menopause). During this transition period, combination therapy could be more effective than either one of the therapies alone.

The field of LH involvement in the maladies of elderly women is in an embryonic stage and much further research is needed to advance our current understanding.

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