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Short Communication

Neurokinin-3 Receptor Antagonists: A Novel Treatment for Hot Flashes in Postmenopausal Women with Estrogen Contraindication

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The most effective treatment for menopausal symptoms, especially hot flashes, is estrogen. Women with formal contraindications to estrogen have available only a few less effective treatments, such as selective serotonin reuptake inhibitors, gabapentin, pregabalin, clonidine, among others. Some of these women, such as patients with positive estrogen receptors breast cancer, are also under anti-estrogenic treatments that worsen the symptoms**.** For this reason**,** they need an effective medication to control the most troublesome effect of hypoestrogenism:-vasomotor symptoms.

The neurohormonal control of the reproductive axis begins in the hypothalamus**.** It is, therefore, very important to understand how the dynamics of the neurons, hormones and neuropeptides control the performance of the GnRH pulse generator. There are three neuropeptides, secreted by the KNDy neurons in the hypothalamic arcuate nucleus (ARC), that control the pulsatile release of GnRH in mammals: kisspeptin, neurokinin B and dynorphin A. Kisspeptin is a peptide that stimulates GnRH release. Neurokinin B is a peptide from the tachykinin family, in conjunction with neurokinin A and substance P. There are three G-Protein-coupled (GPC) receptors for the tachykinins: NK1, NK2 and NK3. Neurokinin B binds mainly to the NK3 receptor (NK3R). Unlike NK1 and NK2 receptors, expressed in the central and peripheral nervous system, NK3R is usually found in the central nervous system, with some expression in the gut, bladder and reproductive tract [1]. Dynorphin A is a family of endogenous opioid peptides.

The communication between the KNDy neurons in the ARC takes place in an autocrine/paracrine manner through neurokinin B/NK3R and dynorphin A/κ-opioid receptor signaling. It has been hypothesized [2] that neurokinin B, through NK3R, initiates KNDy neuronal activity releasing kisspeptin that stimulates GnRH release through GPR54 (a GPC receptor) in the GnRH neurons. In opposition, Dynorphin A ends KNDy neurons activity via κ-opioid receptors, so, neurokinin B stimulates and dynorphin A terminates GnRH pulse generation through kisspeptin (Figure 1A). The homeostatic mechanism of regulation of reproductive endocrinology is part controlled by the stimulation of the KNDy neurons by neurokinin B and the inhibition by estrogen, so in menopause women, the lack of estrogen leads to an imbalance of this control, especially in certain parts of the brain where these neurons are present, such as the thermoregulatory control center in the median preoptic nucleus [1].

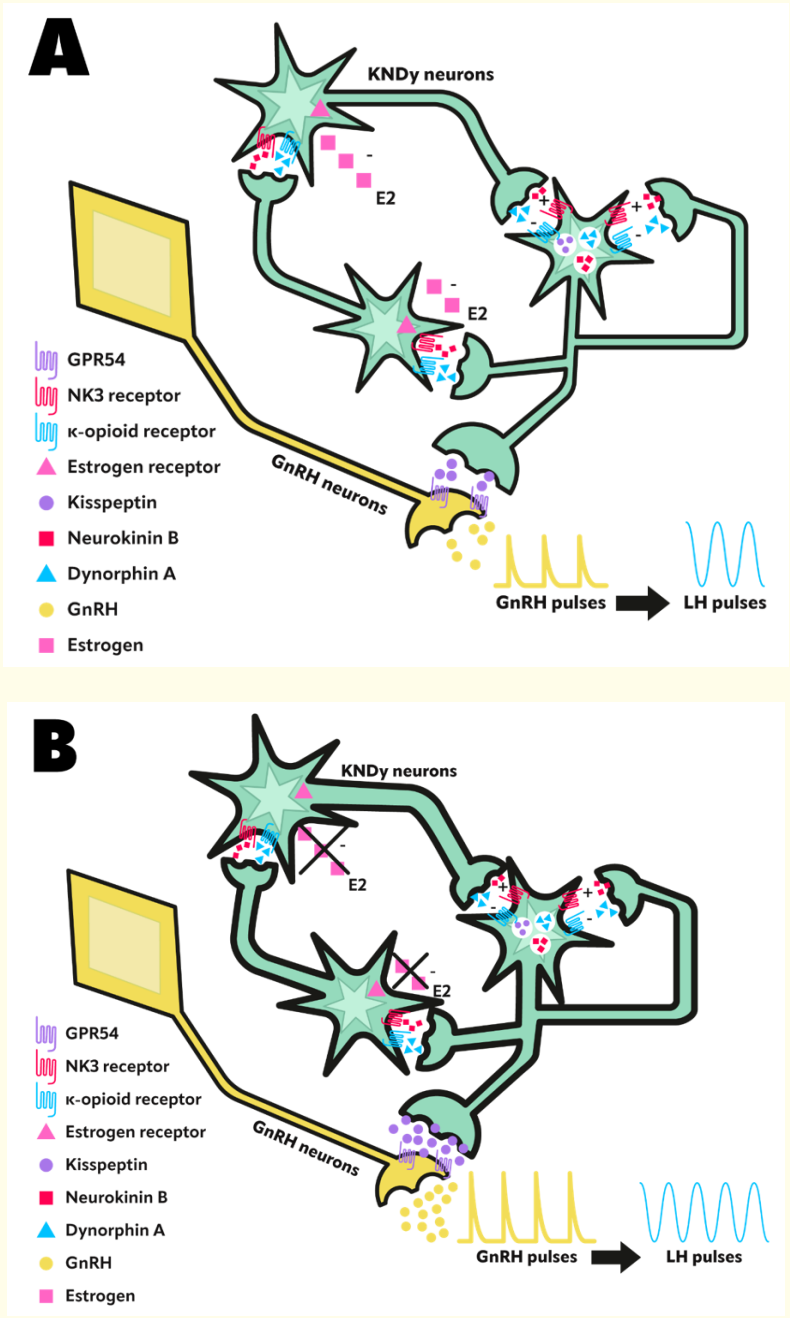

Figure 1: *A. GnRH pulse secretion control by KNDy neurons. Neurokinin B stimulates and dynorphin A inhibits kisspeptin secretion and Kisspeptin stimulates GnRH secretion. Estrogen and Dynorphin A, inhibits kisspeptin secretion. B. Hypoestrogenism causes KNDy neurons hypertrophy with increased Neurokinin B, kisspeptin, GnRH and LH secretion (from 2, modified).*

The menopause is caused by the depletion of the ovarian follicles leading to a diminished estrogen production. This hypoestrogenic state can cause many symptoms, but hot flushes are the most bothering and frequent of them, beginning right after, and sometimes before, the last menstruation. The hot flushes are caused by a dysfunction of the hypothalamic thermoregulator. It has been hypothesized that an increased temperature sensitivity of the thermoregulatory pathways that control heat dissipation mechanisms can trigger the hot flushes [3], with a shift towards a low temperature of the thermoregulatory zone. The pulses of the pituitary gonadotropin LH are closely related to the hot flushes production, and the LH pulses are closely related to GnRH pulses so, since the KNDy neurons are involved in the GnRH pulse generator, are also related to the hot flushes produced by hypoestrogenism.

Hypertrophy of hypothalamic neurons has been observed in menopausal women, specially NKDy neurons (expressing estrogen receptor alpha), and an increase in the expression of NKB and kisspeptin [3], both suppressed by the action of estrogen in women during reproductive life (Figure 1). Estrogen has shown to increase dynorphin mRNA and decrease NKB and kisspeptin expression in animal models. NKDy neurons are projected to the preoptic regions that control heat dissipation effectors. NKB and its receptor (NK3R) have been implicated in hot flushes during menopause, since it has been observed that NKB infusion in patients of reproductive age induces this phenomenon with the same characteristics as those occurring in menopausal patients. Studies in ovariectomized monkeys demonstrated that the enlargement of the hypothalamic neurons and a higher NKB and kisspeptin production are a consequence of the hypoestrogenism. The control of reproductive axis by the estrogen is probably driven through NKDy neurons and the regulation of the GnRH pulse release in the hypothalamus, thus, the lack of estrogen no longer inhibits the neurokinin B stimulation of kisspeptin secretion by the KNDy neurons in the postmenopausal women [3,4].

Julia Prague and colleagues [5] in May 2017 published in *The Lancet*, a randomized Phase 2, double-blind, placebo-controlled study evaluating the use of a neurokinin 3 receptor antagonist (NK3Ra), the MLE4901, in the control of hot flushes in menopausal patients. The results were encouraging because the use of MLE4901 (pavinetant), significantly reduced the number of hot flushes compared to placebo: 49.01 weekly episodes with placebo (95% CI: 40.81 - 58.56) and 19.35 episodes with MLE4901 (15.99 - 23.42), $p < 0.0001$, with a 45% reduction in the vasomotor symptoms. The treatment also reduced severity, associated discomfort and interference in the daily activities with hot flushes. Compliance with treatment was adequate, despite dosing twice daily, and no serious adverse events were reported. A small group of participants had a transient elevation of transaminases, apparently without clinical significance.

In other study, Skorupskaite., *et al*. [6] found a reduction in pituitary LH, but no FSH, secretion after administration of MLE4901 (pavinetant), and a reduction in frequency and severity of hot flushes and sleep disturbance. This provides indirect evidence of a link between NKB pathway with high GnRH pulses and vasomotor symptoms. Studies on pavinetant have been discontinued due to transaminases elevation [7].

Recently, Santoro., *et al*. [8], published a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study (the VESTA study), comparing fezolinetant, a NK3Ra, with placebo, to evaluate efficacy and safety in controlling vasomotor symptoms. More than 80% of the postmenopausal women experiencing moderate/severe vasomotor symptoms, significantly improved response rates and PRO measures of daily life interference, associated symptoms, and health-related quality of life with the use to fezolinetant. There is an ongoing phase 3 trial with fezolinetant (NCT05033886 and EudraCT 2018-003529-27) whose results would be ready by May 2023.

Trower., *et al*. [9], published RELENT-1 study, that was a multicenter, double-blind, randomized, placebo-controlled, multiple-ascending-dose study comparing NT-814 (Elinzanetant), in ascending doses with placebo in 76 postmenopausal women. NT-814 is a dual NK1 and NK3 receptor antagonist, that reduced hot flushes and sleep disturbance symptoms with a 150-daily dose with no safety concerns.

Menown., *et al*. [10], published a systematic qualitative review comparing NK3as and serotonin norepinephrine reuptake inhibitors (SNRIs). NK3as had a higher efficacy and tolerability than SNRIs.

Early and the ongoing studies, with the future availability of these treatments, would allow women with hypoestrogenism, especially after cancer treatment and endocrine treatments -that worsen the symptoms associated with hypoestrogenism- to have an effective solution that guarantees a quality of life and the return to their normal activities despite their condition. Hormonal cancer therapy often must be taken up to 10 years to avoid, in the case of breast cancer, relapses from this disease, so, the management of vasomotor symptoms is an important matter. However, more studies are pending to reassure the efficacy and safety of these drugs to be use them securely in post-menopausal women.

In brief, the availability of NK3Ra is very good news for the treatment of climacteric symptoms in women who want or need a nonhormonal therapy, and a better choice that the available non-hormonal treatment.

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