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NEUROKININ 3 RECEPTOR ANTAGONIST ACTIVITY ON HORMONAL THERAPY FOR MENOPAUSAL HOT FLUSHES

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ABSTRACT

Neurokinin 3 receptors (NK3R) plays a crucial role in menopausal hot flushes, contributing to thermoregulation and vasomotor symptoms. NK3R, found in the central nervous system in brain especially in hypothalamus, peripheral tissues and other course, is activated by neurokinin B (NKB). Hot flushes, impacting nearly 90% of ovariectomized women, involve complex physiological changes linked to estrogen decline. Clinical trials with NK3R antagonists like Fezolinetant show promise in reducing hot flash frequency and severity, May 2023, the FDA-approved non-hormonal fezolinetant for VMS. Presenting non-hormonal alternatives along with the hormonal replacement therapy its complications and benefits. Understanding NK3R's role in thermoregulation provides a basis for targeted therapies, offering relief from menopausal symptoms and improving overall quality of life. Ongoing research aims to establish long-term safety and efficacy, marking a significant advancement in menopausal symptom management are included in this review article. The neurokinin 3 receptor (NK3R) has emerged as a significant target for understanding and potentially treating menopausal symptoms, particularly hot flushes. NK3 receptors are found in various parts of the body, including the brain, gastrointestinal tract and reproductive system. They play a crucial role in regulating body temperature, hormone release, neurotransmission, and inflammation.

KEYWORDS

Tachykinin, G protein coupled receptor, N-terminus, Radiotelemetry, Astellas Pharma and Venous thromboembolism.

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INTRODUCTION

NEUROKININ RECEPTORS (NK) are the three kinds of receptors present in the central nervous system specially located in hypothalamus and brain stem cells which have specific physiology functions.

NEUROKININ 1 RECEPTOR (NK1R)

NK1 RECEPTORS is primarily involved in mediating pain and inflammation responses, as well as regulating mood and emotions.

NEUROKININ 2 RECEPTOR (NK2R)

NK2 RECEPTORS are mainly found in the gastro intestinal tract, where they play role in regulating smooth muscle contraction and secretion.

NEUROKININ 3 RECEPTOR (NK3)

NK3 RECEPTORS are involved in regulation of body temperature, including the occurrences of hot flushes.

Most recently, the neurokinin 3 (NK3) signalling pathway has been implicated in the development of vasomotor symptoms, and researchers are now exploring the potential of pharmacologic agents which modulate NK3 activity to ameliorate menopausal symptoms[1].

MENOPAUSAL HOT FLUSHES

Hot flashes, a hallmark of menopause, often cause sudden heat sensations, sweating, and skin flushing, disrupting daily life. In ovariectomized women, nearly 90% experience these symptoms. The theory suggests that elevated core body temperature may trigger hot flashes by inducing sweating and peripheral vasodilation. The exact cause remains complex, involving factors such as declining estrogen, genetics, lifestyle and individual differences, motivating ongoing research for more effective interventions[2].

A hot flush is marked by a sensation of extreme heat, accompanied by visible signs of skin blood vessel dilation and a subsequent core temperature drop. It results from inappropriate activation of heat dissipation mechanisms, often due to abrupt hormonal changes during menopause, primarily the decrease in estrogen. These thermoregulatory alterations typically persist until the individual adapts to lower estrogen levels, and hot flushes may gradually diminish[3].

Kronenberg's study (1990) of 506 women with hot flashes found that 87% experienced daily symptoms, with one-third reporting over 10 episodes a day lasting 1-5 minutes. Approximately 40% had a premonition of an impending hot flash. Recent research uses ingested radiotelemetry pills for core body temperature measurements, offering faster response times than traditional methods like esophageal and rectal measurements.

During this process, the ingested pill emits signals, which are captured and transmitted through a wire antenna, with data stored in a digital recorder. The recorder samples data at 30-second intervals during the 24-hour transit through the digestive system, providing a comprehensive understanding of core body temperature variations.

Furthermore, the study employs a separate device to document hot flashes, using sternal skin conductance levels as markers. This integration of methods provides a comprehensive understanding of physiological changes and patterns in corebody temperature fluctuations during the testing period[2].

LOCATION AND FUNCTIONS OF NEUROKININ 3 RECEPTOR

We are specifically discussing about neurokinin3 receptors found in the brain particularly in area such as the hypothalamus amygdala and hippocampus and other body parts. They also present in peripheral tissues such as gastrointestinal tract and the reproductive system. NK3R are a subtype of G protein coupled receptor (GPCR) these are specifically activated by the neuropeptide neurokinin B (NKB) (A4). It is now recognized to have a key role in the regulation of gonadotropin releasing hormone (GnRH) secretion in humans and thus acts as a major regulator of the hypothalamopituitary-gonadal (HPG) axis[4] also they are involved in regulating various physiological processes, including neurtransmission, hormone release, and inflammations where they are involved in the modulation of emotional and cognitive processes. We can also call NK3 receptors as tachykinin receptors 3. Substance p (SP), Neurokinin A (NKA), Neurokinin B (NKB) are mammalian neurokinins showing limited selectively towards, respectively, NK-1, NK-2, NK-3 receptors[5].

STUCTURE OF NEUROKININ RECEPTOR

The structure of the nk3 receptor consists of seven transmembrane domains (TMDs) connected by intra-and extracellular loops. The extracellular N-terminus is responsible for ligand binding, while the intracellular C-terminus facilitates signalling through G-protein and other downstream effectors. The TMDs are crucial for maintaining the receptors structural integrity and mediating signal transduction upon ligand binding. It's a protein that is embedded in the cellmembrane. It consists of a chain of amino acids folded into a specific shape that allows it to interact with other molecules, such as neurotransmitters. The specific arrangement of amino acid in the NK3 receptor determines its function and how it responds to various signals in the body[6].

ROLE OF NK3 RECEPTORS IN THERMOREGULATION

Hypothalamic control

The NK3 receptors play a role in the CNS, particularly in the hypothalamus, where they contribute to the regulation of body temperature and help maintain a stable internal environment.

Temperature modulation

Activation of NK3 receptor by NKB influences the hypothalamic control of thermoregulation, affecting heat production and dissipation processes to maintain a stable body temperature.

Menopausal changes and hot flushes

In the context of menopause, the fluctuation in estrogen level can affect the functioning of the hypothalamus, leading to disruptions in thermoregulation and contribuiting to the occurrence of hot flushes.

Therapeutic implications

Understanding the involvement of NK3R in thermoregulation has prompted research into the development of NK3R targeted therapies for conditions involving distrupted body temperature regulation, such as menopausal hot flushes[7].

PHARMACODYNAMIC ACTIVITY

NK3 signaling through its receptors plays a crucial role in the Ensuring a stable hot flash pattern in trials is essential to avoid misattributing spontaneous reductions to a study drug. Most trials required a consistent 50% change over 1-2 baseline weeks, but two SNRI trials failed to assess baseline stability, potentially affecting their reliability. One SNRI and one NK3Ra trial demanded 50 HFs over 7 consecutive days during screening but used the pre-randomization week as baseline, potentially leading to underestimated comparisons.

Development of menopausal vasomotor symptoms (VMS), commonly known as "hot flashes". Excessive NK3 signaling in the brain's preoptic area disrupts thermoregulation, particularly in estrogen-depleted conditions like the post-menopausal state, leading to an excessive heat dissipation response, symptomatic of VMS.

This disruption in thermoregulation emphasizes the intricate connection between hormonal changes and the central nervous system in the emergence of VMS. Understanding these mechanisms is vital for ongoing research aimed at improving interventions to alleviate this common menopausal symptom and enhance the quality of life for individuals experiencing menopause[4].

NK3 RECEPTOR ANTAGONISTS

The first to be tested on people was the NK3R antagonist MLE4901. In a four-week randomised, double-blind, placebo-controlled crossover experiment, women with hot flashes aged 40 to 62 who took MLE4901 orally were treated for four weeks. On day three, the hot flash frequency in women receiving MLE4901 decreased by 72% (95 percent confidence interval [CI], 81.3 to 63.3 percent), while the placebo group only saw a 20% reduction in hot flash frequency. Over the course of the first two weeks of the trial, hot flash frequency and severity improved and eventually stabilised[1].

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Selective Serotonin Reuptake Inhibitors (SSRIs), clonidine, gabapentin and pregabalin are examples of nonhormonal therapy for menopausal

symptoms. When it comes to addressing menopausal symptoms, SNRIs and SSRIs are often the most recommended alternative among them[2].

Senktide injection causes elevated c-Fos expression in the medial preoptic region (mPOA) and Arc in ovariectomized, estrogen-primed rats, especially when administered centrally (intracerebroventricularly). This underscores the function of c-Fos in thermoregulation. The activation of heat dissipation systems is suggested by the increased neuronal activity in the mPOA. Senktide is also able to successfully lower core body temperature without interfering with thermoregulation or cold-induced thermogenesis when infused into the rat median preoptic nucleus[3].

A centrally active competitive antagonist of the human nk3 receptor is called sojonox-653 (sjx-653)[8].

Fezolinetant and NT-814 have been investigated in clinical trials as potential treatments for postmenopausal women's hot flash symptoms. According to Depypere *et al*, (2017), fezoileant, an NK3R antagonist, demonstrated impressive outcomes, reducing hot flush frequency by 93% and severity by 70% (compared to 54% and 23% reduction with a placebo, respectively). Additionally, everyday interference, sleep quality, and functional impairment were among the subjective quality-of-life elements that were improved by fezolinetant treatment[9].

Astellas Pharma created fezolinetant, which will be sold under the Veozah brand. Fezolinetant blocks the neurokinin 3 receptor, which helps the brain regulate body temperature. Veozah is a once-daily 45 mg tablet. It is the first NK3 receptor antagonist medication licenced by the FDA. The FDA mandates liver function tests at the 3-, 6-, and 9-month intervals since the medication is processed in the liver and there may be drug-drug interactions[10].

Elinzanetant (NT-814) is an orally active nk1 and nk3 antagonist that was developed by Bayer, Glaxosmithkline. Its formula is C33 H35 F7 N4 O3 and its molar mass is 668.65g.mol-1. It is administered orally. It relieves sex hormone abnormalities and hot flashes. Phase 2 clinical trials are ongoing[10]. In cycle 1, the median menstrual cycle duration varied between 27.0 and 28.0 days among the treatment groups. Menstrual cycle duration increased significantly with elinezanetant 120mg administration, with a median increase of 7.0days (P =.023). Menstrual cycle length did not alter in the groups treated with elinzanetant 40mg, elinzanetant 80mg, or placebo. Duration of the menstrual cycle and biochemical indicators of ovulation in women receiving a placebo or elinzanetant during the study The duration of the menstrual cycle varied between cycles 1 (C1) and 2 following treatment with placebo (N = 8, red), elinzanetant 40mg (N = 7, blue), 80mg (N = 8, green) and 120mg (N = 8, orange) (C2). * Wilcoxon rank sum test, P <.05. B, the mean variation in menstrual cycle duration (days) between cycles 1 and 2 in healthy women after elinzanetant 40mg (N = 7, blue), 80mg (N = 8, green), and 120mg (N = 8, orange) treatments. The graphs' data also display the group median and interquartile range in addition to within-participant paired raw data. The percentage of healthy women with blood progesterone levels higher than 30nmol/L after cycle 2 with placebo (N = 8 red), elinzanetant 40mg (N = 7 blue), 80mg (N = 8 green) and 120mg (N = 8 orange). Chi-square test, P <.05.

Pavinetant (AZD-2624) –The molar mass of Formula C26 H25 N3 O3 S is 459.56g.mol-1. AstraZeneca and Millendo are developing oral, selective, and active nk3 antagonists. It addresses polycystic ovarian syndrome and hot flushes. Its ineffectiveness led to the discontinuation of its development[11].

MECHANISM OF NK3 RECEPTOR ANTAGONISTS

In hypoestrogenic situations, KNDy neurons release higher concentrations of NKB (menopause). KNDy neurons project to thermoregulatory neurons expressing NK3Rs in the median preoptic nucleus and use NK3 receptors to communicate with one another and control GnRH pulses. Thus, thermoregulatory heat dissipation mechanisms are

inhibited at two sites by NK3R antagonism. Hot flashes are controlled by the NKB and NK3R pathway in the hypothalamus, especially in women going through menopause. GnRH pulses and thermoregulation are impacted by NK3R activation caused by NKB produced by KNDy neurons. Hot flashes are caused in part by increased NKB expression as a result of decreased oestrogen during menopause. Hot flashes are brought on by thermoregulatory neurons activating NK3R, which opens heat dissipation pathways. Hot flash frequency and intensity are decreased when NK3R antagonists, such as pavinetant, are used to block this route[12]. It has been demonstrated that NK-3 receptors may be found in the cerebral cortex and myenteric plexus membranes of guinea pigs, as well as in brain slices from rats and mice[13]. Research on both people and animals has demonstrated that loss-of-function mutations in the genes encoding kisspeptin and NKB, or its receptors, Kiss1r and neurokinin 3 receptor, are the cause of impaired sexual development and infertility (NK3R). The arcuate nucleus (ARC) neurons, also called kisspeptin/NKB/Dyn (KNDy) neurons, are known to co-express dynorphin A, NKB, and kisspeptin[14].

TREATMENT TO CURE

It indicates that neurokinin B, which is frequently co-expressed with kisspeptin in hypothalamic neurons, is important in regulating both systems. The therapy of menopausal hot flashes may benefit from the development of neurokinin B antagonists. These drugs have a noticeable effect on both daytime flushes and sleep disturbances and they show a remarkably quick beginning of action, frequently within the first 1-2 days of use. But more investigation is required to ensure their long-term efficacy and safety. If successful, these innovative therapies could represent a substantial improvement in the management of menopausal hot flashes. There is an increasing demand for safe, effective alternatives to hormone replacement therapy (HRT) for menopausal hot flashes due to the possible hazards involved[3]. Kisspeptin is a neuropeptide that stimulates the hypothalamic-pituitary-gonadal axis and is essential for human reproduction[15].

Over the course of the four-week treatment period, positive effects persisted.

Lessons on hormone replacement therapy and coronary heart disease total four.

First lesson: pay attention to contradictions.

Second lesson: resist the pull of mechanism.

Third lesson: set aside faith

Fourth lesson: continue to be sceptical[16]

Contraindications to hormone replacement treatment (HRT) include endometrial hyperplasia, pregnancy, thrombophilic diseases, venous thromboembolism, arterial thromboembolic illness, endometrial malignancy, and active liver disease. These factors establish if HRT is suitable for a certain patient[17,18].

HORMONAL REPLACEMENT THERAPY

What is hormone replacement therapy?

Menopause, which strikes women at a median age of 51, is a normal physiological event. Hormone replacement therapy (HRT) combines progestogen with oestrogen to protect the endometrium in women who are still in their uterus and relieve menopausal symptoms. The oestrogen can be applied topically, intravaginally, or orally. It can also be oestradiol, oestradiol 17β, oestrone, or conjugated equine oestrogen. The progestogen can be administered intrauterinally, transdermally, or orally (Mirena, Bayer Schering). Progesterone can be added either continuously (continuous combined regimen) or progressively (cyclic regimen) to oestrogen, which is taken daily in HRT regimens. Tibolone is a synthetic steroid preparation used orally that functions as a HRT agent and has oestrogenic, androgenic, and progestogenic effects. Although extra testosterone can be given to HRT, its function won't be discussed in this instance[19].

Prior to 2002, when the first results of the Women's Health Initiative (WHI) trial were made public, hormone replacement therapy (HRT) was the accepted treatment for menopausal management. In clinical settings, HRT is often started close to menopause. A separate hypothesis was explored in

the WHI, which was that the effects of HRT began ten years or more after menopause. It turns out that a key factor in assessing the risk and benefit of HRT is age at onset. Many different medical disorders can be effectively treated with HRT, possibly reducing the need for separate treatments for different issues[20].

POTENTIAL ADDITIONAL BENEFITS OF NK3RECEPTOR

Neuromodulators are one type of input that regulates GnRH neuronal output. It has been demonstrated that neurokinin B (NKB) significantly modulates the neuroendocrine function of the reproductive system and may regulate GnRH neurons[21].

Sleep Quality/Concentration

In three NK3Ra studies, there was an improvement in sleep efficiency and focus. The attenuation of NK3R actions in melanin-concentrating hormone neurons (involved in the sleep–wake cycle) and in the prefrontal cortex, an important area for concentration, as well as the reduced disruption of sleep caused by HFs are likely the causes of this. On the other hand, the additional NK1Ra action of NT-814 may attenuate substance P-induced arousal and facilitate sleep. Since SNRIs do not cause drowsiness, their ability to reduce HF and anxiety is probably the reason for their ability to reduce nighttime awakenings.

Mood

SNRIs elevate melancholy mood (another common menopausal symptom). Despite the lack of evidence linking NK3Ras to mood, NT-814's NK1Ra activity might be advantageous. If mood is a very limiting issue, it may be worthwhile to explore cognitive behavioural therapy (CBT) in addition to medication, as the benefits of CBT seem to last over time.

CV Safety

The risk of CVD rises after menopause. NK3Ras in rats reversed spontaneous hypertension and lowered heart rate via lowering midbrain dopaminergic transmission in the ventral tegmental area that highly expresses NK3Rs, in contrast to SNRIs, which may be associated with hypertension leading to increased CV risk. NK3Rs are also expressed by vasopressin neurons, and thromboxane A2 increases NKB activity. These properties make NK3Ras potentially valuable targets for therapeutic intervention[4].

ARTIFRACTURE EFFICACY OF MENOPAUSAL HORMONE THERAPY

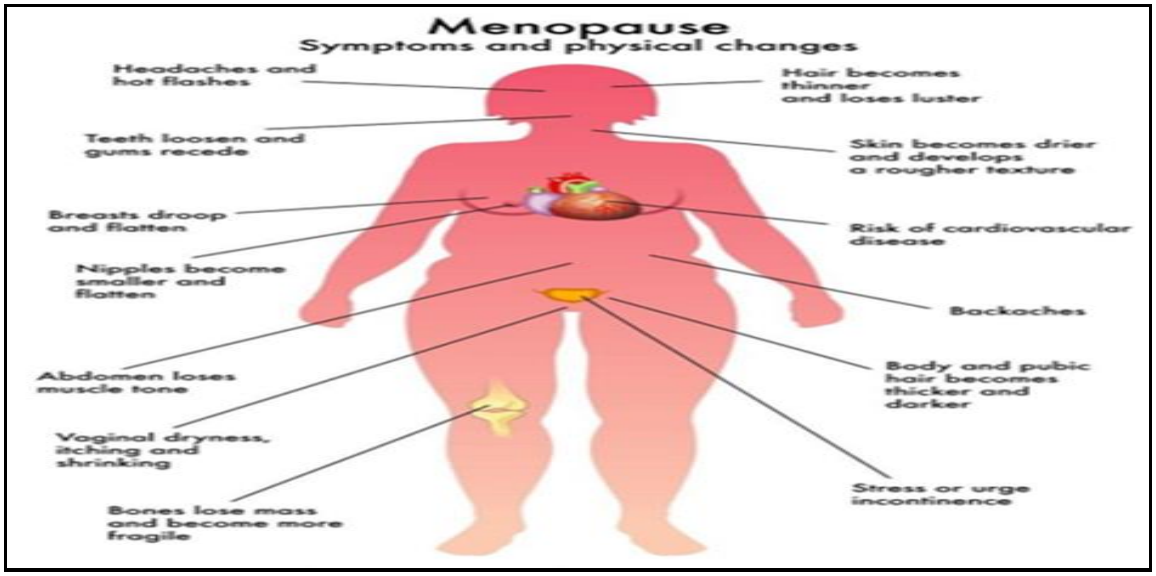
A meta-analysis of multiple randomised clinical trials conducted between 1973 and 2000 found that MHT significantly reduced the number of vertebral fractures by 33 percent and the number of nonvertebral fractures by 27 percent. Women under 60 had a considerably lower pooled relative risk (RR) of nonvertebral fractures, hip fractures and wrist fractures. A substantial increase in bone mineral density (BMD) has been established in further double-blind, randomised, placebo-controlled studies when comparing women on MHT to those in the placebo group[6-12]. In 875 healthy postmenopausal women, a prospective postmenopausal estrogen/progestin intervention (PEPI) research assessed the impact of MHT on BMD (age 45 to 64 years). Women who received conjugated equine estrogens (CEE), 0.625mg/day with a progestin, or CEE alone, increased their bone mineral density (BMD) in the proximal femur and lumbar spine by a substantial amount after three years compared to those who received a placebo[22].

Adverse reactions

Asymptomatic increased in hepatic transaminases
Blood glucose elevations
Abdominal pain
Diarrhea
Insomnia
Backpain
Thermo fluctuations
Risk of breast cancer
Endometrial and Ovarian Cancers
Risk of strokes
Pulmonary thromboembolism[23]
Sleeping disturbances
Depressive moods

Headache, migraines increase during perimenstrual days[24]
Metabolic activities[25]
Creutz feldt-Jakob disease in childrens
Hypertension
GH stimulation cell multiplication[26]
Many possible therapeutic indications for selective NK3 receptor antagonists are proposed, including CNS disorders, pain and inflammation, lung and skin illnesses, based on receptor distribution and thepharmacological effects of these agents. Overall, there has been a noticeable upsurge in interest in and research on NK3 receptors in recent years.

However, in order to clearly define the pathophysiological role of NK3 receptors and to more solidly establish the potential therapeutic utility of potent and selective NK3 receptor antagonists, extensive additional medicinal chemistry and pharmacology studies including preclinical and clinical evaluation of appropriate compounds from distinct structural classes are needed[27] Anatomical data that suggests NKB neurons may interact with NK3R in the rat median eminence to affect GnRH production. On the other hand, NK3R staining was only seen in 16 percent of GnRH-irsomata. These findings imply that NKB neurons may operate through a receptor other than NK3R to indirectly affect anterior pituitary function through inputs to arcuate neuroendocrine neurons[28].



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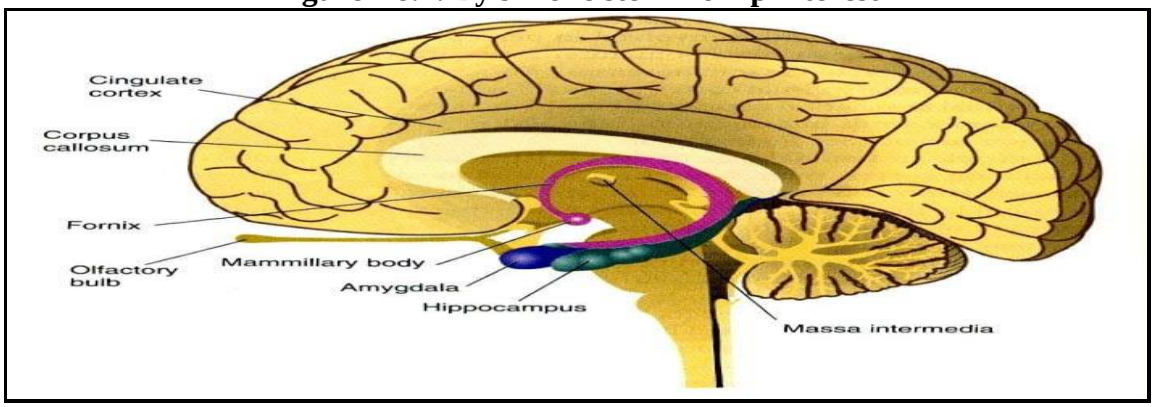

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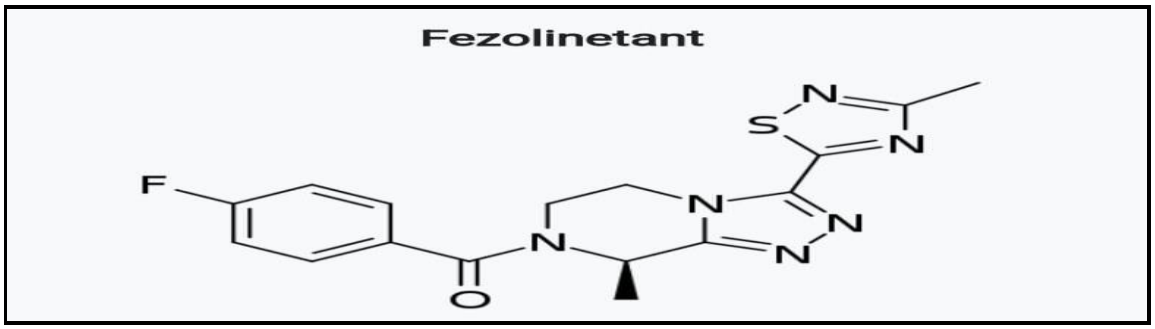

Figure No.3: Manish Modi, Waljit S. Dhillo. Neurokinin 3 receptor antagonism: A Novel treatment for menopausal hot flushes, *Neuroendocrinology,* 109, 2019, 242-248

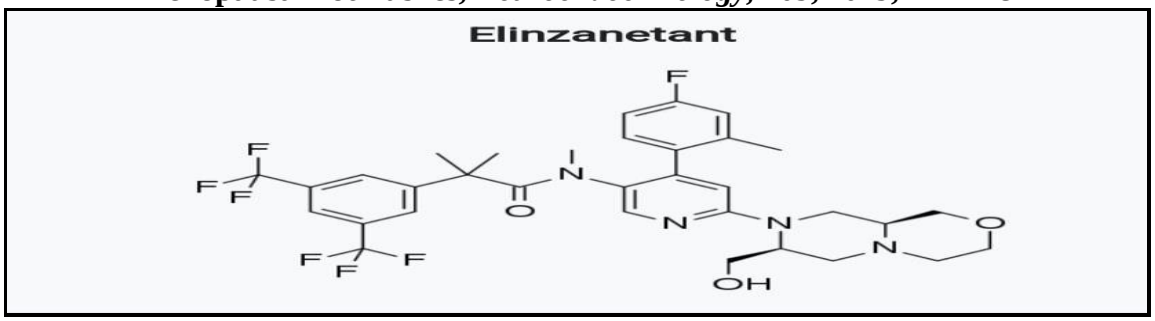

Figure No.4: Manish Modi, Waljit S. Dhillo. Neurokinin 3 receptor antagonism: A Novel treatment for menopausal hot flushes, *Neuroendocrinology,* 109, 2019, 242-248

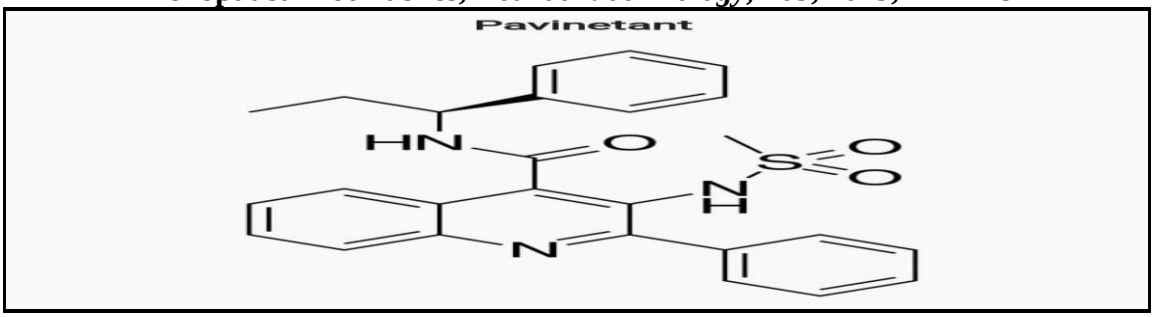

Figure No.5: Manish Z, Waljit S. Dhillo. Neurokinin 3 receptor antagonism: A Novel treatment for menopausal hot flushes, *Neuroendocrinology,* 109, 2019, 242-248

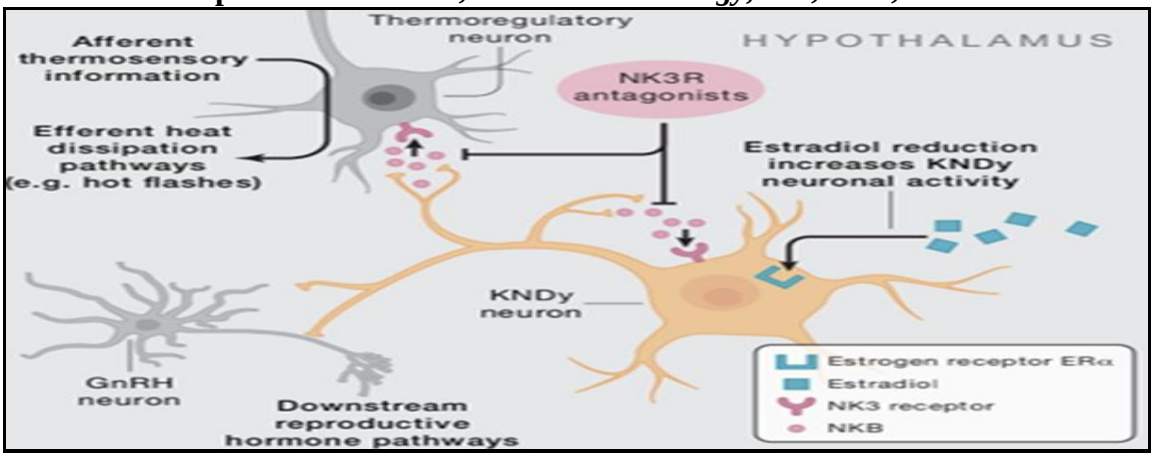

Figure No.6: Alexander n. comninos and dhillo, neurokinin 3 receptor antagonism for menopausal hot flashes

CONCLUSION

In conclusion, neurokinin 3 receptors (NK3R) play a crucial role in regulating various physiological processes, with a particular focus on their involvement in thermoregulation and menopausal hot flushes. These receptors are primarily located in the central nervous system, including the hypothalamus, and are activated by the neuropeptide neurokinin B (NKB). The decline in estrogen levels during menopause can disrupt the functioning of NK3 receptors, contributing to the occurrence of hot flushes. Research has explored the use of NK3 receptor antagonists as a potential therapeutic approach for managing menopausal symptoms, particularly hot flashes. Drugs such as Fezolinetant and Elinzanetant have shown promising results in reducing the frequency and severity of hot flushes in clinical trials. These antagonists work by inhibiting the NK3 signaling pathway, which is implicated in the thermoregulatory disruptions associated with menopausal hot flashes. The development of NK3 receptor antagonists represents a significant advancement in non-hormonal treatment options for menopausal symptoms, offering an alternative to hormone replacement therapy (HRT). These antagonists have demonstrated efficacy in improving sleep quality, concentration and mood, addressing multiple aspects of menopausal symptomatology. Despite their potential benefits, it's important to consider potential adverse reactions associated with NK3 receptor antagonists, such as hepatic transaminase increases, blood glucose elevations, and gastrointestinal symptoms. Long-term safety and effectiveness still require further investigation. In summary, the modulation of NK3 receptors presents a promising avenue for managing menopausal hot flushes, and ongoing research aims to refine and expand the use of NK3 receptor antagonists, offering hope for improved quality of life for individuals experiencing menopause.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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