Physiology: Hormonal changes during menopause, the importance of KNDy, NKB signaling, Neurokinin and antagonists

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Definitions

- Perimenopause – Menopause transition
- Menopause
- Postmenopause

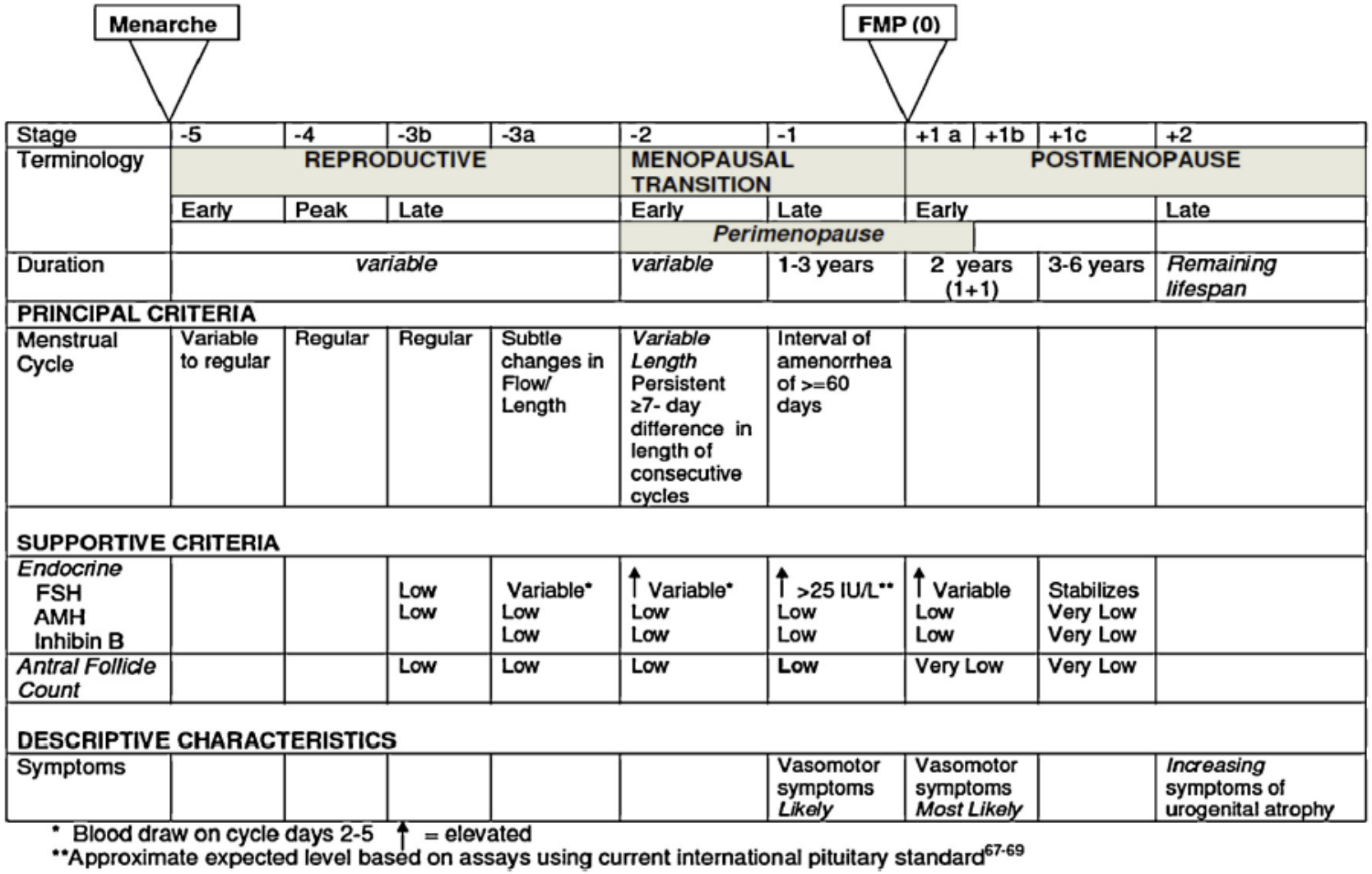
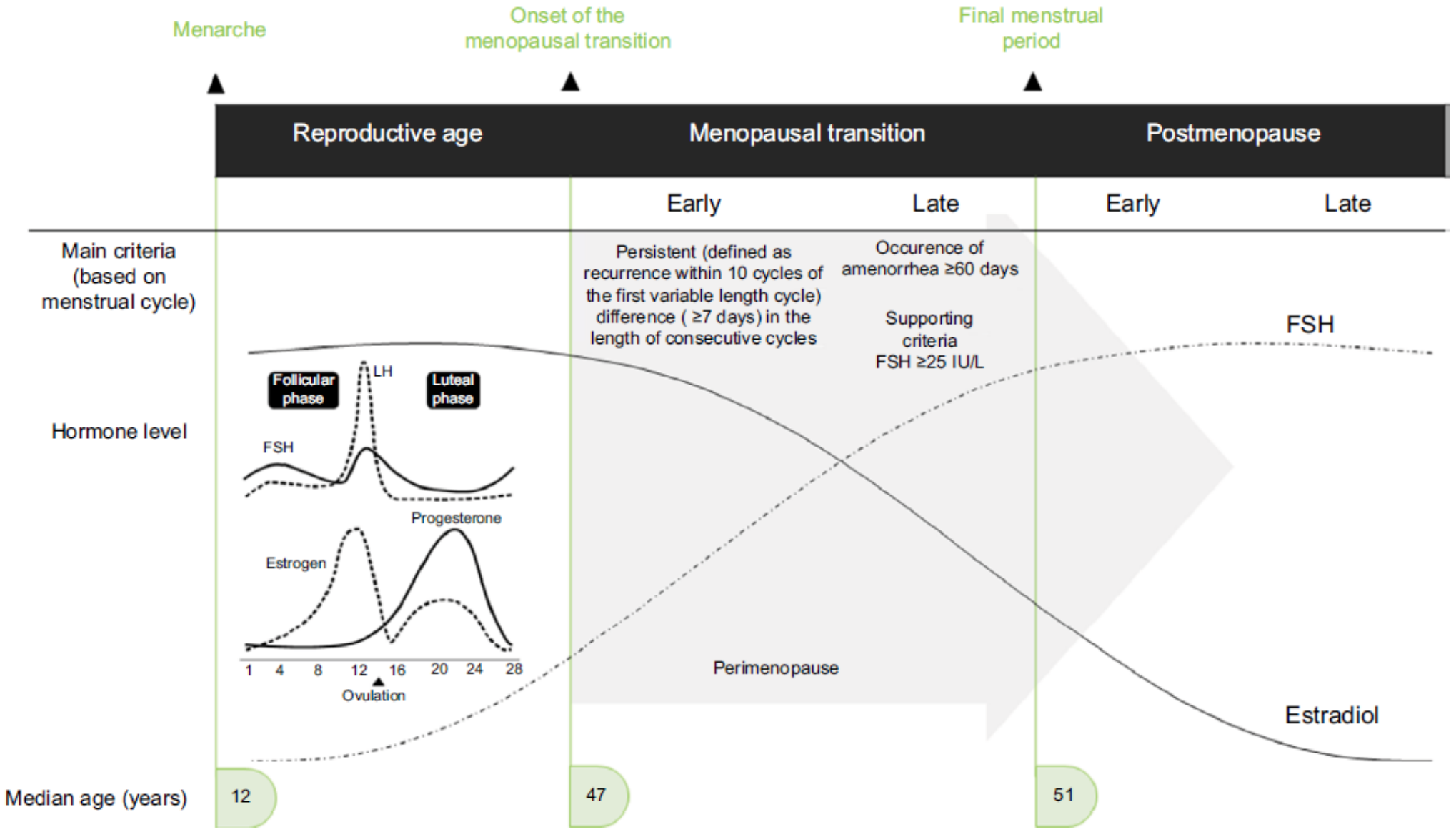
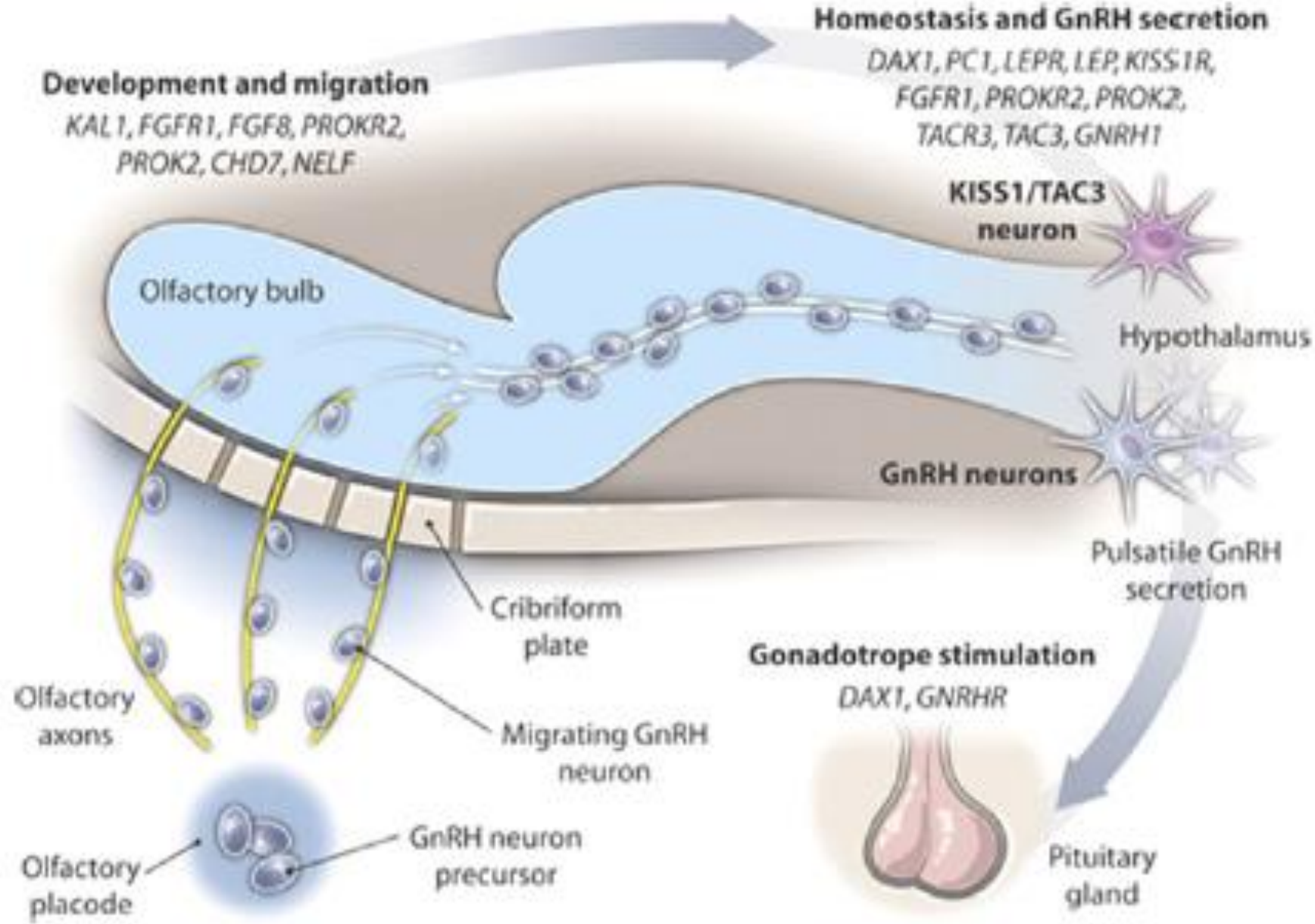


Fig. 1. The 2011 Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

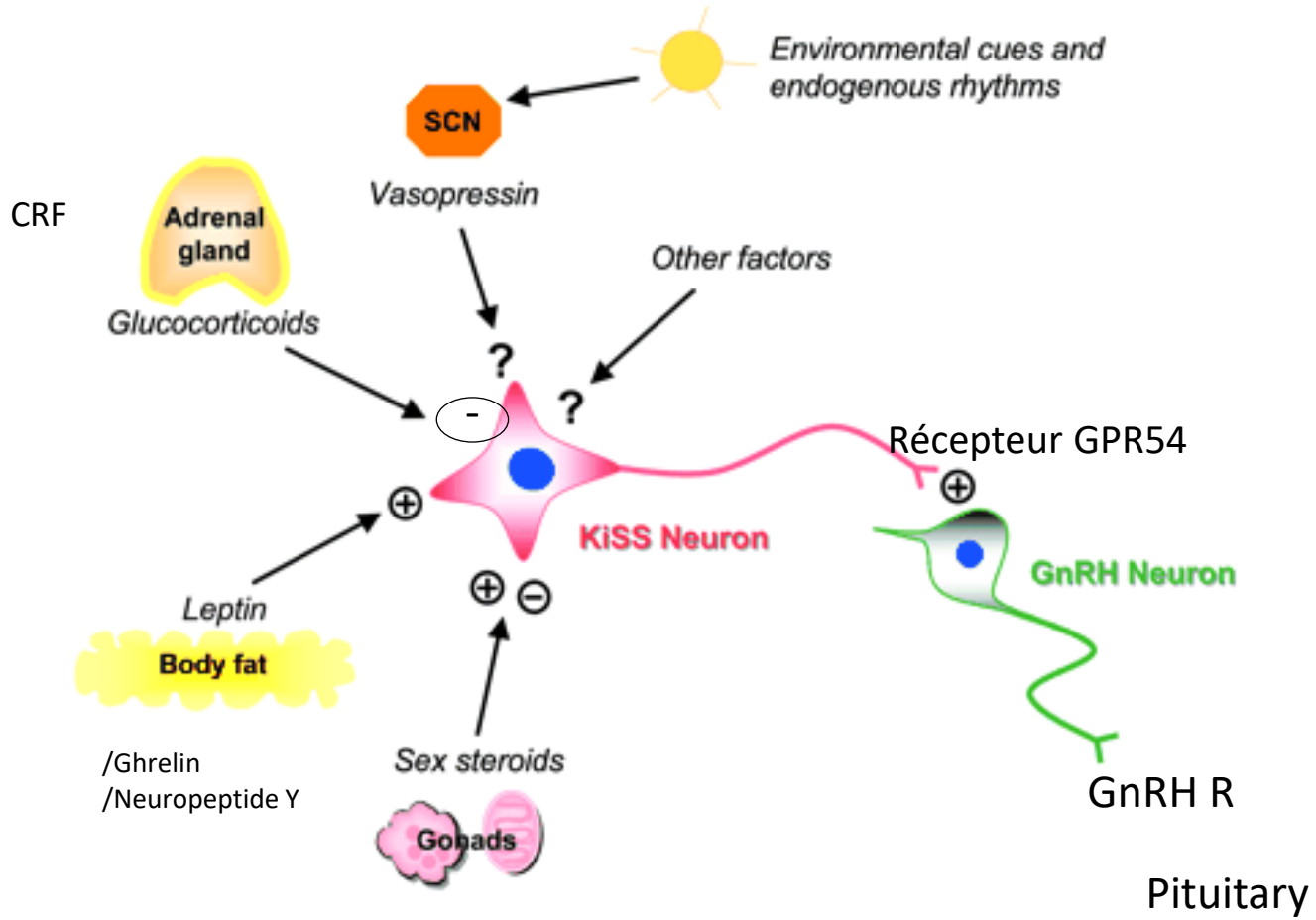


Nature and Science of Sleep 2018:10

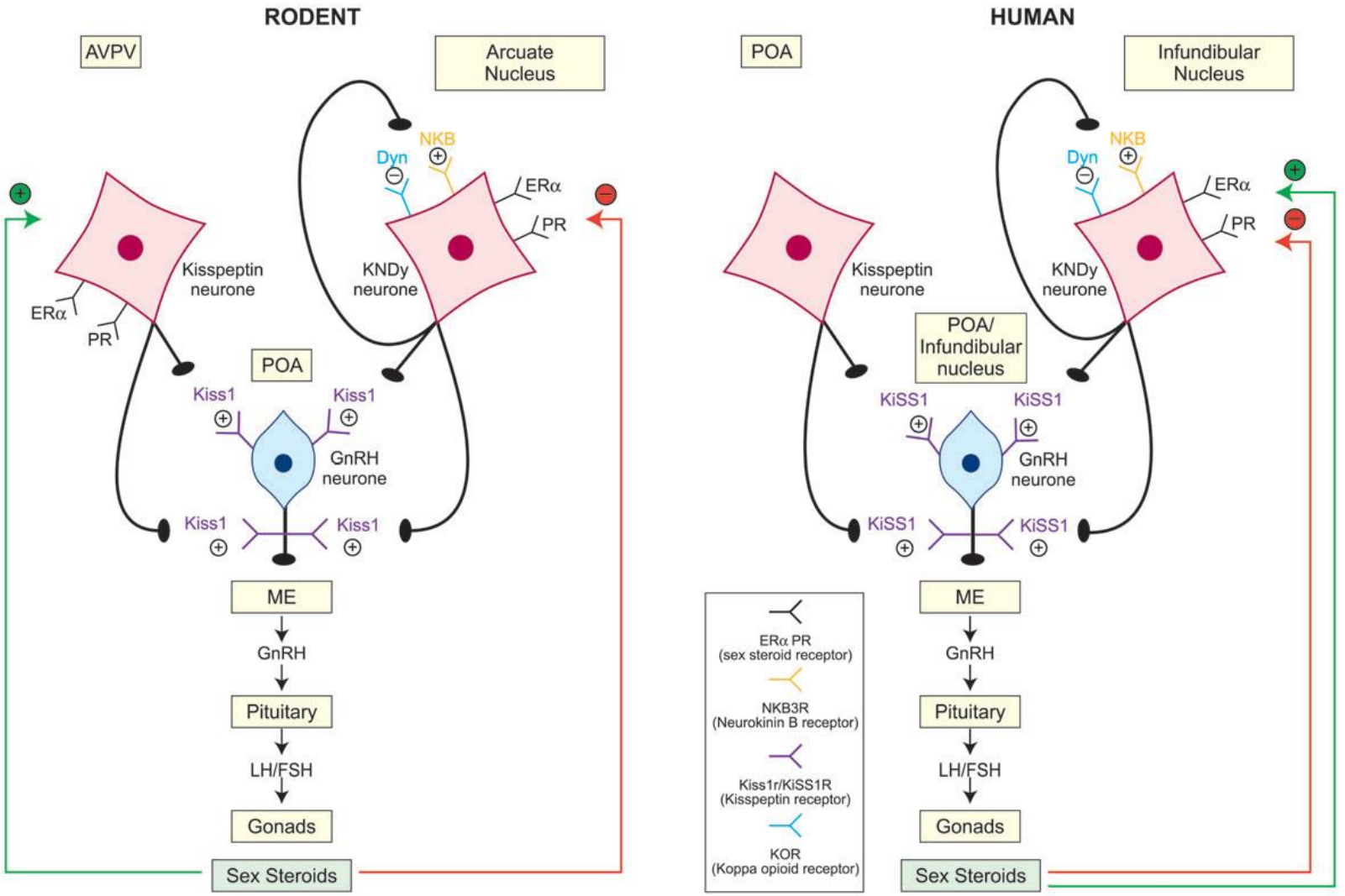
MT begins four to six years before cessation of menses, and a physiologic deterioration of hypothalamic-pituitary-ovarian axis function associated with fluctuating hormone levels


Homeostasis and GnRH secretion
DAX1, PC1, LEPR, LEP, KISS1R, FGFR1, PROKR2, PROK2, TACR3, TAC3, GNRH1
Development and migration
KAL1, FGFR1, FGF8, PROKR2, PROK2, CHD7, NELF
KISS1/TAC3 neuron
Olfactory bulb
Hypothalamus
GnRH neurons
Pulsatile GnRH secretion
Cribriform plate
Gonadotrope stimulation
DAX1, GNRHR
Olfactory axons
Migrating GnRH neuron
GnRH neuron precursor
Olfactory placode
Pituitary gland

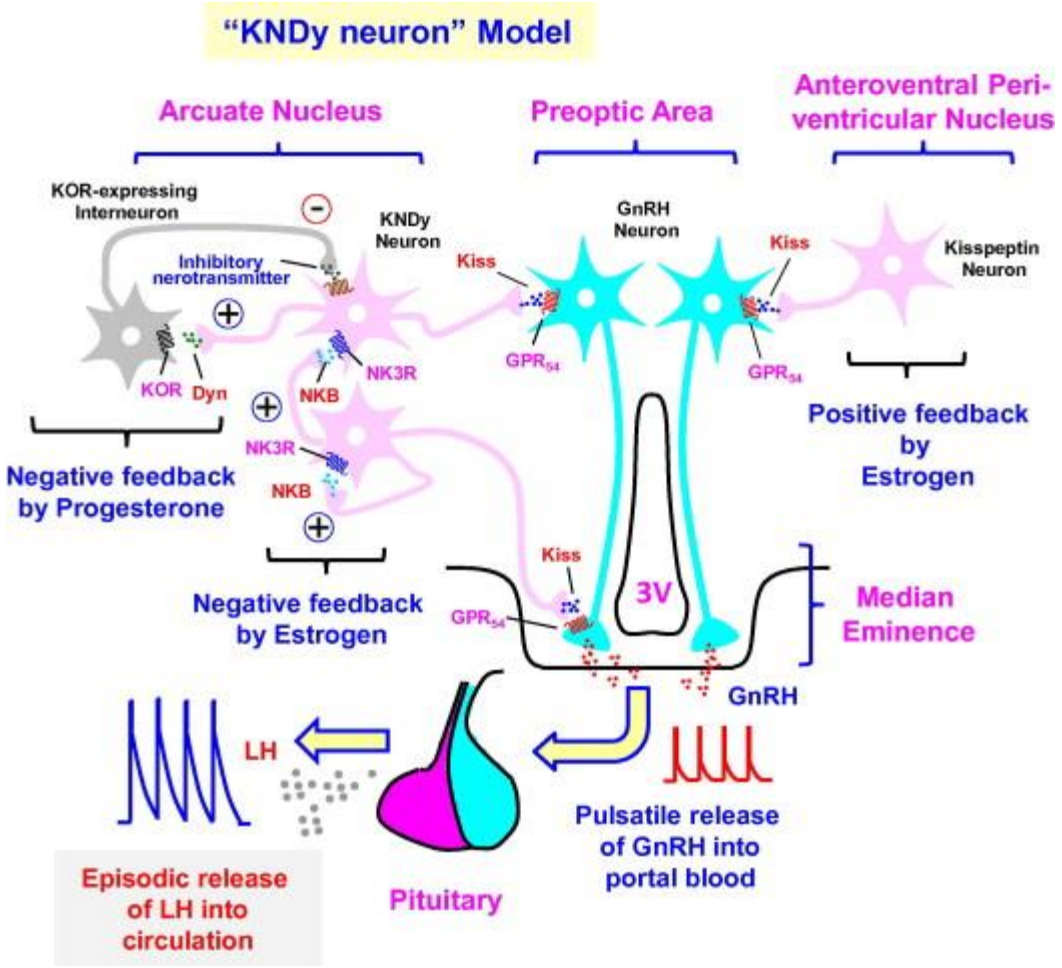
Kiss neuron



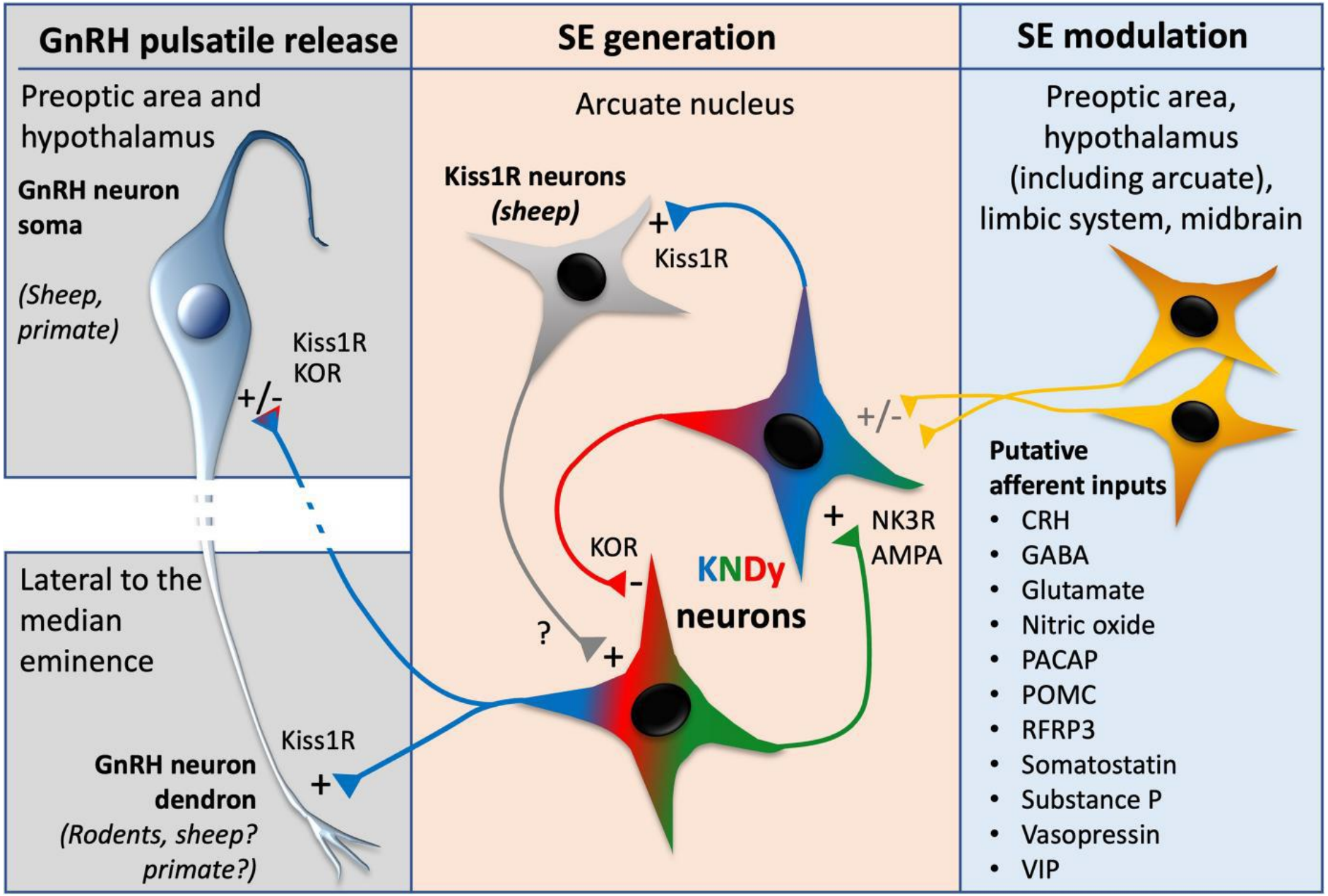
Kisspeptin, a key factor in the neuroendocrinological regulation of animal reproduction, is a peptide product encoded by kiss genes, which act as the natural ligand of GPR54.



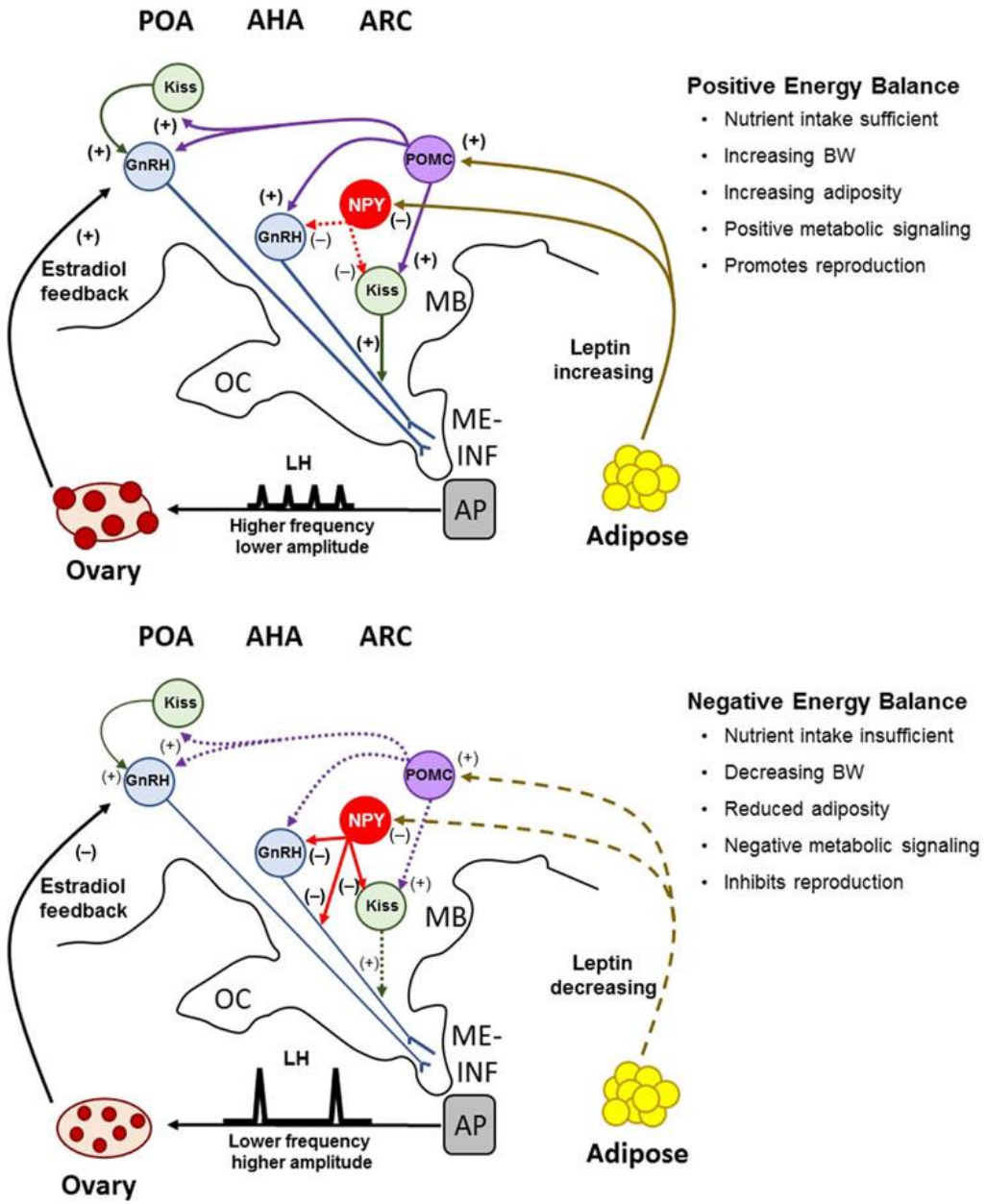
Karolina Skorupskaite, Human Reproduction Update, Vol.20, No.4 pp. 485–500, 2014



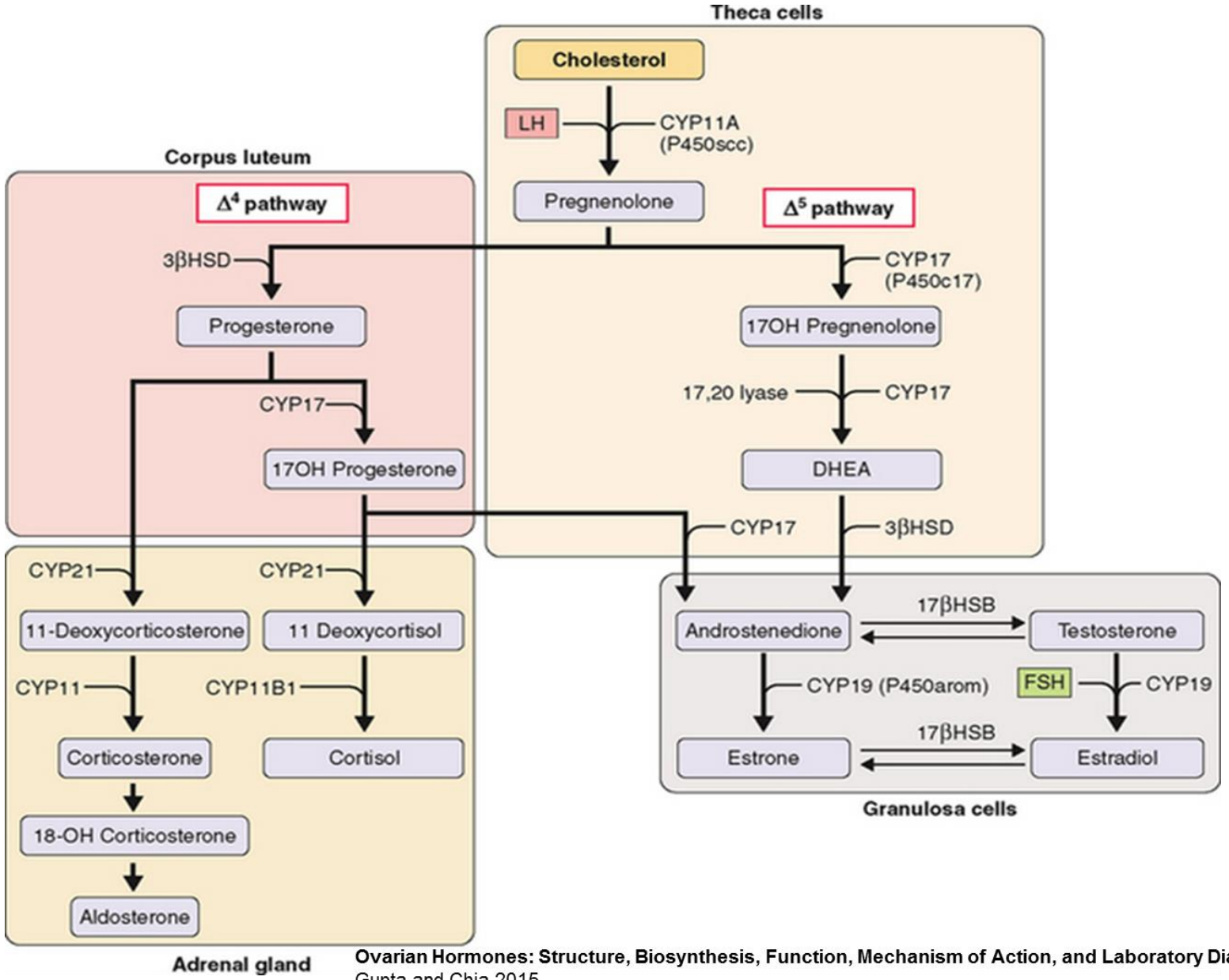
Guangfu Hu,General and Comparative Endocrinology 208 (2014) 94–108



Aleisha M. Moore, *Endocrinology*, 2024, Vol. 165, No. 2



Animal (2019), 13:12, pp 2986–2999



Ovarian Hormones: Structure, Biosynthesis, Function, Mechanism of Action, and Laboratory Diagnosis
Gupta and Chia 2015

Flushes, blushing or hot flushes

- Apart from physiological flushes represented by emotional or prudish blushing, post-prandial flushes and menopausal hot flushes, various pathologic flushes exist of various etiologies: endocrine, dysmetabolic, histaminic and iatrogenic.
- Their pathogenicity is based mainly on local metabolites secretion provoking vasodilatation.

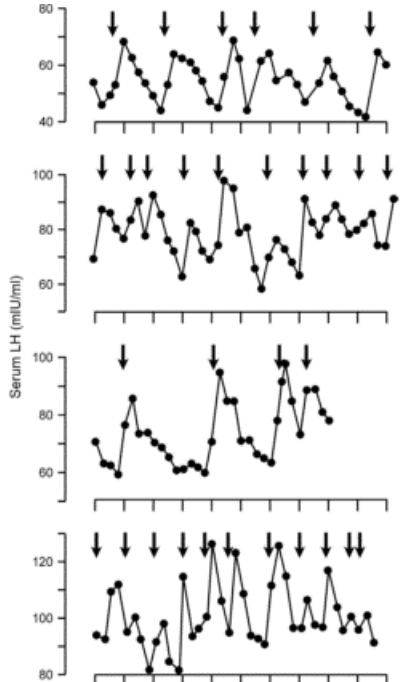
J F Merlen, J M Coget ,J Mal Vasc. 1987;12(3):285-90

The menopausal hot flush

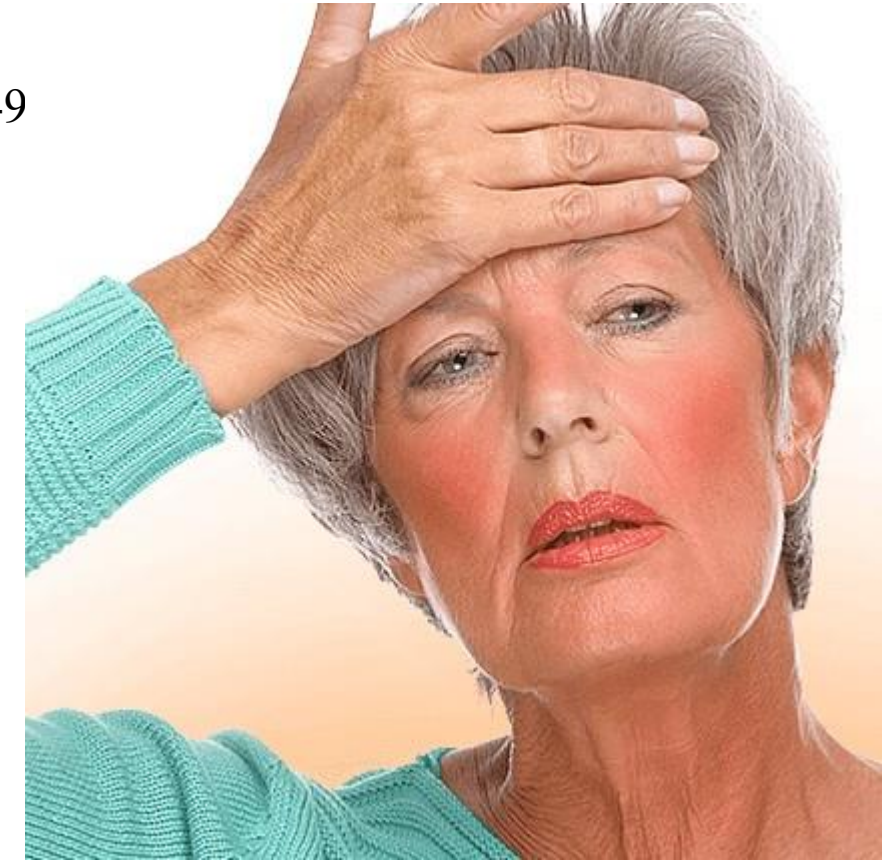
- Although the hot flush is generally recognised by women and the medical profession as the most characteristic and often a very distressing symptom of the climacteric, it remains **an enigma**
- It is probable that the flush is initiated by a supra-pituitary mechanism which is influenced by the **hypothalamic factors** responsible for pulsatile LH release

David W. Sturdee, Maturitas 60 (2008) 42–49

Pattern of pulsatile LH release and associated flush episodes in four postmenopausal women.
The arrows indicate flush onset.

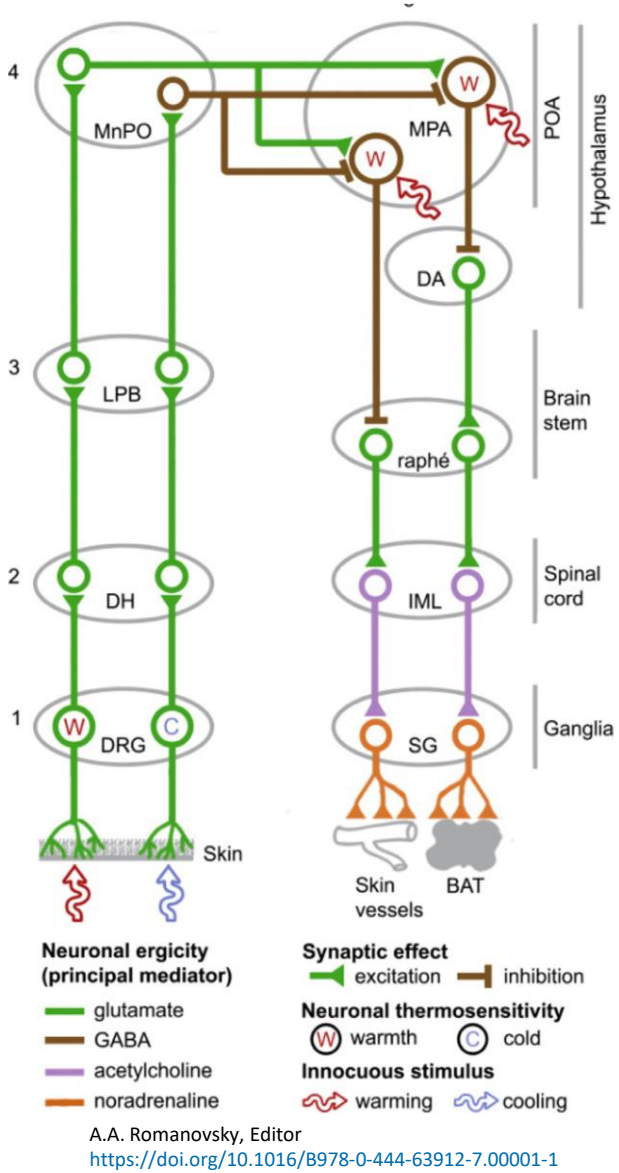


Casper et al. (1979).



Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes

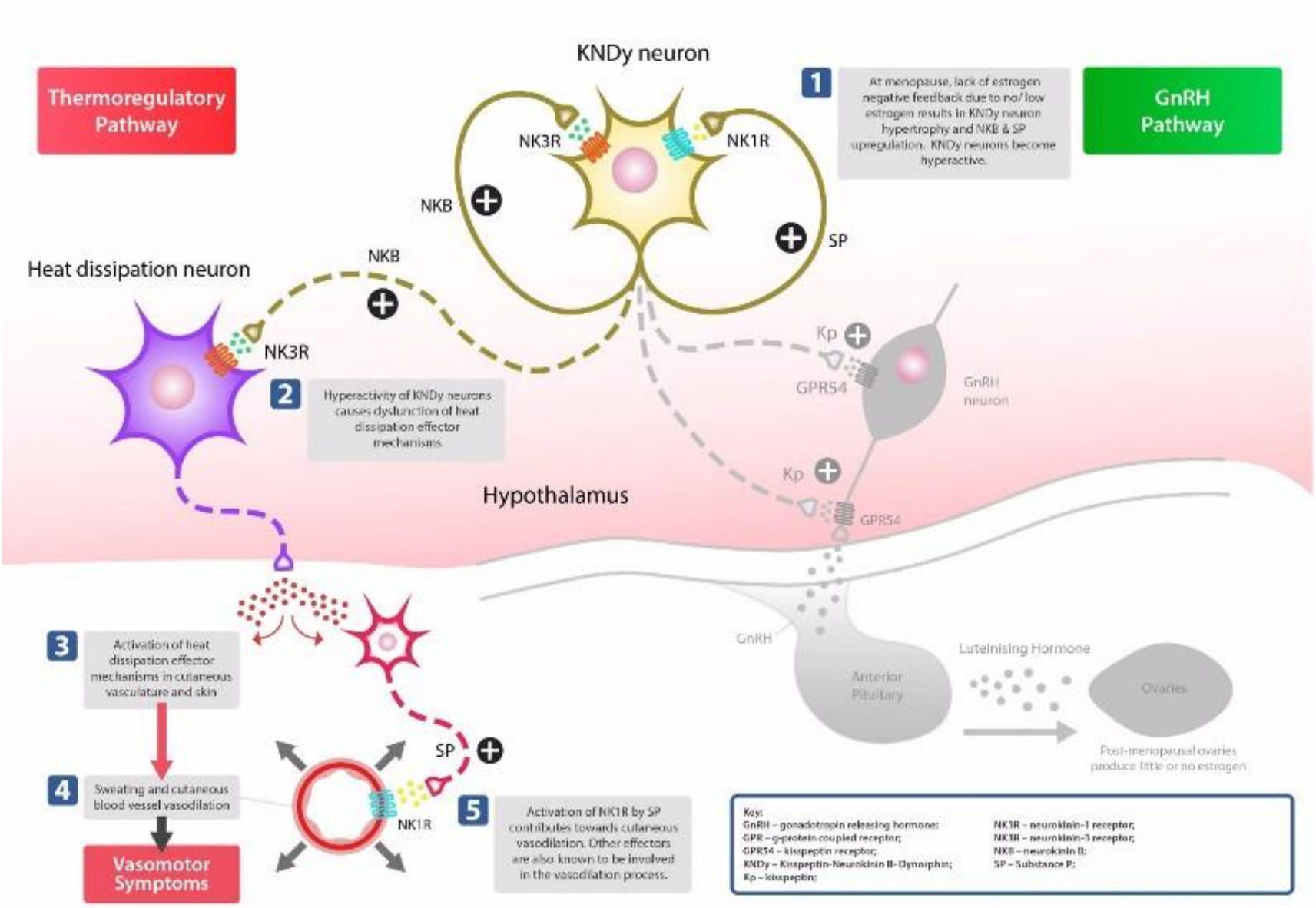
- Based on the marked changes in hypothalamic kisspeptin, neurokinin B and dynorphin (KNDy) neurons in postmenopausal women, we hypothesize that KNDy neurons play a role in the mechanism of flushes.
- In the rat, KNDy neurons project to preoptic thermoregulatory areas that express the neurokinin 3 receptor (NK3R), the primary receptor for NKB. Furthermore, activation of NK3R in the median preopticonucleus, part of the heat-defense pathway, reduces body temperature.
- Finally, ablation of KNDy neurons reduces cutaneous vasodilatation and partially blocks the effects of estrogen on thermoregulation



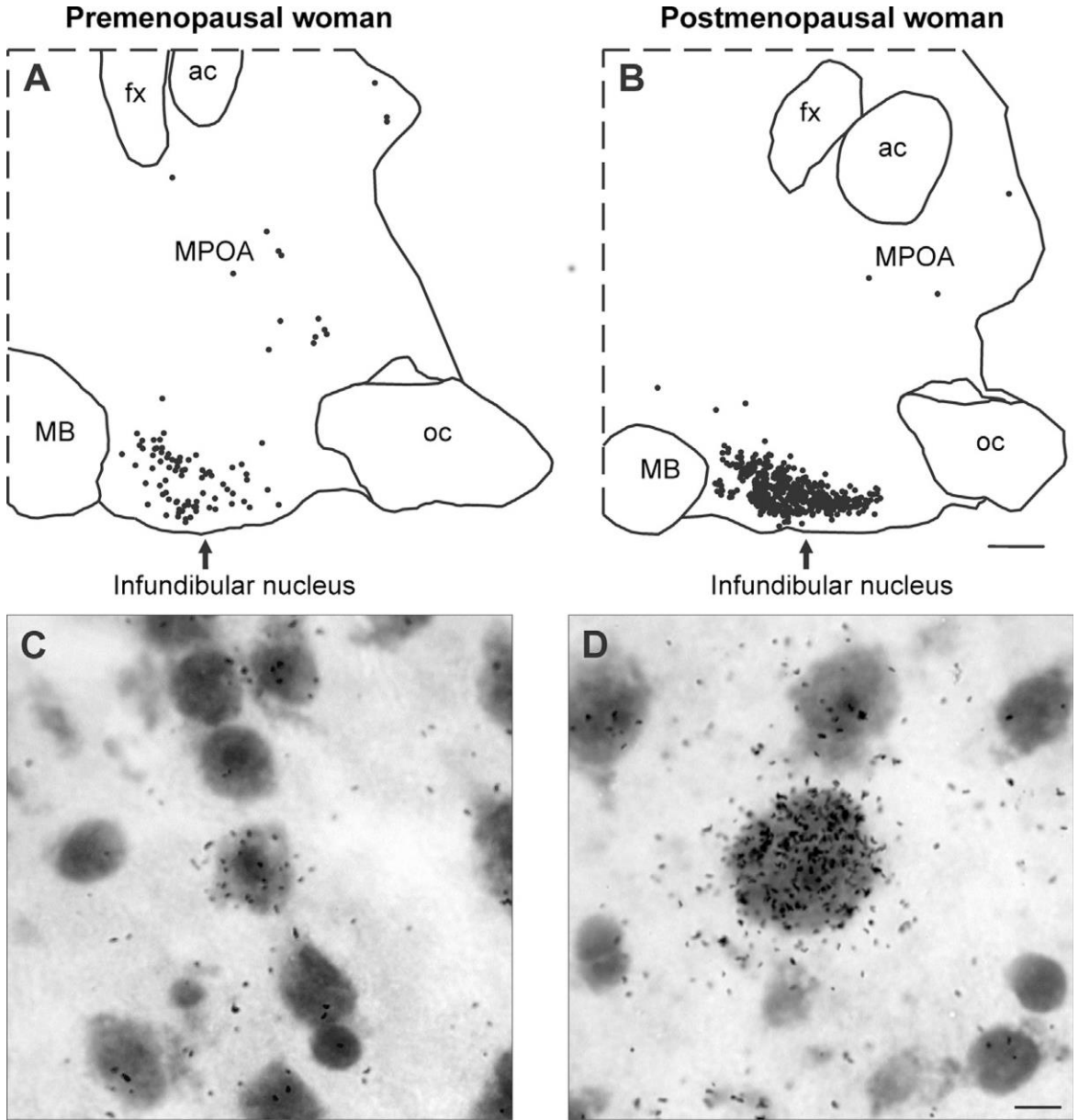
A.A. Romanovsky, Editor
https://doi.org/10.1016/B978-0-444-63912-7.00001-1

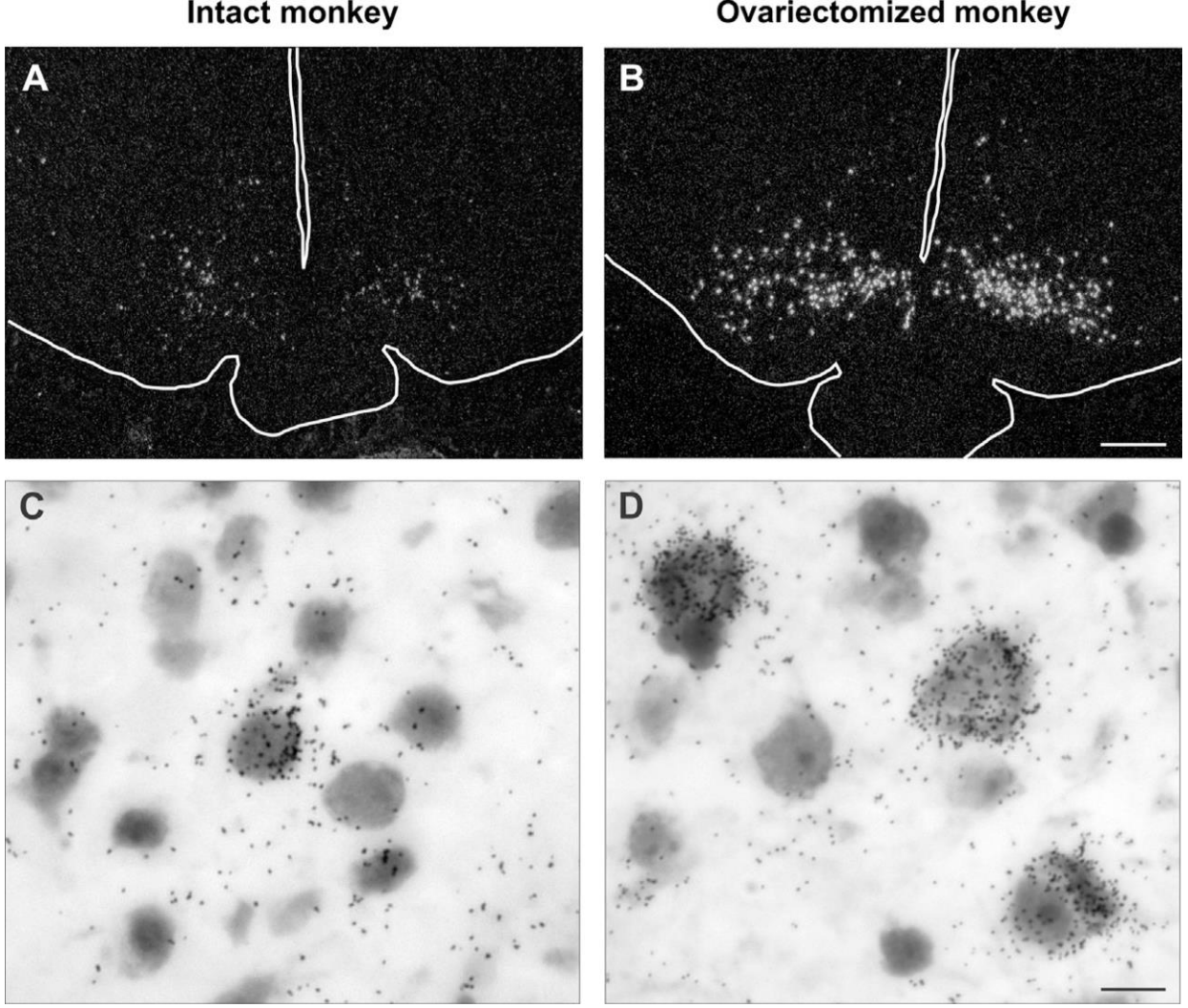
Naomi E. Rance- Front Neuroendocrinol. 2013 August ; 34(3): doi:10.1016/j.yfrne.2013.07.003.

Menopause transition : a neuroendocrine storm



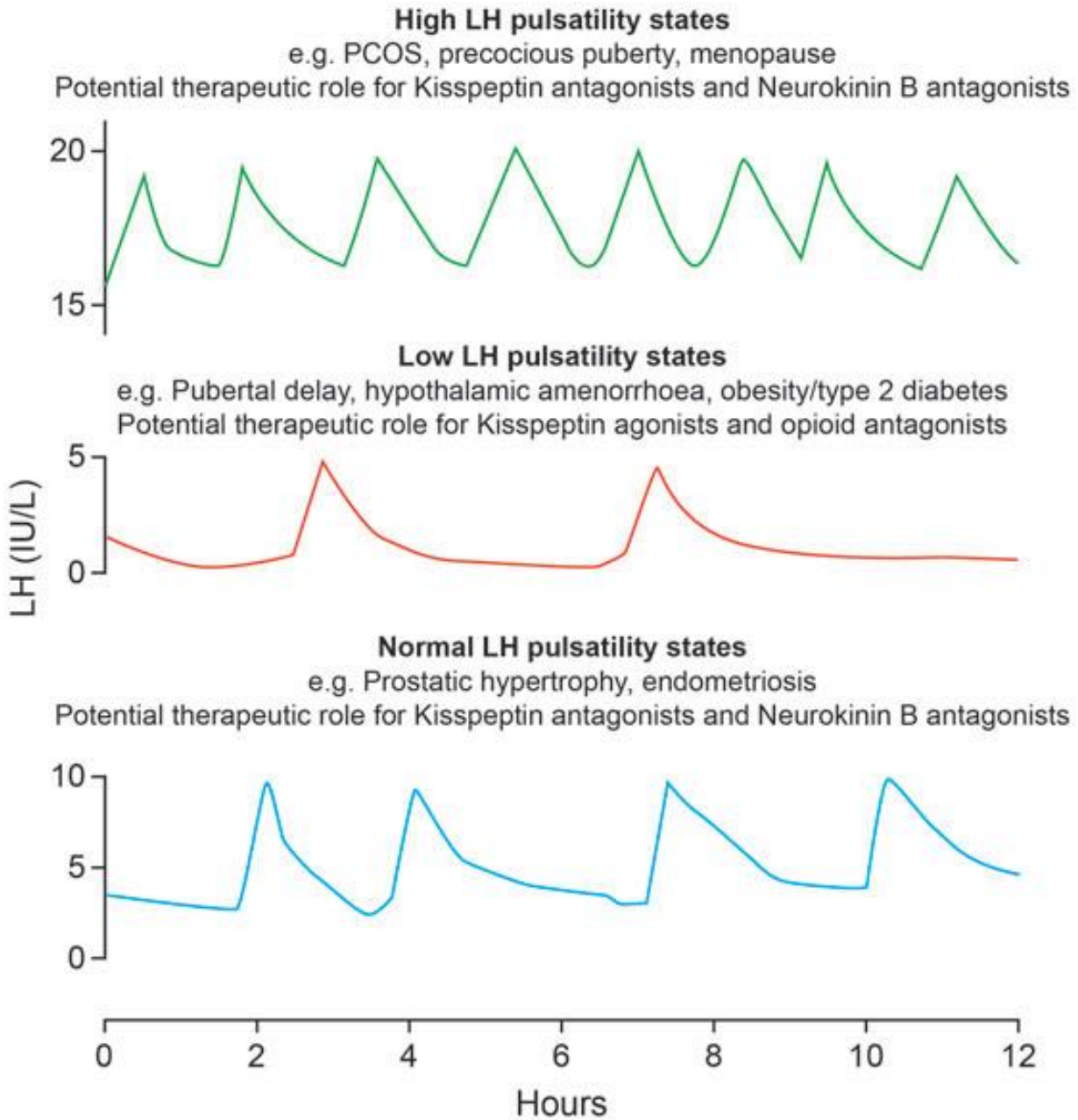
In postmenopausal women, kisspeptin neurons are hypertrophied and display increased numbers of audioradiographic grains, indicative of increased gene expression. Nearly identical changes can be seen in NKB neurons in the infundibular nucleus of postmenopausal women (Rance and Young, 1991).





(A and B) Darkfield photomicrogaphs of coronal hypothalamic sections from an intact (A)or ovariectomized (B) cynomolgus monkey hybridized with cDNA probes complimentary to NKB mRNA (Tac3 in the monkey) and visualized using autoradiography

Brightfield photomicrogaphs of neurons expressing NKB mRNA visualized using in situ hybridization in the arcuate nucleus of an intact (C) or ovariectomized (D) cynomolgus monkey

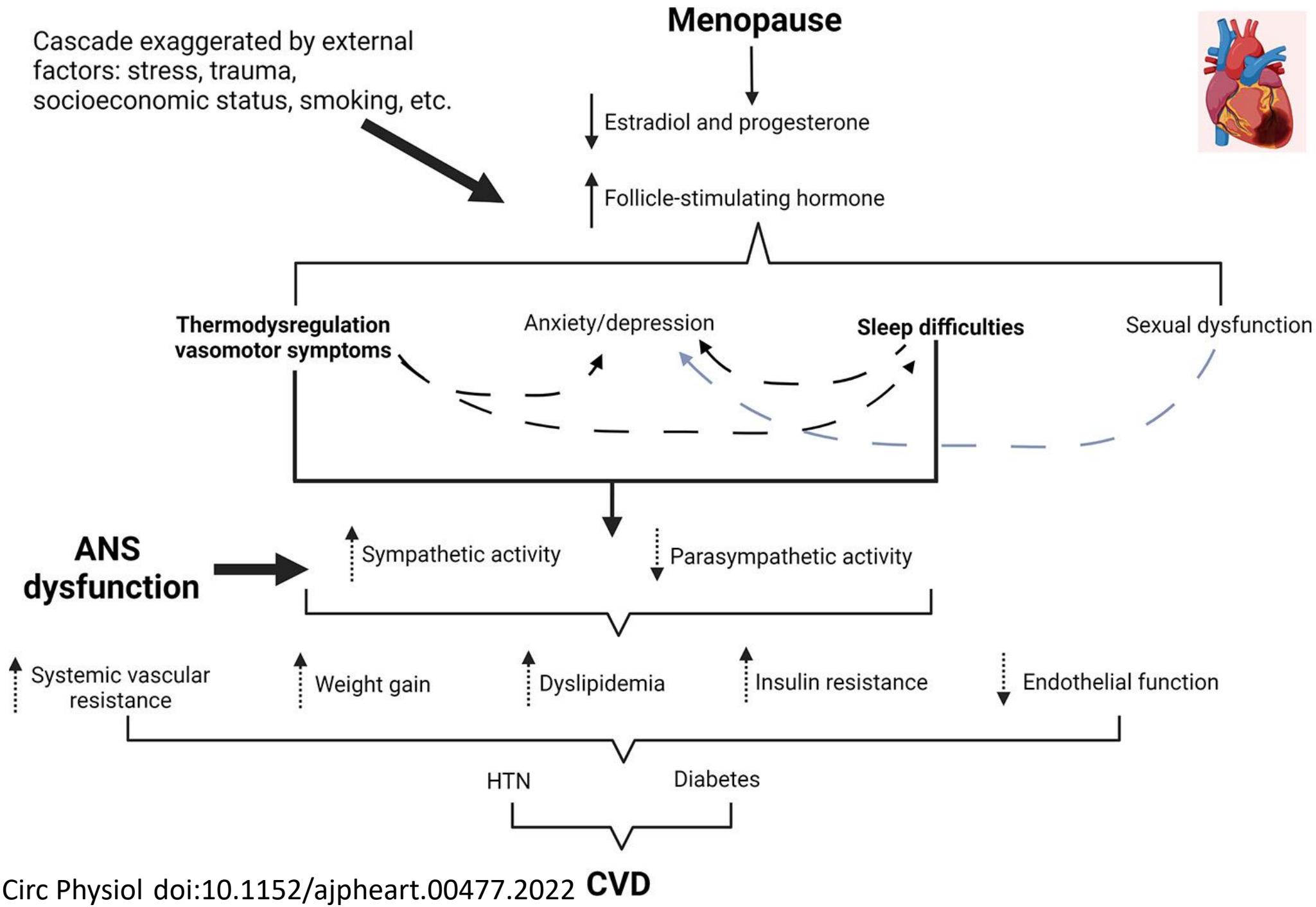


Karolina Skorupskaite, Human Reproduction Update, Vol.20, No.4 pp. 485–500, 2014

Vasomotor symptoms of menopause, autonomic dysfunction, and cardiovascular disease

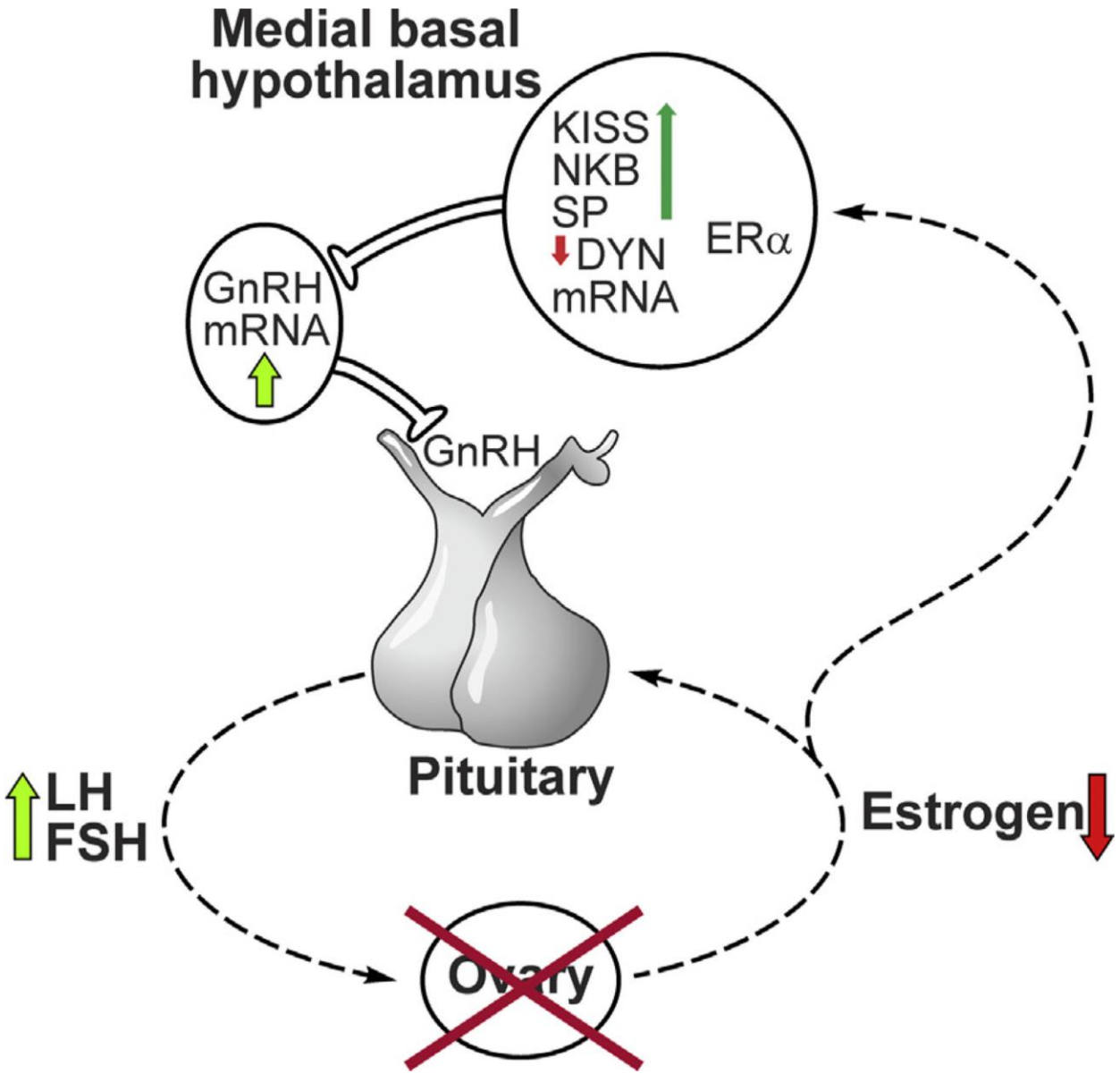
- Vasomotor symptoms of menopause (VMS; hot flashes/flushes and night sweats) are common among females undergoing menopausal transition and have been associated with elevated blood pressure (BP) and increased CVD risk.
- Autonomic dysregulation of BP has been posited as a contributing factor to the elevated CVD risk in menopausal females with VMS.
- Disruption of autonomic function associated with VMS might provide a mechanistic pathway to CVD development.

Am J Physiol Heart Circ Physiol 323: H1270–H1280, 2022

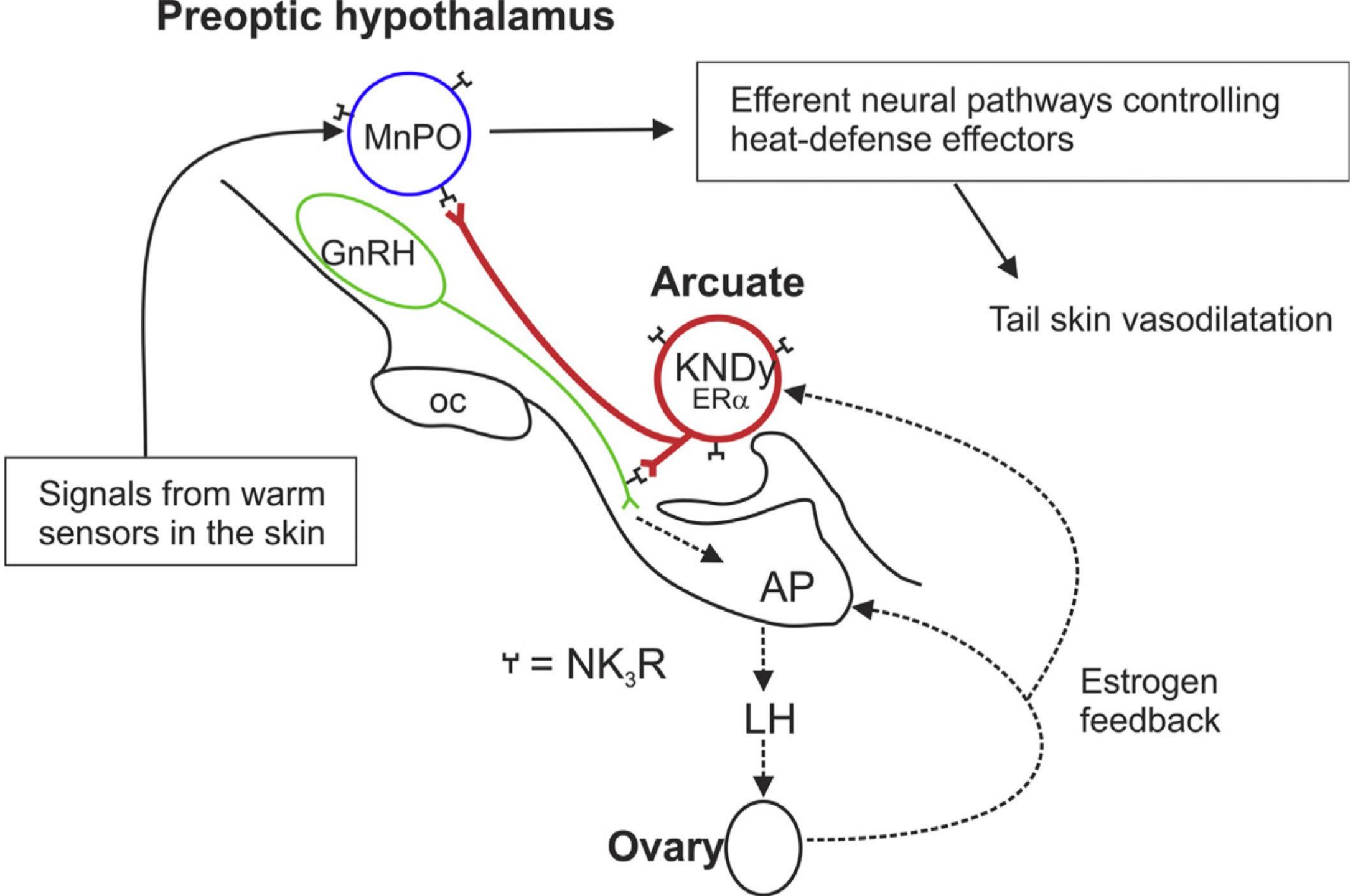


AJP-Heart Circ Physiol doi:10.1152/ajpheart.00477.2022

Schematic diagram showing the relationship between KNDy neurons and the neuroendocrine circuits controlling LH secretion in postmenopausal women



Naomi E. Rance,Front Neuroendocrinol. 2013 August ; 34(3): . doi:10.1016/j.yfrne.2013.07.003.


Preoptic hypothalamus
MnPO
Efferent neural pathways controlling heat-defense effectors
GnRH
Arcuate
Tail skin vasodilatation
KNDy
ERα
OC
Signals from warm sensors in the skin
AP
ϒ = NK3R
LH
Estrogen feedback
Ovary

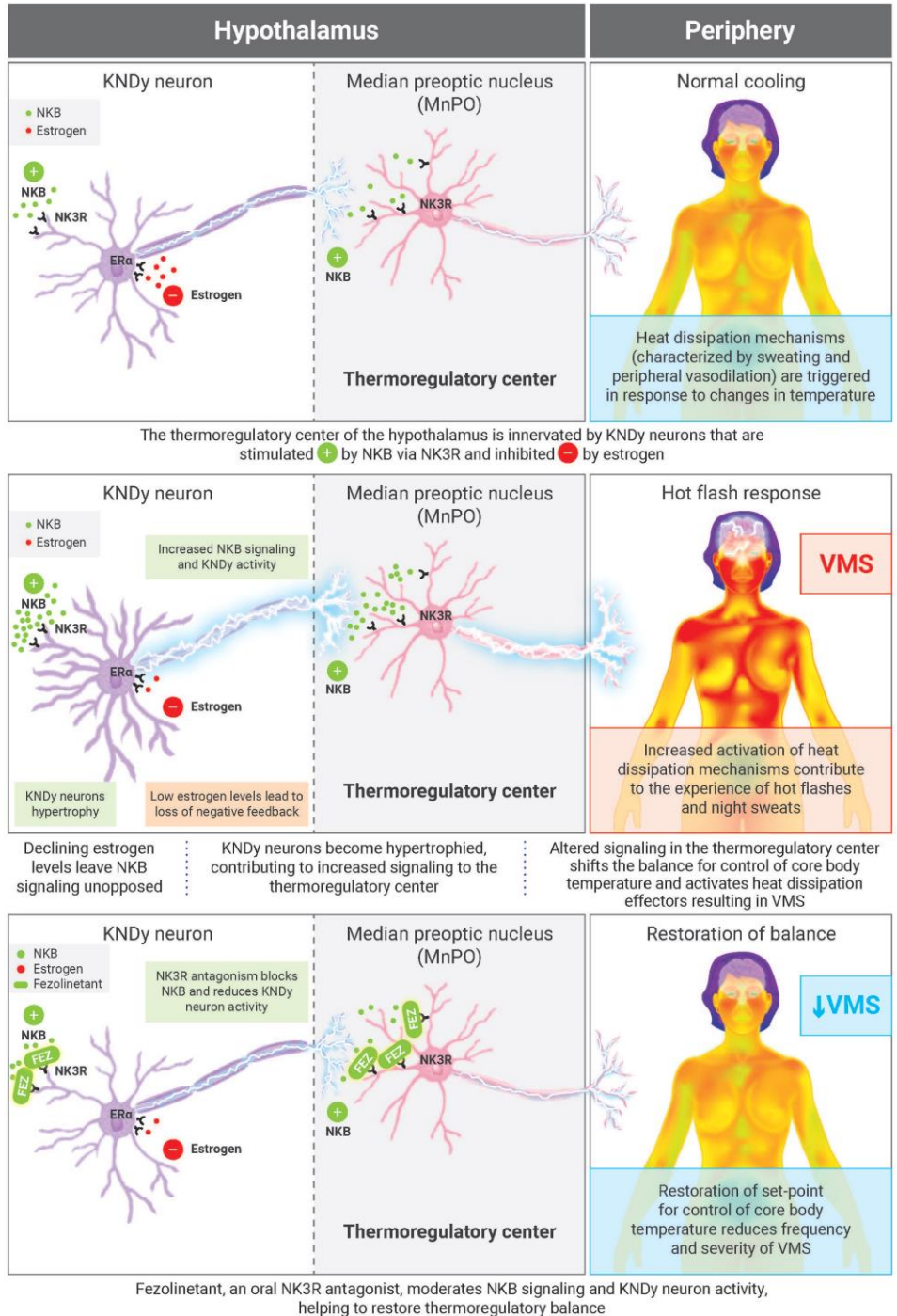
Additional effects ??

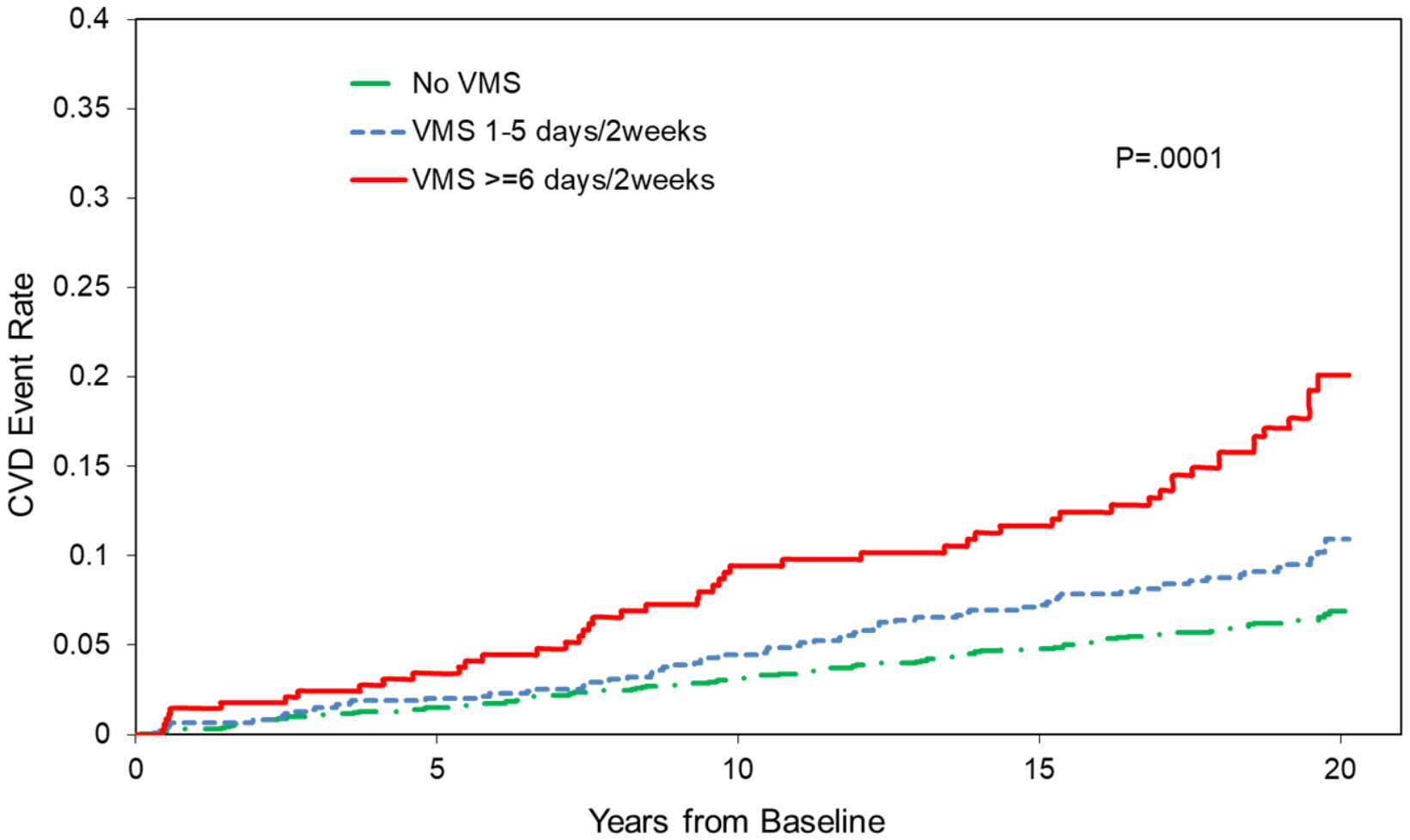
- hypothalamic neurons that express NK3R are implicated in the estrogen modulation of body weight
- cardiovascular disease is increased in menopausal women but pre-clinical evidence suggests that manipulation of neuronal signaling in the ventral tegmental area, which highly expresses NK3R, using an NK3R antagonist reduces heart rate and reverses spontaneous hypertension in rats
- specific metabolic/cardiovascular endpoints. ??

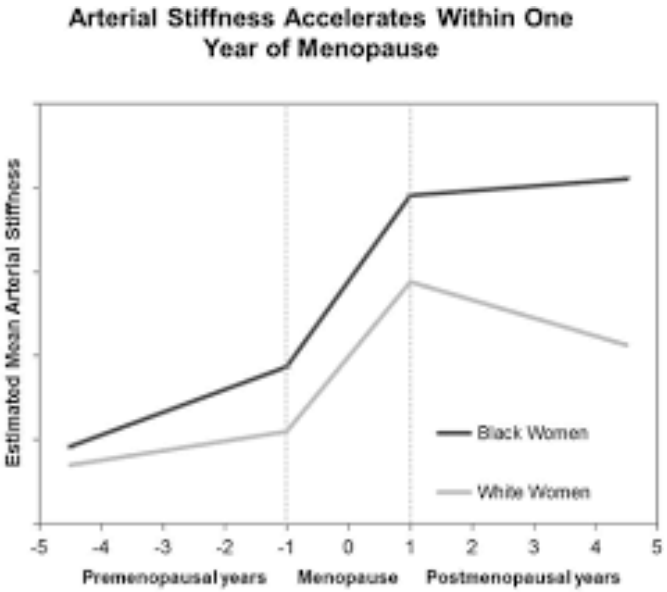
Noel S, Sorlet C, Hospied S, et al. Suppression of weight gain in ovariectomized high-fat diet rats and in female monkeys by treatment with ESN364 (NK3 antagonist). Endocrine Rev 2017;38:OR19-6

Lessard A, Campos MM, Neugebauer W, Couture R. Implication of nigral tachykinin NK3 receptors in the maintenance of hypertension in spontaneously hypertensive rats: a pharmacologic and autoradiographic study. Br J Pharmacol 2003;138:554–63

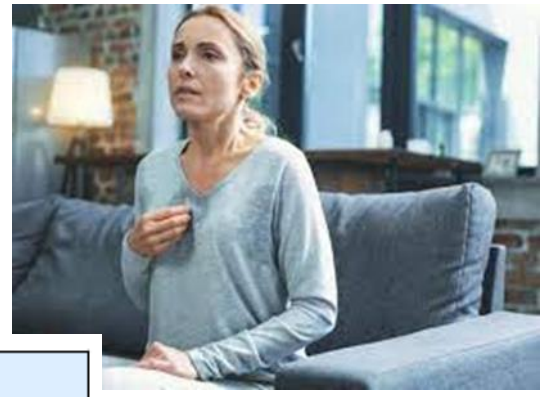
De Brito Gariepy H, Couture R. Blockade of tachykinin NK3 receptor reverses hypertension through a dopaminergic mechanism in the ventral tegmental area of spontaneously hypertensive rats. Br J Pharmacol 2010;161:1868–84


Hypothalamus
Periphery
KNDy neuron
Median preoptic nucleus (MnPO)
Normal cooling
NKB
Estrogen
NK3R
ERα
Thermoregulatory center
Heat dissipation mechanisms (characterized by sweating and peripheral vasodilation) are triggered in response to changes in temperature
The thermoregulatory center of the hypothalamus is innervated by KNDy neurons that are stimulated by NKB via NK3R and inhibited by estrogen
Hot flash response
VMS
Increased NKB signaling and KNDy activity
KNDy neurons hypertrophy
Low estrogen levels lead to loss of negative feedback
Increased activation of heat dissipation mechanisms contribute to the experience of hot flashes and night sweats
Declining estrogen levels leave NKB signaling unopposed
KNDy neurons become hypertrophied, contributing to increased signaling to the thermoregulatory center
Altered signaling in the thermoregulatory center shifts the balance for control of core body temperature and activates heat dissipation effectors resulting in VMS
Restoration of balance
↓VMS
Fezolinetant
NK3R antagonism blocks NKB and reduces KNDy neuron activity
FEZ
Restoration of set-point for control of core body temperature reduces frequency and severity of VMS
Fezolinetant, an oral NK3R antagonist, moderates NKB signaling and KNDy neuron activity, helping to restore thermoregulatory balance


No VMS
VMS 1-5 days/2weeks
VMS >=6 days/2weeks
P=.0001
CVD Event Rate
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
Years from Baseline


Arterial Stiffness Accelerates Within One Year of Menopause
Estimated Mean Arterial Stiffness
Black Women
White Women
-5
-4
-3
-2
-1
0
1
2
3
4
5
Premenopausal years
Menopause
Postmenopausal years

Tailored Care



Key Points

- Perimenopause is defined as a period encompassing physiologic changes that result in the onset of menstrual irregularities and other symptoms, until a woman reaches menopause
- Commonly encountered symptoms in the perimenopausal period include hot flashes, vaginal or sexual symptoms, sleep and mood changes, and bleeding
- Menopausal symptoms may long precede the final menstrual period, and earlier onset may predict a longer duration of symptoms
- Evaluation and treatment of symptoms should be personalized based on type and severity of symptoms and contraceptive need, using a shared-decision making model

Delamater and Santoro, Clin Obstet Gynecol. 2018 September ; 61(3): 419–432.

Objectives- Discussion

- Differential diagnosis : menopause versus other conditions
- Differential diagnosis between transition or perimenopause and menopause
- Menopause diagnosis in patients with IUD-LNG, or endometrial ablation or interovarian hysterectomy
- Diagnosis Tools ? Anamnesis ? Biology ? Progestin test ? Echography ?
- When to start a treatment (not to late , not to early) ? How to select the treatment ? Which treatment ?
- Which additional examinations ?