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Research Article

Has The Enigma of Steroid Feedback Effects on GnRHR Liberation Been Resolved with the Illustration of Estrogen Receptor-A on the Hypothalamic Kisspeptins Neurons-A Narrative Review

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Abstract

Earlier we had reviewed the roles of Kisspeptins in reproduction in 2012 and subsequently the confusion over progesterone in positive feedback effects with challenges in the earlier explanations offered. Since then, a lot of work has been done in rodents as the mammalian species to explain the part of epigenetics further . Estrogen generated by the ovarian follicles possess a crucial part in the central mode regulating reproduction through control of gonadotropin releasing hormone(GnRH) liberation via its negative along with positive feedback effects in case of female mammals. It has been well acknowledged that estrogen receptor-α(ER-α) modulates both negative along with positive feedback effects, however precise targets have continued to be enigmatic for over20 yrs. Subsequent to the invention of Kisspeptin(Kp) neurons in the form of afferent neurons which express ER-α to control GnRH neurons, the modes which modulate estrogen feedback are slowly getting revealed .Here we have tried to explain how Kp neurons in the arcuate nucleus (Arc), that are thought to bring about pulsatile GnRH/gonadotropins liberation along with folliculogenesis modulating the negative feedback effects the part of Kp neurons residing in the anteroventroperiventricular nucleus -periventricular nucleus((AVPV-PeN),that are believed to be implicated led in bringing about GnRH/ luteinizing hormone(LH) surge along with ovulation as a sequel, in modulating the positive feedback effects. This posit has been validated by studies which illustrated that estrogen bound ER-α both resulting in upregulation as well as downregulation of KISS 1 gene(KISS 1) in the Arc along with AVPV-PeN Kp neurons respectively . Furthermore, here the molecular along with epigenetic modes that modulate the KISS 1 expression control by estrogen is detailed. The role of afferent neurons which express ER-α in control of Kp liberation is further detailed.

Key words: Estrogen receptor-α; Kisspeptin neurons; negative; positive feedback effects; Arc /AVPV-PeN Kp neurons

Introduction

It has been well acknowledged that estrogen generated by the ovary possesses an essential part in the female reproductive system through its feedback effects on gonadotropin releasing hormone(GnRH) liberation in case of mammals. The central mode of the estrogen feedback effects on GnRH liberation has continued to be enigmatic for over decades .This had been in view of no illustration

regarding expression of estrogen receptor-α(ER-α),which is a key receptor isoform needed for estrogen feedback effects in the hypothalamic GnRH neurons. Extensive evaluation regarding hypothalamic Kisspeptins(Kp) neurons that are acknowledged to be expressing ER-α isoform have aided over time in getting insight about the central negative in addition to positive feedback effects of estrogen on GnRH liberation. Earlier we had reviewed the roles of Kp in reproduction in 2012along with controversies in the estrogen feedback effects on mode of ovulation in normal menstrual cycle including the historical perspective[1,2]. Here the physiological importance of this estrogen negative in addition to positive feedback effects on the tonic pulsatile as well as surge mechanisms of GnRH liberation that aids in the regulation of folliculogenesis as well as ovulation in case of female mammals respectively is detailed. Moreover, the molecular along with epigenetic modes modulating the control of Kisspeptin gene (KISS1) expression by estrogen, namely signaling of ER-α along with afferent neurons which express ER-α which might modulate the estrogen-based manipulation of Kp liberation from hypothalamic Kisspeptins(Kp) neurons is further detailed.

Methods

Thus, a narrative review was carried out did a using the using the search engine PubMed, Web of Science , Medline, Embase, Cochrane reviews, and Google Scholar, Search engine with the MeSH Terms; GnRH; Kisspeptins(Kp); estrogen feedback; negative& positive feedback effects; estrogen receptor-α(ER-α); reproduction; GnRH / gonadotropins liberation; brain targets from 1980 to 2023 till date.

Results

We found a total of 250 articles ,out of which we selected 96 articles for this review. No meta-analysis was done.

Estrogen feedback effects on pulsatile as well as surge mechanisms of GnRH / gonadotropins liberation

The mammalian reproduction is controlled by the hypothalamic-pituitary-gonadal (H-P-G)axis. Estrogen that gets liberated from the ovary, that exists downstream of this axis provides feedback to the higher centers inclusive of hypothalamus along with pituitary for controlling GnRH / gonadotropins liberation. Estrogen generation gets stimulated by the tonic pulsatile liberation of gonadotropins(like luteinizing hormone(LH) along with follicle stimulating hormone (FSH)) produced from the anterior pituitary gland, undergoing regulation from the GnRH pulses. At the time of follicular generation, circulating estrogen causes fine tuning of pulsatile liberation of GnRH for ensuring enough quantities of FSH , LH. These estrogen effects have been labelled as the negative feedback effects of estrogen'' on GnRH pulses. Once there has been enough stimulation by FSH , LH generation of large mature antral follicles takes place in the ovary. The generation along with liberation of estrogen takes over time slowly ,escalation occurring in parallel with follicular generation as well as in the form of sequelae, greater quantities of circulating estrogen obtained from the mature antral follicles (alias graafian follicles) which in turns leads to large bolus of hypothalamic GnRH liberation with subsequent pituitary LH(GnRH / LH) surge. This estrogen effect known as the so termed' positive feedback effect of estrogen' on GnRH liberation followed by ovulation induction. We are skipping the historical aspect of how part of GnRH got unearthed. Till date the pulsatile as well as surge mechanisms of GnRH liberation have been posited to get governed by independent hypothalamic modes known as the so termed ''GnRH pulses as well as surge developers' respectively[3].

Essential part of estrogen receptor-α regarding mammalian reproduction

Collecting proof has pointed to the key part regarding ER-α being the key estrogen receptor central isoforms implicated in both negative along with positive feedback effects of estrogen on GnRH / LH liberation . Actually , Esr1 (that encodes ER-α) knockout mice[4], besides rats[5], illustrated that hyper liberation of LH along with estrogen, that pointed to ER-α basically being implicated in modulation of estrogen negative feedback effects. Moreover, the Esr1 knockout mice as well as rats did not illustrate ovulation, however enhanced cystic follicles were observed in Esr1 knockout mice as well as rats. This pointed to ER-α being further implicated in positive feedback effects as well [4,5]. Conversely reproductive working of Esr2(that encodes ER-β) knockout animal model was documented to vary amongst animal models. Esr2 knockout mice illustrated normal liberation of LH along with estrogen[4] as well as were sub fertile , generating smaller litter size [6] while Esr2 knockout rats present with infertility along with have absence of ovulation [7]. Additionally, prior studies illustrated that selectively antagonizing ER-α signaling, however not estrogen-ER-β signaling deleted the endogenous LH surge in rats [8].In toto these observations pointed that ER-α basically modulates both negative along with positive feedback effects on GnRH / LH liberation.

Generally, ER-α is acknowledged to be a ligand activated transcription factor which activates or suppresses the target genes getting expressed. This estrogen bound ER-α has been documented to bind with estrogen response element(ERE) in the target genes for regulating gene expression [9]. Additionally, it has been pointed that estrogen bound ER-α cross talks with other transcription factors like activator protein1 (AP1) as well as nuclear factor κB(NFκB) along with this complex regulates target genes expression through binding to non-ERE response elements via the transcriptional partners [10]. Interestingly, a prior study illustrated that ER-α knock in/ knockout(KIKO) mice where a mutant ER-α(E207A/G208A) possesses absence of binding capacity to ERE , however possesses the capacity of cross talks with other transcriptional partners [11], illustrated the negative, however absence of positive feedback effects of estrogen on liberation of LH [12].These observations pointed that the negative feedback effects of estrogen on GnRH pulses is probably modulated through certain genes regulated by the ERE independent estrogen-ER-α signaling, whereas positive

feedback effects of estrogen is probably modulated through certain genes regulated by the ERE based estrogen-ER-α signaling.

Probable targets of negative along with positive feedback effects of estrogen in the Brain

The exact targets regarding negative along with positive feedback effects of estrogen on GnRH pulses as well as surge production has continued to be enigmatic for not only decades but whole 20th century in view of lack of documentation of expression of ER-α in GnRH neurons [13]. Hence the maximum acceptable reasoning is that some hypothalamic neurons that express ER-α act in the form of targets of the negative along with positive feedback effects of estrogen on GnRH pulses as well as surge production in addition to that these neurons that express ER-α transfer the estrogen signals to the GnRH neurons. A great quantity of cells that express ER-α were observed in variable hypothalamic nuclei -like maximum (anteroventroperiventricular area (AVPV), preoptic area(POA), arcuate nucleus (Arc),ventro medial nucleus(VMH)-at the mRNA along with protein levels besides the paraventricular nucleus(PVN)-as well as suprachiasmatic nucleus(SCN) in whom ER-α expression was basically observed at the mRNA levels in rats [14]. Akin to that, ER-α expression was observed at the mRNA along with protein levels in the POA, Arc along with VMH, besides in the PVN at the mRNA levels in sheep [15] . These observations were in agreement with prior studies which illustrated that radio labelled estrogen accrual took place in the POA, Arc along with VMH in rats [16].

Prior studies pointed to Arc being the maximum probable target of the negative feedback effects of estrogen. Smith as well as Davidson[17], illustrated that estrogen effect implants in the medio basal hypothalamus(MBH) inclusive of Arc repressed plasma quantities in ovariectomized (OVX)rats in 1974. Akeme et al. [18], demonstrated that estrogen implants in the Arc repressed LH pulses in OVX rats in 1983. Moreover, Nagatani et al. [19], demonstrated that estrogen micro implants in the Arc repressed LH pulses in fasted along with refed OVX rats, whereas estrogen implants in the PVN or brainstem A2 area repressed LH pulses in just fasted rats in 1994. These observations pointed that the negative feedback effects of estrogen might be modulated by neurons that express ER-α that reside in the Arc in case of normal nutritional situations as well as by numerous neurons that express ER-α that reside in the Arc, PVN along with Brainstem A2 area in case of malnutritional situations. The negative feedback effects of estrogen in case of malnutritional situations are probably modulated by de novo generation of ER-α in PVN along with brainstem A2 area, in view of 48h fasting escalates the quantities of ER-α immunoreactive cells in PVN along with Brainstem A2 area in OVX rats[20].

Prior studies pointed to neurons that express ER-α in AVPV along with/or POA were the maximum probable targets of the positive feedback effects of estrogen. Kawakami et al. [21], along with Goodman [22], illustrated in the latter 1970's that estrogen implants into the AVPV or adjacent area POA resulted in induction of LH surge in OVX rats. Wiegand et al. [23], illustrated in the latter 1980's that electrolytic damage around AVPV ameliorated the estrogen stimulated LH surge in OVX rats. Petersen et.al. [24], illustrated in the latter 1980's that implants possessing estrogen antagonists like LY -10074or keoxifene in the AVPV / POA area avoided estrogen stimulated LH surge in OVX rats . These observations pointed out that cells that express ER-α in the AVPV / POA area act in the form of targets of the positive feedback effects of estrogen for the induction of GnRH / LH) surge.

Kisspeptins neurons in the form of targets of the positive feedback effects of estrogen

Extensive work in the last 2 decades have illustrated that ER-α expression is clearly seen in the hypothalamic-Kisspeptins neurons in case of rodent [25-27] along with sheep [28] as well as Kisspeptin works in the form of a robust stimulant of gonadotropin liberation in rodents [26,29,30], in ruminants [31] along with primates [32,33].Till date it has been well acknowledged that Kisspeptin neurons that are ER-α expressing are the ones that basically bring about the positive feedback effects over GnRH liberation in case of mammals. Initially Kisspeptins were invented to start with in the form of endogenous ligands for GPR54 that represents an orphan Gq-coupled G-protein coupled receptor(GPCR) in case of humans in 2001 [34]. Further in 2003 two independent groups documented those inactivating mutations in the GPR54 gene resulted in hypogonadotropic hypogonadism in humans [35,36]. These significant observations pointed out that Kisspeptin-GPR54 signaling possesses a key part in the brain modes regulating GnRH / gonadotropins liberation in addition to puberty along with fertility in mammals[35,36]. This way anticipated inactivating mutations in the KISS 1 gene((that encodes Kisspeptin) further resulted in hypogonadotropic hypogonadism in humans [37]. In the case of humans the infertile phenotype who are carriers of inactivating mutations in the KISS 1 /GPR54 gene got re generated in case of KISS 1 /GPR54 knockout rodent models [36,38-40]. GPR54 expression is apparent in GnRH neurons in case of rodents [38,41-54] that pointed that Kp directly results in stimulation of GnRH liberation. Moreover, KISS 1 knockout caused untraceable quantities of LH along with FSH despite following OVX, that pointed to absence of tonic pulsatile LH liberation [40]. Additionally, KISS 1 knockout rats further did not illustrate estrogen stimulated LH surge. These observations pointed out that Kisspeptin-GPR54 signaling is necessary for both GnRH pulses along with surge production besides modulation of estrogen feedback effects on GnRH/ LH liberation.

Histological studies in case of rodents illustrated that cell bodies of Kp neurons are basically placed in anterior hypothalamic areas like AVPV periventricular nucleus continuum(AVPV-PeN) along with in the posterior hypothalamic areas in Arc [25,26,42,43]. Significantly ER -α was observed in both populations of hypothalamic Kp neurons, along with Kp expression is regulated by estrogen in a brain area particular manner in rodents [25,26,42].

More particularly, the Arc KISS 1 expression quantities were greater at the time of diestrus along with got repressed following estrogen treatment [25,26,42]. While the AVPV-PeN KISS 1 expression quantities were greater in the afternoon of proestrus along with got escalated following estrogen treatment in rodents [25,27,42]. These observations pointed out that the Arc Kp neurons repress the negative feedback effect of estrogen, whereas AVPV-PeN Kp neurons are the targets of the positive feedback effect of estrogen.

Figure 1demonstrates the brain modes [44].

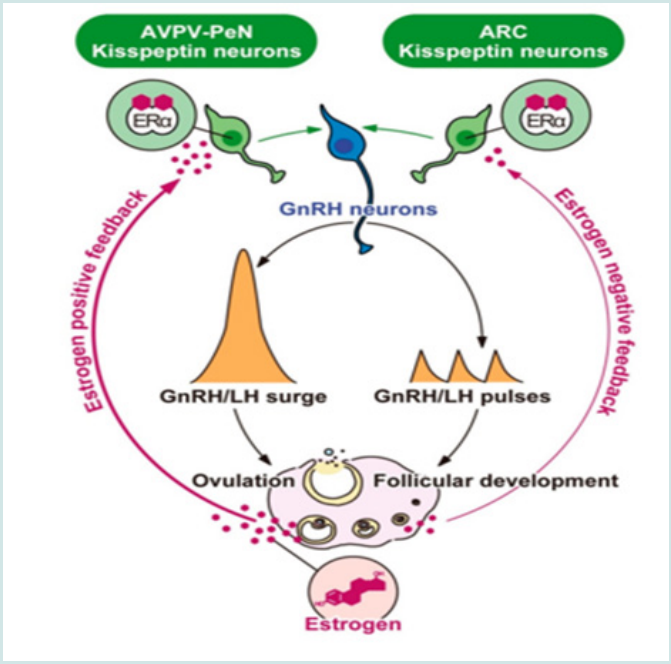

Figure 1: Courtesy ref no-44-Central mechanisms underlying the negative and positive feedback actions of estrogen on pulsatile and surge modes of gonadotropin-releasing hormone (GnRH)/luteinizing hormone (LH) release in female rodents. Estrogen production along with follicular development is stimulated by GnRH/gonadotropin pulses. During the follicular development period, low levels of circulating estrogen fine-tune GnRH/LH pulses via the negative feedback action of estrogen. The estrogen negative feedback action is considered to be mediated by estrogen receptor α (ERα)-expressing kisspeptin neurons located in the arcuate nucleus (ARC). Estrogen production and release gradually increase along with the follicular development, and consequent high levels of circulating estrogen derived from mature follicles, in turn, induce GnRH/LH surge and hence ovulation via the positive feedback action of estrogen. The estrogen positive feedback action is likely mediated by ERα-expressing kisspeptin neurons located in the anteroventral periventricular nucleus–periventricular nucleus continuum (AVPV-PeN).

Molecular along with Epigenetics Modes modulating the control of Arcuate KISS 1 expression by Estrogen along with part of arcuate Kisspeptins neurons in the form of GnRH Pulse Generator in Mammals

Till date the Arc Kp neurons have been believed to be targets of the negative feedback effect of estrogen over GnRH pulse generation, along with akin populations of Kp neurons have been observed in the Arc of other species(spp) or infundibular nucleus of primates(= Arc in other spp)of various mammalian spp inclusive of human [45]macaque monkeys [45-48], sheep [28,49-51],goats [31,52,53]cattle [54],horse [55],pigs [56],along with musk screws [57].The studies of Uenoyama group along with other prior studies illustrated that estrogen treatment basically caused repression of Arc KISS 1 expression in rodents[25,26]. Akin to that in rodents, prior studies illustrated estrogen-based suppression in the Arc Kp neurons in sheep[58], along with the infundibular nucleus of primates inclusive of human [45]. These observations pointed out the negative feedback effects of estrogen on Arc Kp neurons would be akin amongst mammalian spp.

As per the rodent model studies estrogen-based suppression of KISS 1 expression in Arc Kp neurons is probably modulated through the ERE independent pathways in view of estrogen suppressed KISS 1 expression in Arc Kp neurons in ER-α KIKO mice as well[59,60]. Additionally, the prior work of Uenoyama group chromatin immunoprecipitation(ChIP) assay with antibodies against ER-α in addition to acetylated Histone H3 documented that estrogen bound ER-α stimulated histone H3 deacetylation of the KISS 1 promoter area in the Arc Kp neurons by demonstrating that the estrogen treatment resulted in reduction of acetylated histone H3 quantities in the KISS 1 promoter area in case of mouse Arc tissue[61]. These observations pointed that estrogen based inactivating manipulation of histone H3 of KISS 1 promoter area

led to suppression of KISS 1 expression. Moreover, in vivo reporter assay, where KISS 1 -GFP reporter mice were used pointed that the 5' intergenic area of the KISS 1gene is needed for the induction of KISS 1 mRNA expression in the Arc of female mice[99]. Actually, reporter mice that were possessing the 5' truncated KISS 1 -GFP transgene(RBRC09415, RBRC09416) did not show the GFP expression in the AVPV-PeN Kp neurons in estrogen's presence . Additionally, other reporter mice that possessed full length KISS 1 -GFP transgene(RBRC09413) illustrated the GFP expression in Arc along with AVPV-PeN Kp neurons in OVX as well as estrogen treated OVX situations respectively [62]. In toto these observations pointed that one could posit that the estrogen -bound (ER-α), might delete the crosstalk, that is in all probability chromatin loop generation amongst the KISS 1promoter as well as 5' intergenic enhancer area that causes the suppression of KISS 1 expression in the Arc Kp neurons despite subsequent to OVX. In toto the molecular modes of negative feedback effects of estrogen on Arc KISS 1 expression are illustrated in Figure 2.The circulating estrogen in maximum probability binds to the ER-α in the Arc Kp neurons followed by estrogen -bound ER-α,that is coupled to yet not clear transcription partners through non-canonical ERE independent pathway in the Arc Kp neurons. The estrogen -bound ER-α might result in induction of histone H3 deacetylation of the KISS 1 promoter area, along with estrogen -bound ER-α along with /or these inactivating modifications of histone might result in unwinding of the chromatin loop amongst KISS 1 promoter along with the 5' intergenic area of the KISS 1 locus leading to suppression of Arc KISS 1 expression in the Arc Kp neurons.

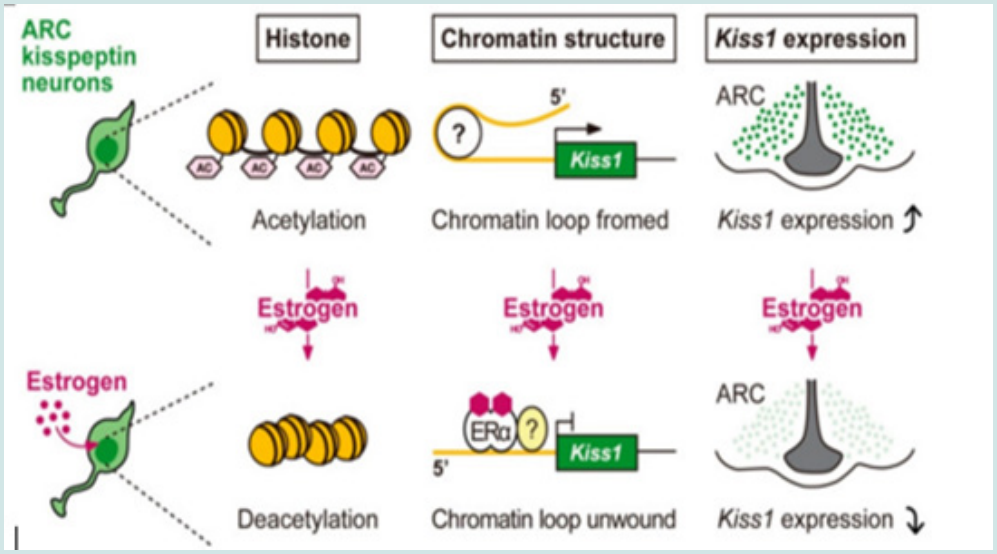

Figure 2: Courtesy ref no-44-Putative molecular mechanism of the negative feedback action of estrogen on Kiss1 expression in the arcuate nucleus (ARC). Circulating estrogen seems to act on ARC kisspeptin neurons, in which estrogen-bound estrogen receptor α (ERα) coupled with an unknown transcriptional partner may repress Kiss1 expression via histone deacetylation and unwinding chromatin loops between the Kiss1 promoter and the 5′-intergenic regions of Kiss1 locus. In the absence of estrogen, ARC Kiss1 expression may be up-regulated by histone acetylation and chromatin loop formation between the Kiss1 promoter and the 5′-intergenic regions of the Kiss1 locus.

Maximum of Arc Kp neurons have been acknowledged to be expressing neurokinin B(NKB) and dynorpinA(Dyn),hence these Arc Kp neurons are further referred to as KNDY neurons[51,52,62,63].Collecting proof points that these Arc KNDY neurons can work in the form of intrinsic pulse generator[65,66]. This belief was recently validated by the study of Uenoyama group that illustrated that rescue of KISS 1 expression in just the Arc Tac3(NKB gene) expressing neurons had the recovery of LH pulses along with follicular generation in case of global KISS 1 knockout rats[67].The multiple unit activity (MUA) recording illustrated that rhythmic escalation of MUA volleys determined from the recording electrodes whose placement was intricate to Arc Kisspeptin(KNDY) neurons got synchronized with LH pulses in goats[31,52]. Additionally, conditionally Arc particular KISS 1 knockout by utilization of Cre-lox P system robustly or partially repressed LH pulses in rats[67], along with mice [68,69],as per the knockout in every subject. Furthermore, fiber photometry recording documented that the mouse Arc Kp neurons displayed that rhythmic escalation of intracellular Ca2+ quantities which were parallel with the LH pulses[70].Hence Kp neurons might liberate Kp in a pulsatile manner followed by stimulation of GnRH / gonadotropins pulses . Actually, Keen et al. [71], along with Kurian et al.[72], illustrated Kp liberation, that in general is parallel with GnRH pulses at the median eminence of rhesus monkeys .Hence, the negative feedback effects of estrogen directly work on the intrinsic source of GnRH pulse generator-that is Arc Kp neurons

along with it is followed by repression of GnRH / LH pulses. Regarding this the robust repression of GnRH / LH pulses prior to the afternoon of LH surge in case of female rodents in the existence of escalated quantities of estrogen might be secondary to the prior detailed epigenetic suppression of Arc KISS 1 expression along with subsequent deficiency of Kp in Arc Kp neurons. Actually, chronic therapy of preovulatory quantities of estrogen robustly represses tonic LH liberation in the morning (prior to LH surge) in case of OVX rats along with this estrogen therapy basically resulted in reduction of KISS 1 expression in addition to Kisspeptin immunoreactivity in the Arc of female rats [27].

Besides hampering the effects of estrogen over KISS 1 expression, estrogen might further hamper the pulsatile action of Arc Kp neurons through other intra-Kp neuronal modes or certain afferent ER-α expressing neurons in Arc Kp neurons. The recurrence of KNDY neuronal action as evidenced by the MUA volley recording was escalated along with reduced by a central delivery of NKB along with Dyn respectively in case of goats [52]. Maximum of KNDY neurons express both tachykinin NK3 receptors, a Gq coupled GPCR for NKB along with kappa-opioid receptor(KOR),a Gi coupled GPCR for Dyn in mice [64,73]rats [74], sheep [75].Taking into account ,the stimulatory or hampering signaling of NKB or Dyn respectively, these observations pointed that the pulsatile action of Arc Kp(KNDY) neurons gets regulated by NKB along with Dyn in an autocrine/paracrine fashion [76]. Prior studies illustrated that estrogen reduced NKB gene (Tac2) in mice, along with Tac3/TAC3 in case of other mammals) expression in the Arc of mice [59,77] as well as sheep [78], infundibular nucleus of rhesus monkeys [79]. Additionally, estrogen reduced Dyn gene(Pdyn) expression in the Arc of mice [31] along with rats [80]. These observations pointed that estrogen might modulate Kp liberation from the Arc KNDY through altering stimulatory NKB as well as hampering Dyn inputs to the KNDY neurons.

Intriguingly, the proestrus quantities of estrogen suppressed Arc KISS 1 expression [26,27],while the diestrus quantities of estrogen that brought about negative feedback effects of LH pulses [44]could not result in repression of Arc KISS 1 expression in female rats [26,27].The dosage of estrogen needed for suppression of Arc KISS 1 expression evokes the probability the some afferent neurons which express ER-α to Arc Kp neurons might be implicated in the negative feedback effects of estrogen on Kp liberation from the Arc Kp neurons .This belief gets validated by a prior study that illustrated that estrogen reduced with efficacy the plasma LH quantities in Kp neurons-particular ER-αknockout mice, in whom Arc KISS 1 expression was not suppressed by estrogen therapy[81]. Thus of the candidates implicated in the negative feedback effects of estrogen would be comprised by Dyn residing in the PVN[74], along with that nor-binaltorphimine(norBNI),a KOR antagonist, escalated LH pulses in estrogen treated OVX rats ,however not in OVX rats without replacing[82]. Moreover ,their study illustrated that suppression of glucoprivation caused repression of LH pulses as well as resulted in induction of fos(encoding C-Fos-a marker of neuronal activation) expression in PVN Dyn neurons-,whereas central glucoprivic repression of LH pulses in estrogen treated OVX rats[74]. These observations pointed out that PVN Dyn neurons might partially modulate negative feedback for repression of Kp liberation through KOR that gets expressed in Arc Kp neurons along with followed by repression of pulsatile GnRH / LH liberation.

The Part of Anteroventroperiventricular Nucleus Periventricular Nucleus((AVPV-PeN), Preoptic area(POA) Kisspeptin neurons in the form of Molecular GnRH / luteinizing hormone (LH) surge generator as well as Molecular along with Epigenetics Modes modulating the control of (AVPV-PeN)-POA KISS 1 expression by Estrogen Positive feedback Effect

The AVPV-PeN Kp neurons have been believed to be the targets of estrogen positive feedback effects over GnRH surge generator in case of rodents as prior outlined. Till date Kp neurons have been isolated in the POA of different mammalian spp, inclusive of macaque monkeys[46,48], sheep[50],goats[53], ,cattle[54],pigs[55], along with musk screw[56], Prior studies illustrated that basically estrogen therapy mostly escalated AVPV-PeN KISS 1 expression[48,9,51,12,8] in addition to stimulated C-Fos expression in AVPV-PeN-Kp neurons in case of OVX rodent models[49,51]. Akin to that prior studies of Uenoyama group as well as other studies illustrated estrogen stimulated KISS 1 along with/or C-Fos expression in the POA/ PeN of macaque monkeys[46,48], sheep[50],goats[54],cattle[55],pigs[56], along with musk screw[57],Hence the POA/ PeN Kp neurons in such spp have been believed to be parallel to AVPV-PeN Kp neurons in rodents in terms of an acute estrogen positive feedback effects area.

The belief regarding AVPV-PeN Kp neurons acting in the form of GnRH surge generator gets further validated by these subsequent studies regarding sex variations in production of LH surge in case of rodent models[83,84].It has been well acknowledged that male rats did not illustrate LH surge despite their treatment with preovulatory quantities of estrogen subsequent to castration in adulthood[85].In agreement male rodents display just occasional Kp neurons in the AVPV-PeN despite presence of estrogen, while females illustrate a clubbing of AVPV-PeN Kp neurons in estrogen existence[51,76,7]. Sex steroids which took origin from the perinatal testis are believed to result in defeminization of the AVPV-PeN Kp neurons in view of neonatal castration aided in the estrogen stimulated AVPV-PeN KISS 1 expression along with LH surge in genetic male rats in adulthood to be illustrated [76,85].Hence these observations pointed that AVPV-PeN Kp neurons acting in the form of targets of estrogen positive feedback as well as work as intrinsic source of GnRH surge generator in case of rodents.

Estrogen stimulated KISS 1 expression in AVPV-PeN-Kp neurons gets probably modulated by the ERE based pathway in view of estrogen therapy did not elicit AVPV-PeN KISS 1 expression along with production of LH surge in ER-α KIKO[12,59].

Furthermore, TomikawaetaI,[61], from the Uenoyama group in their prior study illustrated utilizing ChIP assay with antibodies against ER-α in addition to acetylated histone H3 documented that estrogen bound ER-α bound to the KISS 1 promoter area in the AVPV-PeN Kp neurons by pointed that the estrogen treatment resulted in reduction of acetylated histone H3 quantities in the KISS 1 promoter area in view of estrogen stimulated ER-α binding along with histone H3 acetylation of the KISS 1 promoter area in the in case of mouse AVPV-PeN tissue[98]. These observations pointed that an estrogen based activating manipulation of histone H3 of the KISS 1 promoter area causes KISS 1 expression getting induced. Moreover, chromatin conformation capture(3C) assay pointed that estrogen stimulated chromatin loop generation amongst the KISS 1promoter as well as 3' intergenic area of the KISS 1 locus works in the form of enhancer for estrogen stimulated KISS 1 expression in the AVPV-PeN Kp neurons. Actually, in vivo reporter assay, where KISS 1 -GFP reporter mice were used pointed that the 3' intergenic area of the KISS 1gene is needed for the induction of KISS 1 mRNA expression by estrogen in the AVPV-PeN of female mice[61].In particular reporter mice that were possessing the3'truncated KISS 1 -GFP transgene(RBRC09417) did not show the estrogen stimulated GFP expression in the AVPV-PeN Kp neurons, however illustrated OVX stimulated GFP expression in theArc Kp neurons. Nevertheless, other reporter mice that possessed full length of KISS 1 -GFP transgene(RBRC09413) illustrated the GFP expression in Arc along with AVPV-PeN Kp neurons in OVX as well as estrogen treated OVX situations respectively.

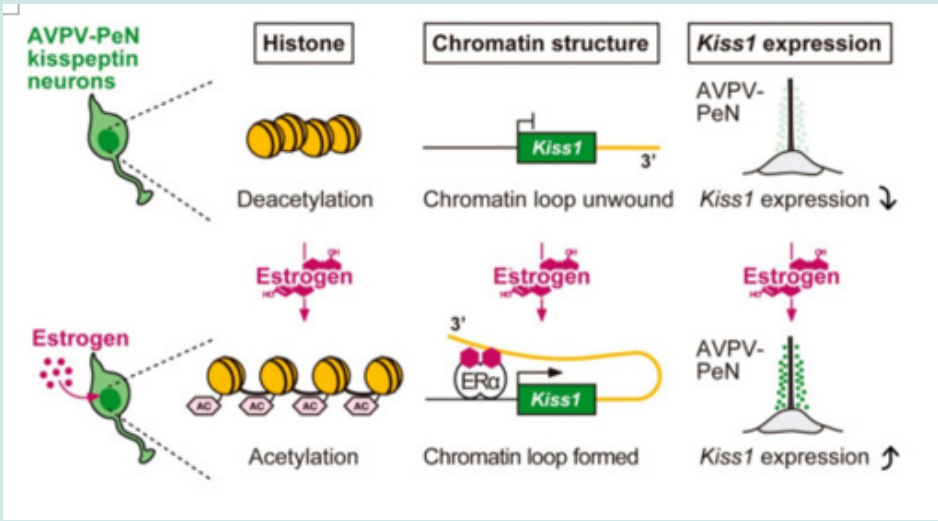

Figure 3: Courtesy ref no-44-Putative molecular mechanism of the estrogen positive feedback action on Kiss1 expression in the anteroventral-periventricular nucleus-periventricular nucleus continuum (AVPV-PeN). Preovulatory levels of circulating estrogen seem to act on AVPV-PeN kisspeptin neurons, in which estrogen-bound estrogen receptor α (ERα) may increase Kiss1 expression via histone acetylation of Kiss1 promotor region and chromatin loop formation between the Kiss1 promoter and the 3′-intergenic regions of Kiss1 locus. In the absence of estrogen, AVPV-PeN Kiss1 expression may be down-regulated by histone deacetylation of the Kiss1 promoter region and unwinding chromatin loops between the Kiss1 promoter and the 3′-intergenic regions of the Kiss1 locus.

Thus, Uenoyama group posited the molecular mode implicated in the estrogen positive feedback effects on AVPV-PeN KISS 1 expression in rodents as illustrated in Figure 3. In brief at proestrus greater quantities of estrogen in case of rodents bind to ER-α in the AVPV-PeN Kp neurons along with estrogen bound ER-α might bind to EREin the KISS 1 promoter area as well as escalate histone H3 acetylation of the KISS 1 promoter area. The estrogen-ER-α binding along with/or the activating manipulation of histones might result in chromatin loop generation amongst the KISS 1promoter as well as 3' intergenic area of the KISS 1 locus causing KISS 1 expression in the AVPV-PeN Kp neurons. Interestingly both the proestrus along with diestrus quantities of estrogen possess the capacity of enhancing AVPV-PeN KISS 1 expression in case of female rats[51], whereas just proestrus quantities of estrogen stimulated LH surge in female rats[51]. These observations evoke a probability that besides enhancing AVPV-PeN KISS 1 expression ,some afferent neurons which express ER-α might be implicated in the positive feedback effects of estrogen on Kp liberation from the AVPV-PeN Kp neurons. Brainstem noradrenergic A2 neurons[86] work in the form of a candidate as illustrated in prior studies that displayed estrogen resulted in C-Fos expression[87] along with alpha1 adrenergic receptor blockade, ameliorated afternoon LH surge in case of proestrus female rats[88]. Furthermore, the SCN, in which ER-α mRNA expression was observed in rats[33], might further work in the form of area for positive feedback effects of estrogen. It is well acknowledged that the timing of LH surge takes place with the aid of a circadian clock which resides in SCN, as well as takes place in the afternoon LH surge of proestrus rodents. A prior

study pointed that SCN vasopressin neurons were implicated in afternoon LH surge induction in view of vasopressin V1 receptor antagonism ameliorated afternoon LH surge in case of proestrus female rats [89]. Intriguingly, an electrophysiological study illustrated that vasopressin therapy stimulated Kp neuronal activity in case of estrogen treated OVX mice ,however not in OVX mice[90], pointing that estrogen might stimulate the sensitivity of AVPV-PeN Kp neurons to vasopressin, into these observations pointed that noradrenergic A2 neurons along with SCN vasopressin neurons might modulate estrogen positive feedback effects to stimulate Kp liberation from AVPV-PeN Kp neurons. Prior studies illustrated that AVPV-PeN Kp neurons basically send their axonal projections to the GnRH cell bodies in the POA of mice[43,91] in addition to Kp impacting a long-lasting excitation of GnRH neurons[92,93]. These observations pointed that Kp liberation from the AVPV-PeN Kp neurons might work on GnRH cell bodies for stimulating GnRH / LH surge.

Conclusions

In total the extensive studies regarding hypothalamic Kisspeptin neurons in the past 20 years have been unravelling the cellular along with molecular modes of negative as well as positive feedback effects of estrogen on GnRH pulses along with surge production in case of female mammals. Dependent on observation of outcomes obtained at present it has been posited that the sustenance of negative feedback effects of estrogen that fine tunes GnRH pulses gets basically modulated by the Arc Kp neurons, where estrogen possesses a direct suppressive effect on KISS 1 expression. Furthermore, estrogen might indirectly hamper pulsatile Kp liberation through afferent neurons which express ER-α . Furthermore, studies regarding clarification of the afferent inputs which relay signals to the Arc Kp neurons are needed. Additionally, it was posited that the positive feedback effects of estrogen that stimulated GnRH surge is basically modulated via the anterior population (AVPV-PeN in case of rodents along with POA/ PeN in case of other mammals)of hypothalamic Kp neurons ,where estrogen directly stimulates KISS 1 expression . Moreover , estrogen might indirectly stimulate surge modes of Kp liberation probably afferent neurons which express ER-α, that are brainstem noradrenergic A2 neurons along with SCN vasopressin neurons. Till now just occasional studies are present which illustrate Kp liberation, other than studies conducted in rhesus monkeys[71,72],as detailed earlier. Greater studies in future are required to illustrate the pulsatile as well as surge modes of Kp liberation , besides clarification of modes of Kp liberation regulated by negative as well as positive feedback effects of estrogen. The same authors from Uenoyama group recently highlighted the roles of various opioidergic neurons inclusive of μOR,κOR[94] etc in regulation of negative as well as positive feedback effects of estrogen which we had attempted earlier as a case report in 2002(unpublished). They further illustrated the crucial part of Kp neurons in coordination of endocrine system and sexual behaviour in mammals[95]. Xie et al.[96],further illustrated the role of Kisspeptin in the regulation of hypothalamic-pituitary-gonadal (H-P-G)axis in reproduction[96] (see Figures 4 & 5 for modes of Kp action and in negative as well as positive feedback effects of estrogen on GnRH liberation).

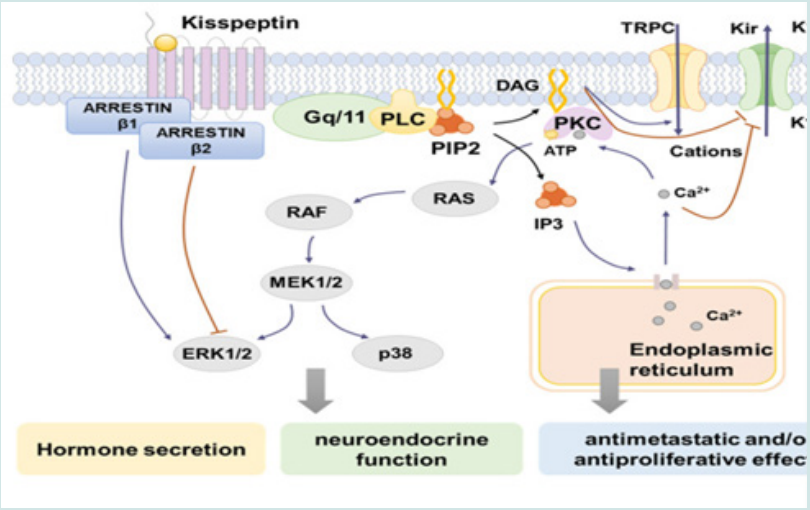

Figure 4: Courtesy ref no-96-Kisspeptin/KISS1R signaling pathways. Kisspeptin binds to KISS1R, inducing the intracellular portion of KISS1R phosphorylates Gq/11. Then PLC is activated, and it hydrolyzes PIP2 to IP3 and DAG. IP3 induces intracellular Ca2+ release from the endoplasmic reticulum, while DAG activates PKC, causing the phosphorylation of MAPK, such as ERK1/2 and p38. Moreover, the activation of KISS1R recruits arrestin-1 and -2, which decreases and increases ERK1/2 phosphorylation, respectively. The increase of intracellular Ca2+ changes ion channel permeability by blocking the inwardly rectifying potassium channel (Kir). The depolarization of GnRH neurons is caused by activation of a nonselective cation channel (TRPC) and suppression of Kir by DAG and increased Ca2+. Through the signaling pathways above, kisspeptins activate different MAPKs and cause the release of Ca2+, which contribute to hormone-releasing regulation, neuroendocrine function, antimetastatic and/or antiproliferative effects.

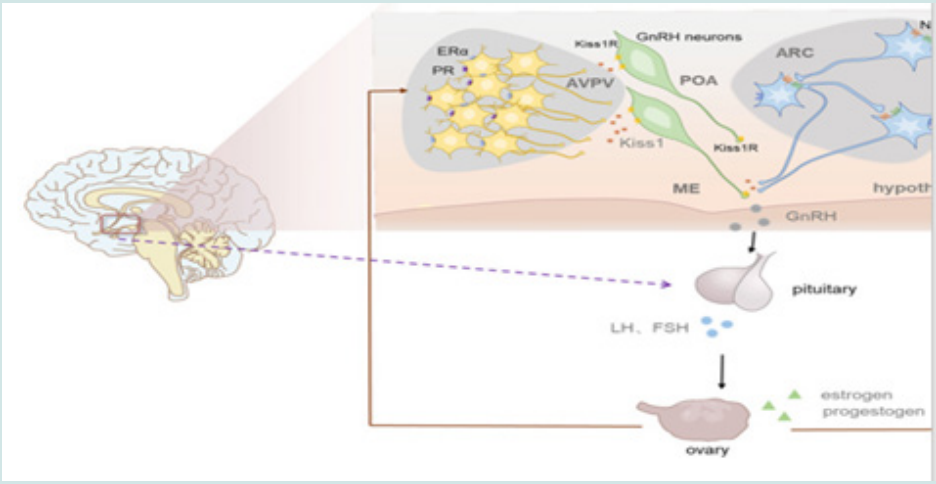

Figure 5: Courtesy ref no-96-The role of kisspeptin in HPG axis and the positive and negative feedback of sex steroids in female. The population of kisspeptin neurons are located in anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC) in rodents. ARC kisspeptin neurons which express NKB and Dyn are named KNDy neurons. Acting in an autocrine/paracrine manner, NKB stimulates kisspeptin secretion while Dyn inhibits it, thus regulates the release of GnRH indirectly. In this way KNDy neurons mediate negative feedback of estrogen and enable the generation and termination of GnRH pulse. AVPV NEURONS regulate the generation of GnRH sulge, thus induce LH surge, which is more significant in female ovulation. Progesterone also plays an indispensable role in the generation of GnRH surge.

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