

Citation	Species	Experimental Design	Evidence of Estrogen Receptor α (ER α) Activation/Exposure (ERA)	Evidence of Change in Kisspeptin(Kiss-1) Expression (CKE)	ERA observed?	CKE observed?	Relevant Notes
Adachi et al., 2007	Adult Wistar-Imamichi strain rats (<i>Rattus norvegicus</i>)	Organisms were ovariectomized(OVX) and castrated(CAS). Females received either a low E2(20 ug/mL estradiol in peanut oil) or high E2 treatment (crystalline E2 enough to produce 514.1 pg/ml of E2 levels). Males received either a testosterone(T) or high E2 treatment; 9 hr-post estrogen exposure	-E2 exposure -90.4% ER α immunoreactivity in the AVPV KiSS-1 cells and 91.7% ER α immunoreactivity in the ARC KiSS-1 cells in the low E2-treatment	15% c-fos activity in the AVPV KiSS-1 cells; 40% c-fos activity in the ARC KiSS-1 cells (high E2 exposure)	Yes	Yes	
		Organisms were ovariectomized(OVX) and castrated(CAS). Females received either a low E2(20 ug/mL estradiol in peanut oil) or high E2 treatment (crystalline E2 enough to produce 514.1 pg/ml of E2 levels). Males received either a testosterone(T) or high E2 treatment.; 14 hr-post estrogen exposure		significant increase in percentage of AVPV KiSS-1 mRNA-positive neurons with c-Fos immunoreactivity was significantly higher in the high E2-treated animals at 14:00 hr compared to 9:00 hr (60% c-fos activity in the AVPV KiSS-1 cells; 45% c-fos activity in the ARC KiSS-1 cells) -significant increase of # of activated ARC KiSS-1 cells in Low-E2 exposure (100 vs 500 cells) -significant difference of c-Fos immunoreactivity between high and low estrogen treatment	Yes	Yes	
		High E2-treated rats received either a brain injection of anti-rat metastin/kisspeptin monoclonal antibody or normal mouse IgG. LH assay done afterwards for LH surge.		-significant increase in relative expression of KiSS-1 post OVX and high(2% vs 0.1%) and low estrogen (2.3% vs 0.1%) exposure in AVPV KiSS-1 cells -significant decrease in relative expression of KiSS-1 cells post OVX and high estrogen exposure (2% vs 12%) and CAS and high estrogen exposure (2% vs 8%) in ARC KiSS-1 cells.	Yes	Yes	
Alcin et al., 2013	Adult Rhesus Monkey (<i>Macaca mulatta</i>)	adult OVX rhesus monkeys divided into 4 experimental groups with empty-filled pills for 28 days, E2-filled pills for 28 days, empty-filled pills for 28 days and progesterone(P)-filled pills for the last 14 days, or E2-filled pills for 28 days and P-filled pills for the last 14 days	Estrogen Treatment	-increased expression of Kiss1 due to OVX -Abolished Kiss1 expression in the ARC Kiss-1 neurons with E2 treatments -Decreased Kiss1 expression but not to the level that E2 treatment did in P-filled treatment	Yes	Yes	-kisspeptin neurons in the ARC of the hypothalamus appears to play a major role in mediating these feedback actions of steroids in non-primate species -ovariectomised monkeys had largely expressed Kiss1 neurons whereas in intact animals, the kisspeptin cell bodies were small in size

Clarkson et al., 2008	Mice (<i>Mus musculus</i>)	Control Mice given implants of 17B-estradiol(1ug/20 g of body weight) which is then injected. 6 days later, mice received an injection of estradiol benzoate (1ug/20g of body weight) or vehicle control at 9 am. mice were treated with progesterone as well (500 ug/20 g of body weight).	Estrogen treatment -The percentages of kisspeptin neurons expressing ER alpha within the AVPV, rPVpo, and cPVpo divisions of the RP3V were 64 + 8%,45 + 8%, and 36 + 7%, respectively	-Kisspeptin neurons were found to express c-FOS in each of the OVX+E mice with mean percentage values of 33 ± 4%, 24 ± 4%, and 35 ± 3% of kisspeptin neurons with c-FOS in the AVPV, rPVpo, and cPVpo, respectively while in the vehicle, none of the kisspeptin neurons expressed c-FOS -the percentage of kisspeptin neurons expressing c-FOS was similar (30 -40%) between Gpr54-null and wild-type mice across the RP3V	Yes	Yes	-strong correlation found between the percentage of c-FOS-positive kisspeptin neurons and percentage of c-FOS positive GnRH neurons -kisspeptin-GPR54 signaling is essential for GnRH neuron activation that initiates ovulation -Estrogen induces 30-40% Kiss1 c-fos expression in both the Gpr54-null and wild type
		Gpr54 knockout mice with above procedure			Yes	Yes	
		Kiss1 knockout mice with above procedure			Yes	Yes	
Dubois et al., 2015	Adult Mice (<i>Mus musculus</i>)	-generated ERalpha knockout mice via Cre recombinase. -ovariectomized mice treated with sesame oil or E2 dissolved in sesame oil(1 mg/mL) exposure -long term OVX-E2 exposure at the same concentration	-E2 exposure(1 mg/ml)	-While E2 significantly suppresses Kiss1 mRNA to undetectable levels in WT mice, it had no effect on Kiss1 mRNA expression in the ARC of ERalpha KO mice. -in the AVPV, Kiss1 mRNA levels were low in the WT mice and undetectable in KO mice 7 days after OVX. E2 significantly increased Kiss1 mRNA to higher levels in WT mice compared with vehicle-treated mice. E2 is able to stimulate a low level of detectable Kiss1 mRNA expression in ERalpha KO mice which did not differ from basal Kiss1 mRNA levels in vehicle-treated WT mice.	Yes	Yes	-estradiol activation of ERalpha in kisspeptin neurons in the ARC suppresses GnRH/LH secretion whereas E2 activation of ERalpha in kisspeptin neurons in the anteroventral periventricular nucleus mediates the release of GnRH/LH surges(positive feedback) -E2 stimulated LH surges in WT mice and no effect in KERalphaKO mice -Kiss1 mRNA completely gone after E2 treatment however normal in ERalpha knockout -this paper signifies there's multiple methods of which estrogen can reduce LH levels -there may be existence of a redundant negative feedback pathways may exist -suggestions that GABA afferents to the GnRH neurons may be involved and POMC expressing neurons as targets of E2 negative feedback actions
Dungan et al., 2007	Adult female Mice (<i>Mus musculus</i>)	-GPR54 KO mice were generated by retroviral mutagenesis. -OVX mice and examined serum LH levels 7 days later, then implanted with empty or E-filled capsules -experiment 3 tests whether GPR54 signaling mediates positive feedback of E on LH secretion	E-filled capsule treatment	-When exposed to estrogen, there was an abolishment of Kiss1 cells in both WT and GPR54 KO in the ARC. -In the AVPV, WT experienced a significant increase of Kiss1 cells whereas GPR54 KO experienced a significant increase to levels equal to OVX WT pre-E exposure.	Yes	Yes	The Role of Kisspeptin–GPR54 Signaling in the Tonic Regulation and Surge Release of Gonadotropin-Releasing Hormone/Luteinizing Hormone
	Adult Female Rhesus Macaques (<i>Macaca mulatta</i>)		estradiol exposure	-Increased Kiss-1 expression (2.2) related to young and middle-aged macaques -OVX causes a significant increase in Kiss1 expression but E2 reverts and abolishes Kiss-1 expression to levels lower than that in young macaques	Yes	Yes	

Eghlidi et al., 2010	Young Female Rhesus Macaques (<i>Macaca mulatta</i>)	tested various ages and E2(long and short-term) treatment with OVX	estradiol exposure	-decreased Kiss-1 expression (0.1) -OVX causes a non-significant increase in Kiss-1 expression(0.1 vs 3.9). E2 reverts the effects of OVX.	Yes	No	questionable? Looks like a significant increase based on graph
Kauffman et al., 2007	Adult Wistar-Imamichi strain rats(<i>Rattus norvegicus</i>)	adult rats were either left intact or gonadectomized(GNX) and implanted with 17 β -estradiol or nothing. Adult female rats were OVX and given estradiol in sesame oil(5 ug) with a second injection of estradiol(50 ug)	estradiol treatment	-In the AVPV Kiss1 neurons, E2 causes a significant increase in Kiss1 cells and mRNA only in female rats. Overall increase in Kiss1 cells in female controls. -In the ARC Kiss1 neurons, E2 causes a significant decrease in Kiss1 cells and mRNA regardless of treatment or sex.	Yes	Yes	Sexual Differentiation of Kiss1 Gene Expression in the Brain of the Rat sexual differentiation in Kiss1 expression in AVPV but not in the ARC
Kim et al., 2011	Mice (<i>Mus musculus</i>)	gonadectomized mice and rats then received an E2-filled implant	estradiol treatment	-Significant increase in Kiss1 cells in both males(70 vs 1) and females(75 vs 1) post-OVX and E2 treatment in the MeA(p<0.05) -significant increase in Kiss1 copies in MeA and AVPV/PeN for both males (150 vs 50; 100 vs 20) and females(100 vs 20; 400 vs 100) post GNX and E treatment -significant increase in Kiss1 cells for males in the MeA and AVPV (50 vs 4; 45 vs 12) -significant decrease in Kiss1 cells for males in the ARC(45 vs 200)	Yes	Yes	- p < 0.05
	Adult Wistar-Imamichi strain rats(<i>Rattus norvegicus</i>)			-Significant increase in Kiss1 neurons and mRNA/cell in both males(50 vs 10; 40 vs 25) and females(40 vs 4; 45 vs 19) post-OVX and E2 treatment in the MeA (p<0.05)	Yes	Yes	
Kinoshita et al., 2005	Adult Female Wistar-Imamichi strain rats(<i>Rattus norvegicus</i>)	-Animals were OVX and either received a varying dose of E2 to produce a low (35.8 pg/mL) or high (514.1 pg/mL) E2 level. Others received nothing. -control rats also received an injection of anti rat metastin or PBS(non immunized mouse IgG) into the third ventricle to determine the effects of metastin on LH surge	low E2 levels (35.8 pg/mL)	-non-significant change in relative expression of Kiss-1 compared to OVX controls -injection of metastin	Yes	No(Yes)	-low estrogen treatment did not induce a change in KiSS1 expression however Kiss1 injection did induce a change in plasma LH along with estrogen. OVX alone with metastin could not produce a LH surge.
		high E2 levels(514.1 pg/mL)	-significant decrease of Kiss-1 expression compared to OVX controls (returns levels to that pre-OVX)	Yes	Yes		
			100 pM E2 exposure	Increased relative luciferase Kiss-1 gene activity but non significant(1.25)	Yes	No	
			1nM E2 exposure	Increased relative luciferase Kiss-1 gene activity but non significant(1.4)	Yes	No	
			10nM E2 exposure	Significant increased relative luciferase Kiss-1 gene activity(1.6)	Yes	Yes	
			100 nM E2 exposure	Significant increased relative luciferase Kiss-1 gene activity(2.5)	Yes	Yes	

Li et al., 2007	MCF-7, 293T and GT1-7 mice cell lines	-site directed mutagenesis of SP and ERalpha and exposure to various concentrations of E2 (0, 100pM, 1nM, 10nM, 100 nM, 1uM) for 6 h	1uM E2 exposure	-Significant increased relative luciferase Kiss-1 gene activity(2) -E2 treatment increased KiSS1 promoter activity approximately 3-fold in the presence of ERa, whereas no hormone-induced effect was observed in the cells without ERa -In the ERa positive hypothalamic GT1-7 cell line, E2 responsive effects of the KiSS1 promoter were observed without exogenous ERa	Yes	Yes	
Neal-Perry et al., 2009	Female Sprague Dawley rats (<i>Rattus norvegicus</i>)	-OVX'ed young and middle-aged rats exposed to estradiol benzoate/progesterone and kisspeptin-10(10 nM)	estradiol benzoate(2ug) + progesterone (500ug) exposure	-hormone treatment significant induces Kiss1 mRNA levels in both age groups but less Kiss 1 mRNA in middle-aged	Yes	Yes	-middle-aged rats exhibiting delayed and attenuated LH surges have reduced levels of Kiss1 mRNA in the anterior hypothalamus under estrogen-positive feedback conditions
Richard et al., 2008	Sprague Dawley rats (<i>Rattus norvegicus</i>)	OVXed and injected with 10 ug of E2 every 2 days for 3 weeks	10 ug of E2 every 2 days for 3 weeks	-Kiss1 mRNA significantly reduced in OVX rats but E2 restores it to levels similar to mestroestrous.	Yes	Yes	-PPT = propylazoletriol -DPN = diarylpropionitrile -GPR54 expression positively regulated by GnRH and negatively controlled by chronic exposure to E2 --administration of the selective oestrogen receptor alpha ligand propylpyrazoletriol, but not the selective ERb ligand diarylpropionitrile, mimics this effect of Kiss-1 expression -increasing the E2 concentration causes a significant increase in Kiss-1 mRNA levels
			1 mg of PPT daily for 3 days	-OVX abolishes Kiss-1 mRNA levels. PPT significantly increases Kiss-1 mRNA levels to levels above Mestoestrous.	Yes	Yes	
		1 mg of DPN daily for 3 days	-OVX abolishes Kiss-1 mRNA levels. DPN is unable to induce any changes in Kiss-1 mRNA levels. significantly increases Kiss-1 mRNA levels to levels above Mestoestrous.	No	No		
		1 mg of PPT and DPN daily for 3 days	-OVX abolishes Kiss-1 mRNA levels. PPT with DPN significantly increases Kiss-1 mRNA levels to levels above Mestoestrous.	Yes	Yes		
	LBT2 gonadotroph cell lines	Tested different concentrations of E2 to see the effect on Kiss-1 mRNA levels(E2 10-9 M vs E2 10-7 M)	10-9 M estradiol exposure	-estradiol exposure does not induce any change in relative Kiss-1 mRNA levels relative to control	Yes	No	
			10-7 M estradiol exposure	-estradiol exposure induces significant increase in relative Kiss-1 mRNA levels relative to control	Yes	Yes	
Smith et al., 2005	Adult Female Mice (<i>Mus musculus</i>)	-female ERalpha null mice were produced through breeding pairs, each carrying a single copy of the disrupted ER gene -female ERbeta null mice were also included in the experiment -mice were ovariectomized and given an E2-filled capsule via implantation at the base of the neck	E2 treatment -when ERalpha was KO, E2 had no effect on expression of Kiss-1 mRNA in OVX mice -when ERbeta was knocked out, the effects of E2 on the expression of Kiss-1 mRNA was similar to that of WT animals	-OVX significantly increased the number of cells expressing Kiss-1 mRNA by 2.6 fold in the ARC and increased the cellular content of Kiss-1 mRNA by 1.7-fold with E2 treatment completely reversing the effects of OVX -in the AVPV, OVX significantly decreased the # of identifiable Kiss-1 mRNA containing cells by 58% and E2 treatment restored. -in the PeN, OVX decreased number of Kiss-1 cells and E2 treatment reversed this effect. -With the ERalpha knockouts, estrogen treatment does induce any changes post OVX.	Yes	Yes	-in the ARC, Kiss-1 expression increased after ovariectomy and decreased with E2 treatment -AVPV, Kiss1 expression was reduced after ovariectomy and increased E2 treatment -ERalpha is essential for mediating the inhibitory and stimulatory effects of E2 as Kiss-1 mRNA did not respond to E2 in either the ARC and AVPV when ERalpha was nonfunction -ERbeta was also made nonfunctional however these mice responded to E2 exactly as wild-type animals -all Kiss-1 expressing neurons in the ARC and AVPV coexpress ERalpha

Tomikawa et al., 2012	Adult Mice (<i>Mus musculus</i>)	OVXed and implanted with E2-filled pill @ 200 ug/mL	E2 treatment @ 200 ug/mL	<p>-E2 treatment causes a significant increase in kisspeptin signal intensity in the AVPV kisspeptin neurons(200 vs 50 & 120 vs 20)</p> <p>-E2 treatment causes a significant decrease in kisspeptin signal intensity in the ARC kisspeptin neurons (50 vs 5 & 75 vs 5)</p>	Yes	Yes	arbitrary unit
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