

IMPACT OF ESTROGEN RECEPTOR A GENE AND OXYTOCIN RECEPTOR GENE POLYMORPHISMS ON FEMALE SEXUALITY

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INTRODUCTION

- Estrogens exert a direct effect on hypothalamic neurons at hyperchiasmatic level, especially on paraventricular nucleus (PVN), ventromedial nucleus (VMN), cortical areas (occipital–temporal cortex, ventral prefrontal cortex and medial prefrontal cortex), hippocampus, central nucleus of amygdala and pedunculopontine nucleus (PPN). Peripheral actions of estrogens also promote female sexuality, including vaginal trophic effects as well as increase in skin sensitivity.
- Rs2234693 (PvuII) polymorphism is a common SNP (42% in Caucasians), located in intron 1 of *ERA* gene in which thymine is substituted by cytosine (T→C). The presence of the dominant T allele of PvuII polymorphism can enhance ERA activity. Although increased reproductive efficiency has been associated with wildtype allele of PvuII polymorphic site, the implication of rs2234693 has not been associated with sexual function.

INTRODUCTION

- Oxytocin is implicated both in social behavioral network (14, 15) and in sexual response. Increased oxytocin levels have been reported during sexual arousal, reaching peak levels during orgasm, whereas increased oxytocin levels have been confirmed immediately after orgasm. Furthermore, oxytocin levels have positively been correlated with intensity of contractions of the pelvic musculature during orgasm.
- Oxytocin receptor (*OXTR*) is a 389 amino acid polypeptide with 7 transmembrane domains that belong to the class I G protein-coupled receptor (GPCR) family (20). Rs53576 is an SNP substitution of guanine by adenine (G→A), which has thoroughly been studied and linked to socially related personality traits and behaviors.

INTRODUCTION

- The aim of the present study was to investigate the correlation of estrogen receptor α (*ER* α) gene polymorphism (rs2234693-PvuII) and oxytocin receptor gene polymorphism (rs53576) with sexuality parameters of young healthy women. This is the first study to investigate the interaction between *ERA* and *OXTR* in relation to sexual function in women.

SUBJECTS AND METHODS

- 133 Greek heterosexual women aged 20–25 years old, sexually active.
- Exclusion criteria: chronic diseases, major psychiatric disorders, oral contraceptive pills (OCs), polycystic ovary syndrome (PCOS), thyroid diseases as well as drugs that are implicated in hypothalamus–pituitary–gonadal axis.
- Hormonal determinations
- Female Sexual Function Index (FSFI) questionnaire
- Age of adrenarche, menarche, age of first intercourse and also number of sexual partners
- Study of genetic polymorphisms
- Statistical analysis

RESULTS

Table 1 Anthropometric and hormonal characteristics
(*N* = 133).

Variable	Mean (S.D.)
Age	21.62 (1.92)
Height (m)	1.64 (0.05)
Weight (kg)	59.88 (12.14)
Body mass index (BMI)	22.09 (4.00)
Estradiol (E ₂) (pg/mL)	43.64 (15.20)
Testosterone (ng/mL)	0.31 (0.08)
FAI (%)	1.98 (1.40)
LH (IU/mL)	5.94 (2.20)
FSH (IU/mL)	6.53 (1.54)
SHBG (nmol/L)	69.54 (29.78)
Progesterone (ng/mL)	9.76 (7.39)

RESULTS

Table 2 Hormonal characteristics and sexual parameters among rs2234693 (PvuII) genotype groups (homozygous for T wild-type allele, homozygous for C polymorphic allele and heterozygous) and rs53576 (OXTR) genotype groups (homozygous for G wild-type allele and carriers of A polymorphic allele) (bold indicates significance level: $P < 0.05$).

	ERA				OXTR		
	TT (N=38)	TC (N=64)	CC (N=31)	P value	GG (N=64)	GA/AA (N=69)	P value
Age	21.42 (2.04)	21.62 (1.96)	21.87 (1.72)	0.299	21.68 (2.08)	21.56 (1.78)	0.987
FSH (IU/mL)	6.57 (1.32)	6.48 (1.77)	6.57 (1.32)	0.952	6.64 (1.58)	6.42 (1.51)	0.402
LH (IU/mL)	5.98 (2.46)	5.89 (2.18)	5.98 (1.97)	0.84	5.91 (2.14)	5.97 (2.28)	0.861
E2 (pg/mL)	43.46 (14.30)	43.50 (14.64)	44.14 (17.71)	0.999	44.46 (16.52)	42.87 (13.94)	0.804
Progesterone (ng/mL)	9.29 (8.35)	10.03 (6.75)	9.79 (7.62)	0.496	9.88 (7.79)	9.66 (7.05)	0.941
Testosterone (ng/dL)	0.32 (0.08)	0.31 (0.08)	0.30 (0.09)	0.61	0.32 (0.08)	0.30 (0.09)	0.183
SHBG (nmol/L)	64.51 (30.91)	70.72 (31.49)	73.27 (24.32)	0.237	68.07 (29.9)	70.90 (29.82)	0.415
FAI	2.24 (1.54)	1.98 (1.49)	1.68 (0.95)	0.126	2.07 (1.44)	1.90 (1.37)	0.208
Desire	4.46 (0.86)	4.19 (0.92)	4.10 (1.07)	0.252	4.11 (0.96)	4.37 (0.92)	0.155
Arousal	5.48 (0.48)	4.96 (1.31)	4.61 (1.38)	0.004	4.95 (1.13)	5.10 (1.24)	0.04
Lubrication	5.58 (0.66)	5.22 (1.33)	5.03 (1.25)	0.046	5.27 (1.19)	5.29 (1.15)	0.993
Orgasm	5.15 (0.96)	4.66 (1.53)	4.55 (1.50)	0.211	4.66 (1.40)	4.88 (1.39)	0.152
Satisfaction	5.44 (0.90)	5.20 (1.20)	4.96 (1.06)	0.058	5.25 (1.14)	5.17 (1.06)	0.39
Pain	4.88 (1.46)	5.02 (1.61)	4.82 (1.53)	0.521	5.05 (1.42)	4.83 (1.65)	0.543
FSFI_full	31.02 (3.21)	29.27 (6.64)	28.10 (6.26)	0.075	29.32 (5.71)	29.67 (5.97)	0.265
Menarche	12.36 (1.14)	12.30 (1.35)	12.45 (1.31)	0.482	12.46 (1.43)	12.26 (1.12)	0.632
Adrenarche	10.36 (1.23)	10.34 (1.35)	10.25 (1.54)	0.769	10.56 (1.51)	10.11 (1.18)	0.172
Age of first intercourse	17.84 (1.91)	17.89 (1.99)	17.70 (1.73)	0.915	18.06 (1.91)	17.62 (1.87)	0.095
Number of sex partners	3.84 (4.73)	3.67 (3.58)	2.93 (2.36)	0.785	3.46 (4.26)	3.62 (3.16)	0.442

RESULTS

Table 3 Comparison of hormonal characteristics and sexual parameters between women who carry both T allele of rs223493 (PvuII) and A allele of rs53576 (OXTR) (T+A group) and the no (T+A) group and between women who carry T allele and no A allele (T+no A group) and those who carry A allele and no T allele (no T+A group) (bold indicates significance level: $P < 0.05$).

	T+A (N=53)	No (T+A) (N=80)	P value	T+no A (N=49)	No T+A (N=16)	P value
Age	21.49 (1.89)	21.71 (1.95)	0.469	21.61 (2.09)	21.81 (1.37)	0.264
FSH (IU/mL)	6.37 (1.60)	6.63 (1.50)	0.351	6.67 (1.62)	6.57 (1.20)	0.827
LH (IU/mL)	5.95 (2.42)	5.93 (2.06)	0.515	5.90 (2.14)	6.02 (1.80)	0.594
E2 (pg/mL)	43.12 (13.20)	43.99 (16.46)	0.748	43.88 (15.81)	42.07 (16.59)	0.695
Progesterone (ng/mL)	9.66 (6.98)	9.83 (7.69)	0.856	9.86 (7.81)	9.65 (7.50)	0.897
Testosterone (ng/dL)	0.30 (0.09)	0.31 (0.08)	0.691	0.32 (0.07)	0.28 (0.09)	0.101
SHBG (nmol/L)	67.45 (29.85)	70.92 (29.84)	0.499	69.44 (33.01)	82.33 (27.61)	0.049
FAI	2.05 (1.47)	1.94 (1.36)	0.748	2.10 (1.56)	1.40 (0.86)	0.019
Desire	4.44 (0.88)	4.11 (0.97)	0.075	4.12 (0.91)	4.12 (1.02)	0.92
Arousal	5.28 (1.02)	4.86 (1.26)	0.004	5.02 (1.18)	4.51 (1.69)	0.464
Lubrication	5.43 (0.97)	5.18 (1.27)	0.181	5.27 (1.29)	4.80 (1.55)	0.07
Orgasm	5.01 (1.31)	4.62 (1.44)	0.033	4.66 (1.41)	4.45 (1.61)	0.689
Satisfaction	5.25 (1.08)	5.19 (1.11)	0.713	5.33 (1.13)	4.92 (0.96)	0.039
Pain	4.98 (1.55)	4.90 (1.54)	0.624	4.95 (1.56)	4.32 (1.92)	0.157
FSFI_full	30.43 (5.24)	28.88 (6.14)	0.026	29.38 (6.08)	27.14 (7.59)	0.229
Menarche	12.22 (1.17)	12.44 (1.34)	0.485	12.43 (1.38)	12.37 (0.95)	0.82
Adrenarche	10.18 (1.14)	10.42 (1.49)	0.637	10.53 (1.45)	9.87 (1.31)	0.16
Age of first intercourse	17.67 (2.00)	17.93 (1.83)	0.242	18.08 (1.89)	17.43 (1.36)	0.171
Number of sex partners	3.79 (3.34)	3.38 (3.95)	0.428	3.67 (4.69)	3.06 (2.46)	0.857

CONCLUSIONS

- In the present study a genetic predisposition of female sexual response was revealed.
- More specifically, T allele (wildtype) of rs2234693 (PvuII) polymorphism of *ERA* gene was correlated with increased levels of arousal and lubrication
- A allele (polymorphic) of rs53576 (*OXTR*) polymorphism was correlated with increased arousal levels.
- The concurrence of T allele (wildtype) of *ERA* rs2234693 polymorphism and A allele (polymorphic) of *OXTR* rs53576 polymorphism was correlated with increased arousal and orgasm levels as well as with higher FSFI_full scores.

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