3

Participation of the Monoaminergic System in the Antidepressant-Like Actions of Estrogens: A Review in Preclinical Studies

Carolina López-Rubalcava[1], Nelly Maritza Vega-Rivera[1,2], Nayeli Páez-Martínez[3] and Erika Estrada-Camarena[2*]

[1]*Departamento de Farmacobiología, Cinvestav-IPN,*
[2]*Laboratorio de Neuropsicofarmacología,*
Instituto Nacional de Psiquiatria Ramón de la Fuente,
[3]*Sección de Graduados, Escuela Superior de Medicina-IPN*
Mexico

1. Introduction

1.1 Estrogen receptors – Classification and distribution

Estrogens are steroid hormones produced by gonads that bind to different receptor types and mediate numerous actions, like growth, development, cognition, neuroprotection and participate in mood regulation (Margeat *et al.*, 2003; Vasudevan & Pfaff, 2007). The classic estrogen receptors (ER) are: ERα and ERβ. These receptors are ligand-activated transcription factors (Kuiper & Gustafsson, 1997) with nuclear and non-nuclear distribution (Monje & Boland, 2001; Weiser *et al.*, 2008). In ovariectomized rats, ERβ and ERα are co-localized in various brain regions, including the bed nucleus of the stria terminalis, the medial and cortical amygdaloid nuclei, the preoptic area, the lateral habenula, the periacueductal gray, the locus coeruleus, the hippocampus and the brain cortex (Shughrue *et al.*, 1997). In these last two structures, ERβ is more abundant than ERα. Other structures that contain only ERβ are the olfactory bulb, the ventral tegmental area, the zona incerta, the cerebellum, the pineal gland and some hypothalamic nuclei (such as the supraoptic, the paraventricular, the supraquiasmatic and the tuberal nuclei). By contrast, brain areas with solely ERα are the ventromedial hypothalamic nuclei and the subfornical organ (Shughrue *et al.*, 1997).

Several reports have described two membrane estrogen receptors unrelated to ERα and ERβ: an orphan receptor coupled to G proteins called GPR30 (Filardo *et al.*, 2002) and another, named ER-X, that posses characteristics of tyrosine-kynase activity (Toran-Allerand, 2004). GPR30 is a seven transmembrane ER that binds estrogens with high affinity and acts independently of ERα and ERβ to stimulate adenyl cyclase and phopholipase C via Gαs proteins, which in turn, generates classic second messengers such as the cyclic

* Corresponding author

adenosine monophosphate (cAMP), inositol trisphosphate and Ca+ and induces the release of the epidermal growth factor (Filardo *et al.*, 2002). On the other hand, the ER-X is a plasma membrane ER enriched in a caveolar-like microdomain that is expressed during development and after ischemic brain injury (Toran-Allerand *et al.*, 2005). ER-X mediates 17α-estradiol and 17 β-estradiol (E2) activation of MAPK/ERK in development neocortical explants, after ischemic injury and in animal models of Alzheimer's disease and Down's syndrome. These characteristics could explain estrogen's rapid actions in the central nervous system.

2. Monoamines and depression

One of the earliest theories in the biology of depression is the monoaminergic hypothesis that proposed a dysfunction of the serotonegic/catecholaminergic function that leads to depression. The neurotransmitters serotonin (5-HT), dopamine (DA) and noradrenaline (NA) (NA) are localized in limbic brain regions involved in the regulation of mood, cognition and anxiety, among others. This theory was proposed in the early 50s, with the observation that reserpine, a drug with antihypertensive activity and that inhibits catecholamine vesiculation, induced signs of depression (Lopez-Muñoz & Alamo, 2009). On the other hand, drugs that facilitate monoamine release were found to be antidepressant. At present, serotonin transporters, noradrenaline transporters and the monoamine oxidase enzyme (MAO) are targets of antidepressant therapy, all of which increase the serotonergic and/or noradrenaline tone through an inhibition of monoamine reuptake or inhibition of monoamine catabolism (MAO inhibition) (Kalia, 2005; Lopez-Muñoz & Alamo, 2009; Osterlund, 2009).

Although the pharmacological and biochemical effects of antidepressant drugs occur rapidly (within minutes), in clinical practice the antidepressants drugs produce their therapeutic actions after at least 10 to 14 days after treatment initiation. This suggests that antidepressants act via a delayed postsynaptic receptor-mediated event (Kalia, 2005). It is hypothesized that the delayed time of onset for antidepressant drugs is due to the feedback mechanism of the somatodendritic 5-HT1A receptor. In this case, increased release of serotonin by acute administration of antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) leads to a dose-dependent inhibition of 5-HT neuronal firing rate (Osterlund, 2009) due to the activation of the presynaptic 5-HT1A receptors, followed by inhibition of neuronal firing and terminal serotonin release. Chronic administration of reuptake inhibitors leads to desensitization of the presynaptic 5-HT1A autoreceptors and thereby restores serotonergic firing and terminal serotonin release (Krishnan & Nestler, 2008). The observed desensitization of presynaptic 5-HT1A autoreceptors is in line with the time course for therapeutic onset of reuptake inhibitors (Maletic *et al.*, 2007; Osterlund, 2009).

Similarly to serotonergic receptors, it has been reported that chronic antidepressant treatments caused subsensitivity of the noradrenergic receptor–coupled adenylate cyclase system in the brain (Vetulani *et al.*, 1976). This work shifted the emphasis from acute presynaptic (α2-adrenergic receptors) to delayed postsynaptic receptor-mediated events in the mode of action of antidepressants. The delayed desensitization of the noradrenergic β-adrenoceptor– coupled adenylate-cylase system in the brain is an action that is common to almost all antidepressant treatments (Kalia, 2005).

3. Depression in women: Role of estrogens

In women, changes in the incidence of mental illnesses (particularly in major depressive disorder) can be found in three important periods of their reproductive life span. These periods are characterized by drastic hormonal oscilations (Girdler & Klatzkin, 2007; Payne *et al.*, 2007). For example, a correlation was found between the onset of depressive and anxiety symptoms and the rapid decrease of progesterone and allopregnanolone levels during the late lutheal phase of the menstrual cycle in vulnerable women (Halbreich & Kahn, 2001; Backstrom *et al.*, 2003); by contrast, when a gradual reduction in progesterone concentrations occurs, a reduction of depression, anxiety, food cravings, mood swings and cramps is observed (Contreras *et al.*, 2006). In addition, a positive correlation between the abrupt fall of hormones levels and post-partum depression has been established (Jensvold, 1996). Hence, some reports indicate that hormones such as estradiol are a useful therapy to relief the postpartum depression symptoms (Soares *et al.*, 2001).

The most characterized endocrine period where hormonal fluctuations influence depressive states is the perimenopause transition. Several reports indicate that follicular stimulating and luteinizing hormones and estradiol oscillations are correlated with the onset or worsening of depression symptoms during early perimenopause (Halbreich & Kahn, 2001; Pae *et al.*, 2009), when major depressive disorder incidence is 3-5 times higher than the male matched population of the same aged (Riecher-Rossler & Geyter, 2007). Several longitudinal studies that followed women across the menopausal transition indicate that the risk for significant depressive symptoms increases during the menopausal transition and then decreases in the early postmenopause (Soares & Zitek, 2008) and in the last years of menopause its incidence is comparable to that shown by men (Payne *et al.*, 2007; Riecher-Rossler & Geyter, 2007). Also, epidemiological studies showed that women vulnerable to hormonal fluctuations, who suffer premenstrual dysphoric disorders, are susceptible to develop post-partum- and perimenopausal-depression (Richards *et al.*, 2006; Payne *et al.*, 2007). The sum of all these depressive episodes results in a long term deficient quality of life due to many years of poor mental health.

Other studies that have shown the participation of estrogens in the etiology of depression are the following: a prospective study showed that women with a lifetime history of depression had high levels of follicle-stimulating and luteinizing hormones levels, but low estradiol concentrations (Harlow *et al.*, 2003). In this case, authors concluded that a lifetime history of major depression may be associated with an early decline of ovarian function, a situation that characterizes menopause transition (Harlow *et al.*, 2003). On the other hand, in a similar study, women with no history of depression, had increased levels of FSH and LH and increased variability of estradiol that were significantly associated with depressive symptoms (Freeman *et al.*, 2006). In fact, it was proposed that the unstable and irregular pattern of hormone production during perimenopausal transition, in susceptible women, may increase vulnerability to mood disorders (Sherwin & Henry, 2008; Rocca *et al.*, 2010).

In addition, it has been reported that in depressive women, high levels of FSH correlate with the severity of depression and the intensity of menopausal symptoms (Rajewska & Rybakowski, 2003). Interestingly, these women presented a transient decreased response to the stimulation of the serotonergic system with D-fenfluramine, suggesting hypoactivity of the serotonergic system during depression (Rajewska & Rybakowski, 2003). Therefore, the

impact of hormone oscillations during perimenopause transition may affect the serotonergic system function and increase vulnerability to develop depression.

4. Antidepressant like actions of estrogens in clinical and preclinical studies

4.1 Effects of estrogens in clinical studies

The participation of estrogens in the etiology of depression is evident when they are used as part of the pharmacotherapy of depression associated to perimenopause. Clinical research has found clear antidepressant effects of various estrogens when given alone (Schmidt *et al.*, 2000; Soares *et al.*, 2001) or in combination with classic antidepressants (Soares *et al.*, 2001; Morgan *et al.*, 2005). However, an equal amount of reports have failed to find antidepressant effects of estrogens administered alone (Coope, 1975; Saletu *et al.*, 1995; Morrison *et al.*, 2004) or a lack of further benefit from that produced by an antidepressant treatment (Shapira *et al.*, 1985; Amsterdam *et al.*, 1999). The nature of such differences is unknown; however, factors, including age, type of compounds, depression scales, duration of treatment, type of depression, endocrine stage and time after cessation of menses, may be responsible for these differences.

For example, in a double-blind placebo-controlled study of 34 perimenopausal women with major depressive disorder or minor depression, 3 weeks of estradiol monotherapy resulted in significant improvement (Schmidt *et al.*, 2000). Furthermore, in another placebo controlled double-blind study of perimenopausal women, 17 β-estradiol delivered transdermally was also efficacious (Soares *et al.*, 2001). An open study also showed that in women with major depressive disorder, estradiol either as monotherapy or added to an SSRI antidepressant was effective after 6 weeks of treatment (Rasgon *et al.*, 2002). However, studies in which menopausal women with or without depression diagnosis were included, estrogens were ineffective to reduce depressive symptoms (Coope, 1975; Strickler *et al.*, 1977).

On the other hand, two out of four studies of varying designs suggest that estrogen may improve responsiveness to antidepressants. A randomized, controlled, multicenter trial of fluoxetine in geriatric depression found that women who were incidentally taking estrogen improved better on fluoxetine than placebo, whereas those who were not taking estrogen showed no difference between fluoxetine and placebo (Schneider *et al.*, 1997). On the negative side, a recent retrospective study found no difference in the proportion of responders to fluoxetine between women who took estrogen replacement therapy and women who did not (Amsterdam *et al.*, 1999). Finally, another study failed to show efficacy for estrogen augmentation of imipramine in either pre- or postmenopausal women with treatment-resistant depression (Shapira *et al.*, 1985). Some examples of estrogens used as therapy for depression alone or in combination with antidepressants or other hormones are illustrated in table 1 and table 2.

4.2 Antidepressant-like effects of estrogens on basic research

In basic research, animal models of experimental depression have been extensively used in the development of novel therapeutic compounds and for the understanding of the neural substrates underlying depressive behavior (Holmes, 2003; Cryan *et al.*, 2005; Markou *et al.*, 2009). Thus, using animal models for the screening of compounds with antidepressant-like properties, estrogens have antidepressant-like effects. For example, it was found that 7 days

of estradiol treatment reduces the immobility behavior in gonadectomized mice in the tail suspension test, suggesting an antidepressant-like action (Bernardi *et al.*, 1989).

Other studies have been performed in rats and mice using the forced swimming test (FST) which has been primarily developed as a test for screening the efficacy of novel antidepressants (López-Rubalcava *et al.*, 2009). It is noticeable that antidepressant-like actions of estrogenic compounds have been detected after acute (1 injection) and chronic treatments (7-14 days) if they are administered close to the time of ovaries elimination, i. e. either immediately or few weeks after estrogens decline. For example, the administration of estradiol benzoate for 7 or 14 days, induces antidepressant-like effects in the FST (Okada *et al.*, 1997; Rachman *et al.*, 1998). Besides, the antidepressant-like action of estrogenic compounds like 17β-estradiol (E2), 17α-ethinyl-estradiol (EE2) and diarylpropionitrile (DPN, an agonist to estrogen receptors type β) was also observed after an acute treatment (Estrada-Camarena *et al.*, 2003; Walf *et al.*, 2004). Interestingly, a selective estrogen receptor modulator, raloxifene, was only effective after 7 days of treatment; whereas tamoxifen, or the ERα agonist, 4,4',4''-(4-Propyl-[1H]-pyrazole-1,3,5-triyl)trisphenol (PPT) were ineffective in the FST after an acute or chronic treatment (table 3). Hence, the antidepressant-like effect of compounds with estrogenic activity depends on the type of compound and on the length of the treatment, suggesting that different mechanisms are involved. In addition, the antidepressant-like effect of estrogens also seems to depend on the time of estrogen restitution after the ovariectomy (OVX) as well as on the age of the animals. In this sense, if the restitution with E2 in young animals is initiated after three weeks post-OVX, but not five or more weeks, antidepressant-like effects are observed (Estrada-Camarena *et al.*, 2011). In contrast, if middle age rats (around 12 months old) are ovariectomized, the antidepressant-like effect of E2 is restricted to one week post-OVX (unpublished data).

5. Actions of estrogens on monoaminergic systems

5.1 Evidence of estrogens interactions with the serotonegic system

In vitro and in vivo studies, with non-stressed animals, have analyzed estrogens' effects on the serotonergic system. For example, in ovariectomized rats, acute and chronic estradiol treatment resulted in increased serotonin levels in specific brain areas such as the dorsal raphe nucleus and hippocampus (Lubbers *et al.*, 2010). Similar results were found in the hypothalamus of guinea pigs (Lu *et al.*, 1999) and in the dorsal raphe nucleus of nonhuman primates (Lu & Bethea, 2002). Furthermore, human studies reported increased serotonin levels in postmenopausal women receiving hormone replacement therapy with estrogens (Blum *et al.*, 1996) and suggest that estradiol enhances 5-HT synthesis in serotonergic neurons (O'Keane *et al.*, 1991).

Estrogens effects on serotonin levels could be related with an increase on tryptophan hydroxylase activity (Donner & Handa, 2009). Thus, in rat´s dorsal raphe nucleus, it has been shown that the tryptophan hydroxylase enzyme expression is directly modulated by estrogens (McEwen, 1999; Donner & Handa, 2009). Furthermore, inmunohistochemical studies revealed the existence of ER-β mRNA in neurons of the dorsal raphe nucleus (McEwen, 1999). Therefore, it is suggested that estrogens might modulate the enzyme's activity or synthesis through ER-β, and consequently have an impact on serotonin levels (McEwen, 1999; Donner & Handa, 2009).

Another site of action through which estrogens can influence serotonin levels is the serotonin transporter (SERT). Studies in monkeys showed that E2 and the selective modulators of estrogen receptors, raloxifene and arzoxifene, increased tryptophan hydroxylase mRNA expression and decreased SERT's mRNA expression (Bethea *et al.*, 2002; Smith *et al.*, 2004). Interestingly, in the FST, raloxifene induced antidepressant-like effects similar to SSRIs such as fluoxetine (Estrada-Camarena *et al.*, 2003; Estrada-Camarena *et al.*, 2010). Studies in rats, analyzing different brain areas, indicate that acute or chronic treatment with estradiol benzoate decreased the number of ^{3}[H] paroxetine binding sites (Mendelson *et al.*, 1993). These results are in agreement with in vitro studies that reported that some estrogenic compounds interact with the serotonin transporter in membranes obtained from cerebral cortex, hippocampus, hypothalamus and striatum (Chang & Chang, 1999).

Reference	Study population	Estrogenic compound	Findings
(Lopez-Jaramillo *et al.*, 1996)	Post-menopausal women	Conjugate equine estrogens, oral	E>placebo ↓ Beck scale
(Soares *et al.*, 2001)	Perimenopausal women with depression (40-45 years old)	17 β-estradiol path	E>placebo ↓ MADRS y BKMI scales
(Montgomery *et al.*, 1987)	Peri, postmenopausal and hysterectomized women without depression (44-50 years old)	17 β-estradiol with or without testosterone	E o E+T > placebo in perimenopausic interview and SRD30
(Strickler *et al.*, 1977)	Perimenopausal and hysterectomized women with unipolar and bipolar depression or healthy (35-66 years old)	Conjugate equine estrogens, oral	E=placebo MMPI y 16PF scales
(Coope, 1975)	Menopausal, hysterectomized and oophorectomized women with depression (40-61 years old)	Conjugate equine estrogens, oral	E=placebo
(Bukulmez *et al.*, 2001)	Postmenopausal women without depression (45-60 years old)	Equine estrogens + medroxyprogesterone or Tibolone, oral	E+MHP o E+tibolone>placebo ↓ Beck scale
(Schmidt *et al.*, 2000)	Perimenopausal women with depression	17 β-estradiol patch	E>placebo

Table 1. Effect of estrogens as antidepressants in clinical practice

Reference	Study population	Antidepressant	Type of estrogen	Results
(Shapira *et al.*, 1985)	Pre and postmenopausal women with depression treatment resistant (26-74 years old)	Imipramine 200 mg/day/3 months	Conjugate equine estrogens, oral 1.25-3.75 mg/day/month	E+imipramine = placebo+imipramine Hamilton and Becker scales
(Amsterdam *et al.*, 1999)	Pre and postmenopausal women with depression with or without treatment with estrogens alone or in combination with progesterone (<45 a > 45)	Fluoxetine 20 mg/day/3 months	Conjugate equine estrogens, oral 0.625 mg/day/3 months with or without progesterone	E+fluoxetine= placebo+fluoxetine Hamilton scale
(Schneider *et al.*, 1997)	postmenopausal women with depression	Fluoxetine	ERT Estrogens 1.5 month	E+FLX >E+placebo, placebo+FLX y placebo+placebo
(Schneider *et al.*, 2001)	postmenopausal women with depression > 60 years old	Sertraline	Conjugate equine estrogones oral (0.625 mg/day) /3 months	E+SERT improves of quality of life
(Soares *et al.*, 2001)	Peri and post-menopausal women with depression	Citalopram 20-40 mg/day/2 months	17 β-estradiol (100 µg/day/1 month + CIT/2 months	E+CIT> E+placebo ↓ MADRS scale
(Joffe *et al.*, 2001)	Peri and post-menopausal women with depression	Mirtazepine 30-45 mg/day 2 months	estrogens+MIRT	E+MIRT ↓ Hamilton scale

Table 2. Effect of estrogens combination with antidepressant drugs in the treatment of depression

Estrogenic compound	Behavioral effect	Test	References
Agonist with more activity on ERα			
Propyl-pyrazol-triol (PPT)	-	FST	(Estrada-Camarena *et al.*, 2003; Walf *et al.*, 2004; Walf & Frye, 2007)
17α-estradiol	-	FST	
17α-Ethynyl-estradiol	+ Low doses	FST	
	- High doses	FST	
Agonist with more activity on ERβ			
Diaryl-propionitrile (DPN)	+	FST	(Walf *et al.*, 2004; Walf & Frye, 2007)
Cumestrol	+	FST	
Agonist of GPR30			
G1	+	TST	(Dennis *et al.*, 2009)
Agonist of ERα and ERβ			
17 β-Estradiol*	+	FST	(Bernardi *et al.*, 1989; Okada *et al.*, 1997; Rachman *et al.*, 1998; Galea *et al.*, 2002; Estrada-Camarena *et al.*, 2003; Dalla *et al.*, 2005; Romano-Torres & Fernandez-Guasti, 2010)
Estradiol benzoate *	+/-	FST, TST	
Diethyl-stilbestrol	-	FST	
Estradiol valerate	+	CMS	
Selective estrogen receptor modulators of ERα and ERβ			
Raloxifene	+	FST	(Estrada-Camarena *et al.*, 2010; Walf & Frye, 2010)
Tamoxifen	-	FST	
Antagonist of ERα and ERβ			
RU 58668	-	FST	(Estrada-Camarena *et al.*, 2006b; López-Rubalcava *et al.*, 2007)
ICI 182780	-	FST	
Phytoestrogens			
Pomegranate (Estradiol, estrone, estriol, cumestrol, genistien)	+	FST	(Mori-Okamoto *et al.*, 2004)

FST=Forced swimming test; TST= tail suspension test; CMS = chronic mild stress. +: decrease of anhedonia or immobility behavior; - : no change of anhedonia or immobility behavior

Table 3. Effect of different types of estrogenic compounds in ovariectomized female rodents tested in different animal models for the screening of antidepressant-drugs.

As for the action of estrogens on serotonergic receptors, an interaction with 5-HT1A, 5-HT1B 5-HT2A/2C and 5-HT3 receptors has been demonstrated (Osterlund & Hurd, 1998; Raap *et al.*, 2000; Hiroi & Neumaier, 2009). In general, it is proposed that estrogens produce a desensitization of 5-HT1A receptors (Lu & Bethea, 2002) which is associated with decreased Gi protein coupled receptors (Mize & Alper, 2000; Raap *et al.*, 2000; Lu & Bethea, 2002). Moreover, another mechanism of action involves the phosphorylation of 5-HT1A receptor via activation of protein kinase-A; this effect is proposed to be mediated through the activation of an estrogen membrane receptor (Mize & Alper, 2002).

Recently, our laboratory found that E2 requires the presence of 5-HT since its depletion or the selective destruction of the presynaptic terminal, partially blocked E2's antidepressant-like effects (López-Rubalcava *et al.*, 2005). Furtheremore, the antidepressant-like actions of E2 and EE2, alone or in combination with fluoxetine require the activation of 5-HT1A receptors, since the selective 5-HT1A antagonist, WAY100635 blocked the antidepressant-like effect induced by these estrogens (Estrada-Camarena *et al.*, 2006a; Estrada-Camarena *et al.*, 2006b). In support of this proposal, the administration of the specific 5-HT1A post-synaptic receptor antagonist MM-77, canceled E2 antidepressant-like effects in the FST (López-Rubalcava *et al.*, 2005).

Results suggest that estrogenic actions on the serotonergic system require estrogen receptor activation. For example, our research group found that RU58688, an estrogen receptor antagonist, blocks E2 antidepressant-like effects in the FST (Estrada-Camarena *et al.*, 2006b); while the desensitization of postsynaptic 5-HT1A receptors located in the hippocampus of the rat requires the participation of a membrane estrogen receptor (Mize *et al.*, 2001). Recently, it was demonstrated that the membrane estrogen receptor GPR30, is involved in 5-HT1A receptor desensitization in the hypothalamus of the rat (Rossi *et al.*, 2010). Taken together, these data may explain why the blockade of ER and 5-HT1A receptor cancels E2 antidepressant-like effects.

In conclusion, it can be proposed that the antidepressant-like effects of E2 are due to its effects on the serotonergic system at both, a pre-and post-synaptic terminals. Thus, in the presynaptic neuron, estrogens are likely to stimulate the activity of the enzyme tryptophan hydroxylase and at the same time inhibit the SERT, this would lead to an increased in the availability of 5-HT in the synaptic cleft. On the postsynaptic site, 5-HT1A and possibly 5-HT2A receptors contribute to trigger signaling cascades that would allowed the modulation of other neurotransmitter systems and processes as complex as the modulation of neuronal plasticity (Fig. 1).

5.2 Evidence of the interaction of estrogens with the noradrenergic system

Several reports, including electrophysiological records (Wagner *et al.*, 2001) and ligand binding studies (Wilkinson & Herdon, 1982) have shown that estrogens can also modulate noradrenergic neurotransmission in the central nervous system (CNS). Several studies reported that estrogenic compounds can influence noradrenergic neurotransmission through an interaction with the noradrenergic transporter and the MAO or tyrosine hydroxylase enzymes. For example, in vitro studies have shown that E2, EE2, DES and some catechol-estrogens such as 2-hydroxy-EE2 (2-OH-EE2) and 2-hydroxy-E1 (2-OHE) inhibit NA reuptake sites in synaptosomes from the cerebral cortex and hypothalamus of rats that resulted in increased levels of NA in the synaptic cleft (Ghraf *et al.*, 1983). In line with these

findings, acute E2 administration to ovariectomized rats decreased NA reuptake rate in the hypothalamus (Hiemke *et al.*, 1985) and increases mRNA levels of tyrosine hydroxylase in the locus coeruleus (Serova *et al.*, 2002). Finally, it has been reported that estrogens increased NA concentration by inhibiting MAO-A activity (Holschneider *et al.*, 1998). These data collectively suggest that estrogens interact with the noradrenergic system through the modulation of NA release, as well as in processes of synthesis and elimination of the neurotransmitter. Thus, E2 given to ovariectomized female rats increased the firing rate of noradrenergic neurons that project to the preoptic area and to the anterior hypothalamus (Kaba *et al.*, 1983). Similarly to some antidepressant drugs, such as desipramine (noradrenergic reuptake inhibitor), E2 decreased mRNA expression and density of α2 receptors (Karkanias *et al.*, 1997); it has been reported that chronic treatment with E2 reduces β adrenergic receptors response (Carlberg & Fregly, 1986).

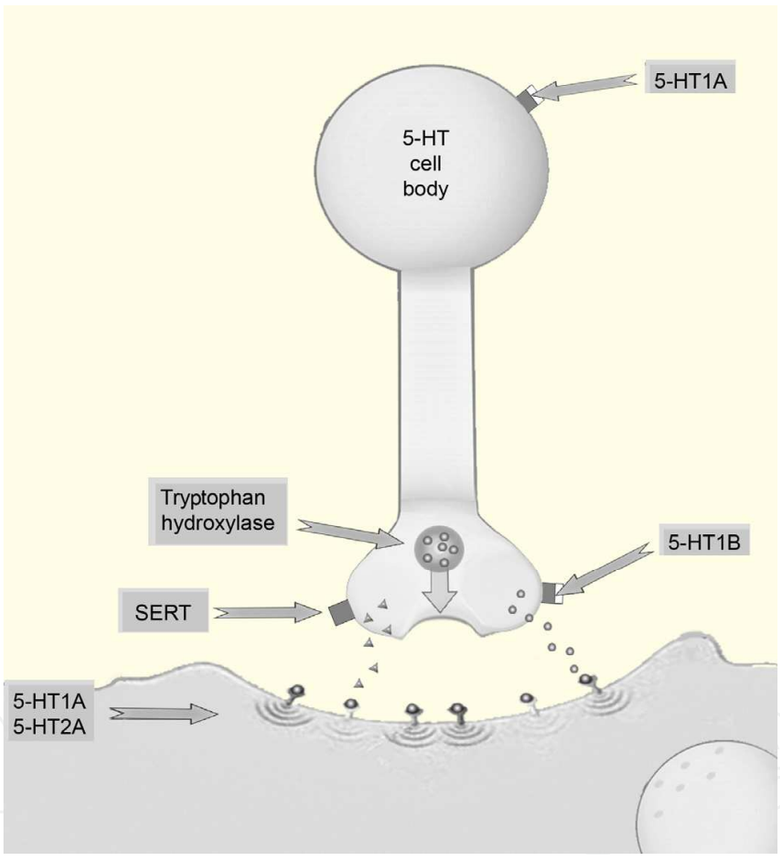


Fig. 1. Esquematic representation of proposed mechanism of action of estradiol's antidepressant-like actions on the serotonergic system in the forced swimming test (an animal model of depression). First, estradiol increases the activity of tryptophan hydroxylase and inhibits the serotonin transporter to induce an increase in serotonin levels in the synaptic clef. Second, estradiol could also induce a desensitization of 5-HT1A and 5-HT1B presynaptic receptors and modulate serotonin release and firing of serotonergic neurons; as a consequence, the increase of serotonin in the synaptic clef may activate 5-HT1A and 5-HT2A postsynaptic receptors and promote the activation of signal transduction pathways. SERT= serotonin transporter.

On the same research line, it has been suggested that EE2 interaction with the noradrenergic system may be mediated through α2 adrenergic receptors, since idazoxan, a selective antagonist of these receptors, is able to block the antidepressant-like effect of EE2 (López-Rubalcava *et al.*, 2007). In addition to these studies, recently we have found that the DSP4, a neurotoxin that selectively destroys noradrenergic nerve terminals in the locus coeruleus was able to blocked the antidepressant-like effects induced by EE2 in the FST (López-Rubalcava *et al.*, 2007). Together, these findings suggest that estrogen may facilitate the noradrenergic transmission by: 1) increasing NA synthesis, 2) by reducing NA reuptake, and by improving NA availability, or 3) through a mechanism involving both proposals.

5.3 Evidence of estrogens interactions with the dopaminergic system

The finding that some estrogens increase the activity of tyrosine-hydroxylase enzymes and inhibit the MAO-A activity may lead to the speculation that an increase in dopaminergic activity could mediate the antidepressant-like effect of estrogens. To our knowledge, there is no direct correlation between brain levels of dopamine or its metabolites and the antidepressant-like effect of these steroids. However, some preclinical reports indicates that agonist to ERα increase dopamine and DOPAC (dopamine metabolite) levels in the hippocampus and the frontal cortex (Lubbers *et al.*, 2010), areas involved in the effect of several antidepressant drugs. In fact, bupropion, a catecholamine enhancer, produces antidepressant-like actions in preclinical models (Reneric & Lucki, 1998; Dhir & Kulkarni, 2008; Bourin *et al.*, 2009).

Evidences in non-stressed animals also support the effect of estrogens on the dopaminergic system. For example, ovariectomy induces a decrease in D1 and D2 receptors density (Bosse & DiPaolo, 1996) which is reverse by 17β-estradiol chronic treatment (Bosse & DiPaolo, 1996; Landry *et al.*, 2002). In acute treatment, estradiol does not alter D2 receptors density but induces changes in the proportion of high to low affinity sites (Levesque & Di Paolo, 1993). In relation to the dopamine transporter (DAT), it has been shown that ovariectomy increases the DAT in the striatum, and this increase was reverted by estradiol chronic treatment (Attali *et al.*, 1997).

It has been reported that D1 and D2 receptor blockade may contribute to reduce negative effects derived from the Hypothalamus-Pituitary-adrenal axis (HPA) activation during stress response (Sullivan & Dufresne, 2006; Belda & Armario, 2009). For example, the administration of dopamine agonists in different brain areas resulted in the increase of plasma corticosterone levels (Ikemoto & Goeders, 1998), whereas the administration of antagonists to D1 and D2 receptors reduces the increase in plasma ACTH and corticosterone concentrations induced by stress (Belda & Armario, 2009). Thus, it is suggested that dopamine receptors are involved in the regulation of the stress response (Belda & Armario, 2009).

In addition, in transgenic mice with functional alterations of the HPA axis, the antidepressant treatment with FLX or amitryptiline corrected the increased binding on D1 and D2 receptors in the striatum and decreased dopamine transporter levels (Cyr *et al.*, 2001). Therefore, if estrogens are able to modulate dopamine receptors and DAT, it is possible that these effects contribute to explain their antidepressant-like effect. Supporting this assumption, a recent report in ovariectomized rats shows that chronic administration of SCH 23390 (D1 antagonist) plus E2 induces robust antidepressant-like actions in the FST (Fedotova & Ordyan, 2011). Additionally, in an experiment performed in male mice it was found that the blockage of D1 or

D2 receptors cancelled the antidepressant-like action of the acute administration of E2 (Dhir & Kulkarni, 2008). Consequently, the information about the specific participation of dopaminergic receptors in the antidepressant-like action of estrogens is yet controversial and need further exploration in order to establish any conclusion.

6. Proposed mechanism of action in the antidepressant-like effects of estrogens

As mentioned earlier, estrogens increases the activity of enzymes involved in the synthesis of 5-HT (tryptophan hydroxylase) and catecholamines (tyrosine hydroxylase and dopamine β-hydroxylase) at the same time that posses the ability to inhibit or decrease the activity of the serotonin and noradrenaline transporters in several brain areas. Interestingly, at the presynaptic terminal, estrogens can also activate the 5-HT1A/5-HT1B and α2-adrenoceptor that regulates the discharge and release of both NA and 5-HT. Together, these effects may contribute to increase the levels of monoamines in the synaptic clef and promote the activation of post-synaptic receptors such as 5-HT2A and β-adrenergic receptors as well as the activation or deactivation of several signal transduction pathways such as cAMP-PKA and IP3-PKC, among others. These signal transduction pathways may contribute to the activation of transcription factors like CREB and promote neuroplastic remodeling and/or neuroprotection processes (Bethea *et al.*, 2009) that could be effective in the development of strategies to cope with stress. Additionally, it has been reported that E2 administration decreases the activity of monoamine oxidase enzymes activity (type A and B) (involved in the degradation monoamines) in several areas of brain (Gundlah *et al.*, 2002).

Recently, it was shown that the monoaminergic neurotransmission is sensitive to modulation of estrogenic compounds, in this sense, the effects of estrogens on monoamine levels may be dependent of the type of estrogen receptor used; thus, ERα or ERβ agonists increases the levels of NA in the frontal cortex and hippocampus; similarly, ERα agonist increase the levels of the metabolites of NA and dopamine, 3-methoxy-4-hydroxyphenylglycol (MHPG) and DOPAC in hippocampus or frontal cortex; and ERβ agonist increase the levels of 5-HIIA in amygdala, hippocampus and ventral tegmental area (Lubbers *et al.*, 2010). It was shown that that the effects of estrogens on cathecolaminergic biosynthetic enzymes are due to the activation of estrogens receptors α and the serotonergic enzyme stimulation has been related with the activation of ER β (Donner & Handa, 2009; Serova *et al.*, 2010). Therefore, it is possible to considerer that the modulation of serotonergic and noradrenergic activity depends in part of the activation of ER. Based on this evidence, it seems possible that ERα are more related with the modulation of the catecholaminergic system, while ERβ with the serotonergic one; notwithstanding future studies are needed to confirm this hypothesis.

It is important to mention that participation of estrogens' membrane receptors in the modulation of monoamines activity needs to be further investigated. For example, it has been shown that the desensitization of 5-HT1A receptor induced by 17 β-estradiol in oxytocin cells of hypothalamus is independent of the activation of ERβ and may involve only the membrane estrogen receptor GPR30 (Rossi *et al.*, 2010); while the desensitization of the same receptors in the ACTH cells are depend of both GPR30 and ERβ (Rossi *et al.*, 2010). This evidence shows the complexity in the relationship between estrogens and monoamines.

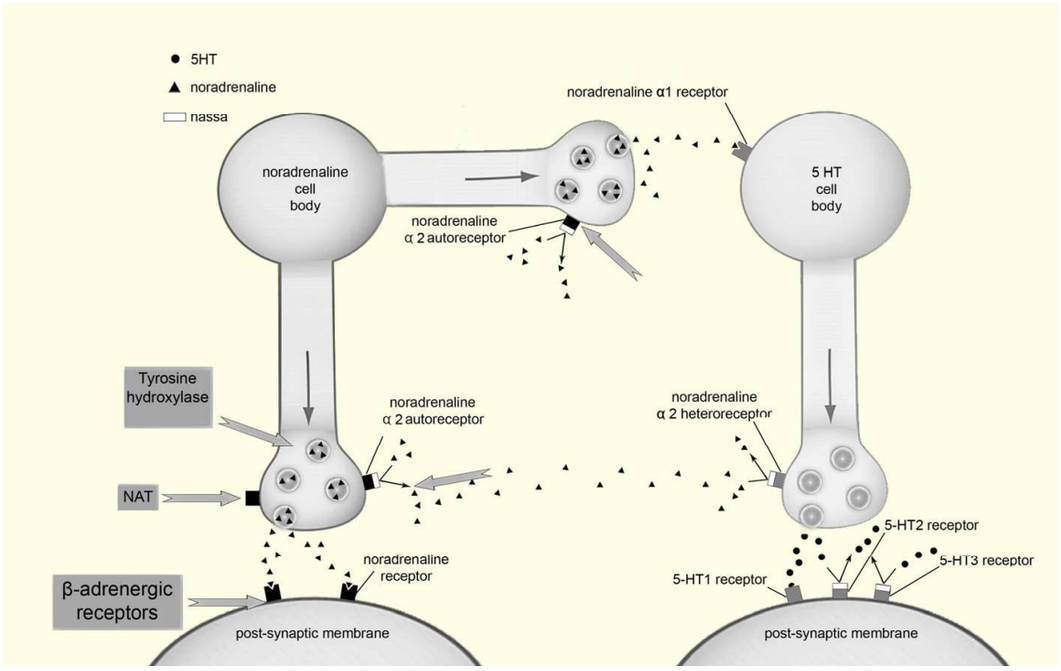


Fig. 2. Esquematic representation proposed for the mechanism of action of ethynyl estradiol's antidepressant-like actions on the noradrenergic and serotonergic systems in the forced swimming test (an animal model of depression). Ethynyl-estradiol increases tyrosine hydroxylase activity and simultaneously inhibits the noradrenergic transporter, facilitating the release of noradrenaline. Increases in NA concentration promote α2-autoadrenoceptors desensitization. In addition, estrogens activate α2-adrenoceptors located on the serotonergic terminals and, therefore, contribute to regulate serotonin release. NAT= Noradrenergic Transporter

7. Possible implications of estrogens actions on the modulation of monoamines activity

The modulation of noradrenergic and serotonergic systems by estrogens could have important physiological implications in the regulation of stress response. It has been reported that corticotrophin releasing factor (CRF) stimulates locus coeruleus activity under stressful situations and this is associated with a heightened arousal (Valentino & Van Bockstaele, 2008; Bangasser *et al.*, 2010). In this case, there is direct evidence that CRF genes expression is regulated by estrogens and that estradiol reduces plasma ACTH and blood pressure increases induced by restrain stress (Bangasser *et al.*, 2010). These responses occurred simultaneously to a differential modulation of cathecolamine biosynthetic enzymes gene expression in the nucleus of the solitary tract and the locus coeruleus (Serova *et al.*, 2005).

Recently, it was reported that an animal model of depression, the FST, increased corticosterone and estrogen plasma concentrations in adult females rats (Martinez-Mota *et al.*, 2011), suggesting that estrogens function as a compensatory mechanism against stress-response. Furthermore, estradiol administration prevented the increase in the percentage of discharge of the locus coeruleus induced by the FST in ovariectomized rats. As a result, it is

possible to considerer that estrogens modulation of the noradrenergic system results in an increase expression of coping behaviors in the FST and in the regulation of HPA function. In addition, it has been reported that stress induced by the FST reduces 5-HT levels in the amygdala and lateral septum in male rats (Kirby *et al*., 1995), while in females, 5-HT is reduced in the prefrontal cortex and in the hypothalamus, but not in the amygdala (Dalla *et al*., 2005). Interestingly, unpublished results from our laboratory showed that E2 administration, previous to the FST, prevented the decline of 5-HT concentration in some brain areas during the FST and at the same time E2 induces an antidepressant-like effect.

Therefore it could be suggested that estrogenic compounds contribute to increase the serotonergic activity and simultaneously decrease noradrenergic activity, improving the behavioral strategies to cope with acute stressful situations. Also these protective actions of estrogens have been shown using animal models of chronic stress; in this case, estradiol administration reversed chronic stress-induced sensitization in the paraventricular nucleus and central amygdala of female rats (Gerrits *et al*., 2006).

8. Acknowledgments

Authors wish to thank Mr. Raúl Cardoso for figure elaboration and Isabel Beltrán Villalobos and José Juan Cruz Martínez for technical assistance. The present work was partially supported by the following Grants: Conacyt-104654 for E E-C and Conacyt-155255 for C L-R.

9. References

Amsterdam, J., Garcia-Espana, F., Fawcett, J., Quitkin, F., Reimherr, F., Rosenbaum, J.&Beasley, C. (1999). Fluoxetine efficacy in menopausal women with and without estrogen replacement. *J Affect Disord* 55, 11-17.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10512601

Attali, G., Weizman, A., Gil-Ad, I.&Rehavi, M. (1997). Opposite modulatory effects of ovarian hormones on rat brain dopamine and serotonin transporters. *Brain Res* 756, 153-159.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9187326

Backstrom, T., Andreen, L., Birzniece, V., Bjorn, I., Johansson, I. M., Nordenstam-Haghjo, M., Nyberg, S., Sundstrom-Poromaa, I., Wahlstrom, G., Wang, M.&Zhu, D. (2003). The role of hormones and hormonal treatments in premenstrual syndrome. *CNS Drugs* 17, 325-342.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12665391

Bangasser, D. A., Curtis, A., Reyes, B. A., Bethea, T. T., Parastatidis, I., Ischiropoulos, H., Van Bockstaele, E. J.&Valentino, R. J. (2010). Sex differences in corticotropin-releasing factor receptor signaling and trafficking: potential role in female vulnerability to stress-related psychopathology. *Mol Psychiatry* 15, 877, 896-904.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20548297

Belda, X.&Armario, A. (2009). Dopamine D1 and D2 dopamine receptors regulate immobilization stress-induced activation of the hypothalamus-pituitary-adrenal axis. *Psychopharmacology (Berl)* 206, 355-365.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19621214

Bernardi, M., Vergoni, A. V., Sandrini, M., Tagliavini, S.&Bertolini, A. (1989). Influence of ovariectomy, estradiol and progesterone on the behavior of mice in an experimental model of depression. *Physiol Behav* 45, 1067-1068.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2780868

Bethea, C. L., Mirkes, S. J., Su, A.&Michelson, D. (2002). Effects of oral estrogen, raloxifene and arzoxifene on gene expression in serotonin neurons of macaques. *Psychoneuroendocrinology* 27, 431-445.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11911997

Bethea, C. L., Reddy, A. P., Tokuyama, Y., Henderson, J. A.&Lima, F. B. (2009). Protective actions of ovarian hormones in the serotonin system of macaques. *Front Neuroendocrinol* 30, 212-238.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19394356

Blum, I., Vered, Y., Lifshitz, A., Harel, D., Blum, M., Nordenberg, Y., Harsat, A., Sulkes, J., Gabbay, U.&Graff, E. (1996). The effect of estrogen replacement therapy on plasma serotonin and catecholamines of postmenopausal women. *Isr J Med Sci* 32, 1158-1162.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9007144

Bosse, R.&DiPaolo, T. (1996). The modulation of brain dopamine and GABAA receptors by estradiol: a clue for CNS changes occurring at menopause. *Cell Mol Neurobiol* 16, 199-212.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8743969

Bourin, M., Chenu, F., Prica, C.&Hascoet, M. (2009). Augmentation effect of combination therapy of aripiprazole and antidepressants on forced swimming test in mice. *Psychopharmacology (Berl)* 206, 97-107.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19517098

Bukulmez, O., Al, A., Gurdal, H., Yarali, H., Ulug, B.&Gurgan, T. (2001). Short-term effects of three continuous hormone replacement therapy regimens on platelet tritiated imipramine binding and mood scores: a prospective randomized trial. *Fertil Steril* 75, 737-743.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11287028

Carlberg, K. A.&Fregly, M. J. (1986). Catecholamine excretion and beta-adrenergic responsiveness in estrogen-treated rats. *Pharmacology* 32, 147-156.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3008199

Contreras, C. M., Azamar-Arizmendi, G., Saavedra, M.&Hernandez-Lozano, M. (2006). A five-day gradual reduction regimen of chlormadinone reduces premenstrual anxiety and depression: a pilot study. *Arch Med Res* 37, 907-913.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16971235

Coope, J. (1975). The post-hysterectomy syndrome. *Nurs Times* 71, 1285-1286. .
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1144136

Cryan, J. F., Valentino, R. J.&Lucki, I. (2005). Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. *Neurosci Biobehav Rev* 29, 547-569.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15893822

Cyr, M., Morissette, M., Barden, N., Beaulieu, S., Rochford, J.&Di Paolo, T. (2001). Dopaminergic activity in transgenic mice underexpressing glucocorticoid receptors: effect of antidepressants. *Neuroscience* 102, 151-158.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11226678

Chang, A. S.&Chang, S. M. (1999). Nongenomic steroidal modulation of high-affinity serotonin transport. *Biochim Biophys Acta* 1417, 157-166.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10076044

Dalla, C., Antoniou, K., Drossopoulou, G., Xagoraris, M., Kokras, N., Sfikakis, A.&Papadopoulou-Daifoti, Z. (2005). Chronic mild stress impact: are females more vulnerable? *Neuroscience* 135, 703-714.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16125862

Dennis, M. K., Burai, R., Ramesh, C., Petrie, W. K., Alcon, S. N., Nayak, T. K., Bologa, C. G., Leitao, A., Brailoiu, E., Deliu, E., Dun, N. J., Sklar, L. A., Hathaway, H. J., Arterburn, J. B., Oprea, T. I.&Prossnitz, E. R. (2009). In vivo effects of a GPR30 antagonist. *Nat Chem Biol* 5, 421-427.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19430488

Dhir, A.&Kulkarni, S. K. (2008). Possible involvement of sigma-1 receptors in the anti-immobility action of bupropion, a dopamine reuptake inhibitor. *Fundam Clin Pharmacol* 22, 387-394.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18705749

Donner, N.&Handa, R. J. (2009). Estrogen receptor beta regulates the expression of tryptophan-hydroxylase 2 mRNA within serotonergic neurons of the rat dorsal raphe nuclei. *Neuroscience* 163, 705-718.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19559077

Estrada-Camarena, E., Fernandez-Guasti, A.&Lopez-Rubalcava, C. (2003). Antidepressant-like effect of different estrogenic compounds in the forced swimming test. *Neuropsychopharmacology* 28, 830-838.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12637949

Estrada-Camarena, E., Fernandez-Guasti, A.&Lopez-Rubalcava, C. (2006a). Participation of the 5-HT1A receptor in the antidepressant-like effect of estrogens in the forced swimming test. *Neuropsychopharmacology* 31, 247-255.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16012533

Estrada-Camarena, E., Lopez-Rubalcava, C.&Fernandez-Guasti, A. (2006b). Facilitating antidepressant-like actions of estrogens are mediated by 5-HT1A and estrogen receptors in the rat forced swimming test. *Psychoneuroendocrinology* 31, 905-914.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16843610

Estrada-Camarena, E., Lopez-Rubalcava, C., Hernandez-Aragon, A., Mejia-Mauries, S.&Picazo, O. (2011). Long-term ovariectomy modulates the antidepressant-like action of estrogens, but not of antidepressants. *J Psychopharmacol*.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21890587

Estrada-Camarena, E., Lopez-Rubalcava, C., Vega-Rivera, N., Recamier-Carballo, S.&Fernandez-Guasti, A. (2010). Antidepressant effects of estrogens: a basic approximation. *Behav Pharmacol* 21, 451-464.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20700047

Fedotova, J.&Ordyan, N. (2011). Involvement of D1 receptors in depression-like behavior of ovariectomized rats. *Acta Physiol Hung* 98, 165-176.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21616775

Filardo, E. J., Quinn, J. A., Frackelton, A. R., Jr.&Bland, K. I. (2002). Estrogen action via the G protein-coupled receptor, GPR30: stimulation of adenylyl cyclase and cAMP-mediated attenuation of the epidermal growth factor receptor-to-MAPK signaling axis. *Mol Endocrinol* 16, 70-84.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11773440

Freeman, E. W., Sammel, M. D., Lin, H.&Nelson, D. B. (2006). Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 63, 375-382.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16585466

Galea, L. A., Lee, T. T., Kostaras, X., Sidhu, J. A.&Barr, A. M. (2002). High levels of estradiol impair spatial performance in the Morris water maze and increase 'depressive-like' behaviors in the female meadow vole. *Physiol Behav* 77, 217-225.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12419397

Gerrits, M., Bakker, P. L., Koch, T.&Ter Horst, G. J. (2006). Stress-induced sensitization of the limbic system in ovariectomized rats is partly restored by cyclic 17beta-estradiol administration. *Eur J Neurosci* 23, 1747-1756.

URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16623831

Ghraf, R., Michel, M., Hiemke, C.&Knuppen, R. (1983). Competition by monophenolic estrogens and catecholestrogens for high-affinity uptake of [3H](-)-norepinephrine into synaptosomes from rat cerebral cortex and hypothalamus. *Brain Res* 277, 163-168.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6315138

Girdler, S. S.&Klatzkin, R. (2007). Neurosteroids in the context of stress: implications for depressive disorders. *Pharmacol Ther* 116, 125-139.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597217

Gundlah, C., Lu, N. Z.&Bethea, C. L. (2002). Ovarian steroid regulation of monoamine oxidase-A and -B mRNAs in the macaque dorsal raphe and hypothalamic nuclei. *Psychopharmacology (Berl)* 160, 271-282.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11889496

Halbreich, U.&Kahn, L. S. (2001). Role of estrogen in the aetiology and treatment of mood disorders. *CNS Drugs* 15, 797-817.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11602005

Harlow, B. L., Wise, L. A., Otto, M. W., Soares, C. N.&Cohen, L. S. (2003). Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. *Arch Gen Psychiatry* 60, 29-36.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12511170

Hiemke, C., Bruder, D., Poetz, B.&Ghraf, R. (1985). Sex-specific effects of estradiol on hypothalamic noradrenaline turnover in gonadectomized rats. *Exp Brain Res* 59, 68-72.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4018199

Hiroi, R.&Neumaier, J. F. (2009). Estrogen decreases 5-HT1B autoreceptor mRNA in selective subregion of rat dorsal raphe nucleus: inverse association between gene expression and anxiety behavior in the open field. *Neuroscience* 158, 456-464.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19049819

Holmes, P. V. (2003). Rodent models of depression: reexamining validity without anthropomorphic inference. *Crit Rev Neurobiol* 15, 143-174.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14977368

Holschneider, D. P., Kumazawa, T., Chen, K.&Shih, J. C. (1998). Tissue-specific effects of estrogen on monoamine oxidase A and B in the rat. *Life Sci* 63, 155-160.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9698044

Ikemoto, S.&Goeders, N. E. (1998). Microinjections of dopamine agonists and cocaine elevate plasma corticosterone: dissociation effects among the ventral and dorsal striatum and medial prefrontal cortex. *Brain Res* 814, 171-178.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9838097

Jensvold, M. (1996). Non-pregnant reproductive-age women. Part II: exogenous sex steroid hormones and psychopharmacology. In: *Psychopharmacology and woman: Sex, gender and hormones*, Jensvold, M., Halbreich, U.&Hamilton, J. (eds), pp 170-190.
URL: Washington, DC: American Psychiatric Press.

Joffe, H., Groninger, H., Soares, C. N., Nonacs, R.&Cohen, L. S. (2001). An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. *J Womens Health Gend Based Med* 10, 999-1004.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11788110

Kaba, H., Saito, H., Otsuka, K., Seto, K.&Kawakami, M. (1983). Effects of estrogen on the excitability of neurons projecting from the noradrenergic A1 region to the preoptic and anterior hypothalamic area. *Brain Res* 274, 156-159.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6412965

Kalia, M. (2005). Neurobiological basis of depression: an update. *Metabolism* 54, 24-27.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15877309

Karkanias, G. B., Li, C. S.&Etgen, A. M. (1997). Estradiol reduction of alpha 2-adrenoceptor binding in female rat cortex is correlated with decreases in alpha 2A/D-adrenoceptor messenger RNA. *Neuroscience* 81, 593-597.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9316013

Kirby, L. G., Allen, A. R.&Lucki, I. (1995). Regional differences in the effects of forced swimming on extracellular levels of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. *Brain Res* 682, 189-196.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7552310

Krishnan, V.&Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature* 455, 894-902.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18923511

Kuiper, G. G.&Gustafsson, J. A. (1997). The novel estrogen receptor-beta subtype: potential role in the cell- and promoter-specific actions of estrogens and anti-estrogens. *FEBS Lett* 410, 87-90.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9247129

Landry, M., Levesque, D.&Di Paolo, T. (2002). Estrogenic properties of raloxifene, but not tamoxifen, on D2 and D3 dopamine receptors in the rat forebrain. *Neuroendocrinology* 76, 214-222.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12411738

Levesque, D.&Di Paolo, T. (1993). Modulation by estradiol and progesterone of the GTP effect on striatal D-2 dopamine receptors. *Biochem Pharmacol* 45, 723-733. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8095140

Lopez-Jaramillo, P., Teran, E., Molina, G., Rivera, J.&Lozano, A. (1996). Oestrogens and depression. *Lancet* 348, 135-136. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8676707

Lopez-Muñoz, F.&Alamo, C. (2009). Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr Pharm Des* 15, 1563-1586. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19442174

López-Rubalcava, C., Oikawa-Sala, J., Chávez-Álvarez, K.&Estrada-Camarena, E. (2005) Analysis of the participation of the serotonergic system in the antidepressant-like action of 17beta -estradiol in the forced swimming test (fst): presynaptic or postsynaptic actions. In: *Society for Neuroscience*, p No. 567.512. Washington, DC.

López-Rubalcava, C., Vega Rivera, N., Cruz-Martínez, J. J. &Estrada-Camarena, E. (2007) Participation of both estrogen and alpha2-adrenergic receptors, in the antidepressant-like actions of ethynil-estradiol in rats tested in the forced swimming test. In: *12th Biennial meeting of the European Behavioral Pharmacology Society*.

López-Rubalcva, C., Mostalac-Preciado, C.&Estrada-Camarena, E. (2009). The rat forced swimming test: an animal model for the study of the antidepressant drugs. In: *Models of Neuropharmacology*, Rocha, L. & Granados, V. (eds): Transworld Res Network.

Lu, N. Z.&Bethea, C. L. (2002). Ovarian steroid regulation of 5-HT1A receptor binding and G protein activation in female monkeys. *Neuropsychopharmacology* 27, 12-24. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12062903

Lu, N. Z., Shlaes, T. A., Gundlah, C., Dziennis, S. E., Lyle, R. E.&Bethea, C. L. (1999). Ovarian steroid action on tryptophan hydroxylase protein and serotonin compared to localization of ovarian steroid receptors in midbrain of guinea pigs. *Endocrine* 11, 257-267. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10786822

Lubbers, L. S., Zafian, P. T., Gautreaux, C., Gordon, M., Alves, S. E., Correa, L., Lorrain, D. S., Hickey, G. J.&Luine, V. (2010). Estrogen receptor (ER) subtype agonists alter monoamine levels in the female rat brain. *J Steroid Biochem Mol Biol* 122, 310-317. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20800684

Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S. G.&Russell, J. (2007). Neurobiology of depression: an integrated view of key findings. *Int J Clin Pract* 61, 2030-2040. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17944926

Margeat, E., Bourdoncle, A., Margueron, R., Poujol, N., Cavailles, V.&Royer, C. (2003). Ligands differentially modulate the protein interactions of the human estrogen receptors alpha and beta. *J Mol Biol* 326, 77-92.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12547192

Markou, A., Chiamulera, C., Geyer, M. A., Tricklebank, M.&Steckler, T. (2009). Removing obstacles in neuroscience drug discovery: the future path for animal models. *Neuropsychopharmacology* 34, 74-89.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18830240

Martinez-Mota, L., Ulloa, R. E., Herrera-Perez, J., Chavira, R.&Fernandez-Guasti, A. (2011). Sex and age differences in the impact of the forced swimming test on the levels of steroid hormones. *Physiol Behav* 104, 900-905.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21658399

McEwen, B. S. (1999). Clinical review 108: The molecular and neuroanatomical basis for estrogen effects in the central nervous system. *J Clin Endocrinol Metab* 84, 1790-1797.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10372665

Mendelson, S. D., McKittrick, C. R.&McEwen, B. S. (1993). Autoradiographic analyses of the effects of estradiol benzoate on [3H]paroxetine binding in the cerebral cortex and dorsal hippocampus of gonadectomized male and female rats. *Brain Res* 601, 299-302.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8431776

Mize, A. L.&Alper, R. H. (2000). Acute and long-term effects of 17beta-estradiol on G(i/o) coupled neurotransmitter receptor function in the female rat brain as assessed by agonist-stimulated [35S]GTPgammaS binding. *Brain Res* 859, 326-333.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10719081

Mize, A. L.&Alper, R. H. (2002). Rapid uncoupling of serotonin-1A receptors in rat hippocampus by 17beta-estradiol in vitro requires protein kinases A and C. *Neuroendocrinology* 76, 339-347.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12566941

Mize, A. L., Poisner, A. M.&Alper, R. H. (2001). Estrogens act in rat hippocampus and frontal cortex to produce rapid, receptor-mediated decreases in serotonin 5-HT(1A) receptor function. *Neuroendocrinology* 73, 166-174.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11307035

Monje, P.&Boland, R. (2001). Subcellular distribution of native estrogen receptor alpha and beta isoforms in rabbit uterus and ovary. *J Cell Biochem* 82, 467-479.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11500923

Montgomery, J. C., Appleby, L., Brincat, M., Versi, E., Tapp, A., Fenwick, P. B.&Studd, J. W. (1987). Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *Lancet* 1, 297-299.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2880114

Morgan, M. L., Cook, I. A., Rapkin, A. J.&Leuchter, A. F. (2005). Estrogen augmentation of antidepressants in perimenopausal depression: a pilot study. *J Clin Psychiatry* 66, 774-780.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15960574

Mori-Okamoto, J., Otawara-Hamamoto, Y., Yamato, H.&Yoshimura, H. (2004). Pomegranate extract improves a depressive state and bone properties in menopausal syndrome model ovariectomized mice. *J Ethnopharmacol* 92, 93-101.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15099854

Morrison, M. F., Kallan, M. J., Ten Have, T., Katz, I., Tweedy, K.&Battistini, M. (2004). Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 55, 406-412.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14960294

O'Keane, V., O'Hanlon, M., Webb, M.&Dinan, T. (1991). d-fenfluramine/prolactin response throughout the menstrual cycle: evidence for an oestrogen-induced alteration. *Clin Endocrinol (Oxf)* 34, 289-292.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1879060

Okada, M., Hayashi, N., Kometani, M., Nakao, K.&Inukai, T. (1997). Influences of ovariectomy and continuous replacement of 17beta-estradiol on the tail skin temperature and behavior in the forced swimming test in rats. *Jpn J Pharmacol* 73, 93-96.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9032138

Osterlund, M. K. (2009). Underlying mechanisms mediating the antidepressant effects of estrogens. *Biochim Biophys Acta* 1800, 1136-1144.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19900508

Osterlund, M. K.&Hurd, Y. L. (1998). Acute 17 beta-estradiol treatment down-regulates serotonin 5HT1A receptor mRNA expression in the limbic system of female rats. *Brain Res Mol Brain Res* 55, 169-172.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9645972

Pae, C. U., Tharwani, H., Marks, D. M., Masand, P. S.&Patkar, A. A. (2009). Atypical depression: a comprehensive review. *CNS Drugs* 23, 1023-1037.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19958040

Payne, J. L., Roy, P. S., Murphy-Eberenz, K., Weismann, M. M., Swartz, K. L., McInnis, M. G., Nwulia, E., Mondimore, F. M., MacKinnon, D. F., Miller, E. B., Nurnberger, J. I.,

Levinson, D. F., DePaulo, J. R., Jr.&Potash, J. B. (2007). Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder. *J Affect Disord* 99, 221-229.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17011632

Raap, D. K., DonCarlos, L., Garcia, F., Muma, N. A., Wolf, W. A., Battaglia, G.&Van de Kar, L. D. (2000). Estrogen desensitizes 5-HT(1A) receptors and reduces levels of G(z), G(i1) and G(i3) proteins in the hypothalamus. *Neuropharmacology* 39, 1823-1832.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10884563

Rachman, I. M., Unnerstall, J. R., Pfaff, D. W.&Cohen, R. S. (1998). Estrogen alters behavior and forebrain c-fos expression in ovariectomized rats subjected to the forced swim test. *Proc Natl Acad Sci U S A* 95, 13941-13946.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9811905

Rajewska, J.&Rybakowski, J. K. (2003). Depression in premenopausal women: gonadal hormones and serotonergic system assessed by D-fenfluramine challenge test. *Prog Neuropsychopharmacol Biol Psychiatry* 27, 705-709.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12787860

Rasgon, N. L., Altshuler, L. L., Fairbanks, L. A., Dunkin, J. J., Davtyan, C., Elman, S.&Rapkin, A. J. (2002). Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry* 63 Suppl 7, 45-48.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11995778

Reneric, J. P.&Lucki, I. (1998). Antidepressant behavioral effects by dual inhibition of monoamine reuptake in the rat forced swimming test. *Psychopharmacology (Berl)* 136, 190-197.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9551776

Richards, M., Rubinow, D. R., Daly, R. C.&Schmidt, P. J. (2006). Premenstrual symptoms and perimenopausal depression. *Am J Psychiatry* 163, 133-137.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16390900

Riecher-Rossler, A.&Geyter, C. (2007). The forthcoming role of treatment with oestrogens in mental health. *Swiss Med Wkly* 137, 565-572.

Rocca, W. A., Grossardt, B. R.&Shuster, L. T. (2010). Oophorectomy, menopause, estrogen, and cognitive aging: the timing hypothesis. *Neurodegener Dis* 7, 163-166.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20197698

Romano-Torres, M.&Fernandez-Guasti, A. (2010). Estradiol valerate elicits antidepressant-like effects in middle-aged female rats under chronic mild stress. *Behav Pharmacol* 21, 104-111.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20168212

Rossi, D. V., Dai, Y., Thomas, P., Carrasco, G. A., DonCarlos, L. L., Muma, N. A.&Li, Q. (2010). Estradiol-induced desensitization of 5-HT1A receptor signaling in the paraventricular nucleus of the hypothalamus is independent of estrogen receptor-beta. *Psychoneuroendocrinology* 35, 1023-1033.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20138435

Saletu, B., Brandstatter, N., Metka, M., Stamenkovic, M., Anderer, P., Semlitsch, H. V., Heytmanek, G., Huber, J., Grunberger, J., Linzmayer, L.&et al. (1995). Double-blind, placebo-controlled, hormonal, syndromal and EEG mapping studies with transdermal oestradiol therapy in menopausal depression. *Psychopharmacology (Berl)* 122, 321-329.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8657828

Schmidt, P. J., Nieman, L., Danaceau, M. A., Tobin, M. B., Roca, C. A., Murphy, J. H.&Rubinow, D. R. (2000). Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 183, 414-420.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10942479

Schneider, L. S., Small, G. W.&Clary, C. M. (2001). Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry* 9, 393-399.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11739065

Schneider, L. S., Small, G. W., Hamilton, S. H., Bystritsky, A., Nemeroff, C. B.&Meyers, B. S. (1997). Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group. *Am J Geriatr Psychiatry* 5, 97-106.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9106373

Serova, L., Rivkin, M., Nakashima, A.&Sabban, E. L. (2002). Estradiol stimulates gene expression of norepinephrine biosynthetic enzymes in rat locus coeruleus. *Neuroendocrinology* 75, 193-200.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11914591

Serova, L. I., Harris, H. A., Maharjan, S.&Sabban, E. L. (2010). Modulation of responses to stress by estradiol benzoate and selective estrogen receptor agonists. *J Endocrinol* 205, 253-262.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20348154

Serova, L. I., Maharjan, S.&Sabban, E. L. (2005). Estrogen modifies stress response of catecholamine biosynthetic enzyme genes and cardiovascular system in ovariectomized female rats. *Neuroscience* 132, 249-259.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15802180

Shapira, B., Oppenheim, G., Zohar, J., Segal, M., Malach, D.&Belmaker, R. H. (1985). Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. *Biol Psychiatry* 20, 576-579.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2985131

Sherwin, B. B.&Henry, J. F. (2008). Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. *Front Neuroendocrinol* 29, 88-113.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17980408

Shughrue, P. J., Lane, M. V.&Merchenthaler, I. (1997). Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. *J Comp Neurol* 388, 507-525.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9388012

Smith, L. J., Henderson, J. A., Abell, C. W.&Bethea, C. L. (2004). Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of macaques. *Neuropsychopharmacology* 29, 2035-2045.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15199371

Soares, C. N., Almeida, O. P., Joffe, H.&Cohen, L. S. (2001). Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 58, 529-534.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11386980

Soares, C. N.&Zitek, B. (2008). Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci* 33, 331-343.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18592034

Strickler, R. C., Borth, R.&Woodlever, C. A. (1977). The climacteric syndrome: an estrogen replacement dilemma. *Can Med Assoc J* 116, 586-587.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=204404

Sullivan, R. M.&Dufresne, M. M. (2006). Mesocortical dopamine and HPA axis regulation: role of laterality and early environment. *Brain Res* 1076, 49-59. URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16483551

Toran-Allerand, C. D. (2004). Minireview: A plethora of estrogen receptors in the brain: where will it end? *Endocrinology* 145, 1069-1074.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14670986

Toran-Allerand, C. D., Tinnikov, A. A., Singh, R. J.&Nethrapalli, I. S. (2005). 17alpha-estradiol: a brain-active estrogen? *Endocrinology* 146, 3843-3850.
URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15947006

Valentino, R. J.&Van Bockstaele, E. (2008). Convergent regulation of locus coeruleus activity as an adaptive response to stress. *Eur J Pharmacol* 583, 194-203. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18255055

Vasudevan, N.&Pfaff, D. W. (2007). Membrane-initiated actions of estrogens in neuroendocrinology: emerging principles. *Endocr Rev* 28, 1-19. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17018839

Vetulani, J., Stawarz, R. J., Dingell, J. V.&Sulser, F. (1976). A possible common mechanism of action of antidepressant treatments: reduction in the sensitivity of the noradrenergic cyclic AMP gererating system in the rat limbic forebrain. *Naunyn Schmiedebergs Arch Pharmacol* 293, 109-114. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=183150

Wagner, E. J., Ronnekleiv, O. K.&Kelly, M. J. (2001). The noradrenergic inhibition of an apamin-sensitive, small-conductance Ca2+-activated K+ channel in hypothalamic gamma-aminobutyric acid neurons: pharmacology, estrogen sensitivity, and relevance to the control of the reproductive axis. *J Pharmacol Exp Ther* 299, 21-30. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11561059

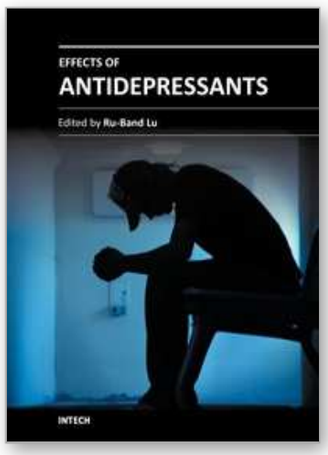
Walf, A. A.&Frye, C. A. (2007). Administration of estrogen receptor beta-specific selective estrogen receptor modulators to the hippocampus decrease anxiety and depressive behavior of ovariectomized rats. *Pharmacol Biochem Behav* 86, 407-414. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16916539

Walf, A. A.&Frye, C. A. (2010). Raloxifene and/or estradiol decrease anxiety-like and depressive-like behavior, whereas only estradiol increases carcinogen-induced tumorigenesis and uterine proliferation among ovariectomized rats. *Behav Pharmacol* 21, 231-240. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20480545

Walf, A. A., Rhodes, M. E.&Frye, C. A. (2004). Antidepressant effects of ERbeta-selective estrogen receptor modulators in the forced swim test. *Pharmacol Biochem Behav* 78, 523-529. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15251261

Weiser, M. J., Foradori, C. D.&Handa, R. J. (2008). Estrogen receptor beta in the brain: from form to function. *Brain Res Rev* 57, 309-320. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17662459

Wilkinson, M.&Herdon, H. J. (1982). Diethylstilbestrol regulates the number of alpha- and beta-adrenergic binding sites in incubated hypothalamus and amygdala. *Brain Res* 248, 79-85. URL:http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6289996



Effects of Antidepressants

Edited by Dr. Ru-Band Lu

ISBN 978-953-51-0663-0
Hard cover, 194 pages
Publisher InTech
Published online 29, June, 2012
Published in print edition June, 2012

Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen