

Non-Reproductive Effects of Estradiol: Brain Behavior

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In addition to reproductive physiological effects and sexual behavior, ovarian steroids, mainly estradiol (E2), also have several other non-reproductive effects. In psychiatry, estradiol has been implicated to exert effects on mood, memory and mental state in human, least in part, through its actions in the serotonergic system activity [1]. Serotonergic signaling has a key role in the generation and modulation of several perceptual, cognitive and behavioral functions such as sleep, addiction, mood, alcohol abuse, depression, anxiety, pain, locomotion, sexual activity, aggression, learning and memory. It has been showed that disruptions in serotonergic systems are involved in the etiology of mental disorders such as schizophrenia, depression, suicidal behavior, obsessive compulsive disorder, eating disorders and infantile autism [2]. Thus, many serotonin receptors have been the target of several treatments of neuropsychiatric disorders.

Some studies have shown that the estradiol receptors are express in the mesencephalic brain such as in the dorsal raphe nucleus (DRN), which contains the largest aggregate of serotonin (5-HT) containing cells in the central nervous system [1]. The demonstration of estradiol receptors in brain structures involved in cognitive and behavioral functions led to idea that estradiol has a direct effect on the mental state, mood and cognition. In fact, various neuropsychiatric disorders in women, such as premenstrual dysphoric disorder, postmenopausal and postpartum depression, anxiety and bulimia are related with low plasma levels of estrogen as well as decreased serotonergic function. Moreover, it is known that the estradiol has significant effects on serotonergic neurotransmission by increasing synthesis of 5-HT as well the expression of the serotonin transporter and affects the functioning of several serotonin receptors [1]. In this context, some clinical studies have reported that estrogen replacement mimics the effect of antidepressants in patients with depression [3].

Furthermore, studies have identified a subpopulation of serotonergic neurons within the dorsomedial subdivision of the DRN that expresses corticotropin-releasing factor (CRF) and that this region of the DR projects to the central nucleus of the amygdala (CeA), a stress-related forebrain structure [4]. Likewise, some serotonergic neurons within DRN projects to CRF neurons from paraventricular nucleus (PVN), a hypothalamus structure involved in mood disorders [5]. The demonstration of projections from DRN to stress-related/mood disorders structures suggests that DRN may play a role in serotonergic modulation of stress-related physiology and behavior in rats and in stress-related neuropsychiatric disorders in humans. In addition to modulation of estradiol on the serotonergic signaling, estradiol also has been implicated in reduction of responsiveness of neurons producers of CRF in the PVN in response to stress stimulus. This result suggests an important role of estradiol in the modulation of stress-related physiology and behavior, protecting the females against the physiological changes known to be induced by increased hypothalamus-pituitary adrenal axis activity [6].

These are just a few examples illustrating the importance of estradiol in the modulation of various non-reproductive perceptual, cognitive and behavioral functions such as mood, depression, anxiety, memory, mental state and cognition. Then, it could be interpreted that the ovarian hormones, mainly estradiol, is very important to several brain functions psychiatric-related physiology and behavior, and its replacement therapy may be used as an adjunct in some neuropsychiatric disorders treatment.

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