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Sex Differences in Brain-Derived Neurotrophic Factor Signaling and Functions

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Abstract

Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family that plays a critical role in numerous neuronal activities. Recent studies report that some functions or action mechanisms of BDNF vary in a sex-dependent manner. In particular, BDNF content in some brain parts and the tendency of developing BDNF-deficient-related diseases like depression is higher in female animals. With the support of other relevant studies, it is suggested that sex hormones or steroids can modulate the activities of BDNF, which may account for its functional discrepancy in different sexes. Indeed, the cross-talk between BDNF and sex steroids has been detected for decades and some sex steroids like estrogen have a positive regulatory effect to BDNF expression and signaling. Thus, the sex of animal models used is critical when studying the functions of BDNF *in vivo*. In this review, we will summarize our current findings on the difference in expression, signaling, and functions of BDNF between sexes. We will also discuss the potential mechanisms in mediating these differential responses with a specific emphasis on sex steroids. By presenting and discussing these findings, we encourage taking sex influences into consideration when designing experiments, interpreting results and drawing conclusions.

Keywords

Brain; BDNF; sex; gene expression; signal transduction

INTRODUCTION

The central nervous system (CNS) is different in structure, activity, development and chemistry between female and male mammals (Forger et al. 2016; Raznahan et al. 2010; Ruigrok et al. 2014). Although these phenomena have long been recognized, the mechanism

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

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that causes the differences is still not clear (Cahill 2006). Some of the sex variations, nevertheless, could be explained by the difference in gonadal steroid (androgens in male and estrogens in female) concentration, which are mainly produced in the testicles in male and the ovaries in female mammals. There are three natural estrogens: estrone (E1), 17β-estradiol (E2) and estriol (E3) in female and a major androgen, testosterone, in male mammals. These hormones act on the brain via multiple mechanisms to shape the differences and part of their actions rely on the interaction with other factors/hormones like neurotrophins. Neurotrophins are a group of growth factors that regulates numerous activities of the nervous system. They consist of 4 members: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin-4/5 (NT-4/5). BDNF is the second neurotrophin identified, which has the most abundant and widespread expression in both developing and mature mammalian brain (Cunha et al. 2010). To date it has been shown that BDNF is involved in every aspect of neuronal activity including neuronal survival, neurogenesis, dendritic branching, neurotransmitter production and release, synapse formation and maturation, and synaptic plasticity, which indicate that BDNF is crucial for the development and maintenance of the brain's activities (Park and Poo 2013). In addition to its contribution in normal brain functions, BDNF has been implicated in various neurological disorders. Lower concentration of BDNF in the blood stream or cerebral fluid has been correlated with the prognosis of diseases like Alzheimer's disease, Parkinson disease, Huntington's disease, Rett Syndrome, and amyotrophic lateral sclerosis (ALS) (Zuccato and Cattaneo 2009). In fact, administration of BDNF is an effective way to improve the neuronal deficits in a number of animal disease models, suggesting BDNF can be a potential therapeutic agent against various traumas like stroke, spinal cord injury, and aging-related neuronal loss (Nagahara and Tuszynski 2011). However, the therapeutic effect of BDNF can be affected by a lot of factors including time and place of administration, age, and even sex of the recipients. Surprisingly, the sex-specific effect on *BDNF* expression, signaling or activities has not raised much concern in most of the BDNF-related research, which may affect our analysis on BDNF's functions or activities. For instance, Li *et al.* has demonstrated that BDNF injection can alleviate the acetic acid-induced pain response in male rats. In contrast, the pain-killing effect of BDNF was abolished when female rats were used in the examination (Li et al. 2010). Thus, the conclusion drawn from an identical study may be completely different, if a different sex of research model is used. Due to the limited amount of studies performed, the mechanism of how sex differences affect the physiological or therapeutic activity of BDNF is still unclear. This mini-review aims to present the findings on the sex effect on the expression, signaling and functions of BDNF. The possible role of sex hormones in these differential activities will also be discussed, and we will close with a brief discussion on some problems that need to be resolved in the future.

SEX DIFFERENCES IN CIRCULATING BDNF AND BDNF EXPRESSION

BDNF is mainly produced in the CNS, and can be detected in almost every brain part (Conner et al. 1997; Katoh-Semba et al. 1997). When comparing the absolute amount of BDNF in various brain regions between male and female, it is reported that female rats have higher BDNF content in the hippocampus, ventromedial hypothalamus, cortex and amygdala than male rats (Bakos et al. 2009; Bland et al. 2005; Liu et al. 2014; Snigdha et al. 2011).

Franklin and Perrot-Sinal also demonstrated a lower level of BDNF in male hippocampus CA3 region (Franklin and Perrot-Sinal 2006). However, the authors also found that the dorsal dentate gyrus of male rats hippocampus has more BDNF than that in the same region of the female brain. (Franklin and Perrot-Sinal 2006). In contrast to rats, male mice have higher BDNF in the hippocampus, cortex and brain stem (Szapacs et al. 2004). In human, there is no significant difference in hippocampal BDNF content between men and women but female subjects have higher BDNF in the prefrontal context (Hayley et al. 2015). Interestingly, sex-dependent expression difference can also be detected in non-mammalian species. For example, male song birds have a higher BDNF level in the high vocal center, which is believed as an important factor to their singing behavior during mating (Rasika et al. 1999). These reports suggest that sex differences on the CNS distribution of BDNF are consistent among various species. Nevertheless, these observations were generated from fragmented and scattered studies, which were not designed primarily to examine the tissue distribution of BDNF in different sexes. Thus, a systematic and comprehensive comparison on the sex- and species-specific BDNF expression in corresponding brain regions should be performed to make a clear picture on this issue.

Besides basal transcription, stress or stimulus-induced *BDNF* expression also shows significant sex-dependent variations. Compelling evidence on such disparity comes from investigations on the effect of environment enrichment on brain functions, which has been shown to increase neuronal BDNF expression probably by epigenetic modifications (Ickes et al. 2000; Kuzumaki et al. 2011; Vazquez-Sanroman et al. 2013). Specifically, enriched environment induces more *BDNF* expression in the prefrontal cortex, hippocampus and hypothalamus of female mice (Bakos et al. 2009; Zhu et al. 2006). Chen *et al.* further demonstrate that environment enrichment only promotes BDNF increase in the female brain after traumatic injury (Chen et al. 2005). Stress-induced responses are also different between male and female. An early stressful event such as isolation, early weaning or mother deprivation decreases *BDNF* transcription solely in the male hippocampus and hypothalamus (Kikusui et al. 2009; Viveros et al. 2010; Weintraub et al. 2010). In contrast, these maltreatments cause a female-specific increase of *BDNF* expression in the amygdala (Hill et al. 2014). In a recent study, Liu *et al.* demonstrate a downregulation of *BDNF* expression in the male ventromedial hypothalamus (VMH) during fasting (Liu et al. 2014). This observation concurs with the function of BDNF as an anorexic factor to suppress appetite in the hypothalamus (Pelleymounter et al. 1995), which may be associated with the food intake behavioral change in response to food availability as male animals have a higher food-anticipatory activity and food intake after refeeding (Li et al. 2015). There is also a sex-specific response to pharmacological-stimulated *BDNF* expression in the brain. For example, NMDA receptor antagonist Dizocilpine increases *BDNF* expression in the cortex of female mice, whereas another NMDA receptor antagonist, Phencyclidine, decreases *BDNF* expression in a variety of brain regions only in female rats (Matsuki et al. 2001; Snigdha et al. 2011). In contrast, male brains are more responsive to GABA receptor agonist Diazepam and canabionoid agonist CP55940 in reducing hippocampal and hypothalamic *BDNF* expression (Kellogg et al. 2000; Lopez-Gallardo et al. 2012). It remains to be explored if the sex-specific *BDNF* expression is responsible for efficacy of these receptor

(ant)agonists, which display obvious sex-specific activities (Feinstein and Kritzer 2013; Tseng and Craft 2001)

Although it has been suggested that most BDNF in the blood is released from the CNS (Rasmussen et al. 2009), the differential BDNF expression in male and female brain does not cause divergence in circulating BDNF. Several studies have reported comparable BDNF levels in circulation between men and women at various ages (Bus et al. 2012; Katoh-Semba et al. 2007; Lang et al. 2009; Ziegenhorn et al. 2007). Presumably, the differences in neuronal *BDNF* expression only affect the autocrine or paracrine activity of BDNF. This autocrine theory is supported by another study performed in skeletal muscle. After electroporating BDNF-overexpressing vector into the tibialis of mouse, Mathews *et al.* found no increase of serum BDNF concentration in the tested mice, although the BDNF content increased 20-fold in their skeletal muscles (Matthews et al. 2009). Nevertheless, the possibility that different platelet activities, the major reservoir of circulating BDNF (Fujimura et al. 2002), may contribute significantly in normalizing the blood BDNF level in different sexes could not be excluded because the hormone uptake and aggregation activities of platelets are different between male and female (Halbreich et al. 1991; Haque et al. 2001).

SEX-SPECIFIC FUNCTIONS OF BDNF

Because of the sex-specific expression in various conditions, it is expected that BDNF may induce different functions or different degrees of action in particular sexes. Comparative studies using male and female animals with ablated *BDNF* gene provides some evidence to support this hypothesis. In one of these studies, it is shown that conditional deletion of *BDNF* gene in the forebrain (cKO) causes hyperactivity in the male mice only. Female *BDNF* cKO mice, in contrast, display anxiety and depression behaviors, which cannot be detected in male animals (Monteggia et al. 2007). This observation of lower BDNF in female mouse brain causes depressive behaviors is an attractive explanation to the high preponderance of depression in women across cultures (Kuehner 2003). In support of this conclusion, a recent examination performed in postmortem samples from depressed women who died by suicide clearly demonstrate reduced BDNF levels within the frontopolar prefrontal cortex compared to their non-psychiatric controls (Hayley et al. 2015). However, the linkage of BDNF level in the brain and depression has not been strongly established as another study, which analyzes *BDNF* and its receptor Tropomyosin kinase receptor B (*TrkB)* expression in postmortem subjects with major depressive disorder does not show any sex-dependent effect in the subgenual anterior cingulate cortex (Tripp et al. 2012).

In contrast to the depression behavior, heterozygous depletion of *BDNF* gene (*BDNF+/−*) alleviates the anxiety behavior only in female serotonin transporter knockout (SERT−/−) mice (Ren-Patterson et al. 2006). This study reveals that female *SERT−/−BDNF+/−* mice have higher serotonin (5-HT) and its metabolites 5-hydroxyindoleacetic acid (5-HIAA) in the hippocampus and hypothalamus, elevated catecholamines [dopamine, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid] in striatum, and augmented hypothalamic *TrkB* expression than *SERT−/−BDNF+/+* mice. Due to an increase in the concentration of 5-HT in the hypothalamus of estradiol implanted male mice, the authors suggest that the availability of estrogen protects female *SERT−/−BDNF+/−* mice from

monoamine depletion and thus reduces the anxiety behavior. In another study performed in neuron-specific *BDNF* knockout mice, Camerino *et al.* show that ablation of *BDNF* in the CNS causes more body adiposity and higher bone mass in female animals (Camerino et al. 2012). Interestingly, these phenotypes show close similarities to that of the neuronal-specific *estrogen receptor* knockout (*ER−/−*) mice (Ohlsson et al. 2012). Thus, the authors postulate that BDNF and estrogen pathways may act synergistically in female mice to modulate the skeletal and metabolic phenotypes.

In a series of studies to explore the role of BDNF signaling in various disorders using our newly identified BDNF mimetic 7,8-dihydroxyflavone (7,8-DHF) (Jang et al. 2010), it was found that this small molecule also displays differential pharmacological activities in different sexes. In the first study performed in mice with hypoxia ischemia (HI)-induced brain injury, 7,8-DHF-treatment has a more pronounced protective effect against HI-induced hippocampal neurodegeneration and astrogliosis in female animals (Uluc et al. 2013). A later study confirmed these findings that 7,8-DHF treatment has a higher potency against HI-induced hippocampal apoptosis in female mice (Cikla et al. 2016). This study also found that the protective effect of 7,8-DHF is ablated in estrogen receptor (*ER)−/−* animals. Together, with other signaling analysis, the authors proposed that post-HI induced *ER* expression in female hippocampus couples the c-Src kinase to augment the TrkB phosphorylation, thereby reduces the cellular apoptosis and neuronal injury. In our recent study, we found that 7,8-DHF initiates the AMPK/CREB/uncoupling protein 1 (UCP1) pathway to increase the lipid oxidation and energy expenditure in muscle cells (Chan et al. 2015). Concurred with these *in vitro* findings, administration of 7,8-DHF increased the energy expenditure of mice under high-fat diet (HFD) feeding, thus protecting these animals from gaining excess body weight. It is intriguing to note that the anti-obesity function of 7,8-DHF could only be detected in female mice as HFD feeding induced similar body mass increase in both control and 7,8-DHF administered male mice. While the TrkB-ER cross-talk proposed by Cikla *et al.* (Cikla et al. 2016) provides an attractive model to explain the sex-dimorphic activities of 7,8-DHF, we should also consider the fact that 7,8-DHF is an aromatase inhibitor (Chen et al. 1997; Kao et al. 1998). Thus, further studies on the role of 7,8-DHF in ER signaling or estrogen production are needed to delineate its sex-dependent activity in both neurological system and peripheral tissues.

SEX-DEPENDENT SIGNALINGS INDUCED BY BDNF

BDNF exerts its biological actions via interaction with its cognate high affinity receptor TrkB. After binding to the transmembrane receptor, BDNF induces TrkB dimerization and autophosphorylation. The phosphorylated residues in TrkB serve as the docking sites for adaptor proteins like Src homology domain 2 (SH2) or polypyrimidine tract-binding protein (PTB), which lead to the activation of phosphoinositide 3-kinase (PI3K)-Akt, mitogen-activated protein kinase (MEK)-extracellular signal regulated kinase (ERK), and phospholipase Cγ1 (PLCγ1)-CRE-responsive element binding protein (CREB) signaling (Longo and Massa 2013). Surprisingly, there is no clear evidence showing a sexual difference in BDNF-induced signaling in cells under physiological conditions, but several indirect studies suggest that female mice have a differential TrkB activation mechanism. Hill and van den Buuse demonstrated a sex-dependent variation in TrkB signaling in *BDNF+/−*

mice. These authors reported that male *BDNF+/−* mice exhibited higher TrkB phosphorylation than female animals in the frontal cortex and striatum (Hill and van den Buuse 2011). Consequently, the downstream ERK signaling was enhanced in the male *BDNF+/−* brain. The mechanism that contributes to this differential TrkB signaling between male and female is unknown, but the authors suspect that the sex steroids may a play significant role. In another study that investigates the distribution of phosphorylated (activated)-TrkB in the hippocampus, Spencer-Segal *et al.* showed that the proesterous female hippocampus CA1 region has more phosphorylated TrkB proteins than the age-matched male (Spencer-Segal et al. 2011). The same research group found in an earlier study that TrkB and the downstream Akt phosphorylations fluctuated during the estrous cycle (Spencer et al. 2008), further confirming estrogen may increase TrkB signaling. In another elegant study to explain the sex-specific pattern of mouse mammary gland development, it is reported that mammary mesenchymal cells express a high level of the truncated TrkB isoform (TrkB-T1) in E13 male embryo in an androgen-dependent manner (Liu et al. 2012). Thus, the BDNF generated by mesenchymal cells in male embryo is sequestered; leading to an inhibition of sensory neuron innervation to the mammary gland, which eventually dampens the development of mammary gland in male mice.

INTERACTION OF SEX HORMONES WITH BDNF EXPRESSION AND SIGNALING

The first linkage between BDNF and sex steroids was reported from a study that showed a co-localization of BDNF and TrkB in the ER mRNA-containing neurons during forebrain development (Toran-Allerand et al. 1992). Subsequent studies performed in animals with ovariectomy reveal that estrogen replacement increases *BDNF* expression in hippocampus, cortex and olfactory bulb, which confirm the BDNF-inducer activity of estrogen (Solum and Handa 2002). It is now generally accepted that estrogen modulates *BDNF* expressions through at least four different mechanisms. First of all, estrogen can directly induce *BDNF* expression by activating ER. This conclusion is supported by the findings that the *BDNF* gene contains a canonical estrogen response element (Sohrabji et al. 1995), and gel shift and DNA foot-printing assays clearly show that estrogen-ER complexes bind to this sequence in the *BDNF* gene (Sohrabji et al. 1995). Second, estrogen modifies the activity of *BDNF* promoter epigenetically as ovariectomy-induced estrogen depletion causes an increase of methylation on *BDNF* promoters IV and V in the hippocampus (Moreno-Piovano et al. 2014). The mechanism of how estrogen epigenetically controls *BDNF* expression is obscure, but a recent study reports that estradiol infusion into the hippocampus specifically increases histone H3 acetylation at *BDNF* promoters II and IV, possibly through decreasing the expression of histone deacetylase 2 (HDAC2) (Fortress et al. 2014). Third, the ER regulates the activity of CREB through non-genomic activity. In cultured hippocampal neurons, estradiol induces an influx of extracellular Ca^{2+} influx, leading to activation of CREB (Zhao et al. 2005; Zhou et al. 2005). Given that CREB is a major transcription factor that controls *BDNF* expression in neurons in response to Ca^{2+} concentration change (Shieh et al. 1998; Tao et al. 1998), it is reasonable to induce that the ER/CREB axis may modulate the expression of *BDNF* (Fig 1). Lastly, ER controls *BDNF* expression indirectly via interneuronal activity. Based on a series of immunofluorescent staining results, it is proposed

that estrogen modulates *BDNF* expression in a cortical neuronal circuit that contains the ERβ-bearing neurons, non-ER-β-bearing GABA(γ-aminobutyric acid)ergic interneurons, and the target BDNF producing neurons (Blurton-Jones and Tuszynski 2006). In this model, estrogen increases GABA activity or production within the ERβ-bearing neurons, which inhibits the activity of non-ER-β-bearing GABAergic interneurons. Since GABA is an inhibitory neurotransmitter *of BDNF* expression (Heese et al. 2000), the reduced GABA production in the interneurons results in an elevation of BDNF transcription in the target cells. This model also provides a possible explanation to the observation that prenatal (gestation days 14–20) exposure to GABA receptor agonist diazepam results in a male-specific reduction of *BDNF* expression in the hypothalamus (Kellogg et al. 2000), because female fetuses of the same gestational age have slightly higher estrogen levels in the hypothalamus (Konkle and McCarthy 2011).

When compared with estrogen, the effect of androgen on BDNF expression is less studied. However, several studies have reported that testosterone, the major component of androgens, is a positive regulator of *BDNF* expression or production in the motor neurons of the spinal nucleus of the bulbocavernosus (SNB), hippocampus CA1 and brain homogenate after middle cerebral artery occlusion (Fanaei et al. 2014; Li et al. 2012; Osborne et al. 2007; Ottem et al. 2007). Progesterone, another important sex steroid produced mainly in the ovary, can also increase the production of BDNF in the cortex explant and glial cells (Kaur et al. 2007; Su et al. 2012). Most studies reporting the positive role of progesterone on *BDNF* expression were performed in injured neurons such as spinal cord injury, traumatic brain injury and ischemic stroke (Cekic et al. 2012; Gonzalez et al. 2005; Jiang et al. 2016). Based on the result of these studies, it has been suggested that progesterone-mediated neuroprotection is BDNF-dependent. Indeed, inhibition of TrkB activity by the kinase inhibitor K252a abolishes the protective effects of progesterone against glutamate-induced neurotoxicity (Kaur et al. 2007). Interestingly, it is also showed that progesterone attenuated the estrogen-induced *BDNF* and *TrkB* expression, although both hormones are *BDNF* expression enhancers (Aguirre and Baudry 2009; Bimonte-Nelson et al. 2004). The physiological significance of the contradictory effect of progesterone is unknown but it suggests that there is a complex interaction network between sex-steroids in regulating *BDNF* expression.

While the relationship between sex steroids and BDNF expression is evident, the interaction between steroid signaling and BDNF/TrkB pathway is largely unexplored. A recent study reported that overexpression of TrkB in Chinese Hamster Ovary (CHO) cells induced transcription of estrogen responsive elements (ERE)-containing reporter by increasing ERα phosphorylation through ERK (Wong et al. 2011), which suggested that the BDNF/TrkB and ER signaling may cross-talk with each other somehow. However, this study does not provide any evidence on the endogenous protein association, which raises a concern of non-specific interaction due to protein over-expression. Nevertheless, estrogen and BDNF trigger several common pathways such as Akt, ERK and CREB individually in neurons (Belcher et al. 2005; Spencer-Segal et al. 2012), which provides indirect evidence to support the TrkB-ER signaling cross-talk (Fig 2). While there is no study performed to investigate if these two factors provoke an additive or synergistic effect in neurons, it has been suggested that estrogen-mediated synaptogenesis and neuroprotection is through BDNF release (Krizsan-

Agbas et al. 2003; Sato et al. 2007). This hypothesis is supported by a study using co-cultured uteri from wild-type or *BDNF* knockout mice with the rat sympathetic ganglia. In this study, the neuritogenesis induced by wild-type uteri was diminished in the presence of estrogen. However, neurite formation in the presence of *BDNF*−/− uteri was not affected by estrogen, indicating that estrogen alters neuritogenic properties of the rodent uterus by regulating BDNF synthesis (Krizsan-Agbas et al. 2003). In another study using *BDNF* heterozygous (+/−) mice, it is reported that estradiol replacement improved the performance on Y-maze and novel-object recognition test in ovariectomized wild-type but not in ovariectomized *BDNF*+/− mice (Wu et al. 2015). Thus, the integrity of BDNF/TrkB signaling is essential to some estrogen-mediated neurological action but how these two pathways interact with each other is still mysterious.

CONCLUDING REMARK

It is now clear that sex difference is more widespread than one may assume in different physiological and pathological conditions. The diversity in body weight and composition, hormonal status, and enzyme activities between male and female interact and contribute to these differences. Since most neuroscience research has been performed using single sex animals, our understanding on the sexual differences in neurological signaling, especially those induced by BDNF, is at the early stage and most information that we have is fragmented and inconclusive. There are still many areas that require further elucidation. An example is to compare if BDNF initiates differential signaling cascades in male and females under physiological or pathological settings. Because a majority of studies were conducted to measure the functional outcome of BDNF administration in animals without elucidating the molecular mechanism or examining the cellular details, we do not have a clear picture on how BDNF causes the differential activities in different sexes. These data are critical for us to better assess the efficacy of employing BDNF therapy in human patients. Another unresolved question lies on sex steroids/TrkB signaling cross-talk. It is also necessary to determine if different sex steroids alter the signaling cascades induced by BDNF, in addition to their role in manipulating BDNF expression. Examining the functional effect of BDNF administration in animals lacking the sex steroid receptors would provide some insights. Without a full understanding on the sex-specific effect, special attention should be made when interpreting the data from studies performed in either male or female animals to conclude the overall activity of BDNF. This information is particularly important when translating the findings into BDNF-based therapeutic strategies in various neurodegenerative, psychiatric and metabolic disorders. Thus, determining and delineating the sex-specific activities of BDNF in both physiological and pathological conditions is highly warranted.

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SIGNIFICANCE

Sex influence on brain function is now being spotlighted in the field of neuroscience. As an important factor that plays a critical role in numerous neuronal activities, the effect of sex difference on the activity of brain-derived neurotrophic factor (BDNF) has not been systemically studied or reviewed. The current article aims to integrate the scattered findings on sex differences in BDNF research and discuss their potential effects on our understanding on BDNF's functions.

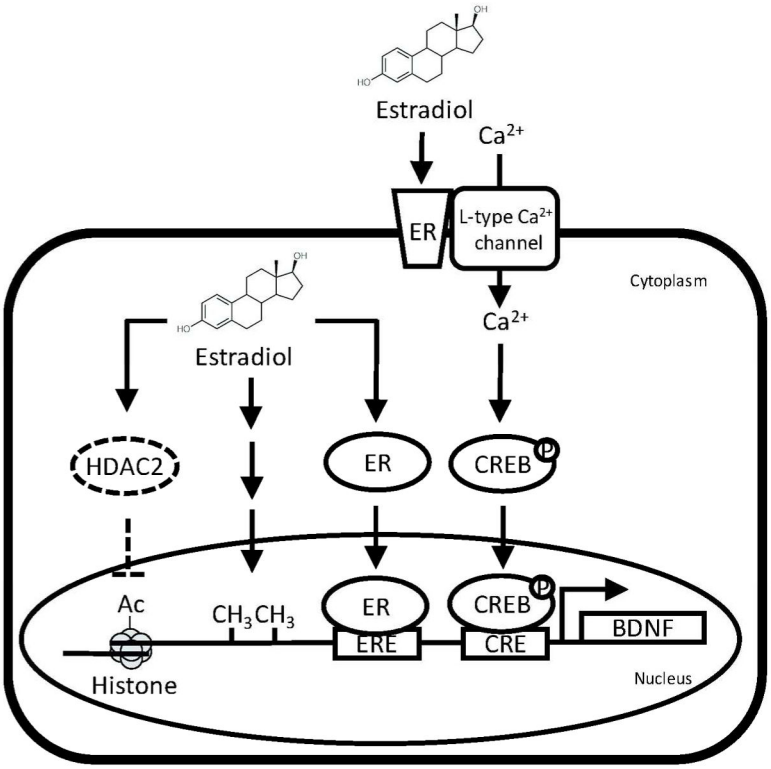

Fig 1. Regulation of *BDNF* expression by estrogen

Estrogen may induce *BDNF* transcription by initiating the ER/DNA tethering, enhancing CREB activity, increasing histone acetylation, and elevating methylation of *BDNF* promoter (CRE: cAMP responsive element; CREB: cAMP responsive element binding protein; ER: estrogen receptor; ERE: ER responsive element; HDAC2: histone deacetylase 2).

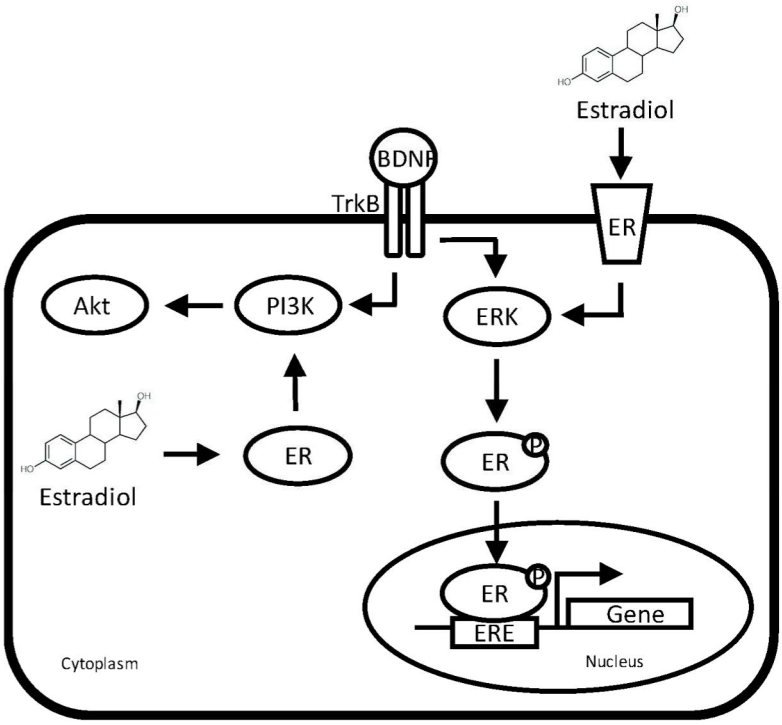

Fig 2.
Common signaling pathways of BDNF and estrogen.