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BDNF-estrogen interactions in hippocampal mossy fiber pathway: implications for normal brain function and disease

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Abstract

The neurotrophin BDNF and the steroid hormone estrogen exhibit potent effects on hippocampal neurons during development and in adulthood. BDNF and estrogen have also been implicated in the etiology of diverse types of neurological disorders or psychiatric illnesses, or have been discussed as potentially important in treatment. Although both are typically studied independently, it has been suggested that BDNF mediates several of the effects of estrogen in hippocampus, and that these interactions play a role in the normal brain as well as disease. Here we focus on the mossy fiber (MF) pathway of the hippocampus, a critical pathway in normal hippocampal function, and a prime example of a location where numerous studies support an interaction between BDNF and estrogen in the rodent brain. We first review the temporal and spatially-regulated expression of BDNF and estrogen in the MFs, as well as their receptors. Then we consider the results of studies that suggest that 17 β -estradiol alters hippocampal function by its influence on BDNF expression in the MF pathway. We also address the hypothesis that estrogen influences hippocampus by mechanisms related not only to the mature form of BDNF, acting at trkB receptors, but also by regulating the precursor, proBDNF, acting at p75NTR. We suggest that the interactions between BDNF and 17 β -estradiol in the MFs are potentially important in the normal function of the hippocampus, and have implications for sex differences in functions that depend on the MFs and in diseases where MF plasticity has been suggested to play an important role, Alzheimer's disease, epilepsy and addiction.

Keywords

neurotrophin; area CA3; dentate gyrus; development; 17 β -estradiol; estradiol; trkB; BDNF

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1. Introduction

Neurotrophins have been shown to play an important role in diverse areas of the CNS. Members of the neurotrophin family include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT-4/5) (Huang and Reichardt, 2001; Teng and Hempstead, 2004; Chao et al., 2006; Reichardt, 2006; Skaper, 2012). Perhaps the most well-studied member of the neurotrophin family is BDNF, which is critical to normal neuronal development and also has many functions in the adult brain (Tyler et al., 2002; Binder and Scharfman, 2004; Bramham and Messaoudi, 2005; Segal and Fishbein, 2005; Lu et al., 2008; Yoshii and Constantine-Paton, 2010).

One of the places in the CNS where BDNF protein and its main receptor, trkB, are expressed in a robust manner is the hippocampus, where numerous studies have shown that BDNF exerts effects on neuronal structure, function and plasticity of hippocampal neurons by activation of trkB (Waterhouse and Xu, 2009; Cohen-Cory et al., 2010; Cowansage et al., 2010; Yoshii and Constantine-Paton, 2010). Several studies have linked dysregulation of hippocampal BDNF with diseases that involve hippocampus (Scharfman and MacLusky, 2006; Arancio and Chao, 2007; Zuccato and Cattaneo, 2007; Scharfman and MacLusky, 2008; Tapia-Arancibia et al., 2008; Zuccato and Cattaneo, 2009; Castren and Rantamaki, 2010; Allen et al., 2011; Autry and Monteggia, 2012; Balaratnasingam and Janca, 2012; Hill, 2012). The actions of BDNF in hippocampus are complex in part because of the diverse ways that the BDNF gene is regulated. There are 9 transcripts, as well as the potential for epigenetic regulation of the BDNF gene (Timmusk et al., 1993; Lubin et al., 2008; Tongiorgi and Baj, 2008). In addition, there is a complex temporal and spatial regulation of BDNF expression, described further below.

Steroid hormones are also robust regulators of hippocampal structure and function (Prange-Kiel and Rune, 2006; Spencer et al., 2008; Walf and Frye, 2008; Ooishi et al., 2012). Since the seminal studies of Woolley and colleagues (Woolley et al., 1990; Gould et al., 1990; Woolley and McEwen, 1992), a great deal of interest has been focused on the potent effects of estrogens on neuronal morphology and plasticity in area CA1 (Mukai et al., 2010; Hojo et al., 2011; Fester et al., 2012; Kramar et al., 2012; Ooishi et al., 2012; Spencer-Segal et al., 2012). However, estrogen receptors (ERs) and trkB are expressed throughout each hippocampal subfield (Drake et al., 1999; Milner et al., 2001; Mehra et al., 2005; Milner et al., 2005), and robust effects of estrogen and BDNF have been observed outside of area CA1, such as the actions of estrogen and BDNF in the dentate gyrus (DG) and area CA3 (Scharfman, 1997; Binder et al., 2001; Tsurugizawa et al., 2005; Zhou et al., 2005; Fester et al., 2006; Gomez-Palacio-Schjetnan and Escobar, 2008; Schjetnan and Escobar, 2012; Spencer-Segal et al., 2012). In fact, BDNF protein levels are highest in the glutamatergic projection from DG granule cells to the hilus and area CA3, the mossy fiber (MF) pathway (Figure 1,2; Conner et al., 1997; Yan et al., 1997). Therefore, we first review what is known about the regulation of BDNF and estrogen synthesis, and their receptors, in hippocampus. One of the intriguing issues we raise is the distinct temporal and spatial regulation of BDNF protein in hippocampus and where information is available, the MFs. We then discuss what is currently understood about the functional interaction between BDNF and estrogen in the MF pathway, and focus on 17 β -estradiol, because it is the major estrogen in the normal brain. Afterwards, implications are discussed, with an emphasis on conditions where estrogen, BDNF and MFs are likely to play a role.

2. BDNF

2.1 BDNF synthesis and its receptors

The BDNF gene consists of nine 5' coding exons, and a common 3' coding exon (IX). The 3'-exon codes for the BDNF preprotein (proBDNF), while the 5' coding regions are linked to individual promoters (Timmusk et al., 1993; Liu et al., 2006; Aid et al., 2007; Sakata et al., 2009). Mature BDNF is synthesized from the precursor proBDNF (Seidah et al., 1996; Lu et al., 2005; Teng et al., 2010). Intracellular cleavage of proBDNF to mature BDNF can occur via furin or by other proprotein convertases (Mowla et al., 1999; Lessmann et al., 2003; Greenberg et al., 2009; Figure 1). Extracellularly, proBDNF can be cleaved by proteases such as metalloproteases or plasmin; tissue plasminogen activator (tPA) is required for the cleavage of plasminogen to form plasmin, a critical step for BDNF-dependent late phase long-term potentiation (L-LTP) (Pang et al., 2004). Mature BDNF binds to the trkB receptor, which exists in both a full-length form (trkB.FL) and truncated forms (trkB.T1 and trkB.T2; Barbacid, 1994; Eide et al., 1996; Fryer et al., 1997). Upon binding of BDNF, autophosphorylation of trkB occurs, leading to activation of signaling cascades such as the mitogen-activated-protein-kinase (MAPK) pathway (Huang and Reichardt, 2003; Binder and Scharfman, 2004; Chao et al., 2006; Yoshii and Constantine-Paton, 2010). Other signaling pathways include phosphatidylinositol 3-kinase (PI₃K)-Akt (Huang and Reichardt, 2003; Binder and Scharfman, 2004; Bramham and Messaoudi, 2005; Chao et al., 2006; Minichiello, 2009; Yoshii and Constantine-Paton, 2010), phospholipase C (PLC) γ (Binder and Scharfman, 2004; Bramham and Messaoudi, 2005; Chao et al., 2006; Minichiello, 2009; Yoshii and Constantine-Paton, 2010), and Ca²⁺/calmodulin-dependent protein kinase (CaMK; Binder and Scharfman, 2004; Minichiello, 2009). Cyclic AMP response element-binding protein (CREB) is also a major target (Huang and Reichardt, 2003; Binder and Scharfman, 2004; Chao et al., 2006; Minichiello, 2009). The effects of these signaling cascades include activation of transcription factors leading to many of the observed effects of BDNF on hippocampal function (Finkbeiner et al., 1997; Minichiello, 2009; Yoshii and Constantine-Paton, 2010). It has been suggested that truncated trkB may also exert biological effects, such as functions related to neuronal development (Fryer et al., 1997; Yacoubian and Lo, 2000; Luikart et al., 2003) or calcium signaling (Rose et al., 2003). Truncated trkB in astrocytes may also serve to regulate the concentration of BDNF at the synapse (Figure 1; Fryer et al., 1997).

Both proBDNF and mature BDNF bind to p75NTR (Barbacid, 1994; Chao, 2003). p75NTR activates intracellular signaling cascades such as nuclear factor- κ B (NF- κ B) and Jun kinase (Casaccia-Bonnel et al., 1996; Casaccia-Bonnel et al., 1999; Zampieri and Chao, 2006; Teng et al., 2010). ProBDNF actions at p75NTR include the regulation of cell survival, pruning of neuronal processes and modulation of synaptic plasticity in hippocampal area CA1 (Lee et al., 2001; Woo et al., 2005; Friedman, 2010; Teng et al., 2010). It has been suggested that mature BDNF acting at trkB has effects that oppose some of the actions of proBDNF at p75NTR (Hempstead, 2006). For example, BDNF appears to facilitate long-term potentiation (LTP) of the Schaffer collateral synapse in area CA1 by actions at trkB (Patterson et al., 1996; Korte et al., 1996; Korte et al., 1998; Bramham and Messaoudi, 2005; Rex et al., 2006), whereas p75NTR facilitates long-term depression (LTD) by actions at p75NTR (Woo et al., 2005). In addition, mature BDNF promotes spine growth and complexity after binding to trkB (Tyler et al., 2002) whereas proBDNF initiates pruning and process retraction by actions at p75NTR (Yang et al., 2009a; Friedman, 2010; Teng et al., 2010). The actions of proBDNF and mature BDNF are likely to be much more complicated than a simple opposition however, because p75NTR can interact with trk receptors to alter the affinity of mature neurotrophins (Esposito et al., 2001).

2.2 Hippocampal expression of BDNF and its receptors

The effects of mature BDNF, proBDNF, trkB and p75NTR are regulated by a complex pattern of spatial and temporal expression. In addition, expression is regulated by many factors so even if mRNA is present, it is not always transcribed. Another complex aspect of expression is trafficking in hippocampal neurons: in the MFs of adult hippocampus, for example, mature BDNF appears to be transported primarily in the anterograde direction (Conner et al., 1997; Altar and DiStefano, 1998) whereas in classic studies of the neurotrophins there is more evidence for retrograde transport (DiStefano et al., 1992). In hippocampus, both appear to occur, and in addition, there is transport to dendrites (Simonato et al., 2002; Tongiorgi and Baj, 2008).

2.2.a. Regional localization of BDNF and its receptors—As mentioned above, both temporal and spatial regulation of hippocampal BDNF expression is complex. Here we discuss spatial expression in the adult rodent. Messenger RNA for BDNF is located in all of the cell layers of the hippocampus, but mature BDNF is primarily synthesized in granule cells and is anterogradely transported to its axons, the MFs (Figures 1,2; Conner et al., 1997; Altar and DiStefano, 1998). The main branch of the MFs forms one of the major glutamatergic inputs to area CA3, where MFs innervate the proximal dendrites of CA3 pyramidal cells in stratum lucidum, forming ‘giant’ boutons (Henze et al., 2000; Jaffe and Gutierrez, 2007). These large boutons are packed with glutamatergic vesicles, and also have dense core vesicles containing BDNF (Dieni et al., 2012). The giant boutons innervate the complex spines (thorny excrescences) of CA3 pyramidal cells, and filamentous extensions that extend from the giant boutons make more conventional synapses on local GABAergic neurons (Acsady et al., 1998). BDNF expression is primarily in the large boutons, but has potential to modulate both pyramidal cells and GABAergic interneurons in area CA3 (Danzon and McNamara, 2004). In the hilar region, axon collaterals of MFs have an analogous pattern: there are giant boutons containing BDNF, which innervate the thorny excrescences of glutamatergic neurons (hilar mossy cells) and filamentous extensions from the giant boutons that innervate GABAergic neurons primarily (Acsady et al., 1998).

Like BDNF, trkB mRNA expression is found in all cell layers (Masana et al., 1993) and trkB receptors are found in diverse cell types (Drake et al., 1999). While many electrophysiological studies in hippocampus have suggested a presynaptic locus of action at axon terminals (Kang and Schuman, 1995; Scharfman, 1997; Xu et al., 2000; Zakharenko et al., 2003), other studies suggest that postsynaptic effects occur. For example, trkB is present postsynaptically on dendritic spines in CA1 pyramidal cells that undergo LTP (Chen et al., 2010). Other studies in cultured hippocampal neurons and area CA1 recordings have suggested a postsynaptic site of action of trkB (Levine et al., 1995; Tanaka et al., 1997). Drake et al. (1999) found that trkB immunoreactivity was located in MF axons and axon terminals, but it was also located outside the MFs. One location that they found which is intriguing is the axon initial segment (of pyramidal cells and GABAergic neurons; Drake et al., 1999), because of actions of BDNF on sodium channels (Blum et al., 2002; Rose et al., 2003).

As one would expect from the high concentration of mature BDNF protein in the MFs (Figure 2), antibodies to proBDNF show prominent immunoreactivity in granule cells (Zhou et al., 2004). Like mature BDNF, proBDNF is anterogradely transported, because immunoreactivity is particularly prominent within the MF projection (Yang et al., 2009b).

As discussed in more detail below, hippocampal expression of proBDNF and p75NTR protein is highest in early life (Yang et al., 2009b). In adulthood, p75NTR expression is relatively low, although this can increase dramatically in astrocytes after seizures (Friedman, 2010). Electron microscopic studies have shown that p75NTR is present in dendrites of area

CA1 pyramidal cells where it appears to mediate LTD in response to proBDNF (Woo et al., 2005). In the DG, Dougherty and Milner (1999) also found postsynaptic p75NTR localization, but most immunoreactivity was in axons and axon terminals - presumably the MFs, consistent with the results using methods besides electron microscopy (Yang et al., 2009b).

2.2.b. Temporal Organization of BDNF and its receptors—Several changes occur in mature BDNF and trkB protein expression throughout development and adulthood, as shown in Figure 3A. Levels of proBDNF and p75NTR also change, and, importantly, are inversely related to levels of mature BDNF and trkB at many points across the lifespan. Figure 3A shows the relationship between mature BDNF, trkB, proBDNF and p75NTR expression as a function of age in the female rodent, although some data comes from studies in which sex was not specified. In Figure 3, the lifespan is divided into several major stages. The first stage is the time between birth and weaning (postnatal day (PND) 0 to approximately PND 21). The second stage is the time between weaning and reproductive maturity, which is reached by approximately PND 50 in the rat and mouse (Spear, 2000). Following these stages are 3) early adulthood (PND 60 until approximately 1 year of age), and 4) later adulthood (approximately 2 years old).

As shown in Figure 3A, levels of mature BDNF protein in whole hippocampus are relatively low at birth and increase during early life (Zhou et al., 1996; Katoh-Semba et al., 1997; Karege et al., 2002). Levels of hippocampal trkB mRNA and protein are also relatively low early in life and increase with time (Masana et al., 1993; Fryer et al., 1996). Both trkB (FL) and trkB.T1 increase during development, with greatest levels after puberty (Masana et al., 1993; Fryer et al., 1996), although not all studies agree (Silhol et al., 2005). In contrast, while mature BDNF and trkB expression increase during development, proBDNF and p75NTR follow an opposite pattern. Using an epitope-tagged BDNF knock-in mouse model, Yang et al. (2009b) demonstrated that whole hippocampal proBDNF protein levels (assayed by Western blot) are highest during early development - with a peak during the second postnatal week. p75NTR immunoreactivity was also highest early in development, i.e., during the first postnatal week (Yang et al., 2009b). During the post-pubertal period, when mature BDNF and trkB expression is relatively high, proBDNF and p75NTR expression has declined (Yang et al., 2009b; Friedman, 2010).

In post-pubertal female rats, BDNF (and most likely, proBDNF) is also temporally regulated, but on a shorter timescale, fluctuating every four days of the estrous cycle (Figures 2-4; Scharfman et al., 2003).

In adulthood, levels of BDNF protein (Karege et al., 2002; Silhol et al., 2005) and trkB receptor mRNA and protein levels generally decrease with age (Croll et al., 1998; Silhol et al., 2005), but less is known about proBDNF and p75NTR in late adulthood.

3. Estrogen synthesis and its receptors

Of the three main physiological estrogens, estrone (E1), 17 β -estradiol (E2) and estriol (E3), 17 β -estradiol is the predominant and most biologically active form (Weichman and Notides, 1980; Kuiper et al., 1997; Blaustein, 2008). The main source of 17 β -estradiol is the gonads, where testosterone is aromatized to estrogen in the ovary in females; in males, significant estrogen is produced in the Sertoli cells (Hess, 2003; Knobil and Neill, 2005; Scharfman and MacLusky, 2006). 17 β -estradiol can also be synthesized in the brain and specifically within the hippocampus (Prange-Kiel et al., 2003; Rune and Frotscher, 2005; Mukai et al., 2010; Azcoitia et al., 2011). Therefore, serum estrogen levels are not necessarily predictive of brain estrogen levels (Hojo et al., 2004). Results of recent studies show that locally

synthesized 17 β -estradiol acts directly upon ERs in hippocampus to exert many of the effects that have been previously attributed to gonadal estrogens (Prange-Kiel et al., 2003; Hojo et al., 2004; Rune and Frotscher, 2005; Fester et al., 2011).

17 β -estradiol is the ligand for two main ER subtypes: ER α and ER β . The affinity of these receptors for 17 β -estradiol is similar (Kuiper et al., 1997), although a variant of ER β , ER β 2, has a lower affinity for the hormone; however, ER β 2 is only a minor component of the ER β found in the brain (Petersen et al., 1998).

In hippocampus, ER α and ER β have been localized to both nuclear and cytoplasmic compartments (Milner et al., 2001; Milner et al., 2005), similar to other regions of the CNS (Blaustein, 1992; Shughrue and Merchenthaler, 2001). Importantly, in addition to acting as transcription factors for target genes (Hall et al., 2001; Klinge, 2001) both of the receptors are also localized to the plasma membrane of hippocampal neurons (Kelly and Levin, 2001; Levin, 2009). Extranuclear ERs can trigger non-genomic events to mediate effects that are faster than those requiring transcription (Foy et al., 1999; Kelly et al., 1999; Bi et al., 2000; Kelly et al., 2002; Bryant et al., 2006; Kramar et al., 2009; Smejkalova and Woolley, 2010; Huang and Woolley, 2012). For example, estrogen exerts neuroprotective effects via a non-transcriptional mechanism (Singh, 2001; Simpkins et al., 2005a).

Interactions between estradiol and BDNF extend to the signaling pathways that they activate. Thus, 17 β -estradiol binding to membrane ER α and ER β can elicit many of the same signal transduction cascades as BDNF-trkB binding: MAPK (Bi et al., 2001; Nilsen et al., 2002; Bi et al., 2003), PI3K-Akt (Zhang et al., 2001), as well as CaMK (Sawai et al., 2002). In addition, phosphorylation of CREB has been implicated in many of the actions of 17 β -estradiol (Panickar et al., 1997; Zhou et al., 2005).

3.1 Regional localization of 17 β -estradiol and its receptors

With respect to 17 β -estradiol, spatial organization is hard to define because, as a steroid, 17 β -estradiol is lipid soluble and therefore readily passes through cell membranes. The fraction of estrogen in hippocampus that is due to gonadal vs. hippocampal synthesis is uncertain (McCarthy, 2008). Therefore, it is more important to discuss its source, the ovaries, testes and the brain (as discussed above, section 3.0). It is also important to consider the localization of ERs in hippocampus, the sites of action for 17 β -estradiol.

Both ER α and ER β are expressed throughout hippocampus (Hart et al., 2001; Milner et al., 2001; Milner et al., 2005). The localization of ER α and ER β in hippocampus is difficult to define conclusively, however, because there are discrepancies between published studies, which may be due to variations in specificities of the antibodies (Pavao and Traish, 2001), as well as differences in the ages, sex and species (Matthews et al., 2000) used in each study.

Hippocampal ER α and ER β have been localized to both presynaptic and postsynaptic compartments. At the light microscopic level, Milner et al. (2001) found nucleic ER α immunoreactivity primarily in GABAergic interneurons, a result also supported by other studies (Weiland et al., 1997; Nakamura and McEwen, 2005), although Solum and Handa (2001) and Kalita et al. (2005) found less ER α interneuronal immunoreactivity in hippocampus. Nucleic ER β immunoreactivity was not found in the rat hippocampus (Milner et al., 2005). In contrast, extranuclear ER α and ER β have been localized to numerous sites. For example, ER α and ER β mRNA and protein have been found in CA3 pyramidal cell and granule cell perikarya and dendrites (Milner et al., 2001; Kalita et al., 2005; Mehra et al., 2005; Milner et al., 2005; Herrick et al., 2006). Ultrastructural studies have also localized ER α and ER β to axons and axon terminals in the DG and CA3, as well as glia (McEwen et al., 2001; Milner et al., 2001; Garcia-Ovejero et al., 2002; Milner et al., 2005; Mitterling et

al., 2010). Taken together, ERs are localized to multiple compartments in neurons and glia in the DG and CA3, including the MFs, suggesting widespread functional effects of ERs in the hippocampus.

3.2. Temporal organization of 17 β -estradiol and ERs

3.2.a. Estrogen

Circulating 17 β -estradiol: Like the fluctuations in pro- and mature BDNF, p75NTR and trkB levels with age, levels of circulating 17 β -estradiol also vary. Figure 3B shows the relative expression of 17 β -estradiol across the lifespan for female rats, and in comparison to levels of BDNF and its receptors (Figure 3A). During early postnatal life, estrogens have a great impact on brain development. 17 β -estradiol is critical to development in both males and females, because it regulates sexual differentiation of the brain (Beyer, 1999; Bakker and Baum, 2008; McCarthy, 2008). At an early point in development, i.e., late gestation/the early postnatal period, males experience a surge in plasma testosterone levels (Weisz and Ward, 1980; MacLusky and Naftolin, 1981; Rhoda et al., 1984; Roselli and Resko, 1997). Testosterone is aromatized to 17 β -estradiol, which causes a “masculinization” of the brain, meaning circuitry responsible for male behavior in adulthood are shaped or “organized” (Wu et al., 2009). Serum levels of 17 β -estradiol are high in both sexes immediately following birth, and decrease during the first postnatal days (Rhoda et al., 1984; Konkle and McCarthy, 2011). Circulating levels of 17 β -estradiol remain equivalent in both males and females during the prepubertal period (Dohler and Wuttke, 1975), and subsequently are higher in females (Luine et al., 2007). How much circulating estradiol actually reaches the brain, however, remains unclear because the fetal rodent liver secretes large quantities of an estradiol binding form of α -fetoprotein, which sequesters the vast majority of serum estradiol in bound form (Vannier and Raynaud, 1975; Puig-Duran et al., 1979).

After puberty, serum 17 β -estradiol levels in female rats fluctuate across the ovarian cycle, which lasts 4 days in the rat (Figure 4). Like the human ovarian cycle (the menstrual cycle), there is a peak of 17 β -estradiol levels in the serum mid-cycle (on the morning of proestrus in the rat; Freeman, 1984). In the rat, serum levels begin to fall as progesterone levels rise at mid-day of proestrus. Subsequently progesterone surges and falls, and both 17 β -estradiol and progesterone levels have returned to baseline by the beginning of the next day of the estrous cycle, called estrus. Following estrus are two days of relatively low serum levels of 17 β -estradiol and progesterone; diestrus-1 and 2 (Figure 4; Freeman, 1984).

In late adulthood, female rats experience “reproductive senescence,” which is characterized by an irregular estrous cycle (“acyclicity”), and/or persistent phases of the cycle (persistent estrus or persistent diestrus). At these times, serum 17 β -estradiol levels have declined, mimicking the decline in mature BDNF and trkB in late adulthood (Figure 3A and B; Huang and Meites, 1975; Lu et al., 1979; Chakraborty and Gore, 2004). A decline in serum 17 β -estradiol levels also occurs in humans during menopause (Burger, 1996; Birge et al., 2001; Simpkins et al., 2005b). Interestingly, in elderly human males, circulating estrogen levels are greater than in postmenopausal women, possibly a result of increased aromatase activity and synthesis of estrogen in adipose tissue (Vermeulen et al., 2002). This is also true of aged male rats compared to aged female rats (Bowman et al., 2006; Luine et al., 2007). In other regions of the brain, such as the hypothalamus and amygdala, it is well established that local estrogen levels in males may not reflect serum 17 β -estradiol concentrations because of the potential for aromatization of circulating androgens (Yuan et al., 1995). Therefore, how much estrogen is actually present in the hippocampus at different stages of life in males and females is not yet clear.

Hippocampal 17 β -estradiol: There is little data available about hippocampal levels of 17 β -estradiol. It has been shown that hippocampal 17 β -estradiol levels in both males and females are highest on PND 0, and decrease rapidly within hours after birth (Amateau et al., 2004; Konkle and McCarthy, 2011). Using radioimmunoassay (RIA), Amateau et al. (2004) found no significant sex difference in hippocampal 17 β -estradiol levels 2 hours post-birth, but females showed a significantly higher concentration of 17 β -estradiol in hippocampus compared to males when measured 32 hours after birth. In contrast, Konkle and McCarthy (2011) found no significant sex difference in hippocampal 17 β -estradiol levels at several time points from PND 0 to 60, although levels were not measured at 32 hours. Male hippocampal 17 β -estradiol levels have been demonstrated to be greater than female levels within the first 32 hours after birth in several other brain areas including the cortex, hypothalamus and preoptic area (Amateau et al., 2004), suggesting that 17 β -estradiol may have a complex spatial regulation - as well as temporal regulation - in males and females during early postnatal life.

Interestingly, adult hippocampal levels of 17 β -estradiol are relatively high in male rats compared to females. Although RIA showed that hippocampal 17 β -estradiol was 35 pM in females (Konkle and McCarthy, 2011), male concentrations in a different study were reported to be much higher – 600 pM (Hojo et al., 2008). Mass spectrometry (MS) also showed that hippocampal 17 β -estradiol concentration was higher in male rats (8 nM), compared to female rats (0.5 to 2 nM; Ooishi et al., 2012). The comparison of 17 β -estradiol levels from hippocampal samples is interesting because it provides an explanation for the finding that males exhibit weak responses to administration of 17 β -estradiol: higher 17 β -estradiol levels in males may saturate ERs and occlude effects of 17 β -estradiol. Indeed, evidence suggests that sex differences in actions of 17 β -estradiol exist. For example, Barker and Galea (2008) found that repeated administration of estradiol benzoate increased cell proliferation and decreased cell death in the DG of female rats, while there was no effect in males. Likewise, membrane ER regulation of CREB phosphorylation in hippocampal neurons is profoundly sexually differentiated, as a result of testosterone exposure of the male during development (Meitzen et al., 2012). However, it is important to note that some discrepancies exist in the measurements of 17 β -estradiol in hippocampus of the male; Konkle and McCarthy (2011) reported levels of hippocampal 17 β -estradiol in the male to be similar to the female (35 pM).

3.2.b. ERs—In males and females, hippocampal ER mRNA and protein are generally expressed at a higher level during development than during adulthood (O'Keefe and Handa, 1990; O'Keefe et al., 1995; Solum and Handa, 2001; Adams et al., 2002; Mehra et al., 2005). For example, O'Keefe and Handa (1990) found a transient increase in hippocampal ERs from PND 4 to 7 in both males and females, and then a subsequent decrease to adult levels. Similarly, Solum and Handa (2001) found an increase in hippocampal ER α from PND 0 to 10 in males and females, with a subsequent decrease in late development and adulthood (only female rats were studied during adulthood).

During adulthood, there is evidence that hippocampal ER levels in female rats vary across the estrous cycle (Mendoza-Garcés et al., 2011). ER α -immunoreactivity was relatively high in CA3 during diestrus-1, while CA3 levels of ER β were relatively high during diestrus-2 (Mendoza-Garcés et al., 2011), possibly to compensate for the low serum levels of 17 β -estradiol during these times of the estrous cycle (Figure 4). ER α and ER β expression decline during late adulthood in female rats (Mehra et al., 2005).

4. Effects of BDNF and estrogen on MF transmission and plasticity

4.1 Actions of BDNF on MF function

Based on the findings discussed above, that mature BDNF and trkB protein expression are high in the MFs of the adult rat, one would predict that mature BDNF influences MF transmission in adult hippocampus by actions at trkB. Several studies support this idea. One of the first studies to evaluate the effects of BDNF in hippocampus used young male rats (approximately PND 30). Bath application of recombinant BDNF to hippocampal slices, at a concentration that was similar to the concentrations used to evaluate neuronal outgrowth in culture, led to a long-lasting potentiation of MF transmission (Scharfman, 1997; Figure 5). Stimuli to the hilus, used to activate MFs preferentially, increased the population spike recorded in the pyramidal cell layer of area CA3, an effect that was long-lasting (Scharfman, 1997). These effects were reminiscent of some of the first studies of BDNF on synaptic transmission, where bath application of recombinant BDNF led to a long-lasting potentiation of the field EPSP evoked by Schaffer collateral stimulation in area CA1 (Kang and Schuman, 1995). Since that time, many studies have replicated the findings in area CA1, and have also shown that they exist *in vivo* when BDNF is focally applied to the molecular layer of the DG (Messsaoudi et al., 1998). Further studies have demonstrated that BDNF enhances LTP in area CA1 (Patterson et al., 1996; Korte et al., 1996; Korte et al., 1998; Zakharenko et al., 2003; Kramar et al., 2004; Rex et al., 2006; Lauterborn et al., 2007).

In addition to the potentiation of MF transmission evoked by single stimuli to the MFs, there also was an effect of BDNF on the activity evoked in area CA3 pyramidal cells in response to a short (2-5 sec) train of paired stimuli (40 msec interstimulus interval) at 1 Hz. In the presence of BDNF, spreading depression (SD) occurred after the train (Scharfman, 1997). Remarkably, this effect was only observed in response to a train of stimuli to the MFs, not stimulation of other pathways such as the fimbria, which suggested afferent specificity (Scharfman, 1997). SD is important because it is considered to reflect hyperexcitability, and therefore it was proposed that the actions of BDNF on MFs may be one of the reasons that the hippocampus is prone to seizures (Scharfman, 1997), which had also been mentioned in relation to a study of kindling previously (Kokaia et al., 1995). Furthermore, it has been suggested that SD is relevant to traumatic brain injury and migraine (Scharfman and MacLusky, 2008). Similar to the effects observed *in vitro* (Scharfman, 1997), BDNF infusion has been shown to enhance MF-evoked responses in area CA3 *in vivo* and are blocked by trkB antagonism (Gomez-Palacio-Schjetnan and Escobar, 2008; Schjetnan and Escobar, 2012).

Additional studies using overexpressing BDNF mice suggested that endogenous BDNF might have similar effects as recombinant BDNF (Croll et al., 1999). Thus, in slices of mice where BDNF was overexpressed using the β -actin promoter, hilar stimuli evoked large population spikes in area CA3, and a short train of stimuli to the hilus at 1 Hz elicited multiple population spikes and SD (Figure 5). The *in vitro* data, suggesting hyperexcitability in the overexpressing mice without adding any recombinant BDNF, were corroborated by *in vivo* studies where kainic acid, a convulsant, was injected into overexpressing mice or controls. The BDNF overexpressing mice exhibited more severe seizures (Croll et al., 1999). Additional studies using infusion of BDNF to adult male rats showed that seizures could be elicited when BDNF was infused into hippocampus but not in response to control infusion (Scharfman et al., 2002). Together the results suggested a robust potentiation of MF transmission by mature BDNF in adult male rats, mediated by trkB receptors, and a predisposition of BDNF-treated tissue to exhibit hyperexcitability. Interestingly, many studies have now suggested a role of mature BDNF and trkB in the type of epilepsy that involves hippocampus - temporal lobe epilepsy (Scharfman, 2005; McNamara and Scharfman, 2012).

4.2 Effects of proBDNF and p75NTR on MFs

Most of the studies to date that have investigated effects of proBDNF and p75NTR have not evaluated effects on the MFs. Instead, area CA1 has been the focus, where exogenously applied proBDNF enhanced LTD following low-frequency stimulation (LFS) to the Schaffer collaterals, an effect mediated by p75NTR (Woo et al., 2005). The experiments used young animals primarily, when proBDNF and p75NTR levels are relatively high (Woo et al., 2005). Other studies have shown that p75NTRs exert adverse effects on structure in both CA1 and the MFs. For example, p75NTR overexpression decreased spine complexity and density of pyramidal cells, whereas young p75NTR knockout mice had greater spine density and complexity (Zagrebelsky et al., 2005). These effects agree with previous studies outside CA3 showing that p75NTR activation can inhibit neurite outgrowth (Yamashita et al., 2002; Sun et al., 2012), and can cause axonal retraction at developing neuromuscular synapses (Yang et al., 2009a). Furthermore, recombinant proBDNF can lead to apoptosis and process retraction in cultured neurons (Teng et al., 2005). Because of the relatively high levels of p75NTR and proBDNF in early development, it has been suggested that proBDNF plays an important role in the developing brain to reduce neuronal number and refine dendrites and axons of emerging circuits (Yang et al., 2009b; Teng et al., 2010).

4.3 Modulation of the effects of BDNF in MFs by estrogen

It was first suggested that there are neurotrophin-estrogen interactions in the CNS in the 1990's (Toran-Allerand et al., 1999). In 1995, Sohrabji and colleagues found evidence for an estrogen-like response element on the BDNF gene (Sohrabji et al., 1995), which suggested that estrogen may exert trophic effects in the female brain by inducing the synthesis of BDNF. Several investigators showed that ovariectomy reduced BDNF levels in various parts of the brain, and estrogen administration restored them (Singh et al., 1995; Sohrabji et al., 1995; Berchtold et al., 2001), although not in all areas of the brain (Sohrabji et al., 1995). Similarly, BDNF mRNA was increased in gonadectomized prepubertal male rats after estrogen treatment (Solum and Handa, 2002).

One question that had not yet been addressed was whether endogenous 17 β -estradiol increased BDNF levels in the MFs, and if the rise in BDNF led to an increase in MF transmission and hippocampal function. Therefore, BDNF immunoreactivity in the MFs was compared using adult female rats that were perfusion-fixed at different stages of the estrous cycle (Figure 2). In addition, females that were intact were compared to females after ovariectomy, and adult males. The results showed that BDNF immunoreactivity in the MFs increased as serum levels of 17 β -estradiol increased to their peak, mid-morning on proestrus (Figure 2; Scharfman et al., 2003). Furthermore, ovariectomy led to a reduction in MF BDNF immunoreactivity relative to the intact female rat (Scharfman et al., 2003) (Figure 2). These data suggested that endogenous fluctuations in serum levels of 17 β -estradiol during the estrous cycle corresponded to endogenous fluctuations in MF BDNF protein levels. The next question was whether increased MF BDNF immunoreactivity corresponded to a physiological change. Using hippocampal slices of female rats at different stages of the estrous cycle, it was demonstrated that MF transmission was increased in animals with relatively high MF BDNF protein levels. For example, stimulation of the MF pathway in a slice from a female rat on proestrous morning (when MF BDNF protein immunoreactivity was high) led to a greater response compared to a female rat on diestrous-2 morning; it was also similar to the effect of adding recombinant BDNF to a slice from a normal adult male rat (Scharfman et al., 2003; Figure 5).

Remarkably, the hippocampal slices of female rats that were examined early on estrous morning were as excitable as proestrous morning, and in some ways more excitable (Scharfman et al., 2003). These findings were correlated with greater transport of MF BDNF

protein to the MF axon terminals on estrous morning (Scharfman et al., 2003). Together the data suggested that the surge in 17 β -estradiol on proestrous morning led to an increase in MF BDNF synthesis that outlasted the surge in 17 β -estradiol itself.

Like the effects of the estrous cycle on responses to single stimuli to the MFs, the responses to repetitive stimulation of the MFs were also increased on proestrous and estrous mornings. SD episodes were readily elicited, similar to the effects of recombinant BDNF in the slices from male rats (Scharfman et al., 2003; Figure 5). In contrast, slices from female rats that were tested at times of the estrous cycle when BDNF immunoreactivity was low, e.g., diestrous-1 morning, had low excitability and behaved like slices from male rats that had not been exposed to BDNF.

The effects of MF stimulation in female rats discussed above suggested that increased BDNF synthesis in MFs caused an effect similar to adding recombinant BDNF, i.e., activation of trkB receptors on MFs. Results of two different experimental approaches suggested that this was true: 1) K252a blocked the effect, and 2) effects only occurred when MFs were stimulated, not when other inputs were electrically activated. Together these data suggested a remarkable cyclic increase in excitability in female rats related to the estrogen-BDNF interactions. Notably, these experiments did not prove that 17 β -estradiol caused the change in BDNF immunoreactivity in the MFs, or that 17 β -estradiol caused the increased excitability in CA3 when BDNF levels were increased in MFs. To prove that 17 β -estradiol was responsible, ovariectomized rats were treated with 17 β -estradiol in a manner that simulated the preovulatory surge in 17 β -estradiol during diestrus-2 and proestrous morning of the estrous cycle (Scharfman et al., 2007). Three injections of estradiol were used: an initial dose that was very low, using a form of 17 β -estradiol (17 β -estradiol benzoate) that was slow acting. A second slightly higher dose was used 12 hrs later; finally, a third dose of rapid-acting estradiol (17 β -estradiol itself) was used to simulate the surge of estradiol on proestrous morning. Serum measurements demonstrated that this dose-regimen reproduced the levels reported for the adult female rat (Freeman, 1984; Scharfman et al., 2007).

Female rats were administered the three doses of 17 β -estradiol approximately 2 weeks after ovariectomy (Scharfman et al., 2007), so that they had recovered from surgery but were not aged too much after the surgical procedure; this is important because the effects of 17 β -estradiol appear to wane as time after ovariectomy increases (Gibbs, 2000; Daniel et al., 2006; Suzuki et al., 2007). The results showed that females that were examined on the simulated mid-morning of proestrus were comparable to intact animals that were examined mid-morning of proestrus: serum 17 β -estradiol levels were similar, BDNF immunoreactivity was elevated in the MF pathway, and responses to MF stimulation in slices were also similar (Scharfman et al., 2007; Figure 2,5). Effects of 17 β -estradiol on responses to MF stimulation were blocked by trkB antagonism (Scharfman et al., 2007). In addition, animals showed improved performance when tested using the object placement or object recognition tests (Scharfman et al., 2007). Together the data supported the hypothesis that serum levels of 17 β -estradiol, as it fluctuates in the normal female rat estrous cycle, increase MF transmission and excitability by a trkB-dependent mechanism - presumably by increasing BDNF synthesis in MFs.

Although these data have implications for understanding the adult female hippocampus, very little was studied with respect to proBDNF and p75NTR. In fact, little is known about the ways in which 17 β -estradiol might influence levels of proBDNF *in vivo*. However, because all BDNF mRNA is first transcribed as proBDNF and then is subsequently cleaved to mature BDNF, any increase in BDNF synthesis that is induced by 17 β -estradiol will first produce proBDNF. Therefore, it seems likely that female rats have a cyclical rise in proBDNF as well as BDNF during the estrous cycle (Figures 2-3). Because p75NTR levels

are relatively low and trkB levels are relatively high during adulthood, synaptic plasticity and neuroprotection mediated by mature BDNF acting on trkB receptors should be favored in adulthood.

4.4 Mechanisms that explain the influence of estrogen on BDNF-dependent effects in the MF pathway

As first described by Sohrabji et al. (1995), the BDNF gene contains a sequence that is similar to the estrogen response element on estrogen-targeted genes. This ERE-like element provides a mechanism for the ER complex to directly bind to the BDNF gene to influence BDNF levels. However, other mechanisms may be important. For example, hippocampal trkB mRNA levels are increased following chronic 17 β -estradiol treatment (Pan et al., 2010) and hippocampal area CA3 stratum radiatum trkB levels fluctuate across the estrous cycle and are highest at proestrus (Spencer et al., 2008). Therefore, increased trkB levels may contribute to the increased excitability on proestrous morning in the studies described above. However, they do not explain the increase on estrous morning, and the elevation in BDNF protein in the MFs does.

Another mechanism is an indirect effect of 17 β -estradiol on GABAergic neurons that in turn increase neuronal activity of granule cells. Because BDNF synthesis increases with neuronal activity, BDNF protein levels in granule cells, and the MFs, would be likely to increase (Blurton-Jones et al., 2004).

5. Implications

5.1 The role of estrogen in BDNF-dependent actions in hippocampus across the lifespan

5.1.a. Early development and adolescence—There are several potential implications of the effects described above for the development of the DG and area CA3, because the MFs develop substantially in the first weeks of life in rodents (Amaral and Dent, 1981; Blaabjerg and Zimmer, 2007), when proBDNF and p75 levels are relatively high (Yang et al., 2009b). proBDNF may be very important because the MF pathway could be refined by proBDNF in early postnatal life.

The observation that some female behavior matures at different rates than males (Cohn, 1991; Chapple and Johnson, 2007) could be related to the changes in BDNF, proBDNF and their receptors during adolescence. In puberty, as circulating levels of 17 β -estradiol begin to rise in females, and proBDNF is still active in shaping neuronal circuitry, higher 17 β -estradiol levels in females may accelerate maturation of neuronal circuitry, and consequently behavior, because it would be likely to increase proBDNF levels. This idea is also relevant to actions of BDNF in areas of the brain outside the hippocampus that are considered to mature considerably during puberty, such as the prefrontal cortex (Spear, 2000).

5.1.b. Aging and Alzheimer's disease—It is also interesting to consider how waning levels of 17 β -estradiol and BDNF might impact women as they age. For example, it has been suggested that declining estrogen levels in elderly women, which has been established (Burger, 1996; Birge et al., 2001; Simpkins et al., 2005b), could explain increased vulnerability of women to Alzheimer's disease (Henderson, 1997; Launer et al., 1999). One reason could be a reduction in BDNF synthesis. Indeed, BDNF levels are decreased in the hippocampi and serum of individuals with Alzheimer's disease (Phillips et al., 1991; Laske et al., 2006a; Laske et al., 2006b; Tapia-Arancibia et al., 2008) and BDNF has been suggested to be therapeutic (Nagahara et al., 2009; Nagahara and Tuszynski, 2011). However it may be that both men and women are vulnerable to Alzheimer's disease (Ott et al., 1996), but for different reasons. In women, declining ovarian production of estrogen -

and therefore BDNF - could be responsible. In men, a decline in gonadal testosterone during aging could lead to a reduced level of testosterone in the brain, and a reduced level of hippocampal estrogen because testosterone is aromatized to estrogen in the brain. Interestingly, the reason for hippocampal vulnerability to low BDNF may not be related to low MF concentrations. It could be related to the fact that an important source of BDNF for the hippocampal principal cells is derived from the perforant path projection, which deteriorates in Alzheimer's disease (Scharfman and Chao, 2012). This concept is at the heart of a new therapeutic approach aimed at delivering BDNF to the entorhinal cortex, where the cells of origin of the perforant path are located (Nagahara et al., 2009).

5.2 Epilepsy, traumatic brain injury, and migraine

5.2.a. Increased excitability in response to 17 β -estradiol and BDNF:

implications for epilepsy—One implication of the findings described above, that increased excitability occurs in the hippocampus of female rats in response to 17 β -estradiol and/or increased BDNF, is that seizure threshold might decline. Seizure threshold is important in the hippocampus, because it is considered to be a region that is relatively susceptible to seizures. The MF pathway is one potential reason for this seizure susceptibility, because the giant boutons of the MFs are densely packed with glutamatergic vesicles. Indeed the MF synapse has been called “the detonator synapse” due to the large depolarizations in CA3 pyramidal cells that are produced by the release of glutamate from MFs (Treves and Rolls, 1992; Henze et al., 2000; Jaffe and Gutierrez, 2007). As a result of the effects of 17 β -estradiol on the MF synapse, one might expect that 17 β -estradiol would cause a susceptibility to seizures that involve hippocampus. In fact, many investigators have suggested that estrogens are ‘pro-convulsant’ and BDNF and trkB activation have also been considered to facilitate seizures (Binder et al., 2001; Scharfman and MacLusky, 2006; McNamara and Scharfman, 2012). Although historically the role of the MFs in the proconvulsant effects of estrogens have rarely been considered, the MFs have been repeatedly implicated in the proconvulsant effects of BDNF: release of BDNF from MFs onto trkB receptors, or transactivation of trkB receptors on CA3 pyramidal cells, have both been suggested to be mechanisms responsible for seizures and epilepsy in rodents (McNamara and Scharfman, 2012). Increased BDNF in MFs has also been noted as early as 1991 as a result of seizures (Isackson et al., 1991), and later was reported in patients with temporal lobe epilepsy (Murray et al., 2000). On the other hand, estrogens and BDNF also increase levels of the anticonvulsant peptide neuropeptide Y (Veliskova and Velisek, 2007; Ledoux et al., 2009), and if estrogens or BDNF concentrations are high, ER and trkB may be internalized (Xu et al., 2004), downregulating effects of the agonist. Therefore, the effects of estrogen and BDNF on seizures are complex.

If an increase in systemic 17 β -estradiol or MF BDNF were able to increase excitability in area CA3, it would be potentially relevant to women with epilepsy, who often experience an increase in the frequency or severity of seizures at a particular phase of the menstrual cycle - typically the periovulatory or perimenstrual phases (or both); this condition is often called catamenial epilepsy (Herzog et al., 1997; Scharfman and MacLusky, 2006). At the periovulatory and perimenstrual phases, an elevation in 17 β -estradiol that subsequently causes a rise in BDNF could explain the increase in seizure susceptibility in women with catamenial epilepsy. Thus, after 17 β -estradiol rises during the preovulatory period, BDNF levels could be high, based on the findings from female rats. BDNF could increase excitability in area CA3, again based on the data from rodents. A similar chain of events might occur at the end of the cycle: after the rise in 17 β -estradiol during the luteal phase in women, BDNF levels may increase, and based on the data from the female rat, the rise in BDNF may persist until just after 17 β -estradiol levels have finished their return to baseline. In women, the time corresponding to the return of 17 β -estradiol to baseline would be the

perimenstrual period. Therefore, a similar mechanism responsible for the periovulatory rise in seizures could also explain the perimenstrual exacerbation of seizures (Scharfman and MacLusky, 2008).

Indirect effects of BDNF may also contribute to an increase in seizure susceptibility. For example, BDNF exerts effects on GABA_A receptors, causing a change in their distribution on neurons (Joshi and Kapur, 2009), an alteration in subunit expression (Joshi and Kapur, 2009) or changes in other aspects GABAergic transmission (Swanwick et al., 2006). A potential mediator of some of these effects is early growth response factor-3 (Egr3), which regulates the α -subunit (Gangisetty and Reddy, 2010), a potentially important regulator of excitability during the perimenstrual period (Smith et al., 2007). Thus, 17 β -estradiol could increase BDNF levels, which would in turn act on GABAergic synapses by effects mediated by Egr3.

Other factors are also likely to be important to catamenial epilepsy besides serum levels of 17 β -estradiol and BDNF, because seizure exacerbation appears to be more common during the perimenstrual phase compared to the periovulatory phase (Herzog et al., 1997). One explanation for the greater seizure severity during the perimenstrual phase relative to the periovulatory phase is that progesterone levels have just declined when the perimenstrual phase occurs. This “progesterone withdrawal” has several possible effects that would increase excitability. First, a reduction in progesterone also reduces its meta bolite allopregnanolone, a ‘neurosteroid’ that facilitates the actions of GABA at GABA_A receptors (Smith et al., 2007; Mitchell et al., 2008; Reddy and Rogawski, 2012). Second, there are decreases in the δ -subunits for GABA_A receptors, which lead to a reduction in tonic GABAergic inhibition, and consequently an increase in neuronal excitability (Maguire and Mody, 2009).

5.2.b. Spreading depression and its relevance to seizures, traumatic brain injury, and migraine—The implications of SD episodes in response to MF stimulation in the presence of high levels of MF BDNF protein are interesting to consider because SD is relevant to epilepsy, traumatic brain injury, and migraine. In epilepsy, SD episodes are somewhat similar to seizures because an SD episode involves a dramatic and synchronous depolarization of principal cells which spreads from one location to another, followed by a slow recovery lasting seconds or minutes (Rogawski, 2012). Although it can be argued that SD episodes are distinct from seizures (Rogawski, 2012), seizures often occur at a similar time as SD (Fabricius et al., 2008) and evoked SD episodes in hippocampal slices have served as experimental models of seizures (Haglund and Schwartzkroin, 1990). Regarding TBI, SD episodes have been described immediately after TBI (Strong et al., 2002; Fabricius et al., 2008; Dreier et al., 2012). Regarding migraine, it has been hypothesized that SD is the neurobiological substrate of migraine (Lauritzen et al., 2011; Rogawski, 2012).

In each of these pathological conditions, exacerbation by 17 β -estradiol and BDNF would seem likely because SD episodes were readily elicited by MF stimulation when 17 β -estradiol levels were elevated and/or BDNF was increased in rodents. However, under normal conditions or vehicle treatment, SD episodes could not be elicited by MF stimulation. The implication is that women would be more susceptible to SD than men. Although it is not clear that women are more susceptible to SD than men, SD episodes do appear to be more prevalent in female rats compared to male rats. For example, a lower threshold for SD was observed in female rats relative to males (Adamek and Vyskocil, 2011). In a transgenic mouse model of familial hemiplegic migraine (type 1), female mice had more SD episodes and greater deficits after SD than male mice (Eikermann-Haerter et al., 2009).

In migraine, incidence is greater in women than men (Silberstein, 1992). Like catamenial epilepsy, there are women who experience a greater susceptibility to migraine attacks during the perimenstrual phase of the menstrual cycle, a syndrome called “menstrual migraine.” A common hypothesis is that a ‘withdrawal’ from estrogen occurs during the perimenstrual period, and this triggers the increase in migraine (Silberstein, 1992). A similar hypothesis exists for the rise in migraine during the perimenopausal period - waning levels of estrogen are responsible (MacGregor, 1997). To the contrary, a rise in estrogen during pregnancy is also associated with increased migraine - the difference being that migraine associated with decreased levels of 17β -estradiol is not accompanied by aura, whereas migraine that occurs when there is an increase in 17β -estradiol levels is associated with aura (MacGregor, 2005). The difference is intriguing because aura is associated with the onset of seizures in temporal lobe epilepsy, and is considered to be a sign that seizure activity is beginning or is about to start. Therefore, migraine associated with seizures may be increased during the perimenstrual period for the same reasons that seizure susceptibility increases in catamenial epilepsy.

5.3 Addiction

Addiction has been suggested to be a form of “pathological plasticity” (Kalivas and Volkow, 2005; Kauer and Malenka, 2007; Kalivas and O’Brien, 2008). It has also been suggested that the hippocampus is part of the network that is involved in addictive behaviors, a network that also involves the nucleus accumbens and amygdala (Tracy et al., 2001; Dong et al., 2006; Ito et al., 2008; Gardner, 2011). One reason the hippocampus has been suggested to play a role in addiction is that it seems likely to be involved in the memory process for the pleasurable experience that facilitates relapse. Perhaps for this reason, it has been shown that there is altered hippocampal activation in clinical studies of drug addiction (Kilts et al., 2001; Volkow et al., 2004).

Area CA3 may be particularly important in this aspect of relapse because of the role of CA3 in memory processes (Kesner et al., 2004; Gilbert and Kesner, 2006). CA3 pyramidal cells make extensive recurrent collaterals (Amaral et al., 1990), unlike principal cells of the DG or CA1 subfields, and it has been suggested that this collateral network allows CA3 to act as an autoassociative network capable of storing patterns that can later be retrieved even if a partial pattern is used as a stimulus for memory retrieval; this function is often termed ‘pattern completion’ (McNaughton and Morris, 1987; Rolls and Treves, 1990; Treves and Rolls, 1994; Kesner, 2007; Myers and Scharfman, 2011).

Inherent in the ideas about pattern completion are a necessity for plasticity in the afferents to the CA3 pyramidal cells, including the MFs. Therefore, it is interesting that MF LTP is increased in rodents following chronic exposure to morphine (Harrison et al., 2002) and there is increased MF excitability following acute ethanol exposure (Newlin et al., 1981) similar to the effects of 17β -estradiol and BDNF on MFs discussed above. BDNF seems likely to play a role in addiction for other reasons also. For example, BDNF serum levels are increased in individuals with addictive behaviors such as pathological gambling (Geisel et al., 2012) and opiate dependence (Heberlein et al., 2011). Serum levels of BDNF are also elevated in naïve individuals following exposure to Δ^9 -tetrahydrocannabinol (THC), the main psychoactive component in marijuana, a commonly abused drug (D’Souza et al., 2009). Studies in rodents have also shown that there is an increase in hippocampal BDNF protein and mRNA expression following ethanol exposure (McGough et al., 2004; Kulkarny et al., 2011), but BDNF mRNA expression has also been found to decrease following ethanol exposure (Tapia-Arancibia et al., 2001; Raivio et al., 2012). Although data directly linking BDNF levels in MFs to addiction is not available, it seems reasonable to suggest that increased BDNF-dependent MF plasticity could contribute to a hippocampal-dependent memory of pleasurable experience that is part of addiction.

Interestingly, there appear to be sex differences in addiction in some studies (Lynch et al., 2002; Carroll et al., 2004; Becker and Hu, 2008; Anker and Carroll, 2011), although results of others are mixed or no sex differences were found (McCance-Katz et al., 1999; Wagner et al., 2007; Feltenstein et al., 2012). When sex differences have been shown, women appear to be more vulnerable to some aspects of addiction compared to males. For example, women show greater dependence on cocaine and psychotherapeutics (Cotto et al., 2010; Becker et al., 2012). Additionally, women report greater craving for opioids relative to men (Back et al., 2011). However, men often consume drugs at higher rates than females (Brady and Randall, 1999) and show greater dependence on alcohol and marijuana (Cotto et al., 2010).

In rodents, females appear to experience a greater reward at lower doses of morphine (Karami and Zarrindast, 2008). Additionally, female rats work harder than male rats for cocaine and opioid rewards, and begin cocaine and opioid self-administration more quickly than males (Roberts et al., 1989; Cicero et al., 2003, Roth and Carroll, 2004, Roth et al., 2004, Lynch, 2006). The differences could involve the hippocampus, because females have a greater impairment in reversal learning, a hippocampal-dependent task, following cannabinoid exposure (Harte and Dow-Edwards, 2010). Therefore, females may be more vulnerable to addiction because when estrogen levels are higher, BDNF-dependent MF plasticity may be greater than males.

Evidence from human and animal studies suggests that fluctuating ovarian hormone levels can indeed influence addictive behaviors (Roberts et al., 1989; Lynch et al., 2000; Feltenstein et al., 2011; Becker et al., 2012). It has been shown that there are increased positive subjective ratings following cocaine administration in women when they are at the time of the menstrual cycle when serum estradiol levels are high (Sofuoglu et al., 1999). In laboratory animals, susceptibility to addictive behaviors may also be especially high during times when estrogen is elevated (Anker and Carroll, 2010). The administration of estrogen to laboratory animals increases drug taking and facilitates the acquisition, escalation, and reinstatement of cocaine-seeking behavior (Anker and Carroll, 2011). Interestingly, female rats during estrus will work harder for cocaine than during any other phase of the estrous cycle (Roberts et al., 1989); this is interesting because during estrous morning, the levels of BDNF in MFs were highest (Scharfman et al., 2003), but at that time serum estradiol levels have returned to diestrous levels (Freeman, 1984; Figure 4). Other studies of female rats during proestrus show greater stress-induced reinstatement of cocaine seeking behavior (Feltenstein et al., 2011). Therefore, high levels of estrogen and in particular high levels of BDNF could be an important factor in facilitating addictive memory: increased BDNF protein levels in the MFs could cause increased potentiation of synaptic transmission, leading to stronger drug-related memory.

6. Summary

17 β -estradiol and BDNF - both mature BDNF and proBDNF - play important roles in the developing hippocampus and in adulthood. Within the MFs, the actions of 17 β -estradiol on BDNF expression appear to have robust effects on MF transmission and plasticity. For the most part, these effects may benefit the female. For example, DG-area CA3 functions may be optimized during times when circulating levels of 17 β -estradiol and BDNF in MFs are elevated. However, the “price” may be a greater susceptibility to some neurological disorders or psychiatric illness.

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Abbreviations

BDNF	Brain-derived neurotrophic factor
CaMK	Ca ²⁺ /calmodulin-dependent protein kinase
CREB	Cyclic AMP response element binding protein
DG	Dentate gyrus
Egr3	Early growth response factor-3
ER	Estrogen receptor
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen-activated kinase
MF	Mossy fiber
PI₃K	Phosphatidylinositol 3-kinase-Akt
PLCγ	Phospholipase C γ
PND	Postnatal day
SD	Spreading depression

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Highlights

17 -estradiol and BDNF have similar effects in hippocampal mossy fibers

17 -estradiol and BDNF synthesis, receptor levels and effects vary with age

In adulthood, 17 -estradiol and BDNF influence synaptic transmission and plasticity

BDNF mediates some of the effects of estrogen in the mossy fiber pathway

17 -estradiol/BDNF interactions influence normal hippocampal function and disease

Figure 1. BDNF and estrogen signaling in the hippocampal mossy fibers

A. A schematic of the hippocampus in horizontal section is shown. The area outlined by the red box is shown at higher magnification in B.

B. The mossy fiber (MF) projection from DG granule cells to area CA3 pyramidal cells is shown. MFs provide a major glutamatergic input to area CA3, with “giant boutons” that innervate complex spines on the proximal apical dendrites of CA3 pyramidal cells called “thorny excrescences” (Henze et al., 2000; Jaffe and Gutierrez, 2007). Filamentous extensions of the giant boutons innervate GABAergic interneurons (Amaral, 1979; Acsady et al., 1998).

C. Estrogen receptors (ERs, blue rectangles) are localized to nuclear compartments in DG granule cells, CA3 pyramidal cells and GABAergic interneurons (Milner et al., 2001; Milner et al., 2005). ERs are also located in MF axons and axon terminals and on the plasma membrane of pyramidal cell dendrites, GABAergic interneurons, and glia (Hart et al., 2001; Milner et al., 2001; Milner et al., 2005). proBDNF (red and black rectangle) is synthesized in the granule cells (1) and can be cleaved to form mature BDNF (black rectangle; 2); BDNF (3) can be anterogradely transported to the terminal, where it is packaged in dense core vesicles (large presynaptic circle in D) like other neuropeptides (Conner et al., 1997; Altar and DiStefano, 1998; Lu et al., 2005; Dieni et al., 2012). proBDNF can also be packaged in dense core vesicles. Due to the overlap in sites containing ERs, BDNF, trkB and p75NTR, ERs can influence BDNF and trkB expression and actions via transcriptional and non-transcriptional mechanisms and vice-versa. The area outlined by the red box is shown at higher magnification in D.

D. Signaling at the MF synapse includes potential sites of action for estrogen at pre or postsynaptic ERs. proBDNF and mature BDNF also have pre and postsynaptic receptors; in addition, truncated trkB on astrocytes could regulate the concentrations of mature BDNF at the synapse (Fryer et al., 1997). Adapted from (Scharfman and Maclusky, 2005)

Figure 2. Fluctuations of BDNF immunoreactivity in hippocampus during the estrous cycle and in ovariectomized rats treated with 17 β -estradiol

A. BDNF immunoreactivity in hippocampal MFs changes across the rat estrous cycle.

1. BDNF immunoreactivity was robust in the MFs of female rats that were perfusion-fixed mid-morning of proestrus, a time when serum levels of 17 β -estradiol peak in the rat (Freeman et al., 1984; Figure 4). DG= dentate gyrus; Calibration = 250 μ m in this and all other parts of the figure. A1-5 are from Scharfman et al. (2003).

2. BDNF immunoreactivity was highest in the MFs of female rats when they were perfusion-fixed on the morning of estrus, when serum levels of 17 β -estradiol have returned to baseline following the surge the previous day (Figure 4).

3. There was less BDNF immunoreactivity in MFs when female rats were perfused on the morning of metestrus, when serum levels of 17 β -estradiol are low.

4. BDNF immunoreactivity in the MFs was decreased following ovariectomy, which eliminates production of 17 β -estradiol in the ovaries.

5. BDNF immunoreactivity in male rats was reduced compared to intact female rats.

B. BDNF immunoreactivity in ovariectomized female rats treated with vehicle compared to 17 β -estradiol.

1. BDNF immunoreactivity in MFs was low following ovariectomy and vehicle treatment. Parts 1-2 are from Scharfman et al. (2007).

2. BDNF immunoreactivity was increased in MFs following ovariectomy and hormone replacement. To simulate the serum levels of 17 β -estradiol during the estrous cycle, a

procedure was used that involved 3 serial injections of estradiol. Rats were perfused at the time that would simulate mid-morning of proestrus.

Figure 3. Comparison of hippocampal proBDNF, mature BDNF, p75NTR, trkB receptor expression and serum 17β-estradiol levels in the female rodent as a function of age

A. Levels of mature BDNF and trkB are inversely related to levels of proBDNF and p75NTR during development and early adulthood.

1. Whole hippocampal levels of mature BDNF protein are relatively low at birth and before puberty, increasing during development (Zhou et al., 1996; Katoh-Semba et al., 1997; Karege et al., 2002). After puberty, BDNF levels fluctuate across the estrous cycle (Scharfman et al., 2003). BDNF protein levels subsequently decrease and are relatively low in late adulthood (Karege et al., 2002; Silhol et al., 2005). trkB expression follows a similar pattern during development and adulthood (Masana et al., 1993; Fryer et al., 1996, but see Silhol et al., 2005), with relatively low levels during late adulthood (Croll et al., 1998; Silhol et al., 2005). In contrast, hippocampal levels of proBDNF and p75NTR were highest during early development, with lower levels after puberty and during adulthood (Yang et al., 2009b). Dotted lines denote estimates of female hippocampal levels where studies have been primarily conducted in studies where sex was not specified or male rats. Question marks denote estimates of proBDNF and p75NTR during late adulthood.

2. Both proBDNF and mature BDNF bind to p75NTR (Chao, 2003). Alternatively, proBDNF can be cleaved to mature BDNF and mature BDNF can then bind to full-length or truncated trkB receptors (Barbacid, 1994; Eide et al., 1996; Fryer et al., 1997).

B. Serum levels of 17β-estradiol vary as a function of age.

1. During early development, serum levels of total (free and bound) 17β-estradiol are relatively high immediately following birth, and decrease during the first postnatal days (Rhoda et al., 1984; Konkle and McCarthy, 2011). Circulating levels of free 17β-estradiol

are lower because estradiol is bound by α -fetoprotein, secreted by the fetal rodent liver, which sequesters the most serum estradiol (Vannier and Raynaud, 1975; Puig-Duran et al., 1979). During early and late adulthood, serum levels of 17β -estradiol fluctuate during the 4-day rat estrous cycle (Freeman (1984; Figure 4). In late adulthood, female rats experience “reproductive senescence,” during which serum 17β -estradiol levels decline (Huang and Meites, 1975; Lu et al., 1979; Chakraborty and Gore, 2004; Bowman et al., 2006; Luine et al., 2007). Dotted line denotes estimated levels of 17β -estradiol during early life; specific levels of free estradiol vary due to α -fetoprotein.

2. 17β -estradiol is the ligand for two estrogen receptors (ER): estrogen receptor α (ER α) and estrogen receptor β (ER β), which have a similar affinity for 17β -estradiol (Kuiper et al., 1997), and may be located in the plasma membrane (mER).

Figure 4. Estradiol and progesterone levels during the human menstrual cycle and the rat estrous cycle

A. A schematic of the human 28-day menstrual cycle is shown. There is a surge in serum levels of 17β -estradiol mid-cycle which ends the first half of the cycle (the follicular phase). Serum levels of progesterone (Progest.) rise and fall during the second half of the cycle (the luteal phase), and are low at the end of the menstrual cycle. Note that there is a rise and fall in 17β -estradiol mid-cycle and during the luteal phase. Adapted from Scharfman and MacLusky (2006).

B. A schematic of the rat 4-day estrous cycle is shown. Serum 17β -estradiol levels begin to rise on the second day of diestrus (diestrus 2) and peak mid-morning of proestrus. Progesterone begins to rise during the middle of the day of proestrus, peaks that night and then falls rapidly, returning to baseline levels by the following morning, estrus. Bars on the x axis indicate nighttime. Adapted from Freeman (1984).

Figure 5. Electrophysiological changes in CA3 following BDNF exposure or overexpression in the male rat compared to female rats at different cycle stages

A. A schematic of the hippocampus in horizontal section showing hippocampal stimulation sites (filled circles) and recording sites (x). Recordings were made in the pyramidal cell layer (PCL) of area CA3b extracellularly and stimuli were triggered to the MFs or fimbria.

B. Responses to single stimuli recorded in CA3b PCL of a slice from a male rat as shown in A, before and 30 min after bath application of recombinant BDNF. The response to MF stimulation was potentiated but not the response to fimbria stimulation, suggesting that the effect of BDNF was specific to the MF pathway, presumably because of effects of BDNF on MF trkB receptors because the effect was blocked by a trk receptor antagonist. Stimulus artifacts are truncated and marked by dots. B-C are from Scharfman et al. (2007).

C. After exposure to BDNF in B, repetitive stimulation (pairs of identical stimuli, 40 msec apart, at 1 Hz) of the MF pathway led to multiple population spikes (arrows) after 3 pairs of stimuli; this did not occur following repetitive stimulation of the fimbria.

D. In slices from BDNF overexpressing male mice, repetitive stimuli led to multiple population spikes after 10 pairs of stimuli without adding recombinant BDNF. Repetitive stimuli did not have this effect in wild type (WT) controls (not shown). From Croll et al. (1999).

E-F. Multiple population spikes were elicited by pairs of MF stimuli (same procedure as C-D, pairs of half-maximal stimuli with a 40 msec interval, at 1 Hz) in female rats that were euthanized during the morning of proestrus (E) or estrus (F). E-F are from Scharfman et al. (2003).