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**Sex differences and the role of estrogen in animal models of schizophrenia:
interaction with BDNF**

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Abstract

Schizophrenia is a severe psychiatric disorder with a complex and variable set of symptoms. Both genetic and environmental mechanisms are involved in the development of the illness and lead to structural and neurochemical abnormalities in the brain. An intriguing facet of schizophrenia is sex differences, which have been described for nearly all features of the illness, including the peak age of onset, symptoms and treatment response. The ovarian hormone, estrogen, may be protective against schizophrenia and evidence is accumulating that estrogen may exert this effect via an interaction with brain-derived neurotrophic factor (BDNF). Both estrogen and BDNF have trophic effects on the developing brain and promote synaptic plasticity and maintain neurons well into adulthood. Major neurotransmitter systems including dopaminergic, serotonergic and glutamatergic pathways are modulated and supported by estrogen and BDNF. Despite their commonalities, estrogen and BDNF have mostly been examined independently but increasing evidence suggests an interaction between the two in brain regions pertinent to schizophrenia. This review will focus on the role of estrogen and BDNF in clinical and animal studies of schizophrenia. We include animal models of neurotransmitter dysfunction and genetic manipulation to show how estrogen may provide a protective effect in schizophrenia, including through mediating BDNF expression and activity. This posited estrogen-BDNF interaction could play a key role in modulating sex-dependent results reported in animal work as well as sex differences in clinical aspects of schizophrenia.

Keywords: Psychiatric disorders, Dopamine, Serotonin, NMDA receptor

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Abbreviations: BDNF, brain-derived neurotrophic factor; 5-HT, serotonin; NMDA, N-methyl-D-aspartate; ER, estrogen receptor; ERE, estrogen response element; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PLC- γ , phospholipase C- γ ; TrkB, tropomyosin-related kinase B; p75^{NTR}, pan-75 neurotrophin receptor; BDNF Het, BDNF heterozygous; PPI, prepulse inhibition; ArKO, aromatase knockout; SSRI, selective serotonin re-uptake inhibitor; SERT, serotonin transporter; 8-OH-DPAT, 8-hydroxy-2-dipropylaminotetralin; PCP, phencyclidine; CREB, cAMP-response-element binding protein.

Introduction

Schizophrenia is a debilitating psychiatric disorder that affects nearly 1% of the world's population (Insel, 2010). It occurs as a syndrome, characterized by positive symptoms such as delusions and hallucinations, negative symptoms such as emotional withdrawal and apathy, as well as cognitive deficits such as impaired attention, learning and memory (Faludi et al., 2011). The pharmacotherapy of schizophrenia started with the serendipitous discovery of chlorpromazine, now classified with several other drugs, such as haloperidol, as a typical antipsychotic (Ban, 2006). The antipsychotic action of these antipsychotics is mediated by blockade of dopamine receptors, in particular the D2 receptor subtype. This in turn led to the dopamine hypothesis of schizophrenia which postulated dopamine hyperactivity in subcortical brain regions (Seeman, 1987). However, in addition to dopamine, other monoamines like serotonin (5-HT) are likely to play a role as well (Meltzer, 1999, Scarr et al., 2004). Indeed, many of the later developed atypical antipsychotics, which were so termed because of their lower incidence of extrapyramidal side effects, show high affinity for receptors other than dopamine, for example 5-HT_{2A} receptors (Meltzer and Nash, 1991). Current antipsychotic drugs are at least partially effective against positive symptoms but they have little effect on the negative symptoms and cognitive deficits of the illness, albeit there is a better functional outcome with the atypical class (Lambert and Castle, 2003). Moreover, not all patients fully respond to treatment and a significant number are non-responders (Pantelis and Lambert, 2003). Better understanding of the pathophysiology of schizophrenia is therefore required for improved drug design and ultimately prevention of illness progression or even illness onset.

Despite several decades of research, the aetiology of schizophrenia remains poorly understood. It appears that a combination of genetic susceptibility and environmental factors

contribute to its expression. Indeed, family, twin and adoption studies have established a genetic link (Kendler and Diehl, 1993). However, the lack of 100% concordance for schizophrenia in monozygotic twins has prompted the search for non-genetic factors. Of these, environmental perturbations during the prenatal or perinatal periods of life such as maternal infection (Buka et al., 2001) or obstetric complications (McNeil et al., 2000) have been shown to be associated with increased risk of the illness. In addition, later stressful life events or drug abuse are widely postulated as triggers for disease onset in late adolescence or young adulthood (Faludi et al., 2011). Schizophrenia is thus considered a multi-factorial neurodevelopmental disorder where disturbances in normal brain growth, through genetic or environmental influences, lead to the structural and neurochemical abnormalities observed in the brains of those afflicted (Rapoport et al., 2012).

Animal and clinical studies suggest that, amongst many other factors, estrogen and the neurotrophin, brain-derived neurotrophic factor (BDNF), are implicated in the pathophysiology of schizophrenia (Häfner et al., 1991, Pillai, 2008). Both of these are well known for their trophic effects on the developing brain and to promote synaptic plasticity and maintain neurons well into adulthood (Scharfman and MacLusky, 2005). Previous studies have mostly examined estrogen and BDNF independently but increasing evidence suggests an interaction between these systems in brain regions pertinent to schizophrenia (Scharfman and MacLusky, 2008). It should be noted that the interaction of BDNF and estrogen has also been linked to mood disorders, including depression and anxiety, which show a higher propensity in females (Ren-Patterson et al., 2006, Lasiuk and Hegadoren, 2007). Schizophrenia and depression often display overlapping symptoms, especially in the cognitive domain, and the relevance of data from animal studies which examined cognitive function is therefore not limited to schizophrenia but may also relate to mood disorders. The

reader is referred to several review papers on the role of sex steroid hormones and their interaction with BDNF in regards to mood disorders (Joffe and Cohen, 1998, Payne, 2003, Scharfman and MacLusky, 2005). The present review will focus on the role of estrogen and BDNF in animal studies of schizophrenia, with an emphasis on the interaction of estrogen- and BDNF-related mechanisms.

1. Estrogen

Estrogens are a group of sex steroid hormones predominantly found in females, but also present in lower concentrations in males. They occur naturally in the body in three forms, estrone (E1), 17 β -estradiol (E2), and estriol (E3). Estradiol is the most potent and bioactive estrogen under normal physiological conditions (Heldring et al., 2007). Besides their control of reproductive functions, estrogens exert profound and diverse effects in the brain (Gruber et al., 2002). While serum estradiol is primarily produced in the ovaries, in the brain, it is synthesized by neurons and astrocytes from cholesterol. This occurs in brain regions where aromatase is expressed, which converts androgens to estrogens (MacLusky et al., 1987, Scharfman and MacLusky, 2006, 2008). In the hippocampus, this *de novo* synthesis of estradiol has been suggested to play a crucial role in synaptic plasticity (Rune et al., 2006, Fester et al., 2011). Several major neurotransmitter systems are modulated by estrogens, including dopaminergic, serotonergic, cholinergic and glutamatergic pathways (Kritzer and Kohama, 1999, Bethea et al., 2002, Cyr et al., 2002, Sanchez et al., 2010). Moreover, numerous studies suggest that estrogens, especially estradiol, have neuroprotective effects. For instance, chronic administration of estrogens improve cerebral blood flow (Greene, 2000) and promote neuronal sprouting (Morse et al., 1986, Kadish and Van Groen, 2002) and myelination (Crawford et al., 2010). Chronic estradiol treatment reverses the deficits in

cytoskeletal plasticity found in the hippocampus of middle-aged ovariectomized rats (Kramar et al., 2009). Acute applications of estradiol also have antioxidant (Goodman et al., 1996) and anti-apoptotic (Garcia-Segura et al., 1998) properties, and induces an increase in the density of N-methyl-D-aspartate (NMDA) receptors which corresponds to an increase in synaptic density and plasticity (Woolley et al., 1997, Woolley, 1998). Induction of synapses has been shown to vary with the estrus cycle in the hippocampus of female rats, with the greatest synaptic density observed during the proestrus phase when estrogen levels are the highest (Gould et al., 1990, Woolley and McEwen, 1992, Gonzalez-Burgos et al., 2005). These pleiotropic effects of estrogens are thus postulated to contribute to the sex differences evident in a variety of neurological and psychiatric disorders including schizophrenia.

Estrogens act via both genomic and non-genomic mechanisms. The genomic effects of estrogen are mediated by two distinct estrogen receptor (ER) subtypes, ER- α and ER- β (Levin, 2001). Binding of estrogen to these receptors, that are either cytoplasmic or nuclear, releases the receptor from its inhibitory complex with heat shock proteins (Knoblauch and Garabedian, 1999). This, in turn, triggers a conformational change, allowing the ER to bind to the estrogen response element (ERE) in the DNA, resulting in activation of the target gene (Levin, 2001). Various genes crucial for normal brain development such as BDNF and the apoptosis regulator protein, Bcl-2, have been reported to contain ERE-like sequences, suggesting that estrogen could modulate their expression via activating this putative ERE (Sohrabji et al., 1995, Teixeira et al., 1995). These genomic effects have a prolonged duration but are usually delayed in onset, with new gene products measurable only after 12-24 hours of hormone exposure (Spencer-Segal et al., 2012). The effects of estrogen can also be rapid and short-lived, occurring via a non-genomic mechanism, presumably through membrane-associated ERs. Acute treatment of ovariectomized rats with membrane-limited estrogen

conjugates (i.e. estradiol bound to bovine serum albumin) have been reported to improve cognitive performance in an inhibitory avoidance task (Walf and Frye, 2008). This effect of estradiol was rapid, occurring within 10 minutes post-hormone exposure. Moreover, blocking putative signalling pathways that are activated by these membrane targets, such as mitogen-activated protein kinase (MAPK), in the dorsal hippocampus blocked the enhancing effects of estradiol in this task (Walf and Frye, 2008). Additionally, Liu and colleagues showed that the non-genomic actions of estradiol may be mediated by intracellular ERs, particularly the ER- β isoform rather than ER- α (Liu et al., 2008). Acute administration of a selective ER- β agonist improved spatial memory in both the radial arm maze and water maze, while an ER- α agonist had no effect in these behavioural paradigms. ER- β activation increased the expression of major synaptic proteins, including PSD-95, synaptophysin and the AMPA receptor subunit, GluR1. These changes were paralleled by increased dendritic branching and increased density of mushroom-type spines in hippocampal neurons *in vivo* (Liu et al., 2008). All of these effects of ER- β activation were likely to be non-genomic, given the relatively short timeframe within which they were found (1-4 hours following a single injection of ER- β agonist). Other studies have started to examine the signalling pathways involved in the ER- β dependent remodelling of dendritic spines. Work by Srivastava and colleagues suggests that the Rap/Erk1/2/AF-6/Afadin pathway may play an important part in the rapid cellular effects of estrogen (Srivastava et al., 2008, Srivastava et al., 2010, Srivastava, 2012).

The ERs are present in high levels in the hypothalamus which conforms with their regulatory role in neuroendocrine events related to reproduction (Taber et al., 2001). The general distribution of ERs is similar across species. However, species and ER subtype differences do exist. For instance, while the human paraventricular nucleus in the hypothalamus predominantly expresses ER- α transcripts rather than ER- β (Osterlund et al., 2000), their

transcript levels are low in this region of the rat brain, with ER- β being the predominant subtype (Osterlund et al., 1998). In human and non-human primates, significant mRNA and protein expression of ERs is found in the basal forebrain, amygdala, dorsal raphe nucleus, mamillary bodies and the hippocampus (Register et al., 1998, Donahue et al., 2000, Gundlah et al., 2000). These distribution patterns support an influence of estrogens on memory, cognition and emotion. In addition, ER transcripts have been found in locomotor regions including the substantia nigra and the subthalamic nucleus (Gundlah et al., 2000, Osterlund et al., 2000).

Sex differences in schizophrenia have been described in many features of the illness, from incidence and mean age of onset to symptomatology, course of illness and response to pharmacological treatments (Aleman et al., 2003, Riecher-Rossler and Kulkarni, 2011). Over a century ago, Kraepelin was the first to show that first-time hospitalization for schizophrenia occurs at a younger age in men than in women (Markham, 2012). This has been replicated in a series of large-scale epidemiological studies by Häfner and others (Häfner et al., 1991, Hambrecht et al., 1992, Häfner et al., 1993, Castle et al., 1998). A significant difference in age of onset between the sexes was reported, with a peak onset age of 15-24 in men and 20-29 in women. Intriguingly, women were found to have a second peak onset after age 45, which may correspond to menopause (Riecher-Rossler et al., 1997). It was proposed that the physiologically higher levels of estradiol in young fertile women contributed to the later age of onset of schizophrenia as compared to men (Seeman and Lang, 1990). Consequently, the second peak of onset in women around menopause may result from the rapid decline and lower production of estradiol. Cohen and colleagues (1999) found that an earlier age of menarche was associated with a later age of first psychotic symptoms and the first hospitalization (Cohen et al., 1999). This association was independent of variables such as

family history and obstetric complications. Moreover, no significant correlation was found between puberty and disease onset in men (Cohen et al., 1999). Female sex hormones thus appear to delay the age of onset in schizophrenia and may provide an overall functional protection against occurrence of the illness.

Clinically, several reports suggest that the symptoms of schizophrenia may present differently among the two sexes. Women tend to have more affective symptoms such as mood disturbances including depression (Goldstein and Link, 1988, Koster et al., 2008), while an amotivational syndrome and negative symptoms seems to prevail in men (Lewine, 1985, Thorup et al., 2007). Men maintain a tonic release of sex hormones from the testes, while female hormones are released from the ovaries in a cyclic pattern, through a feedback loop involving the hypothalamus and the pituitary (Seeman and Lang, 1990). Clinical data suggest that this fluctuation of female hormones may affect the occurrence and severity of psychotic symptoms (Hallonquist et al., 1993, Bergemann et al., 2007). Psychopathology scores in premenopausal women with schizophrenia fluctuate across the menstrual cycle, with symptom deterioration during the low-estrogen phases of the cycle (Hendrick et al., 1996, Bergemann et al., 2007, Seeman, 2012). Reports also indicate that chronic psychoses improve during pregnancy, when estradiol levels are 200-fold higher than normal (Chang and Renshaw, 1986). Conversely, women become more vulnerable to psychosis at the perimenstrual phase of the menstrual cycle (Hallonquist et al., 1993), post partum (Kendell et al., 1987), post menopause (Häfner, 2003), and following abortion (Mahe et al., 1999), all representing periods of estrogen withdrawal (Mahe and Dumaine, 2001).

Women have been found to show a less severe course of illness and a better response to antipsychotics compared to men (Seeman and Lang, 1990). However, it is unclear whether these findings are due to the later age of onset or simply the better compliance to medication

in women (Koster et al., 2008). Alternatively, their pre-menopausal sex hormones may play a part and serve as an endogenous antipsychotic agent. Indeed, Seeman and colleagues (1983) found that women with schizophrenia at 20-40 years were protected from relapse and achieved maximal functioning at lower doses of antipsychotics than older women or men of comparable age (Seeman, 1983). Estrogens cross the blood-brain-barrier and modulate several neurotransmitter systems. For example, estrogens can have post-synaptic anti-dopaminergic effects (Dufy et al., 1979, Sanchez et al., 2010). It is therefore not surprising that their rapid decline may result in detrimental changes in central neurotransmission and thus psychotic symptoms. Ahokas and co-workers (2000) found that the chronic administration of estradiol significantly diminished psychotic symptoms in post-partum women with low levels of circulating estradiol (Ahokas et al., 2000). A more recent study showed that the long term addition of transdermal estradiol for 28 days in pre-menopausal women with schizophrenia significantly improved the positive and general psychopathological symptoms compared to women receiving antipsychotics alone (Kulkarni et al., 2008). Estrogen is therefore not only a mediator of sex differences in schizophrenia but also a potential therapeutic mechanism.

2. BDNF

The molecular targets of estrogen action in schizophrenia are diverse but accumulating data suggest that growth factors, especially BDNF, may play a major role. BDNF is a member of the neurotrophin family which includes nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). Neurotrophins are essential for the survival and differentiation of neurons and in the maintenance of their synapses during development and throughout life (Thoenen, 1995). BDNF, in particular, is involved in regulating synaptic

plasticity and long term potentiation, which have been considered as major cellular mechanisms underlying learning and memory (Xu et al., 2000, Yoshii and Constantine-Paton, 2010). BDNF has been shown to be one of the most potent modulators of neuronal and synaptic morphology (Chapleau et al., 2008). For instance, in cell culture studies, stimulation with BDNF induces dendritic spine formation in hippocampal neurons (Tyler and Pozzo-Miller, 2003, Ji et al., 2005) and increases dendritic arborization, soma size and axon length of striatal neurons (Gavalda et al., 2004). Late-onset, forebrain-specific BDNF knockout mice, where BDNF is mainly lost from the cortex and hippocampus in young adulthood, show a significant reduction in cortical dendritic spine density (Vigers et al., 2012). These effects of alterations in BDNF signalling on the dendritic spine pathologies (Faludi et al., 2011, Glausier and Lewis, 2012) may therefore be involved in alterations in major neurotransmitter systems.

BDNF is first synthesized as a 30-35 kDa precursor, known as pro-BDNF, which is proteolytically cleaved to form mature BDNF that is approximately 13 kDa in size (Mowla et al., 2001). The cellular response to BDNF is mediated by at least two receptor systems, tropomyosin-related kinase B (TrkB) and pan-75 neurotrophin receptor (p75^{NTR}). Binding of mature BDNF to TrkB induces receptor dimerization which stimulates its intrinsic tyrosine kinase activity. This then leads to autophosphorylation of the receptor at multiple tyrosine residues and activation of three signalling cascades including MAPK, phosphatidylinositol 3-kinase (PI3K), and the phospholipase C- γ (PLC- γ) pathways (Figure 1A) (Huang and Reichardt, 2003). These signalling cascades are well known for their regulation of cell survival and cell death (Huang and Reichardt, 2003). BDNF interacts with p75^{NTR} to trigger a different set of intracellular signalling, such as nuclear factor-kappa B (NFkB), c-jun kinase and acidic sphingomyelinase (Kaplan and Miller, 2000), albeit it is the pro-BDNF which

preferentially binds to this receptor (Teng et al., 2005). However, the majority of BDNF-induced effects are attributed to TrkB signalling (Lu, 2003). In addition to the full length TrkB, truncated isoforms generated by alternative splicing of the protein have also been identified (Luberg et al., 2010) which lack the cytoplasmic kinase domain but contain unique short C terminal sequences (Klein et al., 1990, Middlemas et al., 1991). Although the role of these truncated TrkB receptors remains elusive, they may function as ligand trapping molecules which take up and store BDNF, thus restricting the amount of BDNF available for the full length TrkB. Alternatively, truncated TrkB may dimerize with a kinase-containing receptor and prevent tyrosine kinase autophosphorylation. In this way, they inhibit full length TrkB signalling by dominant negative inhibition (Eide et al., 1996, Haapasalo et al., 2001).

BDNF is widely distributed in the cerebral cortex, hippocampus, basal forebrain, striatum, hypothalamus, brainstem and cerebellum. BDNF is most abundant in the hippocampal formation, amygdaloid complex and prefrontal cortex (Ernfors et al., 1990, Hofer et al., 1990, Murer et al., 2001, Pillai, 2008). It is also expressed in various cell types including neurons, astrocytes, microglia and endothelial cells, and is localized to the soma, dendrites and fibers (Pillai, 2008). BDNF transcripts increase throughout brain development (Friedman et al., 1991) and its expression does not appear to decline with age, indicating an essential role for maintaining the adult CNS (Narisawa-Saito and Nawa, 1996, Katoh-Semba et al., 1997).

It has been suggested that altered synthesis and/or release of neurotrophins may contribute to the development of schizophrenia (Angelucci et al., 2005, Autry and Monteggia, 2012, Balaratnasingam and Janca, 2012). The Val66Met polymorphism, which results in a substitution from valine to methionine at codon 66 in the human BDNF gene, is associated with disrupted intracellular trafficking and release of BDNF (Chen et al., 2004). Several studies have shown an association of this polymorphism with aspects of schizophrenia

(Rybakowski, 2008, Buckley et al., 2011). For example, homozygous carriers (Met/Met) show an increased risk of schizophrenia relative to the heterozygous state (Gratacos et al., 2007). This variant has also been reported to show a lower ability to perform verbal episodic memory tasks, accompanied by abnormal cerebral blood flow in medial temporal regions including the hippocampus (Egan et al., 2003). In a separate study, both patients with schizophrenia and healthy participants carrying the Met allele showed poorer verbal memory than their Val homozygous counterparts (Ho et al., 2006). Furthermore, the Met allele was associated with visuospatial impairments that were specific to schizophrenia patients but not healthy participants (Ho et al., 2006). The Val66Met genotype also shows significantly lower structure volume in the dorsolateral prefrontal cortex and hippocampus (Pezawas et al., 2004, Szeszko et al., 2005). Transcranial magnetic and direct current stimulation studies have found abnormal motor cortex plasticity in healthy subjects with the Val66Met polymorphism (Cheeran et al., 2008). These studies support a critical role for BDNF signalling in neural plasticity and the pathophysiology of schizophrenia.

Studies on post-mortem tissue from patients with schizophrenia showed a significant reduction in both BDNF and TrkB transcripts as well as BDNF protein in the dorsolateral prefrontal cortex, compared to controls (Weickert et al., 2003, Weickert et al., 2005, Thompson Ray et al., 2011). Another study, measuring protein concentrations determined by ELISA, showed decreased BDNF levels in the hippocampus, but increased BDNF levels in the neocortex, and unchanged BDNF levels in the cingulate gyrus and thalamus of schizophrenia patients (Durany et al., 2001). In contrast, other studies examining the hippocampus of schizophrenia patients showed increased immunostaining of BDNF and TrkB proteins (Iritani et al., 2003) or increased BDNF protein but decreased TrkB protein, as measured by ELISA and western blots respectively (Takahashi et al., 2000). It is unclear why

there are these opposite and inconsistent findings between studies although different methods used to measure BDNF and TrkB could be responsible.

BDNF can cross the blood-brain barrier (Pan et al., 1998) and its serum protein levels in the periphery are strongly correlated with CNS protein concentrations (Karege et al., 2002). A significant correlation has also been found between BDNF protein levels in plasma and cerebrospinal fluid of antipsychotic-naïve subjects with schizophrenia (Pillai et al., 2010). Most studies show significantly reduced serum BDNF protein levels in chronic and medicated patients with schizophrenia compared to healthy controls (Toyooka et al., 2002, Tan et al., 2005, Grillo et al., 2007, Ikeda et al., 2008, Xiu et al., 2009). This is also true in first-episode and antipsychotic-naïve patients with schizophrenia compared to healthy controls (Palomino et al., 2006, Rizos et al., 2008, Chen et al., 2009). However, increased BDNF serum protein levels have also been reported (Reis et al., 2008), while other studies have failed to find any differences in serum BDNF protein concentrations between healthy controls and those of drug-free and drug-naïve patients with schizophrenia (Shimizu et al., 2003, Huang and Lee, 2006). Despite discrepancies among these clinical studies, overall the results point to a dysregulation of BDNF signalling in schizophrenia (Green et al., 2011).

Differential effects of antipsychotic treatment have been found on serum BDNF protein levels (Yoshimura et al., 2007), with significantly higher concentrations of BDNF protein found in clozapine-treated patients with schizophrenia than in risperidone-treated patients (Tan et al., 2005). In contrast, Grillo and colleagues (2007) found no significant difference in BDNF serum protein levels between patients on clozapine and those on typical antipsychotics. However, there was a robust and positive correlation between serum BDNF protein levels and clozapine dose (Grillo et al., 2007). A comparison of plasma BDNF protein levels in schizophrenia patients at baseline and after 1 year of olanzapine treatment showed a

significant increase in BDNF protein levels, which were associated with a reduction in positive symptoms (Gonzalez-Pinto et al., 2010). Similar treatment-induced increases in plasma BDNF protein levels were observed in other studies and this appeared to parallel positive and negative symptom improvements (Lee et al., 2011).

Komulainen and co-workers (2008) found that a reduction in plasma BDNF protein levels were associated with cognitive impairment in a large sample of 57-79 year old women, but not in men (Komulainen et al., 2008). Further, women who reported using sex hormones performed better in tests of general cognitive function, memory and executive function (Komulainen et al., 2008). Taken together, existing clinical data support a role for BDNF in schizophrenia and that antipsychotics may exert their effect, at least in part, by modifying BDNF expression. However, less is known about sex differences in the involvement of BDNF in schizophrenia, either at the clinical level or in animal models of the illness.

3. Interaction of Estrogen and BDNF in schizophrenia

3.1 Sex differences in the behavioural effects of BDNF mutations

Mice completely lacking BDNF develop severe sensory deficits and usually only live to the second postnatal week. In contrast, BDNF heterozygous mice (BDNF^{+/-}, Het) show a 50% reduction in BDNF expression (Szapacs et al., 2004, Hill and van den Buuse, 2011), depletion levels similar to those seen in schizophrenia patients (Weickert et al., 2003). Some studies showed no overt behavioural abnormality in BDNF Het mice (Ernfors et al., 1994) and no major changes in behavioural tests for anxiety and depression (MacQueen et al., 2001, Chourbaji et al., 2004). However, other studies reported inter-male aggressiveness and hyperphagia during young adulthood (Lyons et al., 1999). In contrast, forebrain-specific,

conditional BDNF knockout mice display sex-dependent behavioural changes with males showing hyperactivity and females showing depression-like behaviours (Monteggia et al., 2007). Similarly sex-specific effects were also found in mice with site-specific deletion of BDNF in the dorsal hippocampus, with only males showing impaired spatial learning and reduced conditioned fear (Heldt et al., 2007). Our laboratory has demonstrated sex-specific behavioural and molecular deficits in a 'two hit' model of developmental stress (Figure 2). The combined effect of reduced BDNF levels and postnatal stress, simulated by chronic young-adult treatment with the stress hormone, corticosterone, led to a profound spatial memory deficit in the Y-maze in male, but not female mice (Klug et al., 2012). In contrast, novel-object recognition was disrupted in female BDNF Het mice, but not males, irrespective of corticosterone treatment (Figure 2). This differential behavioural phenotype in BDNF Het mice was accompanied by significant sex-specific alterations in NMDA receptor subunit protein expression in the dorsal and ventral hippocampus (Klug et al., 2012). Sex differences have also been shown in another 'two hit' rat model where the combined effect of maternal deprivation and chronic unpredictable stress during periadolescence, led to memory impairments that were more pronounced in males than in females (Llorente et al., 2011). While BDNF protein levels were reduced in both males and females, serum concentrations of testosterone and estradiol were significantly reduced in male, but not female two hit animals (Llorente et al., 2011). These studies show clear sex differences in the behavioural effects of animal models with altered BDNF levels. The profound sex-specificity of the effect of neurodevelopmental corticosterone treatment or unpredictable stress in these mice is suggested to be related to marked differences in regional peripubertal variations of BDNF and TrkB protein expression in the cortex and striatum vs. the hippocampus between male and female mice (Hill et al., 2012). For example, in male mice, but not female mice, we observed a marked increase in BDNF protein expression in the frontal cortex from 7 weeks of

age and this change was correlated with an increase in serum testosterone levels in these animals at this age. In contrast, in female mice, but not male mice, a peak of BDNF protein levels was seen in the dorsal hippocampus at 6 weeks of age although this change did not appear to be correlated with serum estradiol levels in these animals. There were also sex-specific peripubertal changes in the striatum and in TrkB signalling which could have played a role in the sex-specific effects of stress (Hill et al., 2012). Also in human studies, sex-specific effects of altered BDNF expression, here caused by the Val66Met polymorphism, were found on the neuroendocrine and physiological effects of social stress (Shalev et al., 2009). However, it remains to be determined which specific neurotransmitter systems mediate these interactions.

The dysregulation of BDNF signalling is also observed in depression and other psychiatric (Thompson Ray et al., 2011) and neurodegenerative disorders (Zuccato and Cattaneo, 2009). For example, recent studies revealed robust molecular changes in the post-mortem amygdala of female subjects with depression, including significant reductions in the expression of marker genes for inhibitory GABAergic interneurons, such as somatostatin and neuropeptide Y (Guilloux et al., 2011). The pattern of these changes was similar to that reported in female mice with reduced BDNF signalling, such as BDNF Het and exon IV knockout mice with low activity-dependent BDNF function (Guilloux et al., 2011). As will be discussed in more detail below (section 4), dysfunction of inhibitory GABAergic interneurons could be a downstream consequence of these changes in BDNF signalling in depression as they have been suggested to be in schizophrenia (Fung et al., 2010, Lewis et al., 2012). BDNF signalling has been reported to up-regulate transcript and protein levels of somatostatin and neuropeptide Y *in vitro* and *in vivo* (Nawa et al., 1993, Nawa et al., 1994) and mice hypomorphic for TrkB show lower mRNA levels for the GABA-synthesizing enzyme,

glutamic acid decarboxylase (GAD67) and parvalbumin (Hashimoto et al., 2005) and have fewer somatostatin mRNA positive neurons (Morris et al., 2008). Dysregulation of BDNF signalling could thus lead to deficient interneuron differentiation or maintenance both in schizophrenia and depression. This is an intriguing point of convergence for these psychiatric disorders given the key role of GABAergic interneurons in regulating cognitive function (Lewis et al., 2005, Woo and Lu, 2006) and the overlapping cognitive symptoms between depression and schizophrenia.

3.2 Association of estrogen and BDNF levels

As discussed earlier, symptoms of schizophrenia fluctuate across the estrous cycle (Hendrick et al., 1996, Bergemann et al., 2007, Seeman, 2012) and it has been suggested that this is caused by varying protective levels of estrogen (Kulkarni et al., 2008). BDNF mRNA expression levels in the frontal cortex and hippocampus of rats also vary with the estrous cycle, with lowest levels found in some studies when circulating estradiol levels were maximum (Cavus and Duman, 2003). Ovariectomy and hormone replacement experiments have extended these findings (for references, see (Scharfman and Maclusky, 2005, 2006). In sharp contrast, in other studies in the hippocampus, BDNF protein levels were higher at the proestrous and estrous phase than in metestrous or after ovariectomy (Scharfman et al., 2003, Scharfman and Maclusky, 2005). Several possibilities have been discussed previously to account for these discrepancies (Scharfman and Maclusky, 2005). Corresponding human data also show significant changes in circulating BDNF protein levels during the menstrual cycle (Begliuomini et al., 2007). However, it is less clear what role alterations in circulating sex steroids and associated BDNF levels play in central neurotransmitter function in schizophrenia. This is important in order to explain the cyclic fluctuations in symptomology

in this illness and to better understand the effects of treatment with estrogen or selective estrogen receptor modulators

3.3 Interaction of estrogen and BDNF with dopaminergic activity

As mentioned above, perturbations in dopamine signalling can lead to schizophrenia-like behavioural deficits. There is considerable evidence that this may be modulated by both sex steroid hormones and neurotrophic factors although it is less clear if this involves a direct interaction.

In animal behavioural models with relevance to schizophrenia, effects of both estrogen and BDNF have been shown. For example, chronic estradiol treatment prevented drug-induced disruptions of prepulse inhibition (PPI) by an action on dopamine D2 receptor and dopamine transporter levels (Chavez et al., 2010, Gogos et al., 2010). PPI is a model of sensorimotor gating that is disrupted in schizophrenia patients (van den Buuse, 2010). Acute estrogen treatment attenuated disruption of PPI in healthy women as well (Gogos et al., 2006b). In female, but not male, estrogen-deficient aromatase knockout (ArKO) mice, the effects of apomorphine and amphetamine on PPI were reduced (Chavez et al., 2009). Latent inhibition is a model of sensory information filtering which is disrupted in schizophrenia patients and in rats treated with amphetamine (Arad and Weiner, 2009). Ovariectomy in rats caused a disruption of latent inhibition, and this was reversed by acute administration of estradiol, clozapine, haloperidol plus estradiol, but not haloperidol alone, suggesting that abnormally low levels of sex steroid hormones can induce a pro-psychotic state resistant to typical antipsychotic treatment (Arad and Weiner, 2009). Further studies on latent inhibition confirmed and extended these observations and suggested that acute estradiol treatment was also efficacious in males (Arad and Weiner, 2010).

Knowledge on the involvement of BDNF in sensory gating mechanisms regulated by dopamine is largely indirect and has not consistently addressed an interaction with sex steroid hormones. Treatment with the dopamine receptor agonist, quinpirole, disrupted PPI and reduced BDNF transcripts in the hippocampus (De Carolis et al., 2010). Both effects were reversed by clozapine pretreatment but there were also other behavioural effects which could have influenced the results. A genetic study using micro-array suggested that the levels of PPI in several mouse substrains were associated with BDNF gene expression in medial prefrontal cortex (Grottick et al., 2005). However, forebrain-restricted BDNF mutant mice did not show changes in PPI (Gorski et al., 2003). Also a large clinical association study did not find clear evidence for a role of BDNF polymorphisms in sensory gating (Shaikh et al., 2011). Our studies in male and female BDNF Het mice did not reveal differences compared to wild-type controls in baseline PPI or its disruption by amphetamine, and additional corticosterone treatment did not induce differences between the groups either (Figure 2). Further experimental interventional studies are needed to directly modulate BDNF expression and assess any sex-specific involvement in PPI and other forms of sensory gating.

Psychotropic drug-induced hyperlocomotion is an animal model of psychosis (van den Buuse, 2010). Female, but not male ArKO mice showed significant reductions in the effect of amphetamine on locomotor activity (Chavez et al., 2009). Also in BDNF Het mice, several studies have observed altered effects of amphetamine and cocaine along with perturbations of dopaminergic activity (e.g. (Hall et al., 2003, Saylor and McGinty, 2008)). In contrast, we did not observe differences between either male or female BDNF Het mice with respect to baseline locomotor activity or amphetamine-induced locomotor hyperactivity (Figure 2).

Several possibilities have been suggested to explain the interaction of dopaminergic behavioural mechanisms, sex steroid hormones and BDNF. Region- and sex-specific co-

localization of mesocortical dopaminergic projections and intracellular estrogen and androgen receptors has been shown in rats (Kritzer and Creutz, 2008). Effects of methamphetamine could be modulated by chronic estrogen treatment (Dluzen and McDermott, 2004). Moreover, they were dependent on the sex of the animals and involved altered levels of BDNF signalling (Dluzen and McDermott, 2004). Chronic injections of estrogen directly stimulated both BDNF transcript and protein levels in mouse midbrain neurons to enhance differentiation of dopaminergic neurons (Ivanova et al., 2001). BDNF has been shown to regulate the binding levels of dopamine D3 receptors in the nucleus accumbens (Guillin et al., 2001) and the uptake activity of dopamine transporters (Hoover et al., 2007). In ER- α knockout mice, dopamine D1 receptor transcript and protein levels were up-regulated in females, but not males, although BDNF transcript and protein levels were reduced in both sexes in this study (Kuppers et al., 2008). Dopaminergic signalling through dopamine D1 and D2 receptors increased immunostaining for the BDNF protein (Hasbi et al., 2009) and chronic treatment of rats with antipsychotic drugs that modulate dopamine signalling, reduced BDNF mRNA expression (Chlan-Fourney et al., 2002, Angelucci et al., 2005, DeCarolis and Eisch, 2010). Despite these findings, the exact neurochemical mechanisms involved in the postulated interaction between estrogens and BDNF, remain to be elucidated.

3.4 Interaction of estrogen and BDNF with serotonergic activity

Serotonin receptors have been implicated in the development of schizophrenia and the action of antipsychotic drugs (Meltzer, 1999, Scarr et al., 2004). Several clinical and preclinical studies have shown interaction of serotonin, BDNF and sex steroid hormones although the results have been variable and these studies have not necessarily focused on schizophrenia (Cyr et al., 2002).

Several experimental manipulations of brain serotonin levels have been shown to alter BDNF expression (Zetterstrom et al., 1999). For example, in mice, chronic treatment with the antidepressant and selective serotonin re-uptake inhibitor (SSRI), fluoxetine, increased BDNF protein levels in the hippocampus and induced sex-specific effects on cell survival and neurogenesis (Hodes et al., 2010). These findings are in line with clinical studies, which show that chronic antidepressant treatment up-regulates serum BDNF protein levels (Kozisek et al., 2008). More recently, it has been suggested that this effect is particularly seen with SSRIs as opposed to antidepressants with another pharmacological mechanism of action (Kozisek et al., 2008, Molendijk et al., 2011). Women had lower serum protein levels of BDNF than men but there were no gender differences in the response to SSRIs (Molendijk et al., 2011). In contrast to antidepressant drugs, the effects of chronic treatment with atypical antipsychotic drugs are less clear. Different to typical antipsychotics, most of these drugs have significant affinity for serotonin receptors in addition to dopamine receptors (Meltzer and Nash, 1991), but in one study there was no effect of olanzapine on serum BDNF protein levels in patients with schizophrenia (Hori et al., 2007) while in another study, quetiapine had a similar effect as the antidepressant, venlafaxine, in preventing a chronic stress-induced reduction of BDNF protein levels in the hippocampus in rats (Xu et al., 2006). Also chronic treatment with risperidone reduced BDNF protein levels in rats and this effect was found in the cortical regions and hippocampus (Angelucci et al., 2000). However, chronic treatment with haloperidol had the same effect as risperidone, suggesting involvement of dopaminergic mechanisms rather than serotonin receptor blockade (Angelucci et al., 2000).

Early studies in BDNF Het mice showed intact serotonergic innervation of the forebrain but increased 5-HT_{1B} and 5-HT_{2A} receptor transcripts in the frontal cortex and decreased 5-HT_{2C} receptor transcripts in the hippocampus (Lyons et al., 1999). However, these effects were

similar in male and female mice. Further studies with conditional forebrain-specific BDNF knockouts confirmed regulation of serotonin receptor binding and function by BDNF (Klein et al., 2010). BDNF Het mice furthermore showed enhanced serotonin release with reduced functional activity of the serotonin transporter (SERT) (Deltheil et al., 2008). However, other micro-dialysis studies did not show changes in serotonin release in the frontal cortex and striatum of BDNF Het mice (Szapacs et al., 2004) and, conversely, mice which were heterozygous or homozygous for a mutation in the serotonin transporter ($SERT^{+/-}$ or $SERT^{-/-}$) did not show altered levels of BDNF protein in the hippocampus and frontal cortex (Szapacs et al., 2004). This lack of a genotype effect was similar in male and female mice, even though male mice displayed overall higher BDNF protein levels than female mice. Male double mutant BDNF Het x SERT knockout mouse displayed a greater decrease in brain serotonin concentrations, increased anxiety and greater adrenocorticotrophic hormone responses to stress than mice with the SERT knockout alone (Ren-Patterson et al., 2006). Interestingly, this phenotype was not evident in female mice that appeared to be protected, presumably by sex steroid hormones. Indeed, chronic treatment of the male double mutants with estradiol increased hypothalamic serotonin concentrations (Ren-Patterson et al., 2006). We produced double mutant 5-HT_{1A} receptor knockout x BDNF Het mice and also found sex-specific effects (Wu et al., 2012). Specifically, female mice, but not males, showed alterations in the phosphorylation of TrkB and downstream ERK2 in the ventral hippocampus (Wu et al., 2012).

Rather than sex differences, other studies have more specifically focused on the interaction of sex steroid hormone treatment, BDNF expression and brain serotonergic activity. Estradiol treatment acutely reduced BDNF gene expression and inhibited the increase of BDNF mRNA levels induced by the 5-HT_{2A/2C} receptor agonist, DOI (Cavus and Duman, 2003). Similar

interactions could be shown in primary cell cultures (Rumajogee et al., 2002). In contrast, in another study, chronic estradiol treatment caused an increase in BDNF protein concentrations and serotonin turnover in the hippocampus (Kiss et al., 2012). Other studies in female ovariectomized rats found that acute estradiol treatment increased SERT and 5-HT_{2A} receptor densities (McQueen et al., 1997, Sumner et al., 1999) although chronic estradiol treatment had no effect on SERT or 5-HT_{1A} and 5-HT_{2A} receptor densities in ovariectomized rats (Chavez et al., 2010). Comparison of the various studies suggests that the duration of estrogen treatment greatly influences the effects on BDNF and serotonin levels.

In terms of behavioural tests with relevance to schizophrenia, treatment of rats with the 5-HT_{1A} receptor agonist, 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT), produced a dose-dependent disruption of PPI and chronic treatment with estradiol prevented this effect (Gogos and Van den Buuse, 2004). Similarly, the absence of estrogen in male ArKO mice leads to a greater effect of 8-OH-DPAT on PPI than in wildtype controls (Gogos et al., 2006a). While the mechanism of this functional interaction remains unclear, studies on ovariectomized mice suggest that estrogen may modulate SERT function. A low estrogen state, induced by ovariectomy, increases SERT activity in the hippocampus despite a reduction in SERT binding density (Bertrand et al., 2005).

5-HT_{2C} receptor knockout mice, which showed marked up-regulation of BDNF protein levels in the hippocampus, displayed mild hyperactivity at baseline (Hill et al., 2011) while 5-HT_{2C} receptors modulate behavioural responses to dopaminergic psychostimulants (Bubar and Cunningham, 2006). Both baseline locomotor hyperactivity and dopamine-mediated locomotor hyperactivity are widely used models of psychosis (van den Buuse, 2010). Overall these studies show a multitude of different ways by which BDNF and the serotonin system interact including sex-specific effects and modulation by sex steroid hormones.

3.5 Interaction of estrogen and BDNF with NMDA receptor activity

Similar to the interaction of BDNF with either dopaminergic or serotonergic mechanisms involved in schizophrenia, also NMDA receptor function appears to be modulated by BDNF in a sex-specific and/or estrogen-dependent manner.

MK-801, phencyclidine (PCP) and ketamine are all NMDA receptor antagonists, which in humans have psychotomimetic actions and cause cognitive impairments similar to those found in schizophrenia patients. These drugs may be utilized in animals to study the NMDA receptor hypofunction hypothesis of schizophrenia (Tamminga, 1999, Carlsson et al., 2001, de Olmos et al., 2008). Chronic treatment with estradiol modulates NMDA and AMPA receptor density in the rat brain (Cyr et al., 2000) and is protective against MK-801-induced PPI disruptions (Gogos et al., 2012). In addition, in a model of cognitive dysfunction induced by treatment with PCP, both a long lasting implant and a single injection of estradiol were protective against cognitive impairments in the novel object recognition task (Sutcliffe et al., 2008, Roseman et al., 2012). Together, these studies suggest an interaction between NMDA receptor signalling and estradiol.

Several studies have shown a link between NMDA/AMPA receptor-induced cognitive deficits and changes in BDNF expression (Woolley et al., 2009, Goulart et al., 2010), however, only few have considered male/female differences or effects of sex steroid hormones. Indeed, a recent study has shown that sex differences in PCP-induced cognitive deficits may be attributed to BDNF expression (Snigdha et al., 2011). In this study, female rats were shown to be more sensitive to PCP-induced deficits in attentional set shifting tasks and showed significant reductions in BDNF mRNA levels in several forebrain regions compared to males (Snigdha et al., 2011). Earlier work showed that administration of the NMDA receptor antagonist, MK-801 (dizocilpine) increased BDNF gene expression in the

rat retrosplenial cortex and that this effect was greater in female rats compared to males (Matsuki et al., 2001). Interestingly, the effect of chronic estrogen treatment both to increase BDNF protein expression and consequently reduce NMDA-mediated cellular toxicity was reversed by progesterone, indicating differential effects of sex steroid hormones on BDNF-mediated mechanisms in the brain (Aguirre and Baudry, 2009). Several other studies have shown that the behavioural and neurochemical effects of NMDA receptor antagonists can be modulated by sex steroid hormones or that the expression of NMDA receptors and other glutamate receptor subtypes can be modulated by sex steroid hormones (e.g. (Woolley et al., 1997, D'Souza et al., 2003, Chavez et al., 2009, Arad and Weiner, 2010, Gogos et al., 2012). Changes in BDNF expression could be involved in these differential effects.

4. Mechanisms of estrogen-BDNF interaction

Overall the above mentioned animal model studies have demonstrated that both BDNF and estradiol play a role in facilitating many of the neurotransmitter mechanisms and behavioural deficits associated with schizophrenia and that an interaction between BDNF and estrogen is likely. The next section will discuss how such an interaction of estrogen and BDNF may occur at the molecular level.

Estrogen may regulate BDNF-TrkB signalling via classical nuclear ER-mediated activation. Estrogen can directly regulate gene expression through binding of estrogen-ER complexes to ERE sequences of the DNA. The rat BDNF gene contains a sequence with close homology to the ERE sequence (Sohrabji et al., 1995), suggesting that estrogen could modulate BDNF expression via activating this putative ERE. Co-localized expression of ER and BDNF is required for this mechanism, and indeed this has been demonstrated in the developing

forebrain (Miranda et al., 1993). However, more recent studies show that BDNF immunoreactive neurons rarely co-express with ERs within the adult rodent neocortex (Blurton-Jones et al., 2004).

Since the co-localization of BDNF with ER- α and ER- β in the hippocampus is controversial, a second indirect mechanism of BDNF-estrogen interaction has been postulated (Figure 1B). Blurton-Jones and colleagues found that ER- β expression is almost exclusively localized to GABAergic parvalbumin-positive interneurons of the perirhinal cortex (Blurton-Jones et al., 2004, Blurton-Jones and Tuszynski, 2006). These GABAergic interneurons were found to innervate other, non-ER bearing GABAergic interneurons. Acute estradiol treatment upregulated GABA immunoreactivity specifically within ER- β bearing GABAergic interneurons, while the majority of non-ER bearing cortical inhibitory neurons showed reduced GABA immunoreactivity after estradiol treatment. Estrogen may therefore lead to increased GABAergic activity or synthesis within ER- β bearing interneurons, which then inhibit non-ER- β bearing GABAergic interneurons. Moreover, since GABAergic neurons were found to innervate cortical BDNF-immunoreactive excitatory neurons, it was hypothesized that this inhibition of GABAergic interneurons by ER- β positive inhibitory neurons results in disinhibition of BDNF-expressing neurons. This, in turn, may lead to increased BDNF synthesis and/or release (Blurton-Jones and Tuszynski, 2006). Supporting this notion are studies which have shown that chronic estradiol treatment decreases GABAergic inhibition in the hippocampus (Murphy et al., 1998) and that BDNF is synthesized in an activity-dependent manner (Castren et al., 1998). In addition, administration of GABA_B receptor antagonists has been shown in rats to increase cortical and hippocampal BDNF transcripts and protein levels by 2-4 folds (Heese et al., 2000).

A third mechanism of interaction is via their converging signalling pathways and activation of common transcription factors. These include the MAPK, PI3K and PLC- γ pathways, cAMP-response-element binding protein (CREB), Src/Fyn, and calcium/calmodulin-dependent protein kinase II (CaMKII) (Scharfman and Maclusky, 2005). Recently, it was found that TrkB further potentiates the effects of estrogen stimulation on ER- α mediated transcription via the MAPK pathway, but signalling via the PI3K pathway inhibited TrkB-dependent transcriptional potentiation at EREs (Wong et al., 2011). This study demonstrates an important reciprocal relationship between BDNF-TrkB and estrogen signalling pathways.

5. Conclusion

A strong body of evidence from clinical and animal data suggests that estrogen signalling is a mediator of sex differences in schizophrenia. Consistent with its trophic effects in the brain, it is hypothesized that some actions of estrogen may be exerted via modulation of BDNF signalling. In this review, we have highlighted involvement of both estrogen and BDNF in schizophrenia and discussed their potential interaction at the functional and molecular level, including specific effects on dopamine, serotonin and glutamate NMDA receptor function. This posited estrogen-BDNF interaction could explain sex-specific findings reported in animal work and help elucidate sex differences in many features of schizophrenia. In addition, the estrogen-BDNF interaction could provide new therapeutic targets.

6. References

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Figure legends

Figure 1

Mechanisms of estrogen-BDNF interaction. Panel A: Estradiol (E2) and BDNF may interact via their converging signalling cascades. E2 binds to membrane estrogen receptors (ER) while BDNF binds to TrkB receptors to activate common MAPK, PI3K, and PLC- γ pathways. These pathways, in turn, activate transcription factors such as CREB which can drive the translation of BDNF to regulate growth, survival and neural plasticity. Alternatively, E2 may bind to classical genomic ER α/β in the nucleus and induce BDNF expression through activation of ERE sites on the BDNF gene. Panel B: Since the colocalization of ERs and BDNF is controversial, it is hypothesized that estrogen may regulate BDNF expression indirectly via disinhibition of ER negative GABAergic interneurons. High E2 levels (red arrow) lead to the stimulation of ER immunoreactive GABAergic interneurons (grey) which innervate other non-ER bearing GABAergic interneurons to decrease their inhibitory activity (blue arrows; surrounding negative signs denote inhibition). These non-ER bearing interneurons innervate BDNF immunoreactive

excitatory pyramidal neurons (orange). Less inhibition may therefore result in increased BDNF synthesis and release (red arrow).

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Figure 2

Summary of the effect of chronic corticosterone (CORT) treatment in the drinking water from 6-9 weeks of age in male and female wildtype (WT) and BDNF heterozygous mice (HET) at 12-15 weeks of age. (A) In the Y-maze, male CORT treated HET did not show any preference towards the novel arm, indicating short-term spatial memory disruption, whereas all other groups showed significantly greater duration of time spent in the novel arm compared to the other two arms (* $P < 0.05$). (B) There were no differences of baseline prepulse inhibition (PPI) between the groups. Treatment with 5 mg/kg of D-amphetamine significantly reduced PPI in all groups (* $P < 0.05$ for main ANOVA effect of drug) but this effect was not different between any of the groups. (C) There were no differences between the groups with respect to baseline locomotor activity or locomotor hyperactivity after injection of 5 mg/kg of amphetamine as measured for two hours post-injection with automated photocell cages. (D) In a novel-object recognition test, female HET showed no

preference for the novel object, indicating a genotype-dependent and sex-specific disruption of recognition memory in these mice. All other groups showed significant preference towards the novel object in a 5-minute retention trial, 1 hour after a 10-minute exploration trial. (E) Body weight was lower in female mice compared to male mice but there were no differences between the experimental groups. For more detailed information on results and methodology, see (Klug et al., 2012, Klug and van den Buuse, 2012). For bar legends in panels D and E, see panels B and C.

Highlights

Estrogen and BDNF have both been implicated in schizophrenia

Estrogen may be protective against schizophrenia by modulating BDNF expression

This may include brain dopaminergic, serotonergic and glutamatergic activity

Estrogen-BDNF interaction could be treatment target in schizophrenia

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