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Neuregulin-1 signalling and antipsychotic treatment: potential therapeutic targets in a schizophrenia candidate signalling pathway

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Neuregulin-1 signalling and antipsychotic treatment: potential therapeutic targets in a schizophrenia candidate signalling pathway

Abstract
Identifying the signalling pathways underlying the pathophysiology of schizophrenia is an essential step in the rational development of new antipsychotic drugs for this devastating disease. Evidence from genetic, transgenic and post-mortem studies have strongly supported neuregulin-1 (NRG1)-ErbB4 signalling as a schizophrenia susceptibility pathway. NRG1-ErbB4 signalling plays crucial roles in regulating neurodevelopment and neurotransmission, with implications for the pathophysiology of schizophrenia. Post-mortem studies have demonstrated altered NRG1-ErbB4 signalling in the brain of schizophrenia patients. Antipsychotic drugs have different effects on NRG1-ErbB4 signalling depending on treatment duration. Abnormal behaviours relevant to certain features of schizophrenia are displayed in NRG1/ErbB4 knockout mice or those with NRG1/ErbB4 over-expression, some of these abnormalities can be improved by antipsychotic treatment. NRG1-ErbB4 signalling has extensive interactions with the GABAergic, glutamatergic and dopaminergic neurotransmission systems that are involved in the pathophysiology of schizophrenia. These interactions provide a number of targets for the development of new antipsychotic drugs. Furthermore, the key interaction points between NRG1-ErbB4 signalling and other schizophrenia susceptibility genes may also potentially provide specific targets for new antipsychotic drugs. In general, identification of these targets in NRG1-ErbB4 signalling and interacting pathways will provide unique opportunities for the development of new generation antipsychotics with specific efficacy and fewer side effects.

Keywords
potential, treatment, antipsychotic, pathway, signalling, candidate, 1, neuregulin, schizophrenia, targets, therapeutic, CMMB

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Keywords: Schizophrenia; neuregulin-1, ErbB4 receptor, antipsychotic, glutamatergic, GABA, dopaminergic, drug target

Abstract

Objectives: *Identifying the signalling pathways underlying the pathophysiology of schizophrenia is an essential step in the rational development of new antipsychotic drugs for this devastating disease. Evidence from genetic, transgenic and post-mortem studies have strongly supported neuregulin-1 (NRG1)–ErbB4 signalling as a schizophrenia susceptibility pathway. NRG1–ErbB4 signalling plays crucial roles in regulating neurodevelopment and neurotransmission, with implications for the pathophysiology of schizophrenia. Postmortem studies have demonstrated altered NRG1–ErbB4 signalling in the brain of schizophrenia patients. Antipsychotic drugs have different effects on NRG1–ErbB4 signalling depending on treatment duration. Abnormal behaviours relevant to certain features of schizophrenia are displayed in NRG1/ErbB4 knockout mice or those with NRG1/ErbB4 over-expression, some of these abnormalities can be improved by antipsychotic treatment. NRG1–ErbB4 signalling has extensive interactions with the GABAergic, glutamatergic and dopaminergic neurotransmission systems that are involved in the pathophysiology of schizophrenia. These interactions provide a number of targets for the development of new antipsychotic drugs. Furthermore, the key interaction points between NRG1–ErbB4 signalling and other schizophrenia susceptibility genes may also potentially provide specific targets for new antipsychotic drugs. In general, identification of these targets in NRG1–ErbB4 signalling and interacting pathways will provide unique opportunities for the development of new generation antipsychotics with specific efficacy and fewer side effects.*

1. INTRODUCTION

Schizophrenia is a devastating psychiatric disorder, affecting 1% of the population worldwide, and ranks among the top ten causes of disability in developed countries (Murray and Lopez 1996). Schizophrenia is clinically characterised by positive symptoms (such as hallucinations and delusions), negative symptoms (such as flat or blunted affect, poverty of speech, and social withdrawal), and cognitive deficits (such as memory deficits, attenuated attention processes, and executive functioning impairment) (Austin 2005). Currently, the symptoms of schizophrenia are principally controlled by pharmacological treatment, i.e., antipsychotic medications that are primarily effective for positive symptoms (Leucht et al. 2009; Vohora 2007). However, current antipsychotics have limited efficacy for negative symptoms and cognitive deficits, and have some severe side effects (Deng et al. 2010; Vohora 2007).

Over the past half century, the discovery and development of antipsychotic drugs were largely dependent on the serendipitous observation of the clinical effects of some compounds, studies on the underlying mechanisms of drug actions, and modifications of previously used drugs for improving efficacy and reducing side effects (Lewis and Gonzalez-Burgos 2006). Unfortunately, these approaches are largely not derived from an understanding of the disease pathophysiology, particularly the aetiology-based molecular pathways of schizophrenia. Although the aetiology and pathophysiology of schizophre nia are still not fully understood, evidence from genetic, post-mortem and animal studies over the past decade have identified a number of susceptibility genes and related pathways for schizophrenia, including neuregulin-1 (NRG1), ErbB4 receptor, disrupted-in-schizophrenia-1 (DISC1), dysbindin-1, catechol-O-methyl transferase (COMT), and Akt (Jaaro-Peled et al. 2009; Karam et al. 2010; Lang et al. 2007). A key question is whether these susceptibility genes and their related pathways have therapeutic potential for the treatment of schizophrenia. Recent evidence suggests that the NRG1–ErbB4 signalling pathway could be a potential target for the development of new generation antipsychotic drugs (Hahn 2011; Karam et al. 2010).

The NRG1–ErbB4 signalling pathway is involved in multiple biological functions in neurodevelopment, including neuronal migration, glial cell development, axon myelination and guidance, dendritic development, and neurotransmitter signalling that have been implicated in schizophrenia (Buonanno 2010; Geddes et al. 2011; Mei and Xiong 2008; Rico and Marin 2011). In fact, the NRG1 and ErbB4 genes have been identified as candidate genes for schizophrenia by many association studies in several ethnic groups (Law et al. 2007; Li et al. 2006; Liu et al. 2005; Lu et al. 2010; Nicodemus et al. 2010; Petryshen et al. 2005; Shiota et al. 2008; Squassina et al. 2010; Stefansson et al. 2003; Williams et al. 2003; Yang et al. 2003); although there are also some contradictory reports (Garcia-Barcelo et al. 2011; Ikeda et al. 2008; Ingason et al. 2006; Jonsson et al. 2009). The studies in both post-mortem brain tissue and blood lymphocytes report altered expression of NRG1 and ErbB4, and their signalling activity in schizophrenic patients (Chong et al. 2008; Hahn et al. 2006; Law et al. 2006; Pan et al. 2011). Studies in transgenic animal models showed that impaired NRG1–ErbB4 signalling leads to behavioural abnormalities relevant to certain features of schizophrenia and that these behavioural deficits could be improved by anti psychotic treatment (Barros et al. 2009; Dejaegere et al. 2008; Kato et al. 2010; Pan et al. 2011; Rimer et al. 2005; Savonenko et al. 2008; Stefansson et al. 2002). Accumulated evidence shows that aberrant NRG1–ErbB4 signalling may contribute to schizophrenia symptoms, particularly positive and cognitive symptoms (Hall et al. 2006; Kang et al. 2012; Roussos et al. 2011; Shamir et al. 2012; Yokley et al. 2012); however, they contribute less to negative symptoms (Rethelyi et al. 2010). In addition, various antipsychotics have different effects on NRG1 and ErbB4 expression and signalling (Pan et al 2011). Accumulated evidence shows that NRG1–ErbB4 signalling is closely interacted with several neurotransmitter pathways (glutamatergic, GABAergic and dopaminergic pathways) that are crucial in the pathophysiology of schizo phrenia and antipsychotic drug efficacy (Buonanno 2010; Lewis and Moghaddam 2006; Neddens et al. 2011; Pitcher et al. 2011). Therefore, NRG1–ErbB4 signalling may provide some important targets for schizophrenia treatment. This article will review the evidence regarding the effects of antipsychotics on alterations in NRG1–ErbB4 function, and provide insight into the potential of the NRG1–ErbB4 signalling pathway as a novel target for the discovery of new antipsychotic drugs.

2. NRG1-ERBB4 SIGNALLING AND ITS INVOLVEMENT IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

2.1 The structures of NRG1 proteins and the downstream signalling pathways

NRG1 is among a family of growth and differentiation factors encoded by four individual genes (NRG1-4). The NRG1 gene generates at least 31 isoforms in humans, presumably due to multiple promoters and alternative splicing, that can be grouped into six types of proteins with different structures and distinct functional properties. Most NRG1 isoforms possess an EGF-like domain, located in the membrane-proximal area of the extracellular part. There are two types of EGF-like domain: α-type EGF-like domain and β-type EGF-like domain. In the NRG1 types I, II, IV and V isoforms, an immunoglobulin (Ig)-like domain connects with the N-terminal sequence and the EGF-like domain. However, the type III isoforms contain a cysteine-rich domain (CRD) that has an additional transmembrane domain (TMN). The N-terminal sequence of NRG1 types III and VI is connected directly to the EGF-like domain. The EGF-like domain is connected with a C-terminal cytoplasmic tail (for review, see Mei and Xiong 2008). Most NRG1 proteins are generated by proteolytic processing (ectodomain shedding) of membrane-anchored precursors (pro-NRG1s) at the membrane-proximal region that lies on the C-terminal side of the extracellular part, which is regulated by three type I transmembrane proteases: tumor necrosis factor-α converting enzyme (TACE, also known as ADAM17) (Montero et al. 2007), β-site of amyloid precursor protein cleaving enzyme (BACE, also known as memapsin 2) (Hu et al. 2006; Willem et al. 2006) and meltrin β (also known as ADAM19) (Wakatsuki et al. 2004; Yokozeki et al. 2007). Eventually diffusible, mature NRG1 proteins are released into the extracellular space (except in the case of NRG1 type III) (Falls 2003). The remaining intracellular membrane-bound NRG1 fragment can be cleaved by Aph1B/C-γ-secretase, generating an intracellular domain that can relocate into the nucleus and regulate gene transcription (Bao et al. 2003).

Diffusible NRG1 binds with a family of type I transmembrane receptor tyrosine kinases called ErbB proteins, including ErbB2, ErbB3 and ErbB4 (Bublil and Yarden 2007). The ErbB protein family consists of four members that are EGF receptors (EGFR), known as ErbB1, ErbB2, ErbB3 and ErbB4. Upon the stimulation of NRG1, ErbB proteins are dimerised to form several types of homodimers (e.g., ErbB4–ErbB4) and heterodimers (e.g., ErbB2–ErbB3, ErbB2–ErbB4 and ErbB4-EGFR) (Falls 2003; Mei and Xiong 2008). NRG1 does not bind to ErbB1 and ErbB2. EGFR, encoded by the ERBB1 gene, cannot bind to NRG1, but forms an activated heterodimer with ErbB4. ErbB2, encoded by the ERBB2 gene, also functions as a coreceptor by forming heterodimers with ligand-bound ErbBs (Falls 2003; Mei and Xiong 2008). The other two ErbB proteins, ErbB3 and ErbB4, can bind to NRG1, in which ErbB4 homodimers can both interact with NRG1 and become activated by it as a tyrosine kinase (Falls 2003; Mei and Xiong 2008). On the other hand, although ErbB3 has been previously considered as kinase-inactive (Falls 2003; Yarden and Sliwkowski 2001), a recent report showed that the ErbB3 kinase domain is competent to bind ATP and catalyse autophosphorylation (Shi et al. 2010). Compared to ErbB3 homodimers (inactive) or ErbB4 homodimers that signal only weakly, ErbB3/ErbB2 and ErbB4/ErbB2 heterodimers contribute to prolonged and enhanced downstream signalling (Yarden and Sliwkowski 2001). The ErbB3 and ErbB4 protein are encoded by the ERBB3 and ERBB4 genes, among them ERBB4 gene has been considered as a

susceptibility gene for schizophrenia (Garcia et al. 2000; Law et al. 2007; Nicodemus et al. 2006; Shiota et al. 2008; Silberberg et al. 2006). Although the ERBB3 gene has also been considered as a potential schizophrenia candidate gene (Li et al. 2009a), the association of the ERBB3 gene with schizophrenia has not been confirmed in several studies (Kanazawa et al. 2007; Li et al. 2009b). Therefore, this review will focus on NRG1 signalling through the ErbB4 receptor. An ErbB4 protein contains two extracellular CRDs, a TMN, an intracellular juxtamembrane (JM) region, a tyrosine kinase domain and a C-terminal cytoplasmic tail (CYT) (Mei and Xiong 2008).
NRG1s with the β-type EGF-like domain have a higher affinity to ErbB receptors (especially the ErbB4 receptor) than NRG1s with the α-type EFG-like domain (Jones et al. 1999; Tzahar et al. 1994; Wen et al. 1994) and promotes the phosphorylation of ErbB receptors 10 times more effectively than NRG1α (Pinkas-Kramarski et al. 1996). In addition, a report by Falls (2003) stated that NRG1β isoforms are 10–100 times more potent than NRG1α isoforms, and that NRG1α is mostly involved in breast development. Therefore, NRG1β isoforms are more likely to be associated with the pathophysiology of schizophrenia than NRG1α isoforms. NRG1 stimulus leads to dimerisation and kinase activation of the ErbB4 receptor, resulting in autoand trans-phosphorylation of the intracellular domains, which activates several signalling pathways. For example, NRG1-induced stimulation of ErbB4 receptor frequently activates the PI3K (phosphatidyl inositol-3-kinase)– Akt–S6K pathway. ErbB4 CYT-1 contains a PI3K-binding site that binds the p85 subunit of PI3K and activates this kinase, which in turn phosphorylates and activates downstream Akt and S6K (Mei and Xiong 2008). The PI3K–Akt–S6K pathway mediates NRG1-induced cell survival, and neuronal and synaptic development (Junttila et al. 2000; Kainulainen et al. 2000; Krivosheya et al. 2008). By acting through the ErbB4-EGFR heterodimer, NRG1 can activate Src family kinases, PLCγ, c-Abl and JNK. Furthermore, NRG1 also activates the Raf-MAPK (mitogen activate protein kinase) pathway (Mei and Xiong 2008).

2.2 Pathological alterations of NRG1-ErbB4 signalling in schizophrenia patients

Both post-mortem studies and behavioural studies in animal models have suggested abnormalities of the NRG1–ErbB4 pathway in schizophrenia (Pan et al. 2011). Several postmortem studies have found an increase in the mRNA expression of NRG1 type I in the prefrontal cortex (PFC) (Hashimoto et al. 2004) and the hippocampus (Law et al. 2006); moreover, an increase of the protein level of the NRG1 intracellular part in the PFC has also been reported (Chong et al. 2008). However, Hashimoto et al. (2004) have shown a decrease in the ratios of type II/I and type II/III mRNA expressions (i.e., a relatively decreased expression of NRG1 type II) (Hashimoto et al. 2004). A study in elderly individuals with schizophrenia has indicated an increased NRG1 type II expression but decreased NRG1 type I expression in the PFC (Brodmann area [BA] 10) (Parlapani et al. 2010). Additionally, Bertram and colleagues (2007) have found using immunohistochemistry and Western blot analysis that the NRG1α isoform is decreased in the white and grey matter of the PFC (Bertram et al. 2007). Barakat et al. (2010) reported that the full-length type III NRG1 precursor did not differ between individuals with schizophrenia and healthy controls, but the levels of NRG1 type III C-terminal fragment significantly decreased in the BA6 of schizophrenia patients (Barakat et al. 2010). Abnormal expression of NRG1 has also been reported in the periphery, although the results were not consistent. For example, the expression levels of NRG1 transcript variants in type I and type III isoforms were significantly increased in peripheral blood lymphocytes (PBLs) in

schizophrenia (Petryshen et al. 2005), whereas a decrease in NRG1 mRNA expression in PBLs and serum NRG1 immunoreactivity were reported by other studies (Shibuya et al. 2010; Zhang et al. 2008, 2011). Decreased peripheral NRG1 mRNA in PBLs has been found in high-risk individuals who later developed psychosis (Kiss et al. 2012). However, a recent study reported no difference in expression of NRG1 mRNA in immortalized lymphocytes between schizophrenia and control subjects (Yamamori et al. 2011). It is worth noting that treatment with the antipsychotics risperidone and quetiapine has been reported to increase NRG1 mRNA expression in PBLs in first-onset schizophrenia patients (Zhang et al. 2008, 2011).

ErbB4 receptor expression has also been shown to be abnormal in post-mortem brain studies. Increases in the protein expression of both the full-length ErbB4 receptor and the isoforms containing CYT-1 domain have been reported in the PFC of schizophrenia patients (Chong et al. 2008; Silberberg et al. 2006). In addition, the mRNA expression of isoforms containing CYT-1 domain and a JM-a domain was also increased in the dorsal PFC of schizophrenia patients (Law et al. 2007). Hahn et al. (2006) found that, although the expression of both NRG1 and ErbB4 receptors was not significantly changed in the PFC of schizophrenia subjects, a marked increase in NRG1-induced activation of the ErbB4 receptor and activity of its downstream signalling components were observed in patients with schizophrenia (Hahn et al. 2006). Although the results are not completely consistent, the majority of studies demonstrate elevated NRG1–ErbB4 signalling in the brain of individuals with schizophrenia (Pan et al. 2011). Furthermore, whether there are developmental differences in NRG1–ErbB4 signalling in patients with psychotic symptoms has not been investigated.

In brief, while not completely consistent, current data from studies in post-mortem brain tissue and PBLs have demonstrated altered NRG1–ErbB4 signalling in schizophrenia. It is worth noting that there are a number of limitations to these studies. Firstly, many reports focused on relative mRNA levels without attempting to address the possible biological significance of the observed difference. For example, what might be the biological relevance of the minor changes in the expression of NRG1 type I and ErbB4 reported previously (Chong et al. 2008; Hashimoto et al.2004)? How might isoform-specific changes in expression affect function that could lead to pathophysiological changes associated with schizophrenia? Recently, Liu et al. (2011) reported the expression of specific NRG1 isoforms in the human and rat post-mortem brain with quantitative data in copies/μg total RNA in addition to normalization of mRNA levels to β-actin (Liu et al. 2011). This provides an important way to further quantitatively analyse of specific NRG1 isoform expression as well as to compare relative ratios to housekeeping genes in schizophrenia postmortem studies. In addition, there are also problems in specificity of antibodies against specific NRG1 isoforms and ErbB4 receptors in terms of interpretation of protein expression in post-mortem tissue (Bare et al. 2011; Fazzari et al. 2010; Vullhorst et al. 2009). Therefore, future postmortem studies using better quality controlled reagents and quantitative measures are required in order to interpret the results and reveal how NRG1–ErbB4 signalling contributes to the pathophysiology of schizophrenia.

2.3 Evidence from studies of transgenetic models with NRG1/ErbB4 knock-out and overexpression relevant to schizophrenia

Along with the findings from post-mortem studies, animals with abnormal NRG1–ErbB4 functioning display behavioural deficits that resemble the symptoms of schizophrenia, including hyperactivity in the novel open-field test and the alternating-Y maze (Barros et al. 2009; Chesworth et al. 2012; Duffy et al. 2008, 2010; Gerlai et al. 2000; Karl et al. 2007; Kato et al. 2010; O'Tuathaigh et al. 2007; Rimer et al. 2005; Stefansson et al. 2002; van den Buuse et al. 2009), deficits in prepulse inhibition (PPI) level (Barros et al. 2009; Chen et al. 2008; Deakin et al. 2009; Dejaegere et al. 2008; Hong et al. 2008; Kato et al. 2010; Savonenko et al. 2008; Stefansson et al. 2002; van den Buuse et al. 2009), and lateral inhibition (Rimer et al. 2005), as well as impaired social activity (Kato et al. 2010; O'Tuathaigh et al. 2007). These transgenic animal models have targeted mutiple mutations in NRG1 genes and the proteolytic processing and cleavage of NRG1 proteins, including mutation or deletion of the Ig-like domain (Rimer et al. 2005), TMN domain (NrgTM) (Chesworth et al. 2012; Karl et al. 2007; O'Tuathaigh et al. 2007; Stefansson et al. 2002), type I (Deakin et al. 2009) and type III of NRG1 (Chen et al. 2008), Aph1B/C-γ-secretase (Dejaegere et al. 2008), and BACE1 (Savonenko et al. 2008). It is worth noting that animals with either reduced (O'Tuathaigh et al. 2010; van den Buuse et al. 2009) or excessive expression (Deakin et al. 2009; Kato et al. 2010) of the NRG1 gene showed similar behavioural deficits. Recently, a knock-out mouse model with ErbB4 ablation specifically in the parvalbumin (PV)positive interneurones (PV-ErbB4−/−) was reported to exhibit schizophrenia-relevant phenotypes similar to those observed in NRG1 or ErbB4-null mutant mice (Chen et al. 2010a; Wen et al. 2010). Together, these studies support the hypothesis that abnormal NRG1–ErbB4 signalling is a potential factor for the behavioural phenotypes of schizophrenia. Moreover, in these models, behavioural phenotypes induced by altered NRG1–ErbB4 signalling are different depending on the mutant domains of proteins, age and gender of animals, and the biological context of the dysregulation (Desbonnet et al. 2009). For example, male NrgTM mice displayed stronger behavioural deficits than female mutants in decreased response to the locomotor-activating effects of acute PCP treatment (O'Tuathaigh et al. 2010), in social withdrawal-like effects of Δ9-tetrahydrocannabinol treatment (Long et al. 2010a,b), and in fear conditioning and recognition of a previously encountered object (Chesworth et al. 2012; Duffy et al. 2010). Sex-specific phenotypic effects were also observed in exploratory and habituation behaviours: female NrgTM mice showed an increase in walkovers and shifting of cage bedding, while male mutants exhibited reduced grooming (O'Tuathaigh et al. 2006, 2008). On the other hand, hypomorphic type II NRG1 (NrgTn) male rats failed to habituate to an open field, while female NrgTn rats exhibited reduced locomotor activity and enhanced habituation to a novel environment; and only female NrgTn rats had impaired PPI (Taylor et al. 2011). Therefore, these results imply that specific personalised treatment may be developed according to the different biological status of patients, although it also implies that the treatment may be ineffective for patients of certain genotypes, ages and genders.

3. INTERACTIONS BETWEEN NRG1-ERBB4 SIGNALLING AND NEUROTRANMISSION: RELATING TO THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

3.1 The role of NRG1-ErbB4 signalling in neurodevelopment in relation to schizophrenia

It has been largely accepted that schizophrenia arises as a consequence of abnormal brain development (Fatemi and Folsom 2009; Jaaro-Peled et al. 2009). NRG1 and ErbB4 are highly expressed in the developing brain (Buonanno 2010; Liu et al. 2011). NRG1 transcripts in the brain are expressed at their highest during embryonic, fetal and early postnatal periods, and expression decreases with age (Buonanno 2010). Considerable evidence has indicated that NRG1–ErbB4 signalling plays critical roles in developmental processes, such as radial glia formation and neuronal migration (Anton et al. 1997; Rio et al. 1997; Yau et al. 2003), glial cell development, axon myelination and axon ensheathment (Calaora et al. 2001; Canoll et al. 1996; Michailov et al. 2004; Nave and Salzer 2006; Schmucker et al. 2003; Taveggia et al. 2005), axon guidance (Bermingham-McDonogh et al. 1996; Gerecke et al. 2004; Lopez-Bendito et al. 2006; Rieff et al. 1999), and dendritic development (Chen et al. 2010b; Gerecke et al. 2004; Rieff and Corfas 2006). NRG1 also affects the development of the dopaminergic system and GABAergic interneurones (Balu and Coyle 2011; Fazzari et al. 2010; Rico and Marin 2011; Roy et al. 2007). For example, peripheral NRG1 administration in neonatal mice activates midbrain ErbB4 receptors and elevates the expression, phosphorylation and activity of tyrosine hydroxylase (TH). This results increases in the level of dopamine and dopamine release, and induces a persistent hyper-dopaminergic state and behavioural impairments in prepulse inhibition, latent inhibition, social behaviours and hypersensitivity to methamphetamine (Kato et al. 2011). NRG1–ErbB4 signalling is critical for the development of inhibitory circuitries and the wiring of GABA-mediated circuits in the postnatal cerebral cortex (Fazzari et al. 2010). Therefore, this evidence further supports the involvement of impaired NRG1–ErbB4 signalling in the development of schizophrenia.

3.2 Effects of NRG1-ErbB4 signalling on synaptic plasticity and neurotransmission in the adult brain in relation to schizophrenia

3.2.1 Interaction between NRG1-ErbB4 signalling and dopaminergic neurotransmission

Dopaminergic dysfunction is one of the most widely accepted neurochemical hypotheses of schizophrenia. It postulates that excess dopaminergic transmission in the mesolimbic and striatal regions, and dopaminergic deficits in prefrontal regions, are responsible for the positive symptoms and negative symptoms of schizophrenia, respectively (Lang et al. 2007). Similarly, Kwon et al. (2008) found that intracerebral infusion of NRG1β into the hippocampus increased extracellular dopamine levels (Kwon et al. 2008). Direct intracerebral infusion of NRG1β into the substantia nigra (SN) evokes an almost immediate overflow of striatal dopamine (Yurek et al. 2004). Since ErbB4 receptors are mainly expressed on the dopamine neurons in the SN, these results suggested that NRG1 can directly modulate the activity of mesostriatal dopaminergic neurons (Abe et al. 2009; Zheng et al. 2009). Carlsson et al. (2011) found that dopamine levels increased in the SN and the striatum of adult mice after systemic administration of NRG1β (Carlsson et al. 2011). Together, these studies

consistently demonstrate that promoted NRG1 signalling is capable of increasing TH levels and dopamine release, enhancing dopaminergic neurotransmission.

3.2.2 Interactions between NRG1-ErbB4 signalling and glutamatergic neurotransmission

considerable amount of research has demonstrated that the ionotropic glutamate receptor N-methyl-D-aspartate (NMDA) plays a critical role in the pathogenesis of schizophrenia, and that hypofunction of NMDA receptors is a major mechanism underlying the pathophysiology of schizophrenia (Kantrowitz and Javitt 2010; Lewis and Gonzalez-Burgos 2006). NMDA receptors are composed of a heterometric assembly of subunits (NR1, NR2 and NR3), where the NR2 subunit shares a common anchoring protein in the post synaptic density (PSD) with the ErbB4 receptor (Chen et al. 2006; Cousins et al. 2009; Geddes et al. 2011). Accumulated evidence supports that NRG1–ErbB4 signalling is capable of regulating the function of the NMDA receptor through the NR2/PSD/ErbB4 complex. For example, MK-801 binding is decreased in the PFC of mice with NRG1 EGF-domain mutation, implying reduced expression of NMDA receptors (Stefansson et al. 2002). Gu and colleagues (2005) reported that NMDA receptor currents and channel activity were significantly decreased in the PFC after perfusion of NRG1, suggesting that elevated NRG1 signalling compromises NMDA function (Gu et al. 2005). Additionally, decreased NR2C expression was found in individuals with schizophrenia that had an NRG1 polymorphism, suggesting deficits in NMDA receptor function (Schmitt et al. 2010).

Hahn et al. (2006) have found that increased NRG1–ErbB4 signalling (enhanced association of ErbB4 receptors with both PSD-95 and the NR1 subunits) was associated with suppressed NMDA receptor activation (reduced phosphorylation of NR2A subunits) in schizophrenia (Fig. 1) (Hahn et al. 2006). It has also been reported that the activation of Src kinases enhances NMDA receptor channel activity and mediates the phosphorylation of NMDA subunits (Yu et al. 1997). This Src-mediated enhancement of synaptic NMDA function could be suppressed by NRG1–ErbB4 signalling through PSD-95, causing hypofunction of NMDA receptors in pyramidal neurons in the PFC and hippocampus under a preparation of blocked GABA neurotransmission; and NRG1–ErbB4 signalling prevents the theta burst-induced phosphorylation of NR2B by inhibiting Src kinase activity (Pitcher et al. 2011). On the other hand, through activation of Fyn and Pyk2 kinases, NRG1–ErbB4 signalling can stimulate phosphorylation of the NR2B subunit of the NMDA receptors (Bjarnadottir et al. 2007).

3.2.3 Interaction between NRG1-ErbB4 signalling and GABAergic neurotransmission

Accumulated evidence supports the contribution of abnormal GABAergic neurotransmission in the pathophysiology of schizophrenia (Benes 2009; Deng and Huang 2006; Lewis and Gonzalez-Burgos 2006). NRG1–ErbB4 signalling plays a critical role in GABAergic interneuron plasticity and transmission. For example, Chen et al. (2010a) found that NRG1 increased GABAA receptor-mediated synaptic currents in CA1 pyramidal cells. NRG1 also increases evoked release of GABA in the PFC by directly activating ErbB4 receptors on presynaptic terminals (Woo et al. 2007). Moreover, impaired NRG1–ErbB4 signalling may induce a reduction of GABA release, resulting in abnormal synchronisation of pyramidal cells, which is related to deficits in working memory in schizophrenia (Lewis and Moghaddam 2006). Another study found that NRG1 increases the function of GABAergic interneurons in

vitro by promoting the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs), which supports the in vivo finding that mice with deletion of ErbB4 receptors in parvalbumin-positive interneurons displayed reduced frequency and amplitude of mEPSCs in interneurones (Ting et al. 2011).

3.3 A key role for NRG1-ErbB4 signalling in integrating dopamine, GABA and glutamate neurotransmission in relation to the pathophysiology of schizophrenia

Given that dopamine, GABA and glutamate systems are responsible for the pathophysiology of schizophrenia and are regulated by NRG1–ErbB4 signalling, a key question is whether NRG1–ErbB4 signalling plays a crucial role in integrating these systems? Also, how does this integrative role contribute to the pathophysiology of schizophrenia? A critical step towards addressing these questions is to identify the precise locations of ErbB4 receptors. A role for NRG1– ErbB4 signalling in glutamatergic transmission between pyramidal cells in the cortex and hippocampus was previously assumed (Barros et al. 2009; Bjarnadottir et al. 2007; Kwon et al. 2005; Mei and Xiong 2008). However, these reports were based on the discovery of ErbB4 expression in pyramidal neurons in the cortex using in situ hybridisation and immunohistological methods with low-specificity antibodies (Bernstein et al. 2006; Thompson et al. 2007), as well as an association between ErbB4 and PSD-95 (Garcia et al. 2000; Huang et al. 2000). A study using whole-cell recording in slice preparations found that NRG1β suppresses Src-mediated EPSP in the pyramidal neurons of mouse hippocampus and prefrontal cortex with blocked GABA neurotransmission, and this effect was not observed in ErbB4 mutant mice (Erbb4−/−HER4heart). This suggested that ErbB4 receptors are required for suppression of Src-mediated EPSP in the pyramidal neurons by NRG1β in this experiment (Pitcher et al. 2011). However, other studies using single cell analysis of electrophysiologically characterised neurons combined with high-specificity antibodies have provided evidence of a lack of ErbB4 expression in any pyramidal cells in the cortex and hippocampus (Fazzari et al. 2010; Neddens and Buonanno 2010; Neddens et al. 2011). Instead, ErbB4 receptors are expressed predominately on the GABA interneurons in the frontal cortex (Neddens et al. 2011), primarily (>98% in the cortex) on the PV-positive interneurons, including basket and chandelier cells that innervate the somata and the axon initial segment of pyramidal cells, respectively (Fig. 1). Small numbers of ErbB4 receptors are expressed on calbindin-positive interneurons that innervate the dendritic region of pyramidal cells (Fazzari et al. 2010; Neddens et al. 2011). According to Neddens et al. (2011), ErbB4 receptors were not detected at the presynapses in any GABA interneurons but are highly expressed postsynaptically at glutamatergic synapses, where it binds to PSD-95 in GABAergic interneurons (Fig. 1). These postsynaptic ErbB4 receptors regulate the formation and/or maintenance of excitatory synapses onto GABAergic interneurons and neuronal network activity (Cooper and Koleske 2011; Fazzari et al. 2010; Neddens et al. 2011). In fact, recent studies have clearly shown that NRG1 regulates pyramidal neuron activity and long-term potentiation (LTP) completely via ErbB4 in PV-positive interneurons in the frontal cortex and hippocampus (Chen et al. 2010a; Wen et al. 2010). It is worthy of note that ErbB4 expression is significantly higher in the ventral than the dorsal hippocampus of mice (Neddens and Buonanno 2010). Consistently, NGR1 type III hypomorphic mice display disrupted activity in ventral hippocampal-accumbens transmission (Nason et al. 2011), and subchronic peripheral NRG1 treatment selectively increases neurogenesis in the ventral hippocampus

(Mahar et al. 2011). In consideration of the fact that neonatal ventral hippocampus lesions are a well-recognised model of schizophrenia (Lipska et al. 2003; Tseng et al. 2009), NRG1–ErbB4 signalling may interact with pyramidal cells and GABA interneurons predominately through the ventral hippocampus. Furthermore, the predominant location of ErbB4 receptors on PV-positive GABA interneurons in the cortex and hippocampus is conserved across species from rodents to primates including humans, which supports the relevance of rodents as an appropriate model to study the mechanisms of NRG1–ErbB4 signalling in the pathophysiology of schizophrenia (Cooper and Koleske 2011; Neddens et al. 2011).

NRG1 elicits a prolonged release of dopamine in the adult hippocampus, which in turn suppresses or reverses LTP at hippocampal glutamatergic synapses (Kwon et al. 2008). Conversely, blockade of ErbB receptors produces a small but significant decrease in dopamine release in the dorsal hippocampus of rats (Neddens et al. 2009). Therefore, NRG1 may regulate hippocampal dopamine release by acting at ErbB4 receptors on dopamine terminals. However, since ErbB4 receptors are primarily expressed on GABAergic interneurons in the hippocampus (as discussed above), it is likely that NRG1-induced dopamine release may be through the action of GABAergic interneurons (Balu and Coyle 2011; Kwon et al. 2008). Since both the cortex and hippocampus are innervated by dopaminergic fibres from the ventral tegmental area (VTA), an alternative mechanism is that NRG1 may regulate dopamine release in the cortex and hippocampus by modulating VTA dopamine neurons. In fact, ErbB4 receptors are located in VTA and SN dopamine neurons of monkeys and humans (Thompson et al. 2007; Zheng et al. 2009). A recent study in rats reported that 66–78% of cells expressing mRNA for ErbB4 are positive for TH in the VTA and SN pars lateralis, and an even higher (94–96%) number of neurons in the SN pars compacta coexpress ErbB4 mRNA and TH (Abe et al. 2009). However, ErbB4 mRNA reportedly does not colocalise with PV immunoreactivity in both the VTA and SN (Abe et al. 2009). These results suggest that NRG1–ErbB4 signalling in the midbrain may regulate the activity of excitatory glutamatergic synapses onto dopaminergic neurons directly, but not through PV-positive interneurones (Fig. 1). Further studies are required to examine whether NRG1–ErbB4 signalling regulates midbrain dopamine neurons through other types of GABA interneurons, and whether it regulates midbrain dopamine neurons through other brain regions.

The evidence discussed above supports the integral role for NRG1–ErbB4 signalling in glutamatergic, GABAergic and dopaminergic neurotransmission; the question is how this signalling pathway contributes to the pathophysiology of schizophrenia? Recently, NRG1–ErbB4 signalling was reported to suppress Src-mediated increase of synaptic NMDA transmission (Pitcher et al. 2011). In view of the fact that NRG1–ErbB4 signalling is altered in the brain of schizophrenic patients (Bertram et al. 2007; Chong et al. 2008; Hahn et al. 2006; Hashimoto et al. 2004; Law et al. 2006; Pan et al. 2011), the altered NRG1–ErbB4 signalling may induce functional changes of the NMDA receptor via the Src pathway. In the case of elevated NRG1–ErbB4 signalling, as shown in many post-mortem brain studies (reviewed above), it may induce NMDA receptor hypofunction via the Src pathway, which may act directly on pyramidal neurons or indirectly through GABAergic interneurons (Fig. 1) (Hahn 2011; Pitcher et al. 2011). However, it should also be noted that some studies reported a decreased expression of NRG1 (Bertram et al. 2007; Hashimoto et al. 2004). As discussed above, NRG1–ErbB4 signalling can activate Fyn and Pyk2 kinases leading to increased

NMDA NR2B phosphorylation (Bjarnadottir et al. 2007), whereas hypofunction of NRG1–ErbB4 signalling will cause decreased activation of Fyn and Pyk2 kinases and NMDA phosphorylation, resulting abnormal modulation of glutamatergic neurotransmission. This may also partly contribute to the pathophysiology of schizophrenia (Bjarnadottir et al. 2007). Therefore, both increased and decreased NRG1–ErbB4 signalling may lead to NMDA hypofunction. As presented in Fig. 1, NMDA hypofunction may lead to deficits in GABAergic transmission by down-regulating GAD67 (67-kDa isoform of glutamic acid decarboxylase) and decreasing GABA production, which in turn cause further decreased excitatory activity of pyramidal cells in the frontal cortex and ventral hippocampus. In fact, GAD67 was decreased in ErbB4 knockout mice (Neddens and Buonanno 2010). Both NMDA hypofunction and decreased excitatory projections from the frontal cortex/hippocampus may lead to deficits of dopaminergic transmission in the midbrain, which may affect pyramidal activity. The interactions between NRG1–ErbB4 signalling and neurotransmission pathways may not only contribute to the pathophysiology of schizophrenia, but also provide potential targets for schizophrenia medication (see below).

4. THE EFFECTS OF ANTIPSYCHOTIC TREATMENT ON NRG1-ERBB4 SIGNALLING

Individuals with schizophrenia that have different NRG1 genotypes respond differently to typical antipsychotic drugs (Kampman et al. 2004). However, to date, there has been no systematic investigation on the effects of antipsychotic treatment on NRG1–ErbB4 signalling, even though several studies have reported antipsychotic drugs affect protein levels and mRNA expression of NRG1 and the ErbB4 receptor in both animals and humans. An in vivo study using haloperidol, clozapine and risperidone for 4 weeks in rats reported that haloperidol increased the protein levels of total NRG1 and ErbB4 receptors, while clozapine reduced the protein expression of NRG1 in the PFC; however all three antipsychotic drugs increased NRG1 and ErbB4 protein expression in the hippocampus (Wang et al. 2008). On the other hand, 12-week treatment with haloperidol significantly reduces NRG1-induced ErbB4 activation in the PFC of mice (Hahn et al. 2006). Additionally, protein expression of NRG1 in the human fetal brain aggregates (in vitro) was increased following a 3-week exposure to clozapine, but not after haloperidol treatment (Chana et al. 2009). Furthermore, 2-week treatment with risperidone and quetiapine significantly increases NRG1 mRNA expression in PBLs in first-onset schizophrenia patients (Zhang et al. 2008, 2011). However, NRG1 type I protein in monkey serum did not change after 8-week treatment with haloperidol (Shibuya et al. 2010). Together, these studies show a trend where short-term treatment with antipsychotics (up to 4 weeks) increases the expression (mRNA or protein) of NRG1 and ErbB4 receptors, while prolonged antipsychotic treatment may decrease their expression. However, different experimental conditions (i.e., different antipsychotics and various types of tissue tested) may explain the contrasting findings reported in these studies. Furthermore, although all current antipsychotic drugs target dopamine D2 receptors, they do have different pharmacological profiles. For example, although haloperidol, risperidone, clozapine and quetiapine are D2 antagonists, haloperidol (Ki=2.6) and risperidone (Ki=3.77) have much higher binding affinities to D2 receptors than clozapine (Ki=210) and quetiapine (Ki=770) (Correll 2010). On the other hand, clozapine displays high affinity to 5-HT2A (Ki=2.59) and 5-HT2C (Ki=4.8) receptors, while

risperidone has a high affinity to 5-HT2A (Ki=0.15) and moderate affinity to 5-HT2C (Ki=32), and quetiapine has a moderate affinity to 5-HT2A (Ki=31), but no affinity to 5-HT2C (Ki=3500) (Correll 2010). It has been suggested that antagonism of serotonin 5-HT2A, 2C receptors (which interact with dopamine D2 receptor antagonism), is a mechanism to achieve clinical efficacy of atypical antipsychotic drugs (Mathews and David 2007; Meltzer and Massey 2011). Therefore, the differential effects of various antipsychotic drugs on NRG1–ErbB4 expression may partly be explained by their distinct pharmacological profiles.

Antipsychotic drugs can not only affect NRG1–ErbB4 signalling, but are also able to reverse abnormal behaviours in animal models of schizophrenia with impaired NRG1– ErbB4 signalling. For example, clozapine is effective at reversing the hyperactivity in TMN domain mutant mice (Stefansson et al. 2002), Ig-like domain mutant mice (Dejaegere et al. 2008), BACE1-knockout mice (Savonenko et al. 2008) and ErbB4-deficient animals (Barros et al. 2009). Clozapine is also effective at normalising abnormal lateral inhibition in NRG1 Ig-like domain mutant mice (Rimer et al. 2005). Furthermore, PPI deficits can be improved by both haloperidol and clozapine in Aph1B/C-γ-secretase-disturbed mice (Dejaegere et al. 2008), and by clozapine in BACE1-knockout mice (Savonenko et al. 2008) and ErbB4-deficient mice (Barros et al. 2009). A recent study has reported that PPI deficits caused by neonatal treatment of NRG1 could be ameliorated by chronic treatment of risperidone (Kato et al. 2011). Although the mechanism underlying antipsychotic corrections of these behavioural deficits is not clear, it is likely to be via modulation of the interactions between NRG1–ErbB4 pathways and neurotransmission pathways. For example, several studies have shown that phosphorylation of the NR2B subunit was inhibited in mice with TMN domain NRG1+/− mutation and ErbB4+/− mutation, and this defect could be reversed by clozapine treatment (Bjarnadottir et al. 2007; Moghaddam 2003).

5. NRG1 AS A POTENTIAL THERAPEUTIC TREATMENT FOR PSYCHOTIC SYMPTOMS

As described above, several mutations in NRG1–ErbB4 signalling genes are associated with different clinically relevant phenotypes, such as prepulse inhibition, startle habituation, working memory, frontal lobe activation, and alterations in other cognitive functions (Greenwood et al. 2012; Hall et al. 2006; Konrad et al. 2009; Munafo et al. 2006; Yokley et al. 2012). Therefore, there is potential for the use of NRG1 as a novel treatment option for patients with psychotic symptoms. Two proof-of-concept studies for NRG1 treatment have been published by two independent laboratories, confirming that peripherally administered NRG1 can pass the blood–brain barrier, most likely via a receptor-mediated transport mechanism (Kastin et al. 2004; Rösler et al. 2011). The rapid uptake of peripheral NRG1 enables time-sensitive treatment schedules, making NRG1 available both for acute and long-term treatment schemes, as shown by neuroprotective effects following intravascular administration in acute stroke models (Xu et al. 2004, 2006).

Animal studies have highlighted the time-sensitive effect of NRG1 administration on neurodevelopment and behaviours. The long-lasting effects of postnatal NRG1 treatment have been assessed by Kato et al. (2011), who peripherally administered NRG1 to newborn mice from postnatal days (PND) 2–10, which triggered an

immediate increase in dopamine content and TH phosphorylation in the frontal cortex, and a similar increase in the striatum at PND 11, with no changes in glutamatergic or GABAergic neurotransmitter system proteins (Kato et al. 2011). The increase in NRG1 activity during the corticolimbic fibre growing period resulted in long-lasting effects beyond adolescence. The dopaminergic system remained altered with increased dopamine metabolite levels in the adult frontal cortex and increased dopamine release in this area (Kato et al. 2011). NRG1-treated mice displayed reduced social interaction in adulthood as well as a lack of latent inhibition and impaired PPI (Kato et al. 2011).

In contrast to the harmful consequences of NRG1 exposure during the developmental period, three recent studies observed a potentially beneficial effect of NRG1 administration during adulthood. Adult mice receiving subcutaneous NRG1 for 3 days showed increased cell proliferation and neurogenesis in the hippocampal dentate gyrus as well as improved performance in the forced swim test (Mahar et al. 2011). The antidepressant-like effect of NRG1 treatment appears to be the consequence of an increase in neurogenesis, with the behavioural differences only visible 4 weeks after treatment cessation and not acutely after administration (Mahar et al. 2011). Recent work on a mouse model for Parkinson's disease provides further evidence for potentially beneficial neurotrophic effects of peripheral NRG1 administration (Carlsson et al. 2011). Modelling the reduction of mesencephalic dopaminergic neurons in patients with Parkinson's disease, Carlsson and colleagues injected NRG1 intraperitoneally (i.p.) to adult mice for 8 days immediately after a neurotoxin 6-OHDA injection into the striatum (Carlsson et al. 2011). Instant treatment onset (6 h after 6-OHDA) of NRG1 attenuated the decrease of dopamine producing neurons in the SN as well as lesion-related behavioural changes (Carlsson et al. 2011). Although no clinical trial has been conducted to test the potential of NRG1 as a treatment option for psychosis in humans, two recent successful phase II chronic trials using NRG1 to treat heart failure strongly support the safety and tolerability of NRG1 treatment in a clinical setting (Gao et al. 2010; Jabbour et al. 2011).

6. POTENTIAL TARGETS IN NRG1-ERBB4 SIGNALLING AND RELATED PATHWAYS FOR NEXT GENERATION OF ANTIPSYCHOTIC DRUGS

As discussed, significant progress has been achieved over the past several years towards revealing the mechanistic roles of NRG1–ErbB4 signalling in the pathophysiology of schizophrenia. These findings have identified potential targets that provide insights for the development of a new generation of antipsychotic drugs. Firstly, the recent finding that peripheral NRG1 treatment displayed antidepressant-like effects in adult animals (Mahar et al. 2011) suggests a potential to develop molecules/ligands that bind to and modulate ErbB receptors. However, this approach should be taken with caution due to the inverted U-shaped relationship between ErbB4 activity and the expression of schizophrenia endophenotypes (Hahn 2011; Role and Talmage 2007; Wen et al. 2010), as well as different effects of NRG1 treatment in developing and adult animals (Kato et al. 2011; Mahar et al. 2011). Secondly, it is possible to examine more specific targets within the downstream pathways of NRG1–ErbB4 signalling. The recent finding, that NRG1–ErbB4 signalling inhibits Src-mediated enhancement of synaptic NMDA function, provides novel targets in the frontal cortex and hippocampus for new antipsychotic drugs (Pitcher et al. 2011),

since the majority of studies have showed that schizophrenia patients have increased NRG1– ErbB4 signalling (Hahn 2011). Therefore, a drug aimed at specifically restoring Src activity in schizophrenia could potentially be a new approach for schizophrenia therapy (Fig. 1) (Hahn 2011; Pitcher et al. 2011). On the other hand, it should be noted that some studies reported decreased expression of NRG1 (as reviewed above); if this is the case, this may lead to different therapeutic approaches in schizophrenia patients with decreased NRG1–ErbB4 signalling by activating Fyn and Pyk2 kinases (Bjarnadottir et al. 2007). Thirdly, the finding that ErbB4 receptors are located on PV-positive GABA interneurons in the frontal cortex and hippocampus, a trait conserved between species from rodents to humans, provides another specific approach for the development of antipsychotics by enhancing the function of PV-positive GABA interneurons. For example, PV-positive interneurons present a 5-fold higher NR2A/NR2B ratio than pyramidal neurons, and these NR2A-containing NMDA receptors regulate the expression of GAD67 in PV-positive GABA interneurons (Kinney et al. 2006). The density of a subset of GABA interneurons with co-expression of GAD67 and NR2A is decreased in the prefrontal and anterior cingulated cortex of schizophrenic patients (Woo et al. 2004, 2008). Therefore, a drug that selectively activates NR2A-containing NMDA receptors in PV-positive interneurons could have therapeutic value to reverse the NMDA hypofunction observed in patients with schizophrenia (Lewis and Gonzalez-Burgos 2006; Rico and Marin 2011). In addition, a drug to modulate interactions between NRG1–ErbB4 signalling and the dopamine pathway may also be a valuable approach to schizophrenia therapy.

Furthermore, the interactive points between NRG1 and other schizophrenia susceptibility factors/pathways should not be excluded as possible future drug targets, as research over the last decade has clearly shown that no single risk factor or related pathway for schizophrenia can cause the disease, instead cumulative or synergistic pathological effects seem likely (Balu and Coyle 2011; Karam et al. 2010). One example is the interaction between ErbB4 and DISC1, due to their co-localisation in the PSD of glutamate synapses and possible functional convergence (Hashimoto et al. 2007; Jaaro-Peled et al. 2009). Targeting both the NRG1–ErbB4 and DISC1–GSK3–Akt pathways may provide specific targets for new antipsychotic drugs (Jaaro-Peled et al. 2009; Ross and Margolis 2009). In addition, other schizophrenia susceptibility factors, such as dysbindin-1, neuronal nitric oxide synthase (nNOS), carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON), and growth factor receptor bound protein (Grb2), are also located in the PSD where signals from neurotransmitters converge, making PSD itself a promising drug discovery target (Hashimoto et al. 2007; Jaaro-Peled et al. 2009). In conclusion, identification of these targets in NRG1–ErbB4 signalling and interacting pathways will provide unique opportunities for the development of new generation antipsychotics with specific efficacy and fewer side effects.

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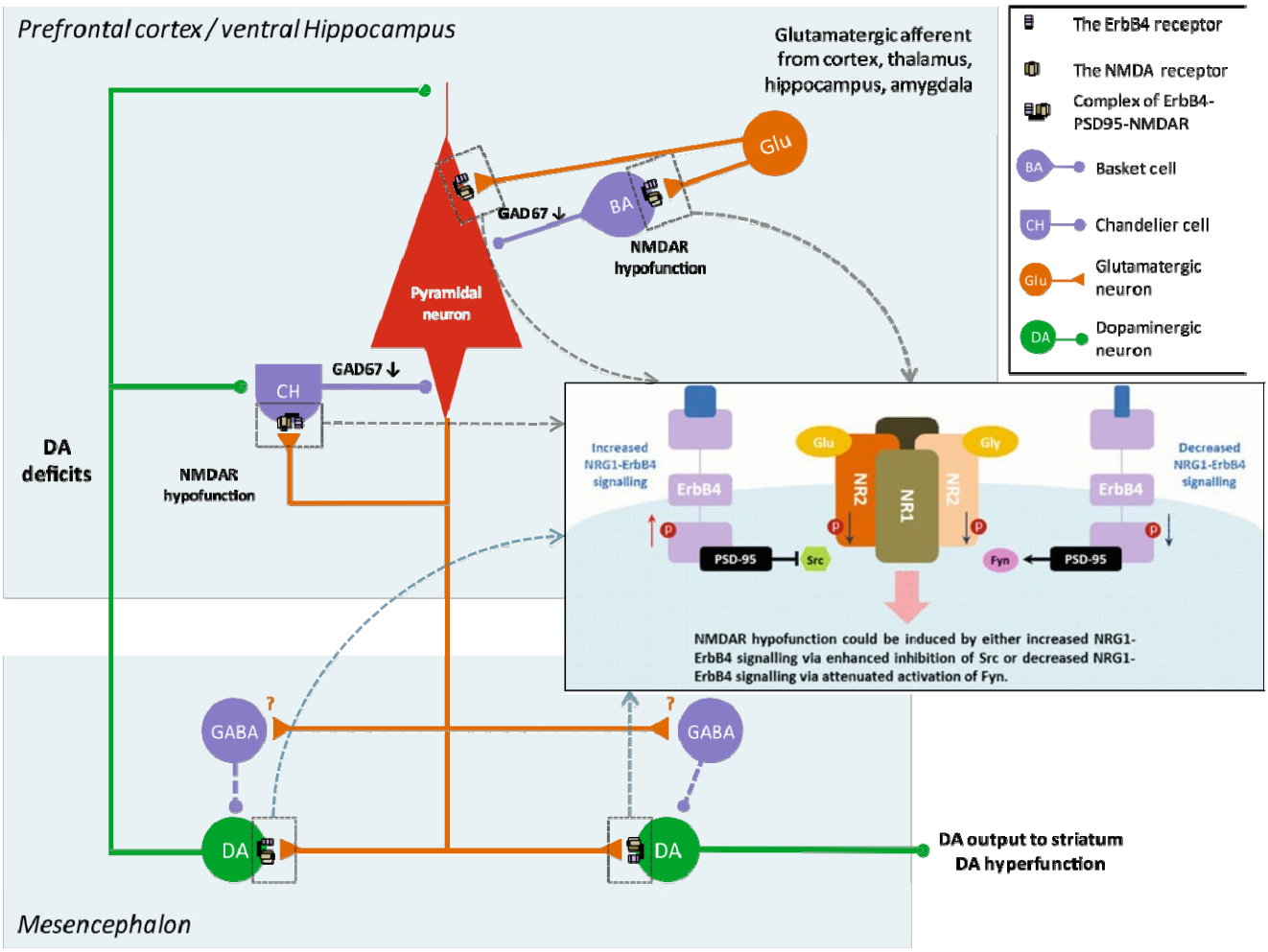

Figure legends

Figure 1. A schematic diagram showing the hypothetical interaction between NRG1-ErbB4 signalling and neurotransmission systems in schizophrenia. The output of pyramidal neurons in the prefrontal cortex and ventral hippocampus is regulated by excitatory glutamatergic neurons (orange colour) and inhibitory GABAergic interneurons (shown in blue). Basket cells (BA) target the somata pyramidal neurons; chandelier cells (CH) terminate at or near the axon hillock of pyramidal neurons. Theses GABAergic interneurons are regulated by glutamatergic projections from various brain regions, including the cortex, thalamus, hippocampus and amygdala. Recent histological studies showed that ErbB4 receptors are located exclusively on PV-positive GABAergic interneurons in the frontal cortex and hippocampus (Fazzari et al 2010; Neddens and Buonanno 2010; Neddens et al 2011b), although an electrophysiological study suggested a direct effect of NRG1 on the pyramidal neurons (Pitcher et al 2011). NRG1 regulates NMDA receptors by activating ErbB4 that co-localise with postsynaptic density (PSD) 95, and then inhibits Src-mediated enhancement of NMDA receptor function. In schizophrenia, in the case of increased NRG1-ErbB4 signalling (as shown in many studies that are summarized in text), it will cause NMDA receptor hypofunction by modulating Src activity, which may directly act on pyramidal neurons or indirectly through GABAergic interneurons. NMDA hypofunction may cause GABAergic deficits by down-regulating GAD67 (67-kilodalton isoform of glutamic acid decarboxylase) and decreasing GABA

production. On the other hand, NRG1-ErbB4 signalling can activate Fyn and Pyk2 kinases leading to increased NMDA NR2B phosphorylation. Therefore, in the case of hypofunctional NRG1-ErbB4 signalling, as observed in several studies in schizophrenia patients, it may cause decreased activation of Fyn and Pyk2 kinases and NMDA phosphorylation, also resulting NMDA hypofunction. In the midbrain, ErbB4 receptors are heavily expressed on dopaminergic neurons, whereas the function of ErbB4 receptors in dopaminergic neurons in the midbrain is controversial. Hypofunction of NMDA receptors may directly affect functioning of the dopaminergic system (shown in green) in the midbrain, or indirectly via GABA interneurons (unclear, shown as question mark), causing hyperfunction of dopamine output to the striatum, and deficits of dopamine output to the cortex/hippocampus.