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Abstract

Evidence from genetic, transgenic and post-mortem studies has strongly supported the critical role that neuregulin 1 (NRG1) and its ErbB4 receptor plays in the pathophysiology of schizophrenia. This article aims to review current evidence regarding the effects of antipsychotic treatment on NRG1−ErbB4 signalling. NRG1 and ErbB4 knockout mice display abnormal behaviours relevant to certain features of schizophrenia, which could be improved by antipsychotic (clozapine/haloperidol) treatment. In contrast to most NRG1/ErbB4 knockout mice with a decreased NRG1−ErbB4 signalling, the majority post-mortem studies showed an increased NRG1−ErbB4 signalling in schizophrenic patients. These differences could be due to degrees of alteration in risk genes (subtle variations in patients vs pronounced alteration in mutant mice) or the duration of the modification on NRG1 signalling. Various antipsychotics have different effects on NRG1 and ErbB4 expression and signalling that are dependent on treatment duration. Current evidence suggests that a chronic (12 weeks) antipsychotic treatment, at least in animal models, could downregulate NRG1−ErbB4 signalling, although an upregulation is seen for a short-term treatment. These effects may be due to multiple binding profiles with various G-coupled protein receptors (e.g. dopamine, and serotonin receptors) of antipsychotics. Studies are needed to investigate the interactions between NRG1−ErbB4 and the other signalling pathways (such as glutamatergic, GABAergic and dopaminergic). Furthermore, the interactions between NRG1/ErbB4 and other schizophrenia suspensibility genes under antipsychotic treatment also require investigation.

Disciplines

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Full Title: Antipsychotic treatment and neuregulin 1-ErbB4 signalling in schizophrenia

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Abstract

Evidence from genetic, transgenic and post-mortem studies have strongly supported the critical role that neuregulin 1 (NRG1) and its ErbB4 receptor play in the pathophysiology of schizophrenia. This article aims to review current evidence regarding to the effects of antipsychotic treatment on NRG1-ErbB4 signalling. NRG1 and ErbB4 knockout mice display some schizophrenia-like behavioural abnormalities, which could be improved by antipsychotic (clozapine/haloperidol) treatment. In contrast to NRG1/ErbB4 knockout mice with a decreased NRG1-ErbB4 signalling, the majority post-mortem studies showed an increased NRG1-ErbB4 signalling in schizophrenia patients. These differences could be due to degrees of alteration in risk genes (subtle variations in patients vs pronounced alteration in mutant mice) or the duration of the modification on NRG1 signalling. Various antipsychotics have different effects on NRG1 and ErbB4 expression and signalling dependent on treatment duration. Current evidence suggests that a chronic (12 weeks) antipsychotic treatment, at least in animal models, downregulates NRG1-ErbB4 signalling, although an upregulation is seen for a short term treatment. Therefore, the dysfunctional NRG1-ErbB4 signalling observed in schizophrenia is unlikely to be due to antipsychotic therapy. Furthermore, multiple-receptor binding profiles (e.g. dopamine, and 5-HT receptors) of antipsychotics may also contribute to their different influences on NRG1-ErbB4 signalling. Studies are also needed to investigate the interactions between NRG1-ErbB4 and the other signalling pathways (such as glutamatergic, GABAergic and dopaminergic).

Abbreviations:

5-HT, Serotonin; BA, Brodmann areas; BACE1, a transmembrane endopeptidase β-Site APP-cleaving enzyme 1; CNS, central nervous system; CYT, C-terminal cytoplasmic tails; ErbB4, a membrane-associated tyrosine kinases, ErbB4 receptor kinases; EGF, epidermal growth factor; Ig, immunoglobulin; NMDA, *N*-methyl-D-aspartate; NRG1, neuregulin 1; PBLs, peripheral blood lymphocytes; PFC, prefrontal cortex; PPI, prepulse inhibition; PSD95, post synaptic density protein 95; SNP, single-nucleotide polymorphism.

1. Introduction

Although the aetiology and pathophysiology of schizophrenia is still not fully understood, it has been widely accepted that both genetic and environmental factors play critical roles in the development of schizophrenia. Over the past decades, the roles of genetic factors have been attracting increased attentions in schizophrenia research. The neuregulin 1 (NRG1) gene has been identified as a candidate gene for schizophrenia in several genetics studies (Li et al., 2006; Liu et al., 2005; Petryshen et al., 2005; Stefansson et al., 2003; Williams et al., 2003; Yang et al., 2003). NRG1 is a group of proteins that contains an epidermal growth factor (EGF)-like domain (α or β) that signals by activating membrane-associated tyrosine kinases, especially the ErbB4 receptor kinases in the central nervous system (CNS) (Falls, 2003). An association between ErbB4 gene and schizophrenia has also been reported (Silberberg et al., 2006). NRG1-induced stimulation of the ErbB4 receptor plays critical roles in the neuronal functions that are closely related to the development of schizophrenia, mainly neuronal specification, neuronal migration, neuron-glial signalling, synapse formation, synaptic transmission, and plasticity of the CNS (for review: see Harrison and Law, 2006). Several studies found that animals with impaired NRG1-ErbB4 signalling displayed schizophrenia-like behavioural abnormalities (Barros et al., 2009; Dejaegere et al., 2008; Rimer et al., 2005; Savonenko et al., 2008; Stefansson et al., 2002).

In clinics, various antipsychotic drugs, including typical and atypical antipsychotics, are widely used to control schizophrenia symptoms. Typical antipsychotics are effective to ameliorate the positive symptoms of schizophrenia mainly through potently and specifically blocking the dopamine receptors (Kapur and Mamo, 2003;

Strange, 2008). Atypical antipsychotics have some effects on positive and negative symptoms, as well as cognitive deficits (Burton, 2006). Atypical antipsychotics have binding profiles not only with dopaminergic receptors, but also with many other receptors, including the serotonin (5-HT), α adrenergic, histamine H_1, and muscarinic M_1 receptors (Mathews and David, 2007). In view of the relationships between NRG1-ErbB4 function and the pathophysiology of schizophrenia, and between antipsychotic treatment and schizophrenia symptoms, the key questions are whether antipsychotic drugs regulate the NRG1-ErbB4 signalling, and how this regulation contributes to their efficacy in controlling schizophrenia symptoms? It is very interesting that schizophrenia patients with different NRG1 genotypes have been reported to respond differently to typical antipsychotics (Kampman et al., 2004). However, to date, not much attention has been paid on the effects of antipsychotic drugs on NRG1-ErbB4 signalling. This paper will focus on reviewing the current evidence regarding to the effects of antipsychotics on the alteration of NRG1-ErbB4 functions.

2. Methods

A reference search was performed across the Medline (January 2000 - November 2010) and ScienceDirect (January 2000 - November 2010) databases. Key words included antipsychotic, individual drug names (chlorpromazine, trifluoperazine, perphenazine, triflupromazine, fluphenazine, thiothixene, zuclopenthixol, haloperidol, pimozide, melperone, loxapine, amisulpride, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, sulpiride, and zotepine), cross-referenced with neuregulin 1, NRG1, and ErbB4. In addition, the reference lists of all papers identified were reviewed.

3. Structures of NRG1 isoforms

The NRG1 gene generates six types of protein (I-VI) and at least 31 isoforms in humans, presumably due to multiple promoters and alternative splicing; each protein type possesses a specific amino-terminal region. All six types of NRG1 isoforms have an EGF-like domain, which is located in the membrane-proximal area of the extracellular part. The type III isoforms contain a cysteine-rich domain (CRD) that has a transmembrane 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 N-terminal sequence of NRG1 types III and VI is connected directly to the EGF-like domain. Then the EGF-like domain is connected with a C-terminal transmembrane domain with or without the linker regions. In the intracellular part, there are C-terminal regions (cytoplasmic tail) (Falls, 2003; Harrison and Law, 2006; Mei and Xiong, 2008). In the proteolytic processing of NRG1, a transmembrane endopeptidase β-Site APP-cleaving enzyme 1 (BACE1) is involved in cleaving the NRG1 molecule, releasing an extracellular domain of the NRG1 molecule (except in the case of NRG1 type III) (Hu et al., 2006; Willem et al., 2006). In addition, the remaining membrane-bound NRG1 fragment can be cleaved by Aph1B/C-γ-secretase, generating an intracellular domain that can relocate into the nucleus to regulate gene transcription (Bao et al., 2003).

4. Abnormal behaviours of animals with deficient NRG1-ErbB4 signalling could be reversed by antipsychotic treatment

In the last decade, animal studies have shown that animals with abnormal NRG1-ErbB4 functions display schizophrenia-like behavioural abnormalities, including

hyperactivities in the novel open-field test and the alternating-Y maze (Barros et al., 2009; Duffy et al., 2008; Gerlai et al., 2000; 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; Dejaegere et al., 2008; Hong et al., 2008; 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 activities (O'Tuathaigh et al., 2007). These reports provided evidence supporting the potential roles of mutations in NRG1 and ErbB4 genes as risk factors for schizophrenia. Importantly, some of the behavioural abnormalities caused by NRG1 and ErbB4 knock-out could be normalised by administration of antipsychotics (Table 1). For example, it has been reported that treatment with clozapine can reverse the hyperactivity of NRG1 TMc-mutant mice in the novel open-field test and in the cross maze test (Stefansson et al., 2002). The effects of clozapine on suppressing hyperactivity have also been observed in open-field and running wheel tests in the NRG1 Ig-like domain mutant mice (Rimer et al., 2005), and in novelty-induced hyperactivity in BACE1-knockout mice. Although the deficits in PPI have been observed in NRG1 EGF- and BACE1-knockout mice, the effects of clozapine on improving PPI have been observed in BACE1-knockout mice (Savonenko et al., 2008), but not in NRG1 EGF-mutant mice (Stefansson et al., 2002). Furthermore, deficits of PPI could be reversed to normal level both haloperidol or clozapine in Aph1B/C-γ-secretase-disturbed mice (Dejaegere et al., 2008). Impaired lateral inhibition in NRG1 Ig-like domain mutant mice could also be improved by clozapine (Rimer et al., 2005). In addition, clozapine could reverse the abnormalities in ErbB4-deficient mice, including decreased anxiety in the open field test, more aggressive activities in the resident-intruder assay and lower PPI level (Barros et al., 2009).

5. Dysregulated NRG1-ErbB4 signalling in schizophrenia: is it caused by antipsychotic treatment?

A number of post-mortem studies examined the expression of NRG1 (including the protein level and its mRNA) in the brain of schizophrenia patients. Although the results are not completely consistent, they did provide evidence to show abnormal NRG1-ErbB4 signalling contributing to the pathophysiology of schizophrenia (Table 2). Hashimoto et al. first reported an increase of the mRNA expression of NRG1 type I isoform, and a decrease in the ratios of type II/I and type II/III mRNA expressions in the prefrontal cortex (PFC) of schizophrenia patients (Hashimoto et al., 2004). These decreased rations of type II/I and type II/III expressions may indicate a relatively decreased expression of type II isoform in schizophrenia (Hashimoto et al., 2004). In a following study, the levels of mRNA for NRG1 type I was confirmed to be elevated (34%) in the hippocampus of schizophrenia patients (Law et al., 2006). Importantly, Chong et al. have also found that the protein level of the NRG1 intracellular part increased by about 20% only in the PFC of schizophrenia patients, but not in patients with bipolar disorders and depression (Chong et al., 2008). In contrast, a recent study demonstrated that the gene expression of NRG1 type I isoform decreased in the PFC, Brodmann area 10 (BA10) (53.2%), and the expression of NRG1 type II isoform increased in BA10 (193%) of elderly schizophrenia patients (Parlapani et al., 2010). In addition, the NRG1α mRNA expression was found to be decreased in the white matter and grey matter of the PFC in schizophrenia patients (Bertram et al., 2007).

ErbB4 receptor expression was also shown to be abnormal in schizophrenia patients. A post-mortem study has shown that the protein expression of the full-length ErbB4 receptor was increased by nearly 30% in the PFC of schizophrenia patients (Chong et

al., 2008). In addition, another study has reported that the expression of ErbB4 receptor isoforms that contain the C-terminal cytoplasmic tails (CYT)-1 domain significantly increased in the dorsolateral PFC of schizophrenia patients (Silberberg et al., 2006). Law and colleagues also pointed out that the mRNA of ErbB4 isoforms containing CYT-1 domain and a metalloprotease cleavable extracellular domain were promoted in the dorsolateral PFC of schizophrenia patients (Law et al., 2007). Interestingly, Hahn et al. (2006) have demonstrated that, although the expression of both NRG1 and ErbB4 receptors did not significantly change in the PFC in schizophrenic subjects compared to normal subjects, the phosphorylation and the activation of downstream signalling of the ErbB4 receptor was elevated. These results suggested an elevated NRG1-ErbB4 signalling in the brain of schizophrenia patients.

NRG1 expression was also studied in the peripheral systems, and the results were not consistent. It was reported that the expression levels of NRG1 transcript variants in type I and type III isoforms significantly increased in peripheral blood lymphocytes (PBLs) from schizophrenia patients (Petryshen et al., 2005). However, another study reported a decrease of NRG1 mRNA expression in PBLs from schizophrenia patients (Zhang et al., 2008).

In brief, although current reports are not completed consistent, the majority of studies in schizophrenia patients suggest an enhanced NRG1-ErbB4 signalling in schizophrenic patients through over expressions of NRG1 and ErbB4, or increased phosphorylation of the ErbB4 receptor leading to the elevated interaction of ErbB4 and postsynaptic density protein 95 (PSD95). It has been suggested that enhanced NRG1-ErbB4 signalling contributes to NMDA hypofunction in schizophrenia (Hahn

et al., 2006). It should be noted that schizophrenia patients usually have undergone chronic antipsychotic treatments, therefore one key question is whether elevated NRG1-ErbB4 signalling observed in post-mortem studies is caused by antipsychotic treatment. However, current results do not support this claim, since the majority of post-mortem studies in schizophrenia have found no correlation between over-expressions of NRG1/ErbB4 and dosages of antipsychotic treatment (Chong et al., 2008; Hahn et al., 2006; Hashimoto et al., 2004; Law et al., 2007; Law et al., 2006). Furthermore, elevated expression of the NRG1 intracellular part was only observed in the PFC of schizophrenia, but not bipolar disorders and depression, although bipolar patients were also exposed to antipsychotics (Chong et al., 2008). Positive associations between intronic SNPs (rs7598440, rs707284, rs839523) and elevated mRNA expressions of ErbB4 isoforms containing a metalloprotease cleavable extracellular domain (JM-a) and CYT-1 domain have been reported, which suggests a splice-variant specific expression of ErbB4 in the brain in schizophrenia (Law et al., 2007). Splice variant-specific alteration of NRG1 gene expression was also observed in schizophrenia (Law et al., 2006). It is important that chronic treatment of antipsychotics has been reported to decrease NRG1-ErbB4 signalling (Hahn et al., 2006; Pan et al., 2010) (see below for details).

6. The effects of antipsychotic treatment on NRG1-ErbB4 signalling

Several studies (Table 3) have also demonstrated that NRG1-ErbB4 expression could be altered by administration of antipsychotic drugs in normal subjects. In an *in vivo* animal study, four-week treatment with haloperidol increased the expression of NRG1 and ErbB4, while clozapine reduced the expression of NRG1 isoforms in the normal rat PFC (Wang et al., 2008). On the other hand, four-week treatment with both haloperidol and clozapine increased NRG1 and ErbB4 expressions in the

hippocampus (Wang et al., 2008). In the same study, four-week treatment with risperidone increased the protein levels of both NRG1 isoforms and ErbB4 receptors in the hippocampus, but not in the PFC (Wang et al., 2008). Additionally, in a clinical study, after a 2-week treatment with risperidone and quetiapine, NRG1 mRNA expression of PBLs of first-onset schizophrenia patients (who has not take antipsychotics before) significantly increased compared to the levels before antipsychotic drug therapies (Zhang et al., 2008). Moreover, an *in vitro* study has shown that NRG1 protein expression increased in human fetal brain aggregates after being exposed to clozapine for three weeks; however, the expression of NRG1 proteins did not change following exposure to haloperidol (Chana et al., 2009). In addition to the finding that NRG1-induced ErbB4 activation was significantly enhanced in the PFC of schizophrenia patients (Hahn et al., 2006), it is very interesting that NRG1-induced ErbB4 activation was significantly reduced by a 12-weeks treatment with haloperidol in mouse brains (Hahn et al., 2006). Recently we examined the effects of short-term or chronic treatment with aripiprazole, haloperidol and olanzapine on the expression of NRG1 and ErbB4 in rat brains (Pan et al., 2010). We found that 1-week treatment with olanzapine significantly increased the protein expression of NRG1 type I, and type III in the hippocampus (unpublished data); however, 12-week treatment with aripiprazole and haloperidol significantly decreased the protein expression of NRG1 types I, II III and the ErbB4 receptor in the PFC. Haloperidol treatment for 12 weeks also significantly reduced NRG1 type III expression in the hypothalamus (Pan et al., 2010). These results suggested that, while relatively short-term (1-4 weeks) treatment with antipsychotics might increase the expression of NRG1 and ErbB4, chronic antipsychotic treatment (12 weeks) would attenuate NRG1-ErbB4 signalling.

7.   Summary

In general, the proposition that dysregulation of NGR1-ErbB4 signalling is involved in the pathophysiology of schizophrenia is supported by evidence from studies in both knockout (Nrg1$^{-/+}$/ErbB4$^{-/+}$) mouse models and post-mortem brains of schizophrenia patients. However, findings from the knowout mouse models are contradictory to those findings obtained from post-mortem studies that, in contrast to NRG1/ErbB4 mutant mice with a decreased NRG1-ErbB4 signalling that present schizophrenia-like abnormal behaviours, schizophrenia patients displayed an increased NRG1-ErbB4 signalling. These differences are partly due to the fact that patients' risk genotypes have only some subtle variations, while transgenic mice have a pronounced gene alteration (Banerjee et al., 2010), or partly due to the duration of the modification of NRG1 signalling (Savonenko et al., 2008). Furthermore, dysregulated NRG1-ErbB4 signalling in schizophrenia might interact with other signalling pathways such as glutamatergic, GABAergic and dopaminergic pathways (Banerjee et al., 2010; Buonanno, 2010). It is important that antipsychotic drugs are able to reverse some abnormal behaviours in NRG1 and ErbB4 mutant mice, and affect the expression of NRG1/ErbB4 and the functioning of NRG1-ErbB4 signalling. It is worth noting that none of the antipsychotic drugs can directly act on ErbB4 receptors; the exact mechanisms of antipsychotics on NRG1-ErbB4 signalling are not clear. Although all antipsychotic drugs largely target dopamine receptors (Kapur and Mamo, 2003), atypical antipsychotics also have binding profiles on other receptors (such as 5-HT and cholinergic receptors), which might explain why various antipsychotics have different effects on NRG1 and ErbB4 expressions. Further studies investigating the exact mechanisms of these regulations, in particular interactions between

NRG1/ErbB4 with other neurotransmitter systems, will improve our understanding of the aetiology of schizophrenia as well as the treatment of this devastating disease.

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Table 1. Effects of antipsychotics on behavioural abnormalities in animals with impaired NRG1-ErbB4 signalling.

Studies	Treatment	Results
Stefansson et al., 2002	Clozapine	Clozapine reversed the increased activity of the NRG1 TMc-mutant mice in the novel open-field test and T-maze test.
Rimer et al., 2005	Clozapine	The activity of the NRG1 Ig-mutant mice was affected by clozapine more than the controls in the open-field and running wheel test.
Dejaegere et al., 2008	Haloperidol, Clozapine	Haloperidol and clozapine normalised PPI deficit in Alph1 B/C γ-secretase-disturbed mice to normal levels.
Savonenko et al., 2008	Clozapine	Clozapine selectively normalised PPI deficits and attenuated novelty-induced hyperactivity occurring in BACE1-knockout mice.
Barros et al., 2009	Clozapine	Clozapine reversed the behavioural defects (such as decreased anxiety in the open field test, aggressive activities in the resident-intruder test and lower PPI level) in ErbB4-deficient mice.

Table 2. Alteration of the expression of NRG1 isoforms and the ErbB4 receptor in schizophrenia

Studies	Results
NRG1 expression in the CNS	
Hashimoto et al., 2004	(1) NRG1 type I expression increased in the PFC of schizophrenia patients. (2) Type II/I and type II/III ratios decreased in the PFC of schizophrenia patients.
Law et al., 2006	NRG1 type I elevated in the PFC and the hippocampus in schizophrenia patients.
Hahn et al., 2006	The expression of NRG1 and the ErbB4 receptor was not different between schizophrenia patients and controls.
Bertram et al. 2007	The NRG1 isoform expression is significantly reduced in white matter and gray matter of the PFC of schizophrenia patients.
Chong et al., 2008	NRG1 expression increased in the PFC of schizophrenia patients.
Parlapani et al., 2010	(1) Expression of NRG1 type I decreased in BA10 of schizophrenia patients. (2) Expression of type II increased in BA10.
NRG1 expression in the peripheral system	
Petryshen et al., 2005	Expression of NRG1 type I and type III increased in PBLs of schizophrenia patients
Zhang et al., 2008	NRG1 expression in PBLs of schizophrenia patients was lower than control groups before any antipsychotic treatment.
ErbB4 receptor expression	
Hahn et al., 2006	ErbB4 expression in the brain of schizophrenia patients did not change, but the phosphorylation of the ErbB4 receptor elevated.
Silberberg et al., 2006	ErbB4 receptors isoforms that contain the CYT-1 domain over-expressed in the dorsolateral PFC of schizophrenia patients.
Law et al. 2007	The mRNA of ErbB4 isoforms containing CYT-1 and JM-a domain increased in the dorsolateral PFC of schizophrenia patients
Chong et al., 2008	ErbB4 protein expression increased in the PFC of schizophrenia patients.

Table 3. Alteration of the expression of NRG1 isoforms and the ErbB4 receptor after antipsychotic treatment.

Studies	Treatment duration	Treatments	Results
Zhang et al., 2008	2 weeks	Quetiapine, risperidone	NRG1 expression in PBLs of schizophrenia patients increased after quetiapine and risperidone treatment.
Wang et al., 2008	4 weeks	Haloperidol, clozapine, risperidone	Haloperidol increased the expression of NRG1 and ErbB4, clozapine decreased NRG1 expression in the rat PFC; haloperidol and clozapine increased NRG1and ErbB4 in the rat hippocampus; risperidone increased NRG1-ErbB4 expression in the hippocampus.
Chana et al., 2009	3 weeks	Clozapine, haloperidol	NRG1 expression in normal human fetal brain aggregates increased after exposure to clozapine, but not haloperidol.
Hahn et al., 2006	12 weeks	Haloperidol	Haloperidol reduced the NRG1-induced ErbB4 activation in mice brain.
Pan et al., 2010	12 weeks	Aripiprazole, olanzapine, haloperidol	Aripiprazole and haloperidol decreased the protein expression of NRG1 types I, II III and the ErbB4 receptor in the rat PFC; haloperidol reduced NRG1 type III expression in the rat hypothalamus.