Effects of prolonged antipsychotic administration on neuregulin-1/ErbB signaling in rat prefrontal cortex and myocardium: implications for the therapeutic action and cardiac adverse effect

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ABSTRACT — Patients with schizophrenia (SCZ) are at higher risk for developing cardiovascular disease (CVD) and neuregulin-1 (NRG1)/ErbB signaling has been identified as a common susceptibility pathway for the comorbidity. Antipsychotic treatment can change NRG1/ErbB signaling in the brain, which has been implicated in their therapeutic actions, whereas the drug-induced alterations of NRG1/ErbB pathway in cardiovascular system might be associated with the prominent cardiac side-effects of antipsychotic medication. To test this hypothesis, we examined NRG1/ErbB system in rat prefrontal cortex (PFC) and myocardium following 4-week intraperitoneal administration of haloperidol, risperidone or clozapine. Generally, the antipsychotics significantly enhanced NRG1/ErbB signaling with increased expression of NRG1 and phosphorylation of ErbB4 and ErbB2 in the brain and myocardium, except that clozapine partly blocked the cardiac NRG1/ErbB2 activation, which could be associated with its more severe cardiac adverse actions. Combined, our data firstly showed evidence of the effect of antipsychotic exposure on myocardial NRG1/ErbB signaling, along with the activated NRG1/ErbB system in brain, providing a potential link between the therapeutic actions and cardiotoxicity.

Key words: Schizophrenia, Cardiovascular disease, Antipsychotics, Neuregulin-1/ErbB

INTRODUCTION

Cardiovascular pathologies are a prominent cause of death in patients with schizophrenia (SCZ). SCZ patients are reported to have a 3-4 fold increased risk of premature death due to cardiovascular disease (CVD) (Kiviniemi et al., 2013; Osborn et al., 2007). The increased cardiovascular mortality has been attributed in part to patients’ unhealthy lifestyle, which includes smoking, poor diet, sedentary behavior and more common substance abuse. However, the use of either typical or atypical antipsychotic drugs is also a major risk factor (Fan et al., 2013). Although it has been well-documented that antipsychotics-induced metabolic side-effects, such as diabetes, obesity and dyslipidemia, can indirectly bring additional burden on cardiovascular system, there is substantial evidence that the drug use can also directly cause cardiotoxicity, including arrhythmia, myocarditis and cardiomyopathy (Citrome et al., 2013; Lin et al., 2014; Stroup et al., 2013). Despite the increased concern over antipsychotic-induced cardiovascular mortality, the underlying mechanism of action of antipsychotics on cardiovascular system remains poorly understood.

Neuregulin-1 (NRG1) and its ErbB receptors are crucial for neuronal and cardiac function, and NRG1/ErbB signaling has been identified as a common susceptibility pathway for both SCZ and CVD (Huertas-Vazquez et al., 2013; Kuksal et al., 2013). In the adult heart, NRG1 receptors ErbB2 and ErbB4, but not ErbB3, are found on cardiomyocytes. Upon the stimulation of NRG1, homo-
and heterodimers of ErbB proteins are formed. The formation of dimers results in tyrosine phosphorylation and activates the corresponding downstream signaling. Although NRG1 does not bind to ErbB2, ErbB2 functions as a co-receptor by forming heterodimers with ligand-bound ErbBs, and heterodimers with ErbB2 are implicated as a more potent signaling complex than homodimers (Mendes-Ferreira et al., 2013). Several post-mortem studies have found abnormal NRG1 and ErbB4 expression in the brain of SCZ patients (Bertram et al., 2007; Geddes et al., 2011), and the altered NRG1/ErbB signaling was also observed in the myocardium of patients with heart failure and in several animal models of CVD (Doggan et al., 2009; Gui et al., 2012; Rohrbach et al., 2005). Additionally, specific disruption of NRG1/ErbB pathway in genetically modified mice leads to abnormal behaviors characterized by certain features of SCZ (Barros et al., 2009) and cardiac defects (Odiete et al., 2012). Taken together, these findings provide evidence linking NRG1/ErbB system to the comorbidity of SCZ and CVD.

While it has been reported that various antipsychotics have different effects on NRG1 and ErbB4 expression in the brain (Deng et al., 2013), the evidence concerning whether these alterations reflect changes in ligand-induced ErbB activation is limited. Moreover, considering the well-known cardiotoxic effects of antipsychotics, we hypothesize that the antipsychotic administration may synchronically alter NRG1/ErbB signaling in the brain and heart, which may provide a potential link between the therapeutic actions and cardiovascular side-effects. To test the hypothesis, we investigated the concurrent changes in the expression of NRG1, ErbB4 and ErbB2 and the phosphorylated status of the two ErbB receptors in the prefrontal cortex (PFC) and myocardium of rats following chronic administration of haloperidol (Hal), risperidone (Ris) and clozapine (Clo).

**MATERIALS AND METHODS**

**Animals**

Male, Sprague-Dawley rats (250-280 g), supplied by the Experimental Animal Center of the Second Xiangya Hospital, were housed individually under standard conditions of temperature (23 ± 2°C) and light (12:12 hr light/dark cycle), with free access to food and water. All animal use procedures were carried out in accordance with the Regulations of Experimental Animal Administration issued by the State Committee of Science and Technology of the People's Republic of China, with the approval of the Ethics Committee in our university.

**Drug treatment**

Rats were randomly divided into four groups (n = 6 in each group) treated with different antipsychotic drugs: normal control (Con), Hal, Ris and Clo. The animals in different groups received daily single intraperitoneal injection of vehicle, 1 mg/kg b.w. Hal, 2 mg/kg b.w. Ris or 20 mg/kg b.w. Clo respectively between 8:00 a.m. and 9:00 a.m. for 4 weeks. The antipsychotic drugs were formulated in 0.9% saline containing 0.2% acetic acid and 0.5% Tween 80 and the dosing solutions were prepared fresh daily. The dosages of the drugs used in this study were chosen to represent physiologically relevant levels in vivo, and therefore based on previously reported behavioral studies in rats, such as reversal of prepulse inhibition (PPI) deficits of the acoustic startle reflex (Boya et al., 2010). All the rats were weighted every 3 days and the doses were adjusted to its body weight change.

**Western blot analysis**

Twenty four hours after the last injection, the rats were sacrificed and tissues were rapidly collected. For western blotting analysis, total protein was prepared and the concentration was analyzed using the Bradford method. Samples were loaded on precast 12% SDS-PAGE gels with approximately 50 μg protein in each lane. Proteins in the gels were transferred to a PVDF membrane and blocked for 1 hr in 5% non-fat dry milk in TBS-T (25 mM Tris, pH 7.5, 150 mM NaCl, 0.05% Tween-20). The following antibodies and concentrations were used over night at 4°C: NRG1 (Santa Cruz (Santa Cruz, CA, USA); 1:400), ErbB4 (Santa Cruz; 1:500), ErbB2 (Cell Signaling (Beverly, MA, USA); 1:1,500), p-ErbB4 (Tyr 1056) (Santa Cruz; 1:300), p-ErbB2 (Tyr 1248) (Cell Signaling; 1:1,500) and β-actin (Proteintech (Chicago, IL, USA), 1:4,000). It was then probed with HRP-conjugated secondary antibody for 40 min. After washing, membranes were dipped in ECL and immunoblots were analyzed by using the Bio-profil Biolight PC software. The signals were normalized to β-actin as an internal standard.

**Serum NRG1 analysis**

Upon killing, trunk blood was collected, and serum was obtained by centrifugation at 3,600 × g for 7 min at 10°C. Serum concentration of NRG1 was determined in duplicate using a specific enzyme-linked immunoabsorbent assay (ELISA) kit (Uscn Life, WuHan, China) according to the manufacturer’s protocols.

**Histopathological studies**

Slices from ventricles of each heart were fixed in 10% neutral formalin solution, and then embedded in paraf-
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Statistical analysis
Results from the experiment were reported as means ± S.D. and analyzed using SPSS version 13.0 software. Statistical differences between groups were determined by using one-way ANOVA with Dunnett’s t test for post hoc comparisons. The prior level of significance was established at \( p < 0.05 \).

RESULTS

Effect of antipsychotics treatment on NRG1/ErbB pathway in PFC
As shown in Fig. 1, a significant higher expression of NRG1 was found in the Hal and Ris groups, whereas Clo did not affect NRG1 status (Fig. 1B). All the three antipsychotics significantly increased ErbB4 (Fig. 1C) expression, but ErbB2 (Fig. 1D) was only increased in the Hal group. Both pErbB4 (Fig. 1E) and pErbB2 (Fig. 1F) expression were enhanced in the three groups compared with vehicle-treated control.

Effect of antipsychotics treatment on NRG1/ErbB pathway in myocardium
In parallel, significant differences in NRG1/ErbB signaling were also found in the myocardium (Fig. 2). Similar to the PFC, only rats receiving Hal and Ris but not Clo showed increased NRG1 expression (Fig. 2B). Hal-treated rats also exhibited higher ErbB4 (Fig. 2C) and ErbB2 (Fig. 2D) levels, whereas these differences were not found in the Ris and Clo groups. As for pErbB4 (Fig. 2E) and pErbB2 (Fig. 2F), only Hal- and Ris-treated rats followed the trend found in the PFC with markedly rise of the phosphorylated status of the two ErbB receptors. In contrast, Clo inhibited ErbB2 phosphorylation without affecting pErbB4 status.

Effect of antipsychotics treatment on serum NRG1 status
Due to the reported variation of serum NRG1 status between SCZ patients and healthy controls (Shibuya et al., 2010), and given that most of the SCZ patients were subjected to long-term antipsychotic medication, we examined whether antipsychotic treatment has an effect on serum concentration of NRG1. Our data showed that serum NRG1 status was comparable among the four groups (Fig. 3), implying that the altered circulating NRG1 level in SCZ patients is unlikely caused by the chronic antipsychotic exposures.

Effect of antipsychotics treatment on histopathological features
As previously reported (Wang et al., 2008a), clo-treated rats showed clear evidence of myocarditis and myo
cardial cellular infiltration in the left ventricle compared to control rats (Fig. 4D). However, Hal (Fig. 4B) and Ris (Fig. 4C) seem to be less cardiotoxic, without causing any significant pathological damage in the myocardium.

**DISCUSSION**

Patients with SCZ have a higher incidence of cardiovascular mortality, which is at least partially, attributed to the use of antipsychotics. Nonetheless, SCZ in itself may also increase the risk of CVD (Scigliano and Ronchetti, 2013), and a disease-inherent vulnerability may put SCZ patients at increased risk for cardiovascular events. Genetic variations in NRG1/ErbB system have been associated with both SCZ and CVD (Huertas-Vazquez et al., 2013). Chronic antipsychotic treatment can exert modulatory effects on NRG1/ErbB pathway and improve the behavioral abnormalities relevant to certain features of SCZ in transgenic mice with impaired NRG1/ErbB signaling (Pan et al., 2011). These findings implicated NRG1/ErbB pathway in the development of SCZ and pharmacological actions of antipsychotics. However, on the other hand, antipsychotics may also produce an unforeseen effect on myocardial NRG1/ErbB signaling, which might be associated with the cardiotoxic side-effects.

In the present study, we firstly evaluated the effect of antipsychotics on NRG1/ErbB system in the PFC and myocardium. Previous findings from animal models and post-mortem studies have yielded inconsistent results concerning the altered expression of NRG1/ErbB system in the brain. An in-vivo study reported that 4-week administration of Hal increases the expression of NRG1 and ErbB4 in rat PFC (Wang et al., 2008b). Consistent with previous findings, we also demonstrated that Hal administration increased NRG1 and ErbB4 expression. However, contrasting to the reported effect in the same study that Clo reduces while Ris doesn’t affect PFC protein levels of NRG1, we found both of the two drugs caused a significant increase of NRG1 and ErbB receptors expression, which is much like the previous findings in the hippocampus. These discrepancies could be attrib-
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Fig. 4. Effect of 4-week administration of antipsychotics on myocardial histopathology. Cardiac tissues were of rats treated with vehicle (A), Hal (B), Ris (C) and Clo (D) stained with haematoxylin and eosin (H&E) (× 400 magnitude).

In parallel to the findings in brain, we also found synchronically altered NRG1/ErbB system in the myocardium: both Hal and Ris enhanced NRG1/ErbB signaling, while Clo intriguingly blocked ErbB2 activation. NRG1/ErbB signaling confers strong cardioprotective properties and is suggested to follow a biphasic course during the progression of CVD. After an initial phase of adaptive activation, that may regulate cardiac adaption to stress, activity of the system becomes maladaptively depressed, which ultimately constitute a detrimental event in the progression of the disease (De Keulenaer et al., 2010). NRG1/ErbB signaling can prevent cardiac apoptosis, promote angiogenesis and has anti-inflammatory and anti-adrenergic effects (Pentassuglia and Sawyer, 2009), while antipsychotic-induced cardiotoxic effects, including arrhythmia, myocarditis and cardiomyopathy, are tightly linked to the aberrance in these cardioprotective pathways regulated by NRG1/ErbB. Thus, the attempt to evoke NRG1/ErbB signaling in the myocardium of Hal- and Ris-treated rats might be involved in the compensatory response to the drug-induced cardiotoxicity.

Nonetheless, chronic administration of Clo failed to activate NRG1/ErbB pathway and partly blocked ErbB2 activation. There is compelling evidence that autonomic nervous system dysfunction, which is intrinsic to SCZ and exacerbated by antipsychotic treatment, is the major cause of CVD in patients with SCZ (Leung et al., 2012). Clo is suggested to produce the most pronounced increase in sympathetic tone, which is implicated in the vulnerability to arrhythmias and higher risk of developing myocarditis and cardiomyopathy (Agelink et al., 2001; Hempel et al., 2009). In mice, treatment with Clo for 14 days induces a dose-related increase in myocardial inflammation that correlated with periphery catecholamine levels (Wang et al., 2008a). Similarly, the hyper-catecholaminergic states were also found in patients on Clo medication (Elman et al., 2002), and Clo is the antipsychotic drug that most frequently associated with myocarditis (Kilian et al., 1999). Given the strong modulating effect of NRG1 on myocardial performance and sympathovagal balance, the enhancement in NRG1/ErbB signaling in the myocardium of Hal- and Ris-treated rats may desensitize the cardiac muscle to adrenergic stimuli, providing a modulatory feedback for the autonomic imbalance, while the blockade of NRG1/ErbB pathway by Clo administration may aggravate the detrimental effect of augmented sympathetic tone and finally lead to myocarditis and cardiomyopathy. In support of this hypothesis, patients on Clo have lower heart rate variability (HRV) compared to those on Hal or Ris and matched control subjects (Huang et al., 2013; Kim et al., 2004; Malaspina et al., 2002; Mueck-
The reduction in HRV reflects increased cardiac response to sympathetic hyperactivity and is a strong predictor of arrhythmias and cardiac death (Wu et al., 2009).

However, it is important to interpret the current results within its limitations. Although the present study provided new evidence that altered NRG1/ErbB signaling in the brain and heart might be associated with therapeutic actions and cardiovascular side-effects of antipsychotic medication, further studies that investigate the underlying molecular mechanisms are urgently needed to fully elucidate the involvement of NRG1/ErbB system in the drug-induced cardiotoxicity. Additionally, given that antipsychotics may exert a dose-dependent effect on NRG1/ErbB pathway, which might also vary with the duration of medication, further studies using various doses of antipsychotics for longer treatment duration will provide more consolidate evidence concerning the relationship between NRG1/ErbB signaling and therapeutic and cardiotoxic effects of antipsychotics.

NRG1/ErbB signaling is a potential shared pathological pathway involved in both SCZ and CVD. In the present study, we firstly showed the changes of NRG1/ErbB system in the heart, along with enhanced NRG1/ErbB signaling in the brain, following various antipsychotics administration, providing new evidence for the involvement of NRG1/ErbB system in the therapeutic actions and cardiovascular side-effects of antipsychotic medication.

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Conflict of interest---- The authors declare that there is no conflict of interest.

REFERENCES

Agelink, M.W., Majewski, T., Wurthmann, C., Lukas, K., Ullrich, H., Linka, T. and Klieser, E. (2001): Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. J. Clin. Psychopharmacol., 21, 8-13.

Barros, C.S., Calabrese, B., Chamero, P., Roberts, A.J., Korzus, E., Lloyd, K., Stowers, L., Mayford, M., Halpain, S. and Müller, U. (2009): Impaired maturation of dendritic spines without disorganization of cortical cell layers in mice lacking NRG1/ErbB signaling in the central nervous system. Proc. Natl. Acad. Sci. USA, 106, 4507-4512.

Bertram, l., Bernstein, H.G., Lendeckel, U., Bukowska, A., Dobrowolny, H., Keilhoff, G., Kanakis, D., Mawrin, C., Bielau, H., Falkai, P. and Bogerts, B. (2007): Immunohistochemical evidence for impaired neuregulin-1 signaling in the prefrontal cortex in schizophrenia and in unipolar depression. Ann. NY Acad. Sci., 1096, 147-156.

Boyd, H.N., Tse, L., Procyshyn, R.M., Wong, D., Wu, T.K., Pang, C.C. and Barr, A.M. (2010): A parametric study of the acute effects of antipsychotic drugs on glucose sensitivity in an animal model. Prog. Neuropsychopharmacol. Biol. Psychiatry, 34, 945-954.

Chana, G., Lucero, G., Salaria, S., Lozach, J., Du, P., Woelk, C. and Everall, I. (2009): Upregulation of NRG-1 and VAMP-1 in human brain aggregates exposed to clozapine. Schizophr Res., 113, 273-276.

Citrome, L., Collins, J.M., Nordstrom, B.L., Rosen, E.J., Baker, R., Nadkarni, A. and Kalsekar, I. (2013): Incidence of cardiovascular outcomes and diabetes mellitus among users of second-generation antipsychotics. J. Clin. Psychiatry, 74, 1199-1206.

De Keulenaer, G.W., Doggen, K. and Lemmens, K. (2010). The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anti-cancer therapy. Circ. Res., 106, 35-46.

Deng, C., Pan, B., Engel, M. and Huang, X.F. (2013). Neuregulin-1 signalling and antipsychotic treatment: potential therapeutic targets in a schizophrenia candidate signalling pathway. Psychopharmacology (Berl), 226, 201-215.

Doggen, K., Ray, L., Mathieu, M., Me Entee, K., Lemmens, K. and De Keulenaer, G.W. (2009): Ventricular ErbB2/ErbB4 activation and downstream signaling in pacing-induced heart failure. J. Mol. Cell. Cardiol., 46, 33-38.

Elman, I., Goldstein, D.S., Green, A.I., Eisenhofer, G., Folio, C.J., Holmes, C.S., Pickar, D. and Breier, A. (2002): Effects of risperidone on the peripheral noradrenergic system in patients with schizophrenia: a comparison with clozapine and placebo. Neuropsychopharmacology, 27, 293-300.

Fan, Z., Wu, Y., Shen, J., Ji, T. and Zhan, R. (2013): Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. J. Psychiatr. Res., 47, 1549-1556.

Geddes, A.E., Huang, X.F. and Newell, K.A. (2011): Reciprocal signalling between NR2 subunits of the NMDA receptor and neuregulin1 and their role in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry, 35, 896-904.

Gui, C., Zhu, L., Hu, M., Lei, L. and Long, Q. (2012): Neuregulin-1/ErbB signaling is impaired in the rat model of diabetic cardiomyopathy. Cardiovasc. Pathol., 21, 414-420.

Hahn, C.G., Wang, H.Y., Cho, D.S., Talbot, K., Gur, R.E., Berrettini, W.H., Bakshi, K., Kamins, J., Borgmann-Winter, K.E., Siegel, S.J., Gallop, R.J. and Arnold, S.E. (2006): Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat. Med., 12, 824-828.

Hempel, R.J., Tulen, J.H., van Beveren, N.J., Röder, C.H. and Hengeveld, M.W. (2009): Cardiovascular variability during treatment with haloperidol, clozapine or risperidone in recent-onset schizophrenia. J. Psychopharmacol., 23, 697-707.

Huang, W.L., Chang, L.R., Kuo, T.B., Lin, Y.H., Chen, Y.Z. and Yang, C.C. (2013): Impact of antipsychotics and anticholinergics on autonomic modulation in patients with schizophrenia. J. Clin. Psychopharmacol., 33, 170-177.

Huertas-Vazquez, A., Teodorescu, C., Reinier, K., Uy-Evanado, A., Chugh, H., Jerger, K., Ayala, J., Gunson, K., Jui, J., Newton-Cheh, C., Albert, C. M. and Chugh, S. S. (2013): A common missense variant in the neuregulin 1 gene is associated with both schizophrenia and sudden cardiac death. Heart Rhythm, 10, 994-998.
Kilian, J.G., Kerr, K., Lawrence, C. and Celermajer, D.S. (1999): Myocarditis and cardiomyopathy associated with clozapine. Lancet, 354, 1841-1845.

Kim, J.H., Yi, S.H., Yoo, C.S., Yang, S.A., Yoon, S.C., Lee, K.Y., Ahn, Y.M., Kang, U.G. and Kim, Y.S. (2004): Heart rate dynamics and their relationship to psychotic symptom severity in clozapine-treated schizophrenic subjects. Prog. Neuropsychopharmacol. Biol. Psychiatry, 28, 371-378.

Kiviniemi, M., Suvisaari, J., Koivumaa-Honkanen, H., Häkkinen, U., Isohanni, M. and Hakko, H. (2013): Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. Schizophr. Res., 150, 274-280.

Kukshal, P., Bhatia, T., Bhagwat, A.M., Gur, R.E., Gur, R.C., Lin, S.T., Chen, C.C., Tsang, H.Y., Lee, C.S., Yang, P., Cheng, K.D., Leung, J.Y., Barr, A.M., Procyshyn, R.M., Honer, W.G. and Pang, Kiviniemi, M., Suvisaari, J., Koivumaa-Honkanen, H., Häkkinen, U., Isohanni, M. and Hakko, H. (2013): Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. Schizophr. Res., 150, 274-280.

Kukshal, P., Bhatia, T., Bhagwat, A.M., Gur, R.E., Gur, R.C., Deshpande, S.N., Nimgaonkar, V.L. and Thelma, B.K. (2013): Association study of neuregulin-1 gene polymorphisms in a North Indian schizophrenia sample. Schizophr. Res., 144, 24-30.

Leung, J.Y., Barr, A.M., Procyshyn, R.M., Honer, W.G. and Pang, C.C. (2012): Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol. Ther., 135, 113-122.

Lin, S.T., Chen, C.C., Tsang, H.Y., Lee, C.S., Yang, P., Cheng, K.D., Li, D.J., Wang, C.J., Hsieh, Y.C. and Yang, W.C. (2014): Association between antipsychotic use and risk of acute myocardial infarction: a nationwide case-crossover study. Circulation, 130, 235-243.

Malaspina, D., Dalack, G., Leitman, D., Corcoran, C., Amador, X.F., Yale, S., Glassman, A. and Gorman, J.M. (2002): Low heart rate variability is not caused by typical neuroleptics in schizophrenia patients. CNS Spectr., 7, 53-57.

Mendes-Ferreira, P., De Keulenaer, G.W., Leite-Moreira, A.F. and Brás-Silva, C. (2013): Therapeutic potential of neuregulin-1 in cardiovascular disease. Drug Discov. Today. Today, 18, 836-842.

Mueck-Weymann, M., Rechlin, T., Ehren gut, F., Rauh, R., Acker, J., Dittmann, R.W., Czekalla, J., Joraschk y, P. and Musselman, D. (2002): Effects of olanzapine and clozapine upon pulse rate variability. Depress. Anxiety, 16, 93-99.

Odiete, O., Hill, M.F. and Sawyer, D.B. (2012): Neuregulin in cardiovascular development and disease. Circ. Res., 111, 1376-1385.

Osborn, D.P., Levy, G., Nazareth, I., Petersen, I., Islam, A. and King, M.B. (2007): Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom’s General Practice Research Database. Arch. Gen. Psychiatry, 64, 242-249.

Pan, B., Huang, X.F. and Deng, C. (2011): Antipsychotic treatment and neuregulin 1-ErbB4 signalling in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry, 35, 924-930.

Pentassuglia, L. and Sawyer, D.B. (2009): The role of Neuregulin-1beta/ErbB signaling in the heart. Exp. Cell Res., 315, 627-637.

Rohrbach, S., Niemann, B., Silber, R.E. and Holtz, J. (2005): Neuregulin receptors erbB2 and erbB4 in failing human myocardium -- depressed expression and attenuated activation. Basic Res. Cardiol., 100, 240-249.

Scigliano, G. and Ronchetti, G. (2013): Antipsychotic-induced metabolic and cardiovascular side effects in schizophrenia: a novel mechanistic hypothesis. CNS Drugs, 27, 249-257.

Shibuya, M., Komi, E., Wang, R., Kato, T., Watanabe, Y., Sakai, M., Ozaki, M., Someya, T. and Nawa, H. (2010): Measurement and comparison of serum neuregulin 1 immunoreactivity in control subjects and patients with schizophrenia: an influence of its genetic polymorphism. J. Neural. Transm., 117, 887-895.

Stroup, T.S., Byerly, M.J., Nasrallah, H.A., Ray, N., Khan, A.Y., Lamberti, J.S., Glick, I.D., Steinbook, R.M., McEvoy, J.P. and Hamer, R.M. (2013): Effects of switching from olanzapine, quetiapine, and risperidone to aripiprazole on 10-year coronary heart disease risk and metabolic syndrome status: results from a randomized controlled trial. Schizophr. Res., 146, 190-195.

Wang, J.F., Min, J.Y., Hampton, T.G., Amend, I., Yan, X., Malek, S., Abelmann, W.H., Green, A.L., Zeind, J. and Morgan, J.P. (2008a): Clozapine-induced myocarditis: role of catecholamines in a murine model. Eur. J. Pharmaco l., 592, 123-127.

Wang, X.D., Su, Y.A., Guo, C.M., Yang, Y. and Si, T.M. (2008b): Chronic antipsychotic drug administration alters the expression of neuregulin 1 beta, ErbB2, ErbB3, and ErbB4 in the rat prefrontal cortex and hippocampus. Int. J. Neuropsychopharmacol., 11, 553-561.

Wu, G.Q., Arzeno, N.M., Shen, L.L., Tang, D.K., Zheng, D.A., Zhao, N.Q., Eckberg, D.L. and Poon, C.S. (2009): Chaotic signatures of heart rate variability and its power spectrum in health, aging and heart failure. PLoS One, 4, e4323.

Zhang, H.X., Zhao, J.P., Lv, X., Li, Q.P., Xu, L., Ouyang, X., Yuan, Z.Q. and Huang, J.S. (2008): Explorative study on the expression of neuregulin-1 gene in peripheral blood of schizophrenic patients. Neurosci. Lett., 438, 1-5.