

# Pathological Implications of Oxidative Stress in Patients and Animal Models with Schizophrenia: The Role of Epidermal Growth Factor Receptor Signaling

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and Hiroyuki Nawa

**Abstract** Proinflammatory cytokines perturb brain development and neurotransmission and are implicated in various psychiatric diseases, such as schizophrenia and depression. These cytokines often induce the production of reactive oxygen species (ROS) and regulate not only cell survival and proliferation but also inflammatory process and neurotransmission. Under physiological conditions, ROS are moderately produced in mitochondria but are rapidly scavenged by reducing agents in cells. However, brain injury, ischemia, infection, or seizure-like neural activities induce inflammatory cytokines and trigger the production of excessive amounts of ROS, leading to abnormal brain functions and psychiatric symptoms. Protein phosphatases, which are involved in the basal silencing of cytokine receptor activation, are the major targets of ROS. Consistent with this, several ROS scavengers, such as polyphenols and unsaturated fatty acids, attenuate both cytokine signaling and psychiatric abnormalities. In this review, we list the inducers, producers, targets, and scavengers of ROS in the brain and discuss the interaction between ROS and cytokine signaling implicated in schizophrenia and its animal models. In particular, we present an animal model of schizophrenia established by perinatal exposure to epidermal growth factor and illustrate the pathological role of ROS and antipsychotic actions of ROS scavengers, such as emodin and edaravone.

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## 1 Oxidative Stress Is Implicated in the Pathogenesis of Schizophrenia

Oxygen radicals are molecules essential for energy production, metabolic processes, and germicide in our body; however, they are also toxic to cellular components, such as membrane lipids and DNA (Brewer et al. 2015). Therefore, our tissues and cells contain a large variety of reducing agents (i.e., scavengers) as well as reactive oxygen species (ROS)-degrading enzymes (Chan 2001; Table 1). This is especially true in the brain, which produces high energy accompanying ROS generation and is enriched with these antioxidants to protect the tissue from oxidative stress. Following brain injury, ischemia, infection, or seizures, NADPH oxidase (NOX) is activated in microglia and GABAergic neurons and produces large amounts of ROS in the brain (Kaur et al. 2015). When ROS is not scavenged immediately, they act not only on cell components (membrane lipids and DNA) but also on the molecules that carry ROS (redox) sensors, such as the protein tyrosine phosphatase PTP1B, nuclear factor kappa B (NF- $\kappa$ B), potassium channels, hypoxia-inducible factors, or *N*-methyl-D-aspartic acid (NMDA) receptor. For example, ROS acts on free cysteine residues of the NMDA receptor, altering its channel conformation to decrease NMDA-mediated cation movements, presumably attenuating neuronal cell death (Sanchez et al. 2000; Dukoff et al. 2014). This anti-ROS process functions as a self-defense system in the brain; however, when ROS generation is prolonged, the reduction in NMDA receptor channel activity can perturb normal neurotransmission and brain function. Chronic suppression of NMDA receptor activity is known to result in abnormal cognition and behaviors relevant to schizophrenia (Mohn et al. 1999; Takahashi et al. 2006).

Several reports on ROS generation show that contents of reducing agents are decreased and oxidizing agents are increased in patients and animal models with schizophrenia (Yao and Keshavan 2011; Bokkon and Antal 2011). For example,

**Table 1** Oxidative and antioxidative agents and enzymes

<i>Reactive oxygen species generators (enzymes)</i>
Cytochromes
NAD(P)H oxidase
Cyclooxygenase
Lipoxygenase
Monoamine oxidase, etc.
<i>Oxidative agents</i>
O <sub>2</sub> <sup>-</sup> : Superoxide anion
·OH: Hydroxyl radical
H <sub>2</sub> O <sub>2</sub> : Hydrogen peroxide
ONOO <sup>-</sup> : Peroxynitrite, etc.
<i>Antioxidative enzymes</i>
Superoxide dismutase
Catalase, etc.
<i>Antioxidants</i>
Thioredoxin
Glutathione
Vitamins C, A, E
N-acetyl cysteine
Cysteine, etc.

the products of reactions between ROS and membrane lipids (i.e., peroxidized lipids) are increased in patients in the acute phase of schizophrenia (Mahadik and Scheffer 1996; Ben Othmen et al. 2008). ROS also reacts with the guanosine residue of DNA in nuclei, converting it to 8-hydroxy-2-deoxyguanosine and leading to DNA fragmentation. The brain contents of 8-hydroxy-2-deoxyguanosine and fragmented DNA are elevated in patients with schizophrenia (Nishioka and Arnold 2004; Buttner et al. 2007). Blood levels of pentosidine, an advanced glycation end product, are also elevated as a result of sugar oxidation and are higher in patients with schizophrenia (Arai et al. 2010, 2014).

Conversely, the total amount of ROS scavengers (TAR, the total antioxidative response) is reduced in patients with schizophrenia (Ustundag et al. 2006). Blood concentrations of vitamins C and E are decreased in patients with schizophrenia (Suboticanec et al. 1990; McCreadie et al. 1995). In addition to these small molecules, the levels of enzymes that produce or degrade ROS are also altered. The activities of superoxide dismutase (SOD) and catalase are downregulated in the erythrocytes of patients with schizophrenia (Ben Othmen et al. 2008). Glutamate cysteine ligase is also decreased in patients with schizophrenia (Gysin et al. 2007). These findings suggest that the magnitude of ROS generation appears to be upregulated in patients with schizophrenia.

The pathologic interactions between ROS and psychosis have been investigated in animal models for drug-induced psychosis to monitor ROS generation following exposure to psychostimulants such as amphetamine, phencyclidine, ketamine, or

the NMDA receptor blocker dizocilpine (MK-801). Behrens et al. (2007) showed that a ketamine-induced abnormality in GABAergic neurotransmission and behavior involves ROS generation by NOX. Zuo et al. (2007) also observed increases in hydroxyl radicals in the brain following MK-801 and ketamine challenges. It is established that psychostimulants upregulate ROS production in the brain and contribute to psychostimulant-driven behavioral impairments.

However, caution is necessary when relating these findings to schizophrenia. One problem is the disease specificity of ROS pathology (Cobb and Cole 2015). The pathologic implications of ROS are not limited to schizophrenia. ROS is also implicated in Alzheimer's disease and Parkinson's disease (Lovell and Markesbery 2007; Nakabeppu et al. 2007). Neural activity itself involves higher energy metabolism and results in higher ROS production, as evident in patients with epilepsy (Puttachary et al. 2015). Medication for schizophrenia also enhances the production of ROS; the metabolism of antipsychotic drugs necessitates cytochrome P450 recruitment and also promotes dopamine release and monoamine oxidase activation, all of which drive ROS generation (Martins et al. 2008; Reinke et al. 2004; Table 1). In this context, the pathologic and pharmacologic roles of ROS generation in patients with schizophrenia are controversial and remain to be characterized further (Naviaux 2012).

## 2 Pharmacologic Actions of Antioxidants in Patients with and Animal Models for Schizophrenia

In contrast to arguments supporting the pathologic role of ROS in patients with schizophrenia, many reports more consistently describe the antipsychotic actions of reducing agents. A variety of reducing agents and radical scavengers, including  $\omega$ -3 fatty acids, *N*-acetyl cysteine, minocycline, and vitamins C and E, have been administered to patients, and their therapeutic effects evaluated. Based on this theory, Sivrioglu et al. (2007) supplemented the food of patients with schizophrenia with  $\omega$ -3 fatty acids and reported a reduction in antipsychotic side effects and an improvement in psychotic symptoms. Farokhnia et al. (2013) administered a more potent antioxidant, *N*-acetyl cysteine, to patients with schizophrenia and observed its effectiveness on negative symptoms. In combination with atypical antipsychotics, minocycline was administered to patients in the acute phase, resulting in an improvement in cognition and negative symptoms (Miyaoaka et al. 2007; Levkovitz et al. 2010).

The antipsychotic effects of reducing agents have also been tested in several animal models. Both MK-801 and methamphetamine induce hyperlocomotion and social interaction deficits and cause neurodegeneration in various parts of the brain (Ozyurt et al. 2007). The administration of vitamin E into MK-801-challenged rats decreased cell death in the cingulate cortex (Zhang et al. 2006; Willis and Ray 2007), whereas the administration of the radical scavenger edaravone inhibited cell

death in striatal neurons (Kawasaki et al. 2006). In addition to cell death, the behavioral deficits induced by phencyclidine are also ameliorated by the scavenger of a SOD mimetic (Wang et al. 2003). Neonatal hippocampal lesions result in behavioral impairments at the postpubertal stage and serve as an animal model of schizophrenia (Lipska et al. 1993). The antipsychotic effects of *N*-acetyl cysteine have been verified in this animal model (Cabungcal et al. 2014). Despite discrepancies in the arguments supporting an etiologic or pathologic role of ROS in schizophrenia, almost all antioxidative agents exhibit beneficial effects on cognitive abnormalities relevant to schizophrenia, although the cellular and molecular mechanisms underlying these pharmacologic phenomena remain unclear.

### 3 Strong Interactions Between ROS and Cytokine Signaling

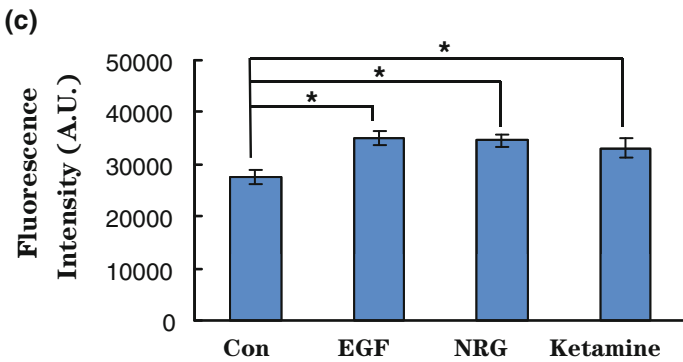
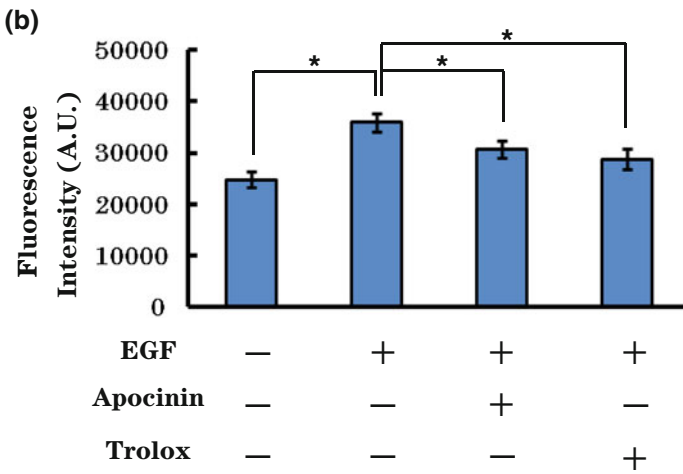
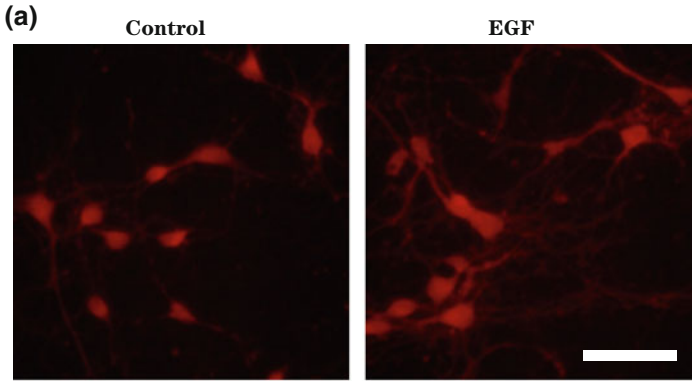
ROS signaling is known to link to cytokine production and cytokine receptor signaling (Landskron et al. 2014). Proinflammatory cytokines and growth factors activate NOX and produce ROS. Brain neurons and microglia release ROS in response to cytokines. Conversely, generated ROS stimulate cytokine production by activating the redox sensor NF- $\kappa$ B (Lian and Zheng 2009) or accelerate cytokine receptor signaling by inhibiting the redox sensor phosphatase. Notably, ROS alone induces the phosphorylation and activation of cytokine receptors in the absence of cytokine ligands such as epidermal growth factor (EGF). In this review, we discuss the interaction between ROS and EGF signaling most extensively demonstrated in the field of carcinogenesis (Chiarugi et al. 2003; Goldkorn et al. 2005).

EGF signaling is highly implicated and serves as a drug target in tumor biology, because this cytokine potently produces ROS, which are known to be DNA mutagens. An EGF challenge to cancer cells and cultured neurons elevates intracellular ROS concentrations (Bae et al. 1997; Cha et al. 2000). Table 2 shows the potency of the cytokines that induce ROS production in cultured neocortical

**Table 2** Comparison of cytokine-induced reactive oxygen species production

DHE oxidation levels (% control)	
Control	100 $\pm$ 6.3
EGF	132 $\pm$ 5.4
Interleukin-1	125 $\pm$ 5.8
Interleukin-6	130 $\pm$ 6.1
Neuregulin-1	130 $\pm$ 8
BDNF	142 $\pm$ 8
Ionomycin (positive control)	153 $\pm$ 8.7

Cultured cortical neurons were exposed to various cytokines in the presence of dihydroethidium. Fluorescence intensity (560 nm) was measured in randomly selected 10 cells (n = 8)  
*DHE* dihydroethidium; *EGF* epidermal growth factor



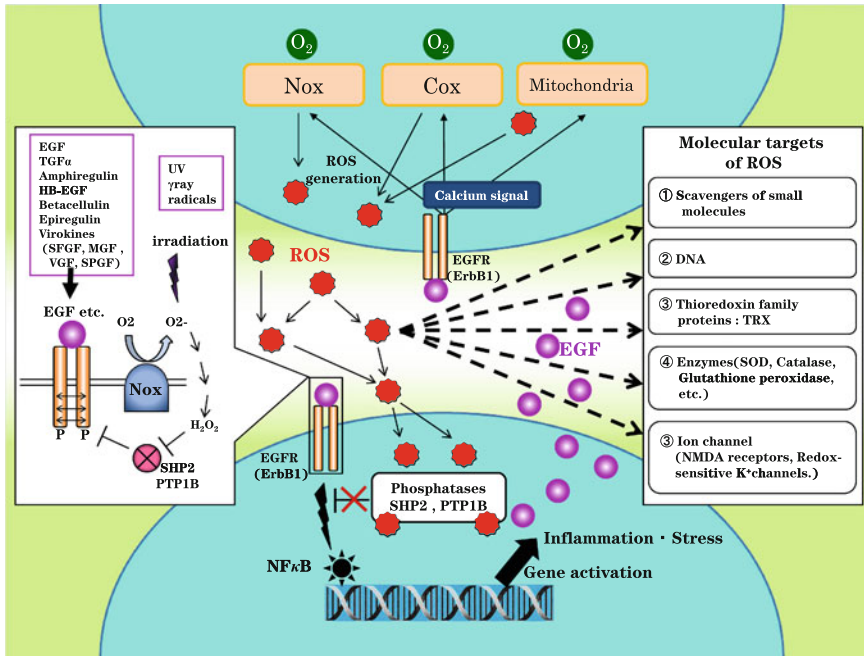
◀ **Fig. 1** The effects of EGF and antioxidants on the levels of ROS in neocortical cultures. **a** Cultured cortical neurons (DIV7) were stimulated with or without 20 ng/ml EGF. ROS production was assessed by mitotracker, which sensed mitochondrial membrane potential. *Scale bar* 50  $\mu\text{m}$ . **b** Cultured cortical neurons were treated with antioxidants (0.5 mM apocynin, 100  $\mu\text{M}$  Trolox) in the absence or presence of 20 ng/ml EGF. **c** Cultured cortical neurons were stimulated with 20 ng/ml EGF, 20 ng/ml neuregulin-1, or 1  $\mu\text{M}$  ketamine. The MitoTracker fluorescence intensity was measured in 10 cells per well using Image J (National Institutes of Health, Bethesda, MD, USA; arbitrary units, A.U.).  $n = 8$ ,  $*P < 0.05$ , EGF epidermal growth factor

neurons. EGF oxidizes the ROS indicator dihydroethidium and changes the indicator to a fluorescent form. This EGF-triggered increase in ROS levels is blocked by the co-application of antioxidants (apocynin, Trolox; Fig. 1). These results indicate that EGF indeed induces ROS production in the brain.

In such inflammatory conditions, the main source of ROS is NOX, which is highly potentiated by EGF signals (Fan et al. 2005a, b; Chen et al. 2008). De Yulia et al. (2005) proposed that hydrogen peroxide is produced by the EGF receptor (EGFR, also known as ErbB1) itself. Conversely, ROS converts the thiol group of a cysteine residue to sulfuric acid in the core region of the tyrosine phosphatase PTP1B, inactivating this enzyme (Yip et al. 2010). Compared with many receptor-type protein tyrosine kinases, the EGFR undergoes a significant amount of basal autophosphorylation in the absence of its ligand and requires phosphatases for its silencing in a basal condition. Thus, the ROS-driven inactivation of PTP1B alone increases phosphorylation of the EGFR, resulting in the activation of EGF signaling without ligands (Lee et al. 1998; De Wit et al. 2001). Thus, hydrogen peroxide-oxidized low-density lipoprotein can also phosphorylate EGFR in the absence of EGF and evoke EGFR signaling (Suc et al. 1998). If acting on peripheral cells, hydrogen peroxide may promote cell proliferation and induce carcinogenesis. In this context, the EGFR signaling cascade appears to be one of the most crucial ROS targets.

Figure 2 summarizes the production of and interaction between EGF and ROS. The ligand EGF binds to EGFR and activates calcium signaling, in turn activating the ROS generators NOX, cyclooxygenase, and cytochromes in mitochondria. The ROS produced acts on phosphatases such as PTP1B and enhances and prolongs the EGF signal transduction. The enhanced phosphorylation of EGFR also hinders its internalization (Ravid et al. 2002). Additionally, ROS acts on the redox site of the transcription factor NF- $\kappa$ B and accelerates NF- $\kappa$ B-mediated gene expression, leading to the synthesis of mRNA for EGF and other cytokines. When ROS reacts with ion channels, neurotransmission in the brain is perturbed unless ROS are trapped by various scavenger molecules (glutathione, thioredoxin, SOD, catalase, etc.).

As shown in Table 2, the EGF homologue neuregulin-1 (NRG-1) triggers ROS production in the brain. In contrast to EGF, NRG-1 binds to the ErbB3 or ErbB4 receptor tyrosine kinases, but NRG-1 signal transduction also involves ROS-mediated autoregulation. However, compared with EGF, NRG-1-driven ROS production is more persistent (Goldsmith et al. 2001).



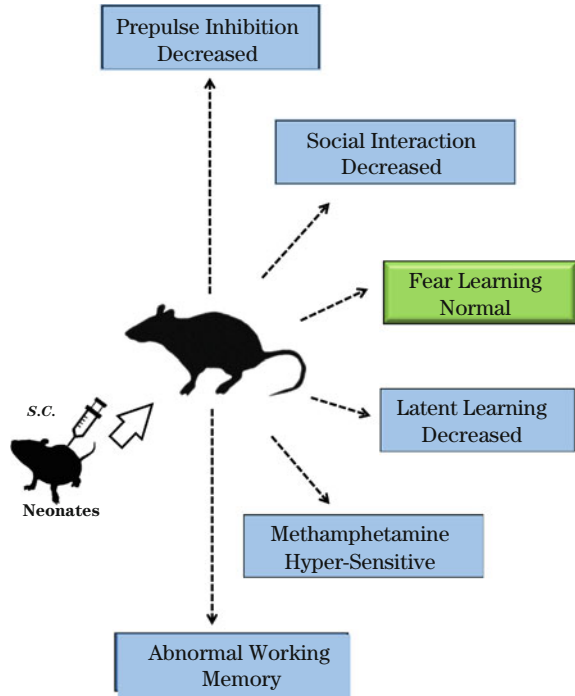
**Fig. 2** Schematic diagram of the interaction between EGF and ROS. EGF and its homologues (transforming growth factor alpha, amphiregulin, heparin-binding EGF-like growth factor, betacellulin, epiregulin, neuregulins 1–6) as well as poxvirus virokines (SMDF, VGF, etc.) directly and indirectly interact with the EGFR (also known as ErbB1) to evoke calcium signaling. This activates NOX, cyclooxygenase (COX), and mitochondrial cytochrome c, which produce ROS. In turn, ROS act on and inhibit protein tyrosine phosphatases (SH2, the protein tyrosine phosphatase PTP1B, etc.) and promote the phosphorylation and activation of EGFR, leading to the production of other cytokines and the further activation of NOX, COX, and mitochondrial cytochromes. *EGF* epidermal growth factor; *EGFR* EGF receptor; *NOX* NADPH oxidase; *ROS* reactive oxygen species

#### 4 Establishment of Animal Models of Schizophrenia by Exposure to EGF and NRG-1

Maternal viral infection and obstetric complication are implicated as environmental risk factors for schizophrenia (Nawa and Takei 2006; Iwakura and Nawa 2013). EGF is known to be highly enriched in human amniotic fluids and contributes to obstetric complication (Varner et al. 1996). EGF derivatives are known to be encoded in viral genome of poxviruses and might be supplied to human fetus and neonates via their infection (Tzahar et al. 1998). Genetic linkage studies and neuropathologic investigations also suggest an association between schizophrenia and EGF and its derivative NRG-1 (Futamura et al. 2002; Anttila et al. 2004; Stefansson et al. 2004; Groenestegge et al. 2007). On the premise of the neurodevelopmental



**Fig. 3** Behavioral impairments in the animal model of schizophrenia established by perinatal exposure to EGF. *EGF* epidermal growth factor. Various behavioral abnormalities emerge at the post-pubertal stage



hypothesis for this illness, therefore, we analyzed animal models of schizophrenia established by perinatal exposure to EGF and its derivatives (Futamura et al. 2003; Tohmi et al. 2004; Watanabe et al. 2004; Tsuda et al. 2008; Kato et al. 2011). Treatment of neonatal rats and mice with EGF, NRG-1, and their homologues and paralogues (i.e., transforming growth factor alpha, epiregulin) all showed the behavioral deficits relevant to schizophrenia at the postpubertal stage (Fig. 3). Injected factors penetrate the immature blood–brain barrier and bind to brain neurons carrying EGFR or ErbB receptors, such as GABAergic and dopaminergic neurons (Abe et al. 2009; Namba et al. 2009). In addition to dopaminergic neurons, GABAergic neurons and glial cells also respond to these cytokines, but their responses gradually diminish after the cessation of cytokine treatment (Nagano et al. 2007; Abe et al. 2011). The most prominent and persistent influences of cytokine treatment are those on dopaminergic neurons, which cause the animals to display cognitive and behavioral impairments (Sotoyama et al. 2011, 2013). These behavioral impairments include abnormalities in sensorimotor gating (prepulse inhibition [PPI]), social interaction, exploratory movement, latent inhibition of learning, and sensitivity to psychostimulants (methamphetamine and/or MK-801), although the directions and magnitudes of these deficits are significantly altered by the genetic background of the animal species used (Mizuno et al. 2004; Tohmi et al. 2005). This observation agrees with the current theory that the onset of schizophrenia involves both genetic and environmental factors.

Although many animal models of schizophrenia have been established, our animal models have the following three characteristic features (Nawa et al. 2014):

- The emergence of behavioral abnormalities occurs not before or during puberty, but around the postpubertal stage. The EGF-exposure-generated monkey model of schizophrenia shows striking behavioral deficits from 5 years of age (Sakai et al. 2014).
- EGF- and NRG-1-exposure-generated models have no apparent deficits in learning. In the eight-arm radial maze test, context fear-learning paradigm, and active avoidance test, these models are indistinguishable from controls (Futamura et al. 2003; Kato et al. 2011).
- Atypical antipsychotics, such as risperidone and clozapine, are effective for the above behavioral deficits, whereas the pharmacologic action of typical antipsychotics (i.e., haloperidol) is limited (Futamura et al. 2003, Sotoyama et al. 2013).

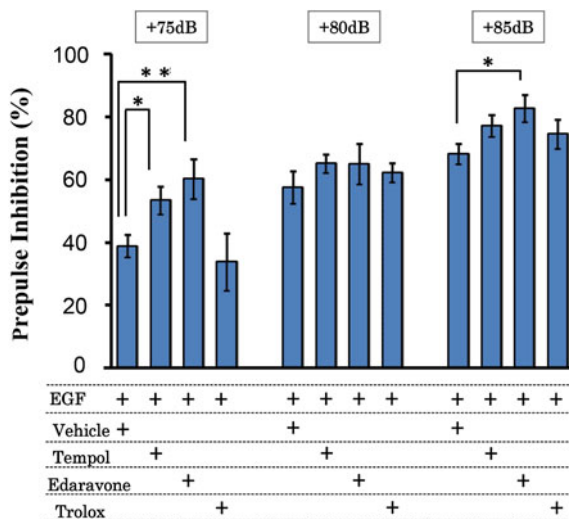
We found similar behavioral abnormalities in transgenic mice in which EGF or NRG-1 was overexpressed from their transgenes (Kato et al. 2010; Eda et al. 2013). However, these approaches to cytokine administration obscure their cellular target (s). The behavioral abnormalities may therefore be ascribed not only to the dysfunction of midbrain dopaminergic neurons but also to that of other peripheral organs. To limit the target organ of the cytokines, we conducted intracerebroventricular administration of EGF into adult rats and verified the reproducibility of the behavioral impairments achieved by perinatal pre-exposure to EGF (Mizuno et al. 2007). This result suggests that peripherally administered EGF targets brain neurons in the neonatal EGF model for schizophrenia.

Subsequent analyses of these models revealed that NRG-1 mainly acts on dopaminergic neurons in the ventral tegmental area of the midbrain, whereas EGF interacts with those in the substantia nigra to promote dopamine synthesis and terminal arborization (Abe et al. 2009; Iwakura et al. 2011a, b). Neonatal mice treated with NRG-1 exhibit a hyperdopaminergic state in the prelimbic cortex (i.e., the medial prefrontal cortex) as adults (Kato et al. 2011). Similarly, neonatal rats treated with EGF display a hyperdopaminergic state in the globus pallidus (Sotoyama et al. 2011). Dopaminergic innervation and release in the globus pallidus are significantly elevated in this model. However, their PPI deficits and abnormal dopamine release are simultaneously normalized by the local administration of an antipsychotic drug to the globus pallidus (Sotoyama et al. 2011, 2013). The globus pallidus is enriched with dopamine D2 receptors and is the major target of antipsychotic drugs in the indirect pathway of the basal ganglia.

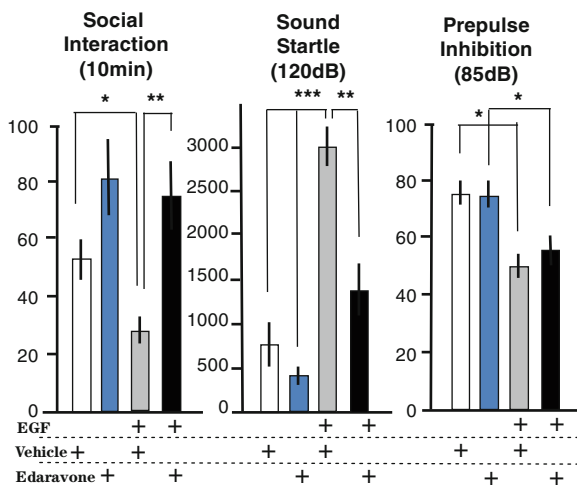
## 5 Pharmacologic Actions of ROS Scavengers in the EGF-Exposure-Generated Model

As mentioned earlier, EGF is a potent ROS producer, and knockdown of protein phosphatases by ROS in turn enhances phosphorylation-based signaling cascades emanating from EGFR. In agreement, Finch et al. (2006) found that catalase degrades hydrogen peroxide and reduces EGF signaling. To assess the direct interaction between ROS production and EGF signaling, we administered the three ROS scavengers (Trolox, edaravone, and 2,2,6,6-tetramethyl-4-piperidinol-N-oxyl [TEMPOL]) during EGF treatment in neonatal rats. The effects of these scavengers on the PPI deficits of EGF-treated rats were evaluated at the adult stage (Fig. 4). Co-administration of TEMPOL and edaravone with EGF resulted in attenuation of the PPI deficits of the EGF-exposure-generated model. This result suggests that ROS production during neonatal EGF treatment is required to generate the model.

We also examined the medication effects of ROS scavengers (emodin, Trolox, edaravone) on the behavioral impairments of the EGF- pretreatment model at the adult stage (Fig. 5). Emodin is a polyphenol ROS scavenger known as 3-methyl-1,6,8-trihydroxyanthraquinone and attenuates EGFR signaling (Mizuno et al. 2008). Edaravone is otherwise known as 3-methyl-1-phenyl-2-pyrazolin-5-one and is prescribed to patients who have suffered a stroke to mitigate the expansion of cerebral ischemic injuries. This drug is verified to reduce EGFR signaling in cancer cells (Suzuki et al. 2005). Subchronic treatment with emodin at



**Fig. 4** Competition by antioxidants with neonatal EGF treatment. Epidermal growth factor (EGF; 0.875  $\mu\text{g/g}$ , administered subcutaneously) or saline was administered daily on postnatal days 2–11 together with antioxidants (3 mg/kg TEMPOL, 10 mg/kg edaravone, and 10 mg/kg Trolox). Interference with the effects of EGF on prepulse inhibition scores was monitored at the adult stage.  $n = 5$  in each group,  $*P < 0.05$  and  $**P < 0.01$ , EGF epidermal growth factor



**Fig. 5** Antipsychotic effects of edaravone on the EGF model relevant to schizophrenia. Epidermal growth factor (0.875  $\mu\text{g/g}$ ) or saline was administered subcutaneously daily on postnatal days 2–11. Adult rats were treated with or without the radical scavenger edaravone (5 mg/kg/day for 7 days, administered intraperitoneally).  $n = 6$ –11 in each group, \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$ . EGF epidermal growth factor

the adult stage suppressed the acoustic startle response and abolished the PPI deficits of the EGF-pretreatment model (Mizuno et al. 2008). The medication effects of emodin on social interaction impairments were undetectable. However, we observed an antipsychotic-like activity of emodin in the methamphetamine model (Mizuno et al. 2010). In contrast to emodin, intraperitoneal injection of edaravone improved social interaction scores and decreased an abnormally high acoustic startle response of the EGF-pretreatment model, although it had no effect on their PPI deficits (Fig. 5). Both the results verified the pharmaceutical effectiveness of ROS scavengers on behavioral impairments relevant to schizophrenia. However, the antipsychotic-like profiles of the individual scavengers differed significantly. Presumably, the preference for the target ROS species differs between those ROS scavengers and results in the diversity between their pharmacologic profiles (Suzuki et al. 2005).

Although the therapeutic mechanism of ROS scavengers remains undetermined, we believe the EGFR signaling cascade to be one of their molecular targets, as suggested by Suzuki et al. (2005). We postulate that an elevation in EGFR signaling (e.g., ErbB1, ErbB2) is sustained until the adult stage even when EGF treatment is completed during the neonatal stage (Futamura et al. 2002). The hypothesis stems from the fact that the administration of specific EGFR blockers also ameliorated the behavioral deficits of the EGF-exposure-generated model (Mizuno et al. 2008, 2013). In light of the strong interaction between EGF signaling and ROS production, further study is warranted into which plays the crucial role in the pathogenesis of both the EGF-exposure-generated model and patients with schizophrenia.

## 6 Conclusion

There are tight interactions between ROS and cytokine signaling. In particular, such interactions are evident for the EGF signal cascade in which basal EGFR autophosphorylation is not negligible. ROS itself inactivates its phosphatases and provokes EGF receptor signaling without any ligands. Conversely, EGFR phosphorylation efficiently activates various ROS-generating enzymes such as NOX and COX to produce excess amounts of ROS. The cytokine–ROS system appears to be recruited in the pathologic conditions of brain injury, infection, and seizures to protect the organ with their given neurotrophic actions as well as to promote the regeneration processes from the insults. When the activation of the cytokine–ROS system is prolonged, the unfavorable side effects emerge in dopaminergic and glutamatergic development/neurotransmission, leading to abnormal brain functions. Our latest results from the EGF model indicate that oxygen radical scavengers are beneficial for the medication of their cognitive deficits. However, the pharmacological profiles differ significantly among scavengers. We hope that safe and novel antipsychotic drugs will be developed from any of oxygen radical scavengers.

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