An emerging role of cGMP in the treatment of schizophrenia: A review

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ABSTRACT

Schizophrenia is a progressive psychotic disorder with devastating effects on the broad aspects of human emotion, perception, thought, and psychosocial interactions. Although treatment with antipsychotic drugs, the mainstay in the treatment of schizophrenia, the large number of patients with schizophrenia respond poorly to the pharmacological and, the large number of patients with schizophrenia poorly respond to the pharmacological treatment. Although a variety of novel therapeutics have long been tested, to date, no drugs clinically efficacious for schizophrenia are available. The multiple lines of evidence strongly suggest that the modulation of cyclic guanosine monophosphate (cGMP) is a promising target in promoting the novel therapeutic strategies of schizophrenia beyond the "receptor-dependent" psychopharmacology. cGMP is modulated via regulating its synthesis by N-methyl-D-aspartate receptor (NMDAR) and nitric oxide (NO), which regulate guannylyl cyclase (GC), the enzyme producing cGMP. cGMP is also regulated by phosphodiesterase (PDE), the enzyme hydrolyzing cGMP. In this review, we critically evaluate the therapeutic potential of agents modulating cGMP activity by regulating cGMP synthesis including NMDAR enhancers, NO enhancers, NO inhibitors including minocycline with anti-inflammatory properties and PDE inhibitors in improving the negative, cognitive and positive symptoms of schizophrenia. We also discuss the possible mechanisms by which these agents produce therapeutic effects on schizophrenia including cGMP signaling pathways, oxidative stress, and neuroinflammation.

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1. Introduction

Schizophrenia is a psychotic disorder that has devastating effects on diverse aspects of human emotion, perception, thought, and cognitive function (American Psychiatric Association, 2013). The clinical features of schizophrenia are commonly classified into distinct clusters of positive, negative and cognitive symptoms (Schultz and Andreasen, 1999). Pharmacological treatment of schizophrenia is a mainstay in the therapeutic strategies of the disorder. The key mechanism of action of the "first-generation" antipsychotic drugs is the blockade of dopamine receptors (Miyamoto et al., 2005). Second-generation agents block serotonin receptors and have a wider variety of other receptor binding profiles (Miyamoto et al., 2005), but despite this advance, approximately 30% of patients respond poorly to currently available treatments (Kennedy

et al., 2014). The field is in need of new treatments targeting novel mechanisms in order to reduce the burden of treatment resistance.

For the last decade, multiple lines of evidence from preclinical and clinical studies suggest that modulation of cyclic guanosine monophosphate (cGMP) could be a new mechanism for the treatment of schizophrenia that extends beyond "receptor-dependent" psychopharmacology (Bernstein et al., 2011; Kehler and Nielsen, 2011). The synthesis of cGMP by the enzyme guannylyl cyclase (GC) is regulated by the N-methyl-D-aspartate receptor (NMDAR), a subtype of the glutamate receptors, and nitric oxide (NO). The enzyme phosphodiesterase (PDE) hydrolyzes cGMP, providing another regulatory pathway. In this review, we critically evaluate the therapeutic potential of NMDAR enhancers, NO enhancers, NO inhibitors, PDE inhibitors (PDEIs) and the anti-inflammatory agent minocycline as they can potentially impact cGMP. We also discuss the possible mechanisms by which these agents could produce therapeutic effects on schizophrenia by means of their impact on cGMP signaling pathways, oxidative stress, and neuroinflammation.

2. Regulation of cGMP and its signaling pathways

cGMP is ubiquitously distributed in cells. It serves as a key second messenger mediating cGMP signaling pathways (Francis et al., 2010; Russwurm et al., 2013). cGMP activates cGMP-dependent protein kinase (PKG), which in turn phosphorylates diverse proteins. These phosphorylated proteins initiate signaling cascades leading to diverse

molecular and cellular effects. cGMP also directly activates multiple proteins such as the cGMP-gated cation channels (Francis et al., 2005). In addition, cGMP binds to the catalytic and allosteric sites of PDE and enhances its own breakdown via a negative feedback mechanism (Francis and Corbin, 2005; Russwurm et al., 2013). cGMP is synthesized from guanosine-5′-triphosphate (GTP) by the catalytic action of guannylyl cyclase (GC) and is degraded to 5′ guanylyl monophosphate (5′-GMP) by PDE (Francis et al., 2005; Russwurm et al., 2013). Thus, GC and PDE are the main regulators in determining the intracellular level of cGMP (Fig. 1). To date, two types of GC have been identified: soluble GC and membrane-bound GC. Membrane-bound GC is activated by extracellular ligands. Only soluble GC is a key factor in regulating the PKG-mediated signaling pathway and other intracellular neurochemical processes (Francis et al., 2010).

PDE is a family of enzymes hydrolyzing cGMP and/or cyclic adenosine monophosphate (cAMP). Of the eleven known PDE families, three enzymes (PDEs 5, 6, 9) selectively hydrolyze cGMP, five enzymes (PDEs 1, 2, 3, 10, and 11) hydrolyze both cGMP and cAMP, and the last three enzymes (PDEs 4, 7, 8) hydrolyze cAMP selectively (Fig. 1) (Omori and Kotera, 2007; Maurice et al., 2014).

3. The NO/cGMP/PKG signaling pathway

Because NO is required to activate soluble GC, soluble GC is called NO sensitive GC (NO-GC) (Francis et al., 2010; Russwurm et al., 2013). NO is generated by NO synthases (NOS) in neurons (nNOS) and endothelial cells (eNOS) (Russwurm et al., 1998). NOS is constitutively inactive and maintains NO at low baseline levels. With calcium influx into a cell, calcium binds to calmodulin and forms the calcium/calmodulin complex (Garthwaite et al., 1989). This complex activates NOS, which converts L-arginine to NO and L-citrulline (Ignarro et al., 1999; Rameau et al., 2004). NOS is a potent enzyme that can induce a several 100-fold increase in the synthesis of cGMP (Derbyshire and Marletta, 2009; Stone and Marletta, 1996). NO-GC catalyzes cGMP synthesis and thus dramatically increases cGMP levels. cGMP initiates cGMP-mediated signaling processes by activating numerous target proteins that trigger diverse signaling cascades (Hofmann and Wegener, 2013)
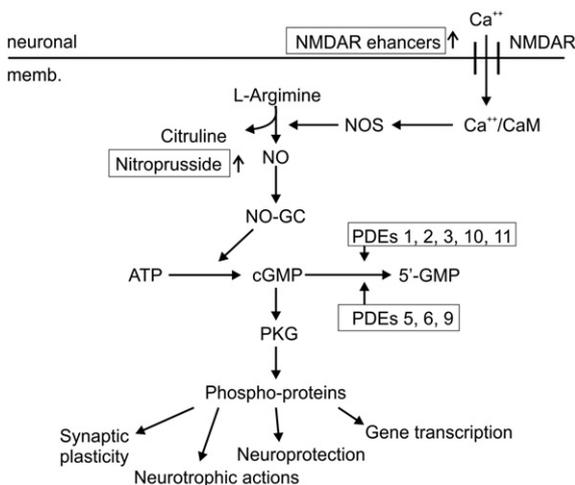
Fig. 1. The NMDAR-NO-cGMP signaling pathway. Ca^{++} influxes via NMDAR and forms Ca^{++}/CaM complex, which activates NOS. The NOS activated catalyzes NO synthesis, and NO activates GC. GC catalyzes cGMP synthesis. cGMP activates PKG, which phosphorylates and thus, activate diverse proteins. The proteins activated initiate diverse bio-molecular processes including the gene expression of many proteins leading to neuroprotection, neurotrophic actions, neuroplasticity and synaptic plasticity. cGMP is degraded by PDE. NMDAR enhancers, nitroprusside and PDEIs up-regulate the cGMP-mediated signaling pathway by enhancing Ca^{++} influx and NO level, and blocking cGMP breakdown, respectively. PDEIs 5, 6, 9 catalyze only cGMP. PDEIs 1, 2, 3, 10, 11 catalyze cGMP and cAMP. NMDAR: N-methyl-D-aspartic acid, Ca^{++}/CaM: Calcium calmodulin complex, NO: nitric oxide, cGMP: cyclic guanosine monophosphate, PKG: cGMP-dependent protein kinase, PDEI: phosphodiesterase inhibitor,

(Fig. 1). At each step in these cascades, interactions are progressively amplified and produce diverse cellular and physiological actions such as neuroprotection, neurotropic actions, synaptic plasticity, endothelial permeability, and smooth muscle relaxation. Recent research has investigated factors activating soluble GC such as NMDAR, NO and PDEI as potential novel therapeutics for schizophrenia.

4. Potentiation of NMDAR improves schizophrenic symptoms

The NMDAR hypo-function theory of schizophrenia proposes that the pathophysiology of the illness is related to diminished function of the NMDAR, and that the enhancement of NMDAR function improves schizophrenic symptoms (Coyle, 2013). Non-competitive NMDAR antagonists, including phencyclidine (PCP), ketamine, and MK-801 can induce a wide range of psychotic symptoms resembling schizophrenia (Domino and Luby, 1981; Krystal et al., 1994; Steinpreis, 1996). In rodents, unique behaviors such as hyperlocomotion, stereotypic behaviors, social isolation and reduced sexual interactions, that are proposed to be preclinical models of some symptoms of schizophrenia, have been observed after administration of non-competitive NMDAR antagonists (Hoffman, 1992; Moghaddam and Adams, 1998; Sams-Dodd, 1997). In the past two decades, there have been a number of augmentation trials in which NMDAR enhancers are added to antipsychotic drugs. There is growing evidence from these studies that agonists of the positive NMDAR allosteric site, glycine and D-serine, as well as sarcosine, a glycine reuptake inhibitor, improve a broad range of schizophrenia symptoms that includes negative and cognitive symptoms, although some results of individual trials are mixed (Shim et al., 2007; and see reviews in Tsai and Lin, 2010; Tuominen et al., 2005.

The mechanism by which NMDAR enhancers may improve schizophrenic symptoms has not been clearly elucidated. The most viable hypothesis is that the enhancement of NMDAR function activates the NO/cGMP/PKC signaling pathway leading to enhanced synaptic plasticity, neuroprotection, and neurotropic actions that exert effects on schizophrenia symptoms (Fig. 1) (Bernstein et al. 2011; Coyle, 2013). It is known that the NMDAR plays a major role in regulating the NO/cGMP/PKC signaling pathway (Bredt and Snyder, 1989; East and Garthwaite, 1991; Jaffrey and Snyder, 1995). NOS, which catalyzes NO synthesis, is tethered to NMDAR (Christopherson et al., 1999). As NMDAR is activated, calcium influxes and activates calcium/calmodulin-dependent protein kinase II (CaMKII) by making a calcium-calmodulin complex, which binds to CaMKII (Garthwaite et al., 1989; Rameau et al., 2004). CaMKII subsequently activates NOS tethered to NMDAR, and activated NOS catalyzes NO synthesis. Thus, NO synthesis is closely linked to NMDAR activity, and the level of NO dramatically increases following NMDAR activation (Bredt and Snyder, 1989). NO activates GC, which catalyzes cGMP synthesis, and cGMP activates the downstream of NO/cGMP/PKG signaling cascade (Hofmann and Wegener, 2013).

5. Can NO activation improve schizophrenic symptoms?

Evidence suggests that NO could be a novel therapeutic target for schizophrenia (Bernstein et al., 2005, 2011; Mizoguchi et al., 2014; Wu et al., 2013). In a recent clinical trial, a single infusion of nitroprusside, an anti-hypertensive drug that converts to NO in the body, was added to stable antipsychotic treatment. The authors reported markedly improved symptoms that emerged within 12 h and lasted for 2–4 weeks (Hallak et al., 2013). Specifically, the single infusion reduced the Brief Psychiatric Rating Scale total scores, the thought disorder, withdrawal–retardation and anxiety–depression subscale scores, and the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale. Although no studies have duplicated these dramatic findings, the results are promising for the treatment of patients with schizophrenia, particularly those with treatment-resistant schizophrenia. The NO/cGMP signaling pathway has been proposed as a plausible mechanism of action of the

drug (Hallak et al., 2013). Thus, nitroprusside, as it converts directly to NO bypassing the downstream process of NMDAR stimulation, may directly stimulate cGMP production and activate NO/cGMP signaling cascades (Fig. 1). Interestingly enough, a recent genetic study reported that glutamate transmission and cyclic GMP were genetically over-presented in individuals with schizophrenia (Docherty et al., 2015) suggesting that genetic factors may contribute to the dysfunction of glutamate transmission/NO/cGMP pathway. This finding is consistent with our proposal that the dysfunction of NMDAR, a subtype of the glutamate receptors /NO/cGMP pathway may contribute to the pathoetiology of schizophrenia, and the up-regulation of cGMP could be a novel therapeutic target for schizophrenia.

6. Does NO blockade improve schizophrenic symptoms?

Other lines of evidence suggest that the blockade of NO formation could be linked to efficacy in the treatment of schizophrenia. The activation of microglial cells plays a crucial role in neuroinflammatory processes such as the release of nitrosactive and oxidative free radicals and pro-inflammatory cytokines (Bessis et al., 2007; Garrido-Mesa et al., 2013). The "oxidative stress" hypothesis of schizophrenia proposes that genetic and developmental factors interacting with psychosocial stressors excessively activate microglial cells and trigger neuroinflammatory processes and release free radicals, including NO free radicals. Prolonged neuroinflammation ultimately produces apoptosis, mitochondrial dysfunction, excitotoxicity, and other neurotoxic processes that may contribute to the pathophysiology of schizophrenia (Fig. 2) (Dean et al., 2012; Mizoguchi et al., 2014; Wu et al., 2013; Zhang and Zhao, 2014). It has been suggested that NO free radical formation as a neuroinflammatory response may contribute to the neuropathology of schizophrenia, and the blockade of NO formation may provide therapeutic benefit (Yong et al., 2004; Zhang and Zhao, 2014).

Evidence supporting the "oxidative stress" theory of schizophrenia mainly comes from animal and clinical studies with minocycline, a tetracycline antibiotic with unique anti-inflammatory and antioxidant actions (Yong et al., 2004; Zhang and Zhao, 2014) (Fig. 2). Over nearly 10 years, minocycline has been actively investigated for its therapeutic potential in a wide range of neurological and psychiatric disorders including ischemia, spinal cord injury, Parkinson's disease, Alzheimer's disease, schizophrenia, and mood disorders (Garrido-Mesa et al., 2013).

7. Animal studies with minocycline: inflammatory models in rodents

Minocycline reduces NO levels and NOS expression in an inflammation state produced by lipopolysaccharide (LPS) or 3-nitropropioic acid (3-NP) or proinflammatory agent (Table 1) (Ahuja et al., 2008; Kim et al., 2004). Minocycline also enhances Bcl-2 level and suppresses caspase expression by blocking the release of cytokines and NO (Thomas and Le, 2004) and activating the PKG pathway downstream (Dean et al., 2012; Tang et al., 2011). Recent studies have shown that minocycline attenuated hyperlocomotion and reversed deficits in social interactions, novel object recognition and prepulse inhibition in rats administered LPS (Zhu et al., 2014b) or granulocyte-macrophage colony-stimulating factor (GM-CSF) (Table 1) (Zhu et al., 2014a). These authors propose that these molecular and behavioral effects in animals could be models of potential therapeutic effects of minocycline in schizophrenia.

8. Studies with minocycline in rodent models of schizophrenia

The therapeutic potential of minocycline for schizophrenia has also been explored as supported by the NMDAR antagonist model of
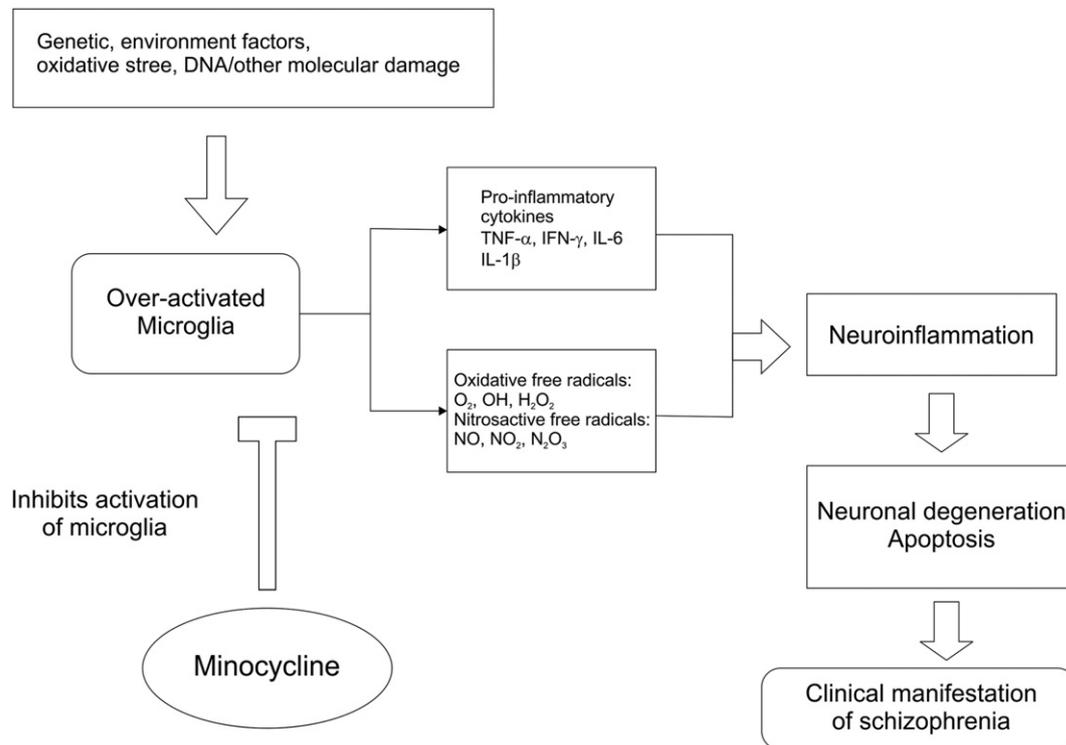
Fig. 2. Proposed mechanism of action of minocycline in the treatment of schizophrenia. Diverse factors including genetic and environmental factors, oxidative stress, DNA and other molecular damages overly activate microglia. The microglia activated triggers neuro-inflammation, releases pro-inflammatory cytokines and oxidative and nitrosactive free radicals. These neurotoxic molecules cause neuroinflammation. The prolonged neuroinflammation leads to chronic neurodegeneration and apoptosis. These neurodegenerative changes ultimately lead to the clinical manifestation of schizophrenia. Minocycline may restore microglia activation at normal levels and block neurodegeneration and apoptosis and ultimately interferes with the development of schizophrenia. TNF: tumor necrosis factor, IFN: interferon, IL; interleukin (The figure is modified from a figure in the article (Zhang and Zhao, 2014).

Table 1
Effects of minocycline on nitrosactive stress and behaviors in normal and schizophrenia-model rats.

Agents producing inflammation/SCZ model	Effects on NO formation or behaviors	Reference
Neuronal culture		
LPS	↓ NO/NO expression	Kim et al. (2004)
Normal rats		
3-NP	↓ NO/nitrite	Ahuja et al. (2008)
LPS, GM-CSF	↓ Hyperlocomotion, ↓ deficits in social interactions/disruption of prepulse inhibition	Zhu et al. (2014a)
Rats administered NMDAR antagonists (NMDA antagonist-model of schizophrenia)		
MK-801	↓ hyperlocomotion, prepulse inhibition deficits	Zhang et al. (2007)
Ketamine	↓ hyperlocomotion, ↓ prepulse inhibition deficits/social isolation/visuo–spatial memory deficits	Monte et al. (2013)
PCP	↓ novel object cognitive deficits	Fujita et al. (2007)
MK-801	↓ visuo–spatial memory deficits	Levkovitz et al. (2007)
Rats administered dopamine receptor agonists (Amphetamine model of schizophrenia)		
Apomorphine	↓ rearing, stereotypic behavior	Dokuyucu et al. (2014a,b)
Methamphetamine	↓ hyperlocomotion	Zhang et al. (2006)

SCZ: schizophrenia.
LPS: lipopolysaccharide.
3-NP: 3-nitropropioic acid.
GM-CSF: granulocyte-macrophage colony-stimulating factor.
PCP: phencyclidine.

schizophrenia. Several recent studies have shown that minocycline mitigates behavioral changes and cognitive impairment induced by the administration of non-competitive NMDAR antagonists (Table 1). For instance, Zhang et al. (2007) reported that minocycline reduced dizocilpine-induced hyperlocomotion and defects in prepulse inhibition of startle. Monte et al. (2013) demonstrated that minocycline prevented and reversed hyperlocomotion, restored prepulse inhibition, reduced social isolation, and improved cognitive deficits induced by ketamine. These findings are consistent with other studies that reported that minocycline improved memory deficits produced by MK801 and phencyclidine (Fujita et al., 2007; Levkovitz et al., 2007).

The mechanism by which minocycline reverses behavioral changes and cognitive deficits in these rodent models has not been well explained. Using the ketamine model of schizophrenia, Monte et al. (2013) showed that minocycline restored normal levels of the antioxidant marker glutathione, that removes oxidative free radicals, and thiobarbituric acid-reactive substances that are products of interactions with oxidative free radicals. Of interest is the fact that these changes occurred in the absence of NO, a typical nitrosactive free radical, generation. This study by Monte et al. (2013) suggests that minocycline may block oxidative stress rather than nitrosactive stress. The findings that minocycline improved visuospatial memory deficits in the non-competitive NMDAR antagonist model of schizophrenia provides encouraging evidence that minocycline could improve cognitive deficits in schizophrenia (Table 1) (Fujita et al., 2007; Levkovitz et al., 2007; Monte et al., 2013). Two studies have shown that minocycline improved hyperlocomotion produced by methamphetamine (Hashimoto et al., 2007; Zhang et al., 2006). A recent study using administration of the dopamine agonist apomorphine reported that minocycline had normalizing effects on rearing and stereotypy, two behaviors that are regarded as models of psychotic symptoms in humans (Dokuyucu et al., 2014a,b).

Animal studies suggest that minocycline block the formation of free radicals, and this action may also contribute to its potential efficacy in the treatment of schizophrenia (Fig. 2) (Yong et al., 2004; Zhang and Zhao, 2014). However, these studies demonstrate that minocycline blocks multiple aspects of inflammation. Accordingly the blockade of free radical formation is only a part of its complicated anti-inflammatory actions. Oxidative free radicals are the main types of free radicals formed. Nitrosactive free radicals, the production of which depends on interactions with NO, comprise a small portion of free radicals formed. Thus, even if minocycline may block NO formation, it is not clear whether this is the main mechanism by which minocycline can exhibit the potential efficacy for schizophrenia. So far, there is no

strong evidence that down-regulation of NO is clearly related to antipsychotic effects of minocycline.

9. Minocycline augmentation trials in patients with schizophrenia

In the past several years, a small number of clinical trials of minocycline augmentation have been conducted (Table 2) (Ghanizadeh et al., 2014; Qurashi et al., 2014). These studies have generally shown that minocycline augmentation of antipsychotic drugs improves negative symptoms of schizophrenia. A recent meta-analysis of four placebo-controlled, double blind trials of minocycline augmentation reported that minocycline reduced the negative symptom subscale score of the PANSS (Chaudhry et al., 2012; Khodaie-Ardakani et al., 2014), reduced the Scale for the Assessment of Negative Symptoms (SANS) score (Levkovitz et al., 2010), or reduced both PANSS and SANS (Liu et al., 2014). Another very recent placebo-controlled, double-blind minocycline augmentation trial showed that the addition of minocycline to risperidone reduced SANS score without changing PANSS-negative symptoms subscale score (Ghanizadeh et al., 2014). Although these data provide hope for the therapeutic potential of minocycline in schizophrenia, these findings need to be confirmed by trials focusing on the long-term effects of minocycline with larger sample sizes of subjects diagnosed only with schizophrenia excluding those with schizophrenia spectrum disorders.

10. PDEIs as a potential target in the treatment of schizophrenia

PDE is a primary regulator that controls intracellular levels of cGMP. Among the 12 families of PDEs, only three PDEs 5, 6, and 9 selectively hydrolyze cGMP (Maurice et al., 2014; Omori and Kotera, 2007). Evidence suggests that the inhibitors of phosphodiesterases (PDEIs) could have therapeutic potential for schizophrenia (Halene and Siegel, 2007; Kehler and Nielsen, 2011). Earlier reviews have focused primarily on PDE regulation of cAMP, with little focus on cGMP regulation (Halene and Siegel, 2007; Siuciak, 2008). Two studies have shown that cGMP levels in the cerebral spinal fluid were lower in drug-naïve patients with schizophrenia than in controls (Ebstein et al., 1976; Gattaz et al., 1983), and treatment of schizophrenia subjects with antipsychotic drugs increased cGMP levels by an average of 50% (Ebstein et al., 1976).

Among PDEIs hydrolyzing cGMP, PDE 5 inhibitors have been studied most extensively. The administration of sildenafil, a PDE 5 inhibitor, was shown to produce significant increases in extracellular cGMP levels in the prefrontal cortex, cerebellum, and hippocampus of rodents (Marte et al., 2008). Goff and his group examined the cognitive effects of

Table 2
Anti-psychotic effects of minocycline augmentation: placebo-controlled, double-blind trials.

Clinical trials	Sample size	Trial duration	Daily doses	Antipsychotics	Rating scales	Outcome
Levkovitz et al. (2010)	54	6 months (early SCZ)	200 mg	Atypical antipsychotics	SANS CGI	↓ negative symptoms ↓ cognitive symptoms
Chaudhry et al. (2012)	94	One year (early SCZ)	200 mg	Unspecified	PANSS	↓ negative symptoms
Ghanizadeh et al. (2014)	35	8 weeks	200 mg	Risperidone	SANS PANSS	↓ negative symptoms → negative symptoms
Khodaie-Ardakani et al. (2014)	38	8 weeks	200 mg	Risperidone	PANSS	↓ negative, positive symptoms; ↓ general psychopathology
Liu et al. (2014)	92	16 weeks (early SCZ)	200 mg	Risperidone	PANSSSANS	↓ negative symptoms

SCZ: schizophrenia.
SANS: Scale for the Assessment of Negative Symptoms.
PANSS: Positive and Negative Syndrome Scale.
CGI: Clinical Global Impression scale.

sildenafil added to antipsychotic drugs in patients with schizophrenia (Goff et al., 2009). This double blind, placebo-controlled crossover trial focusing on the acute effects of sildenafil showed no significant changes in schizophrenia symptoms or cognition. A subsequent randomized, double blind, placebo-controlled trial found that sildenafil augmentation of risperidone in schizophrenia subjects improved positive and negative symptoms (Akhondzadeh et al., 2011). A placebo-controlled study of another PDE 5 inhibitor, vardenafil, examined changes in sensory gating in rats and humans, but failed to find sensory gating changes in either rats or humans (Reneerkens et al., 2013). Zaprinast, a PDE 5 inhibitor with additional affinity for PDE9, was studied in a mouse model for schizophrenia via assessment of prepulse inhibition (Issy et al., 2014). The study showed that zaprinast failed to modify the disruption of prepulse inhibition produced by amphetamine and, when given alone, did not affect prepulse inhibition.

Among PDE inhibitors, PDE 9 inhibitors display the greatest affinity for cGMP and are located in the hippocampus, cortex and cerebellum (Wunder et al., 2005). Since the novel PDE 9 inhibitor PF-4447943 has been shown to reverse disruptions in auditory gating and working memory and inhibit mescaline-induced scratching in a similar fashion to many psychotropic drugs (Kleiman et al., 2012), a potential role for use of PDE 9 inhibitors as antipsychotics has been considered (Hutson et al., 2011). However, a low selectivity for the rat striatum combined with a lack of effect on behavioral assays such as the conditioned avoidance response or spontaneous locomotor activity has led to the exclusion of PDE 9 inhibitors from consideration in treatment of schizophrenia (Kleiman, 2010).

11. Conclusion

An increasing body of evidence indicates that cGMP is an emerging target for developing novel therapeutics for schizophrenia (Bernstein et al., 2011; Kehler and Nielsen, 2011). For the last two decades, clinical trials and animal studies have shown that NMDAR enhancers are likely to be efficacious in treating features of schizophrenia, particularly negative symptoms. Nitroprusside, a prodrug of NO, and PDEIs, shows some promise for improving a range of symptoms in schizophrenia. The common molecular action among these drugs is likely to be the upregulation of cGMP that activates cGMP signaling cascades leading to diverse neuroprotective and neurotropic actions postulated to have clinical efficacy in schizophrenia. On the other hand, the "oxidative stress" theory of schizophrenia suggests that minocycline, an antibiotic drug with antioxidant and anti-inflammatory properties, may improve schizophrenia symptoms by blocking neuroinflammatory processes including the formation of NO free radicals (Zhang and Zhao, 2014). However, whether NO modulation is beneficial or toxic for schizophrenia is not clear at present. Since only a limited number of studies have addressed this question, further research in this area is warranted.

References

Ahuja, M., Bishnoi, M., Chopra, K., 2008. Protective effect of minocycline, a semi-synthetic second-generation tetracycline against 3-nitropropionic acid (3-NP)-induced neurotoxicity. Toxicology 244 (2–3), 111–122.

Akhondzadeh, S., Ghayyoumi, R., Rezaei, F., Salehi, B., Modabbernia, A.H., Maroufi, A., Esfandiari, G.R., Naderi, M., Ghebleh, F., Tabrizi, M., Rezazadeh, S.A., 2011. Sildenafil adjunctive therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled trial. Psychopharmacology 213 (4), 809–815.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. fifth ed. American Psychiatric Association, Arlington, VA.

Bernstein, H.G., Bogert, B., Keilhoff, G., 2005. The many faces of nitric oxide in schizophrenia. A review. Schizophr. Res. 78 (1), 69–86.

Bernstein, H.G., Keilhoff, G., Steiner, J., Dobrowolny, H., Bogerts, B., 2011. Nitric oxide and schizophrenia: present knowledge and emerging concepts of therapy. CNS Neurol. Disord. Drug Targets 10 (7), 792–807.

Bessis, A., Béchade, C., Bernard, D., Roumier, A., 2007. Microglial control of neuronal death and synaptic properties. Glia 55 (3), 233–238.

Bredt, D.S., Snyder, S.H., 1989. Nitric oxide mediates glutamate-linked enhancement of cGMP levels in the cerebellum. Proc. Natl. Acad. Sci. U. S. A. 86 (22), 9030–9033.

Chaudhry, I.B., Hallak, J., Husain, N., Minhas, F., Stirling, J., Richardson, P., Dursun, S., Dunn, G., Deakin, B., 2012. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J. Psychopharmacol. 26 (9), 1185–1193.

Christopherson, K.S., Hillier, B.J., Lim, W.A., Bredt, D.S., 1999. PSD-95 assembles a ternary complex with the N-methyl-D-aspartic acid receptor and a bivalent neuronal NO synthase PDZ domain. J. Biol. Chem. 274 (39), 27467–27473.

Coyle, J.T., 2013. Nitric oxide and symptom reduction in schizophrenia. JAMA Psychiatry 70 (7), 664–665.

Dean, O.M., Data-Franco, J., Giorlando, F., Berk, M., 2012. Minocycline: therapeutic potential in psychiatry. CNS Drugs 26 (5), 391–401.

Derbyshire, E.R., Marletta, M.A., 2009. Biochemistry of soluble guanylate cyclase. Handb. Exp. Pharmacol. (191), 17–31.

Docherty, A.R., Bigdeli, T.B., Edwards, A.C., Bacanu, S., Lee, D., Neale, M.C., Wormley, B.K., Walsh, D., O'Neill, F.A., Riley, B.P., Kendler, K.S., Fanous, A.H., 2015. Genome-wide gene pathway analysis of psychotic illness symptom dimensions based on a new schizophrenia-specific model of the OPCRIT. Schizophr. Res. 164 (1–3), 181–186.

Dokuyucu, R., Kokacya, H., Inanir, S., Copoglu, U.S., Erbas, O., 2014a. Antipsychotic-like effect of minocycline in a rat model. Int. J. Clin. Exp. Med. 7 (10), 3354–3361.

Dokuyucu, R., Kokacya, H., Inanir, S., Copoglu, U.S., Erbas, O., 2014b. Antipsychotic-like effect of minocycline in a rat model. Int. J. Clin. Exp. Med. 7 (10), 3354–3361.

Domino, E.F., Luby, E., 1981. Abnormal mental states induced by phencyclidine as a model of schizophrenia. In: Domino, E.F. (Ed.), Abnormal Mental States Induced by Phencyclidine as a Model of Schizophrenia. NPP Books, Ann Arbor, MI, p. 537.

East, S.J., Garthwaite, J., 1991. NMDA receptor activation in rat hippocampus induces cyclic GMP formation through the L-arginine-nitric oxide pathway. Neurosci. Lett. 123 (1), 17–19.

Ebstein, R.P., Biederman, J., Rimon, R., Zohar, J., Belmaker, R.H., 1976. Cyclic GMP in the CSF of patients with schizophrenia before and after neuroleptic treatment. Psychopharmacology 51 (1), 71–74.

Francis, S.H., Corbin, J.D., 2005. Phosphodiesterase-5 inhibition: the molecular biology of erectile function and dysfunction. Urol. Clin. North Am. 32 (4), 419–429.

Francis, S.H., Blount, M.A., Zoraghi, R., Corbin, J.D., 2005. Molecular properties of mammalian proteins that interact with cGMP: proteinkinases, cation channels, phosphodiesterases, and multi-drug anion transporters. Front. Biosci. 10, 2097–2117 (2005).

Francis, S.H., Busch, J.L., Corbin, J.D., Sibley, D., 2010. cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. Pharmacol. Rev. 62 (3), 525–563.

Fujita, Y., Ishima, T., Kunitachi, S., Hagiwara, H., Zhang, L., Iyo, M., Hashimoto, K., 2007. Phencyclidine-induced cognitive deficits in mice are improved by subsequent sub-chronic administration of the antibiotic drug minocycline. Prog Neuropsychopharmacol Biol. Psychiatry 32 (2), 336–339.

Garrido-Mesa, N., Zarzuelo, A., Gálvez, J., 2013. What is behind the non-antibiotic properties of minocycline? Pharmacol. Res. 67 (1), 18–30.

Garthwaite, J., Garthwaite, G., Palmer, R.M., Moncada, S., 1989. NMDA receptor activation induces nitric oxide synthesis from arginine in rat brain slices. Eur. J. Pharmacol. 172 (4–5), 413–416.

Gattaz, W.F., Cramer, H., Beckmann, H., 1983. Low CSF concentrations of cyclic GMP in schizophrenia. Br. J. Psychiatry 142, 288–291.

Ghanizadeh, A., Dehbozorgi, S., Sigaroodi, M.O., Rezaei, Z., 2014. Minocycline as add-on treatment decreases the negative symptoms of schizophrenia; a randomized placebo-controlled clinical trial. Recent Patents Inflamm. Allergy Drug Discov. 8 (3), 211–215.

Goff, D.C., Cather, C., Freudenreich, O., Henderson, D.C., Evins, A.E., Culhane, M.A., Walsh, J.P., 2009. A placebo-controlled study of sildenafil effects on cognition in schizophrenia. Psychopharmacology 202 (1–3), 411–417.

Halene, T.B., Siegel, S.J., 2007. PDE inhibitors in psychiatry—future options for dementia, depression and schizophrenia? Drug Discov. Today 12 (19–20), 870–878.

Hallak, J.E., Maia-de-Oliveira, J.P., Abrao, J., Evora, P.R., Zuardi, A.W., Crippa, J.A., Belmonte-de-Abreu, P., Baker, G.B., Dursun, S.M., 2013. Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. JAMA Psychiatry 70 (7), 668–676.

Hashimoto, K., Tsukada, H., Nishiyama, S., Fukumoto, D., Kakiuchi, T., Iyo, M., 2007. Protective effects of minocycline on the reduction of dopamine transporters in the striatum after administration of methamphetamine: a positron emission tomography study in conscious monkeys. Biol. Psychiatry 61 (5), 577–581.

Hoffman, D.C., 1992. Typical and atypical neuroleptics antagonize MK-801-induced locomotion and stereotypy in rats. J. Neural Transm. Gen. Sect. 89 (1–2), 1–10.

Hofmann, F., Wegener, J.W., 2013. cGMP-dependent protein kinases (cGK). Methods Mol. Biol. 1020, 17–50.

Hutson, P.H., Finger, E.N., Magliaro, B.C., Smith, S.M., Converso, A., Sanderson, P.E., Mullins, D., Hyde, L.A., Eschle, B.K., Turnbull, Z., Sloan, H., Guzzi, M., Zhang, X., Wang, A., Rindgen, D., Mazzola, R., Vivian, J.A., Eddins, D., Uslaner, J.M., Bednar, R., Gambone, C., Le-Mair, W., Marino, M.J., Sachs, N., Xu, G., Parmentier-Batteur, S., 2011. The selective phosphodiesterase 9 (PDE9) inhibitor PF-04447943 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one) enhances synaptic plasticity and cognitive function in rodents. Neuropharmacology 61 (4), 665–676.

Ignarro, L.J., Cirino, G., Casini, A., Napoli, C., 1999. Nitric oxide as a signaling molecule in the vascular system: an overview. J. Cardiovasc. Pharmacol. 34 (6), 879–886.

Issy, A.C., Pedrazzi, J.F., Yoneyama, B.H., Del-Bel, E.A., 2014. Critical role of nitric oxide in the modulation of prepulse inhibition in Swiss mice. Psychopharmacology 231 (4), 663–672.

Jaffrey, S.R., Snyder, S.H., 1995. Nitric oxide: a neural messenger. Annu. Rev. Cell Dev. Biol. 11, 417–440.

Kehler, J., Nielsen, J., 2011. PDE10A inhibitors: novel therapeutic drugs for schizophrenia. Curr. Pharm. Des. 17 (2), 137–150.

Kennedy, J.L., Altar, C.A., Taylor, D.L., Degtiar, I., Hornberger, J.C., 2014. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. Int. Clin. Psychopharmacol. 29 (2), 63–76.

Khodaie-Ardakani, M.R., Mirshafiee, O., Farokhnia, M., Tajdini, M., Hosseini, S.M., Modabbernia, A., Rezaei, F., Salehi, B., Yekehtaz, H., Ashrafi, M., Tabrizi, M., Akhondzadeh, S., 2014. Minocycline add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized double-blind placebo-controlled study. Psychiatry Res. 215 (3), 540–546.

Kim, S.S., Kong, P.J., Kim, B.S., Sheen, D.H., Nam, S.Y., Chun, W., 2004. Inhibitory action of minocycline on lipopolysaccharide-induced release of nitric oxide and prostaglandin E2 in BV2 microglial cells. Arch. Pharm. Res. 27 (3), 314–318.

Kleiman, R.J., 2010. Comparison of PDE9 and PDE10 inhibitors in preclinical schizophrenia models. Presented at the New York Academy of Sciences, New York, NY (Online. Available at http://www.nyas.org/Publications/Media/VideoDetail.aspx?cid=2cce36ba-5fd6-4de1-b84e-8b018624bf17).

Kleiman, R.J., Chapin, D.S., Christoffersen, C., Freeman, J., Fonseca, K.R., Geoghegan, K.F., Grimwood, S., Guanowsky, V., Hajós, M., Harms, J.F., Helal, C.J., Hoffmann, W.E., Kocan, G.P., Majchrzak, M.J., McGinnis, D., McLean, S., Menniti, F.S., Nelson, F., Roof, R., Schmidt, A.W., Seymour, P.A., Stephenson, D.T., Tingley, F.D., Vanase-Frawley, M., Verhoest, P.R., Schmidt, C.J., 2012. Phosphodiesterase 9A regulates central cGMP and modulates responses to cholinergic and monoaminergic perturbation in vivo. J. Pharmacol. Exp. Ther. 341 (2), 396–409.

Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers Jr., M.B., Charney, D.S., 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry 51 (3), 199–214.

Levkovitz, Y., Levi, U., Braw, Y., Cohen, H., 2007. Minocycline, a second-generation tetracycline, as a neuroprotective agent in an animal model of schizophrenia. Brain Res. 1154, 154–162.

Levkovitz, Y., Mendlovich, S., Riwkes, S., Braw, Y., Levkovitch-Verbin, H., Gal, G., Fennig, S., Treves, I., Kron, S., 2010. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J. Clin. Psychiatry 71 (2), 138–149.

Liu, F., Guo, X., Wu, R., Ou, J., Zheng, Y., Zhang, B., Xie, L., Zhang, L., Yang, L., Yang, S., Yang, J., Ruan, Y., Zeng, Y., Xu, X., Zhao, J., 2014. Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double blind, randomized, controlled trial. Schizophr. Res. 153 (1–3), 169–176.

Marte, A., Pepicelli, O., Cavallero, A., Raiteri, M., Fedele, E., 2008. In vivo effects of phosphodiesterase inhibition on basal cyclic guanosine monophosphate levels in the prefrontal cortex, hippocampus and cerebellum of freely moving rats. J. Neurosci. Res. 86 (15), 3338–3347.

Maurice, D.H., Ke, H., Ahmad, F., Wang, Y., Chung, J., Manganiello, V.C., 2014. Advances in targeting cyclic nucleotide phosphodiesterases. Nat. Rev. Drug Discov. 13 (4), 290–314.

Miyamoto, S., Duncan, G.E., Marx, C.E., Lieberman, J.A., 2005. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol. Psychiatry 10, 79–104.

Mizoguchi, Y., Kato, T.A., Horikawa, H., Monji, A., 2014. Microglial intracellular Ca(2+) signaling as a target of antipsychotic actions for the treatment of schizophrenia. Front. Cell. Neurosci. 8, 370.

Moghaddam, B., Adams, B.W., 1998. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 281 (5381), 1349–1352.

Monte, A.S., de Souza, G.C., McIntyre, R.S., Soczynska, J.K., dos Santos, J.V., Cordeiro, R.C., Ribeiro, B.M., de Lucena, D.F., Vasconcelos, S.M., de Sousa, F.C., Carvalho, A.F., Macêdo, D.S., 2013. Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: possible involvement of antioxidant and nitrergic pathways. J. Psychopharmacol. 27 (11), 1032–1043.

Omori, K., Kotera, J., 2007. Overview of PDEs and their regulation. Circ. Res. 100 (3), 309–327.

Qurashi, I., Collins, J., Chaudhry, I., Husain, N., 2014. Promising use of minocycline augmentation with clozapine in treatment-resistant schizophrenia. J. Psychopharmacol. 28 (7), 707–708.

Rameau, G.A., Chiu, L.Y., Ziff, E.B., 2004. Bidirectional regulation of neuronal nitric-oxide synthase phosphorylation at serine 847 by the N-methyl-D-aspartate receptor. J. Biol. Chem. 279 (14), 14307–14314.

Reneerkens, O.A., Sambeth, A., Van Duinen, M.A., Blokland, A., Steinbusch, H.W., Prickaerts, J., 2013. The PDE5 inhibitor vardenafil does not affect auditory sensory gating in rats and humans. Psychopharmacology 225 (2), 303–312.

Russwurm, M., Behrends, S., Harteneck, C., Koesling, D., 1998. Functional properties of a naturally occurring isoform of soluble guanylyl cyclase. Biochem. J. 335 (Pt 1), 125–130.

Russwurm, M., Russwurm, C., Koesling, D., Mergia, E., 2013. NO/cGMP: the past, the present, and the future. Methods Mol. Biol. 1020, 1–16.

Sams-Dodd, F., 1997. Effect of novel antipsychotic drugs on phencyclidine-induced stereotyped behaviour and social isolation in the rat social interaction test. Behav. Pharmacol. 8 (2–3), 196–215.

Schultz, S.K., Andreasen, N.C., 1999. Schizophrenia. Lancet 353 (9162), 1425–1430.

Shim, S.S., Hammonds, M.D., Kee, B.S., 2007. Potentiation of the NMDA receptor in the treatment of schizophrenia: focused on the glycine site. Eur. Arch. Psychiatry Clin. Neurosci. 258 (1), 16–27.

Siuciak, J.A., 2008. The role of phosphodiesterases in schizophrenia: therapeutic implications. CNS Drugs 22 (12), 983–993.

Steinpreis, R.E., 1996. The behavioral and neurochemical effects of phencyclidine in humans and animals: some implications for modeling psychosis. Behav. Brain Res. 74 (1–2), 45–55.

Stone, J.R., Marletta, M.A., 1996. Spectral and kinetic studies on the activation of soluble guanylate cyclase by nitric oxide. Biochemistry 35 (4), 1093–1099.

Tang, C.M., Hwang, C.S., Chen, S.D., Yang, D.I., 2011. Neuroprotective mechanisms of minocycline against sphingomyelinase/ceramide toxicity: roles of Bcl-2 and thioredoxin. Free Radic. Biol. Med. 50 (6), 710–721.

Thomas, M., Le, W.D., 2004. Minocycline: neuroprotective mechanisms in Parkinson's disease. Curr. Pharm. Des. 10 (6), 679–686.

Tsai, G.E., Lin, P., 2010. Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr. Pharm. Des. 16 (5), 522–537.

Tuominen, H.J., Tiihonen, J., Wahlbeck, K., 2005. Glutamatergic drugs for schizophrenia. Schizophr. Res. 72 (2–3), 225–234.

Wu, J.Q., Kosten, T.R., Zhang, X.Y., 2013. Free radicals, antioxidant defense systems, and schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 46, 200–206.

Wunder, F., Tersteegen, A., Rebmann, A., Erb, C., Fahrig, T., Hendrix, M., 2005. Characterization of the first potent and selective PDE9 inhibitor using a cGMP reporter cell line. Mol. Pharmacol. 68 (6), 1775–1781.

Yong, V.W., Wells, J., Giuliani, F., Casha, S., Power, C., Metz, L.M., 2004. The promise of minocycline in neurology. Lancet Neurol. 3 (12), 744–751.

Zhang, L., Zhao, J., 2014. Profile of minocycline and its potential in the treatment of schizophrenia. Neuropsychiatr. Dis. Treat. 10, 1103–1111.

Zhang, L., Kitaichi, K., Fujimoto, Y., Nakayama, H., Shimizu, E., Iyo, M., Hashimoto, K., 2006. Protective effects of minocycline on behavioral changes and neurotoxicity in mice after administration of methamphetamine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 30 (8), 1381–1393.

Zhang, L., Shirayama, Y., Iyo, M., Hashimoto, K., 2007. Minocycline attenuates hyperlocomotion and prepulse inhibition deficits in mice after administration of the NMDA receptor antagonist dizocilpine. Neuropsychopharmacology 32 (9), 2004–2010.

Zhu, F., Liu, Y., Zhao, J., Zheng, Y., 2014a. Minocycline alleviates behavioral deficits and inhibits microglial activation induced by intrahippocampal administration of granulocyte-macrophage colony-stimulating factor in adult rats. Neurobiologia 266, 275–281.

Zhu, F., Zheng, Y., Ding, Y.Q., Liu, Y., Zhang, X., Wu, R., Guo, X., Zhao, J., 2014b. Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats. PLoS One 9 (4), e93966.