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SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS (AK PANDURANGI, SECTION EDITOR)

Recent Advances in the Early Intervention in Schizophrenia: Future Direction from Preclinical Findings

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Abstract

Purpose of Review In the past decade, there has been increasing interest in the potential benefit of early intervention in schizophrenia. Patients with schizophrenia show cognitive impairment for several years preceding the onset of psychosis. The author discusses the recent topics on prevention of schizophrenia.

Recent Findings Preclinical findings suggest that maternal immune activation (MIA) produces cognitive deficits as a prodromal symptom in juvenile offspring in rodents. Treatment with anti-inflammatory compounds, such as D-serine, 7,8-dihydroxyflavone (a TrkB agonist), sulforaphane (or its precursor glucoraphanin), and TPPU (1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea: a soluble epoxide hydrolase inhibitor), during adolescence might prevent the onset of behavioral abnormalities and parvalbumin immunoreactivity in the medial prefrontal cortex of adult offspring after MIA.

Summary Based on the role of inflammation and cognitive impairment in the prodromal state, early intervention using anti-inflammatory compounds (i.e., D-serine, sodium benzoate, TrkB agonist, Nrf2 agonist, soluble epoxide hydrolase inhibitor) may reduce the risk of subsequent transition to schizophrenia.

Keywords D-Serine · Keap1-Nrf2 · Sodium benzoate · Soluble epoxide hydrolase · Sulforaphane · TrkB agonist

Introduction

The World Health Organization reports that schizophrenia affects more than 21 million people worldwide [1]. Cognitive impairment is the core feature of schizophrenia that is present across the course of the illness [2–4]. Accumulating evidence suggests that cognitive impairment is apparent in childhood and adolescence, many years prior to the onset of psychosis [5••, 6, 7]. Interestingly, later transition to psychosis was associated with even more marked deficits in verbal fluency and memory functioning in people at clinical high risk of psychosis [5••]. A meta-analysis showed that neuropsychological performance deficits in people at clinical high risk for psychosis who converted to psychosis are greater than in those who did not convert to psychosis [8]. In addition, cognitive deficits are independent predictors of both transition to psychosis and functional outcomes within those at ultra-high risk [9]. Collectively, it is possible that treatment of cognitive impairment in people at clinical high risk for psychosis could prevent the conversion to psychosis.

A positron emission tomography (PET) study demonstrated marked microglial activation in the brain from patients with schizophrenia and people at ultra-high risk for psychosis, suggesting that inflammation (i.e., microglial activation) is linked to the risk of psychosis [10]. In contrast, subsequent PET studies showed no significant differences in microglial activation between people at clinical high risk for psychosis and healthy controls [11, 12]. A recent meta-analysis suggests that there is evidence for a moderately increased effect size for microglial activation in the brain from schizophrenia and that the potential methodological differences between PET studies may contribute to the discrepancy for these PET studies [13]. Given the role of inflammation (i.e., microglial activation), cognition, and progressive brain changes in schizophrenia [14], there is an increasing interest in the benefit of early intervention in the prodromal state [15]. In this review article,

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the potential of compounds with anti-inflammatory activity in the prevention of schizophrenia is discussed.

Neurodevelopmental Model of Schizophrenia

Epidemiological studies suggest that maternal infection during pregnancy increases the risk of neurodevelopmental disorders such as schizophrenia in offspring [16, 17•, 18••, 19, 20]. A recent nationwide Danish cohort study demonstrated that maternal infections during pregnancy were associated with an increased risk of mental disorder in the offspring [21]. In rodents, maternal immune activation (MIA) using the synthetic double-stranded RNA analogue polyriboinosinic-polyribocytidylic acid (poly(I:C)), a Toll-like receptor 3 agonist, yields offspring with schizophrenia-like behavioral abnormalities [17•, 18••, 20]. Offspring after prenatal poly(I:C) injection mimic schizophrenia-like behavioral abnormalities in adulthood, although MIA model using poly(I:C) does not reproduce the full spectrum of immune responses normally induced by infectious pathogens [18••, 22]. Previously, we reported that juvenile offspring of poly(I:C)-treated pregnant mice displayed cognitive deficits and the reduction of parvalbumin (PV) immunoreactivity in the medial prefrontal cortex [23•, 24••, 25], suggesting that cognitive deficits in juvenile mice after neonatal poly(I:C) exposure may be core symptoms of a prodromal state. It is reported that juvenile male offspring exposed to poly(I:C) at an early gestation day showed a significant alteration in social interaction [26], suggesting that MIA during late gestation from the earlier exposure causes long-term behavioral changes (i.e., cognitive deficits) in adulthood [26].

NMDAR Co-agonist D-Serine

The *N*-methyl-D-aspartate receptor (NMDAR) plays a key role in the pathophysiology of schizophrenia [27–33]. D-serine is a physiological co-agonist of the NMDAR that plays a role in synaptic plasticity neurodevelopmental processes which are involved in schizophrenia (Fig. 1) [34–37]. In physiological conditions, D-serine is synthesized principally in neurons, but not in glia, by serine racemase in the adult brain [38–41]. In contrast, pathogenic inflammation causes D-serine to come from reactive astrocytes [41, 42]. The oxidative stress induced by inflammation is suggested to promote the NMDAR hypofunction associated with schizophrenia [41]. Recently, we reported that deletion of serine racemase in mice confers D-serine-dependent resilience to chronic social defeat stress [43]. Collectively, it seems that D-serine might produce anti-inflammatory actions through NMDAR activation.

Levin et al. [44] reported that D-serine reduces subjective feelings of sadness and anxiety and has precognitive effects in healthy control subjects, suggesting that D-serine has beneficial effects on cognitive functions. A double-blind, placebo-controlled study showed that D-serine (60 mg/kg) caused significant improvement in mismatch negativity (MMN) frequency and clinical symptoms in schizophrenia [45]. There is also a relationship between gamma-band auditory steady-state response and plasma levels of D-serine in schizophrenia [46]. In the cognitive training group, increased D-serine was positively correlated with improvements in global cognition in patients with schizophrenia, suggesting that D-serine may play a role in the cognitive training–induced neurophysiologic changes in schizophrenia [47]. Although multiple NMDAR-enhancing agents have demonstrated beneficial effects for cognitive impairment in schizophrenia, a recent meta-analysis showed no significant effect of NMDAR-enhancing agents on overall cognition [48]. However, the NMDAR-enhancing agents may offer benefit in young patients with schizophrenia [48]. Collectively, it seems that D-serine may treat prodromal state in subjects with high risk for psychosis.

Previously, we reported that neonatal disruption of serine racemase in mice caused schizophrenia-like abnormal behaviors in adulthood and that chronic administration of D-serine during adolescence might prevent the onset of behavioral abnormalities in adulthood [49], suggesting that early intervention with D-serine may prevent the onset of psychosis in adult (Table 1). Furthermore, we reported lower levels of D-serine in the frontal cortex and hippocampus from adult mouse offspring after MIA whereas D-serine levels in these brain regions of juvenile offspring remained the same [23•]. Interestingly, D-serine (600 mg/L from P28 to P56) in drinking water could prevent the onset of cognitive deficits in adult offspring after MIA (Table 1) [23•]. This preclinical study suggests that supplementation with D-serine during adolescence could prevent the onset of psychosis in adult offspring after MIA. Therefore, it is of great interest to investigate whether early intervention with D-serine could prevent the conversion to psychosis in people with high risk for psychosis.

The Concert Pharmaceutical Inc. (Lexington, MA, USA) has been developing CTP-692, a deuterated form of D-serine, which is expected to have similar pharmacology as D-serine with the potential for an improved safety profile [55]. In December 2018, the company initiated phase 1 clinical trial of CTP-692. Therefore, it may be of interest to investigate whether early intervention with CTP-692 could prevent the conversion to psychosis in subjects with high risk for psychosis.

Sodium Benzoate

Sodium benzoate, the common food preservative, is a D-amino acid oxidase (DAAO) inhibitor (Fig. 1). Lane et al.

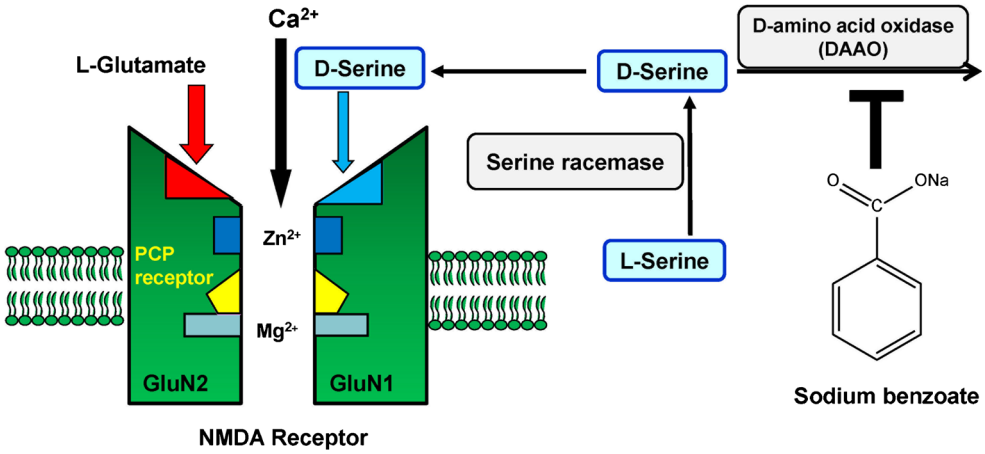

Fig. 1 NMDAR, D-serine, and sodium benzoate. Phencyclidine (PCP) is an ion-channel blocker of the NMDAR. D-serine is an endogenous co-agonist of the glycine modulatory site on the GluN1 subunit of NMDAR. Glutamate is an endogenous agonist at glutamate sites on the GluN2 subunit. D-Serine is synthesized from L-serine by serine racemase and is metabolized by D-amino acid oxidase (DAAO). Sodium benzoate is an inhibitor of DAAO

[56••] reported that add-on treatment of sodium benzoate significantly improved a variety of symptom domains and cognition in patients with schizophrenia. Subsequently, Lin et al. [57] reported that adjunction of sodium benzoate improved symptomatology of patients with clozapine-resistant schizophrenia. Although sodium benzoate has antipsychotic-like effects in the phencyclidine (PCP)-induced mouse model of schizophrenia [58], it did not increase brain or cerebrospinal fluid levels of D-amino acids (i.e., D-serine or D-alanine) in mice or dogs [58, 59]. Thus, it is unlikely that the action of sodium benzoate may be mediated through DAAO inhibition in the brain although further study on the role of DAAO in the beneficial effects of sodium benzoate is needed. In contrast, sodium benzoate is thought to have a potent anti-inflammatory effect [60]. Collectively, it is suggested that sodium benzoate may produce beneficial effects through a potent anti-inflammation effect [58]. A randomized control trial of sodium benzoate in early psychosis is currently underway (Table 1) [50].

TrkB Agonist 7,8-Dihydroxyflavone

Brain-derived neurotrophic factor (BDNF) and its high-affinity receptor tropomyosin receptor kinase B (TrkB) signaling play a crucial role in neurodevelopment [61]. A recent meta-analysis showed that decreased peripheral BDNF levels are significantly associated with schizophrenia, thereby supporting the neurobiological hypothesis of BDNF in schizophrenia [62]. We reported that the levels of BDNF in the parietal cortex from schizophrenia group were lower than those from the control group, whereas the levels of BDNF pro-peptide in the same region were higher than those from the control group. By contrast, the protein levels of proBDNF and BDNF pro-peptide in the cerebellum of the schizophrenia group were lower than those of the control group [63•]. Collectively, it seems that abnormalities in BDNF -TrkB signaling might play a role in etiology of schizophrenia [63•, 64].

Accumulating evidence demonstrated that 7,8-dihydroxyflavone (7,8-DHF) has TrkB agonism with potent inflammatory activity [65–68]. Previously, we reported that

Table 1 Potential candidates for intervention of psychosis

Potential compounds	Mechanisms of action	Animal models	References
D-Serine	NMDAR agonist	MIA model Neonatal exposure model by phenazine	Fujita et al. [23•] Hagiwara et al. [49]
Sodium benzoate	DAO inhibitor	No report of animal model. Clinical trial is underway.	Ryan et al. [50]
7,8-Dihydroxyflavone (DHF)	TrkB agonist	MIA model	Han et al. [24••] Han et al. [25] Han et al. [51]
Sulforaphane (SFN) or its precursor glucoraphanin	Nrf2 agonist	Repeated PCP model MIA model	Shirai et al. [52] Matsuura et al. [53••]
TPPU	Soluble epoxide hydrolase inhibitor	MIA model	Ma et al. [54••]

MIA, maternal immune activation; *DAO,* D-amino acid oxidase; *NMDAR*, *N*-methyl-D-aspartate receptor; *PCP*, phencyclidine

7,8-DHF could attenuate behavioral abnormalities and dopaminergic neurotoxicity in mice after administration of methamphetamine [69, 70]. Furthermore, 7,8-DHF was reported to have potent antidepressant effects through potent anti-inflammatory actions in rodent models of depression [71–73]. Collectively, it seems that 7,8-DHF elicits beneficial effects through potent anti-inflammatory actions.

We reported that the juvenile offspring of poly(I:C)-treated pregnant mice displayed cognitive deficits, as well as decreased BDNF-TrkB signaling in the prefrontal cortex [24••]. Interestingly, drinking water of 7,8-dihydroxyflavone (1 mg/mL; a TrkB agonist) during adolescence could prevent the behavioral abnormalities (i.e., cognitive deficits, prepulse inhibition deficits) and decreased BDNF-TrkB signaling in the prefrontal cortex and PV immunoreactivity in the medial prefrontal cortex in the adult offspring after MIA (Table 1). These data suggest that decreased BDNF-TrkB signaling in the prefrontal cortex may play a role in cognitive deficits of juvenile and adult offspring after MIA [24••].

Complement protein C1q (complement component 1, q subcomponent) is known to play a key role in pregnancy where its deficiency and dysregulation can have adverse effects, leading to preeclampsia, missed abortion, miscarriage or spontaneous loss, and various infections [74, 75]. We found higher expression of C1q in the prefrontal cortex of adult offspring after MIA. We also found that treatment with 7,8-DHF during juvenile and adolescent stages might attenuate an increase of C1q in the prefrontal cortex of adult offspring after MIA (Table 1). It is likely that increased C1q expression in the prefrontal cortex might be involved in the behavioral abnormalities of adult offspring after MIA [51].

Furthermore, drinking water of 7,8-dihydroxyflavone in poly(I:C)-treated pregnant mice from pregnancy to weaning could prevent the onset of cognitive deficits and decreased BDNF-TrkB signaling in the prefrontal cortex of adult offspring after MIA (Table 1) [25]. Taken together, it seems that early intervention by a TrkB agonist (i.e., 7,8-DHF) in people with high risk for psychosis might potentially reduce the risk of subsequent transition to schizophrenia.

Transcription Factor Nrf2 Activator Sulforaphane

The Kelch-like ECH-associated protein 1-NF-E2-related factor 2 (Keap1-Nrf2) system forms the major node of cellular and organismal defense against oxidative and electrophilic stresses of both exogenous and endogenous origins [76•]. The Keap1-Nrf2 system plays a key role in the oxidative stress and inflammation which are involved in psychiatric disorders [77]. Previously, we reported that the Keap1-Nrf2 system might contribute to stress resilience which plays a role in the pathophysiology of psychiatric disorders such as schizophrenia and depression [78•, 79, 80]. Interestingly, the expressions of Keap1 and Nrf2 proteins in the parietal cortex from schizophrenia patients were lower than those of controls [80], suggesting that reduced Keap1-Nrf2 signaling (i.e., inflammation and oxidative stress) may play a role in the pathophysiology of schizophrenia.

Sulforaphane (Fig. 2), found in cruciferous vegetables (i.e., broccoli sprout), is an Nrf2 activator with potent antioxidant and anti-inflammatory effects. It was reported that sulforaphane could attenuate behavioral abnormalities in mice after administration of methamphetamine [81] or PCP [82]. Furthermore, pretreatment with sulforaphane could attenuate cognitive deficits, the increase in 8-oxo-dG-positive cells, and the decrease in PV immunoreactivity in the medial prefrontal cortex and hippocampus after repeated PCP administration. Moreover, PCP-induced cognitive deficits were improved by the subsequent repeated administration of sulforaphane. Interestingly, the dietary intake of glucoraphanin (a glucosinolate precursor of sulforaphane) (Fig. 2) during the juvenile and adolescence prevented the onset of PCP-induced cognitive deficits as well as the increase in 8-oxo-dG-positive cells and the decrease in PV immunoreactivity in the brain in adulthood (Table 1) [52].

In addition, we also found that dietary intake of glucoraphanin during juvenile and adolescence could prevent cognitive deficits and loss of PV immunoreactivity in the medial prefrontal cortex of adult offspring after MIA (Table 1) [53••]. Interestingly, gene set enrichment analysis by RNA sequencing demonstrated that MIA caused higher expression of centrosome-related genes in the prefrontal cortex and hippocampus of adult offspring after MIA and that dietary intake of glucoraphanin could improve these abnormal gene expressions. In particular, we found an increased expression of suppressor of fermentation-induced loss of stress resistance protein 1 (*Sfi1*) mRNA in the prefrontal cortex and hippocampus of adult offspring after MIA, and dietary intake of glucoraphanin prevented the expression of *Sfi1* mRNA in these regions. Thus, it is likely that centrosome-related genes may play a crucial role in both prodromal symptoms and psychosis in offspring after MIA [53••].

Interestingly, there are altered expressions of SFI1 protein in the postmortem brains and *SFI1* mRNA in hair follicle cells from schizophrenia patients compared with controls [53••]. Taken together these data, it is likely that dietary intake of glucoraphanin-rich vegetables in subjects with high risk for psychosis may prevent the transition to psychosis in young adulthood. Therefore, it is of great interest to investigate whether dietary intake of glucoraphanin-rich vegetables in subjects with high risk for psychosis may prevent the transition to schizophrenia.

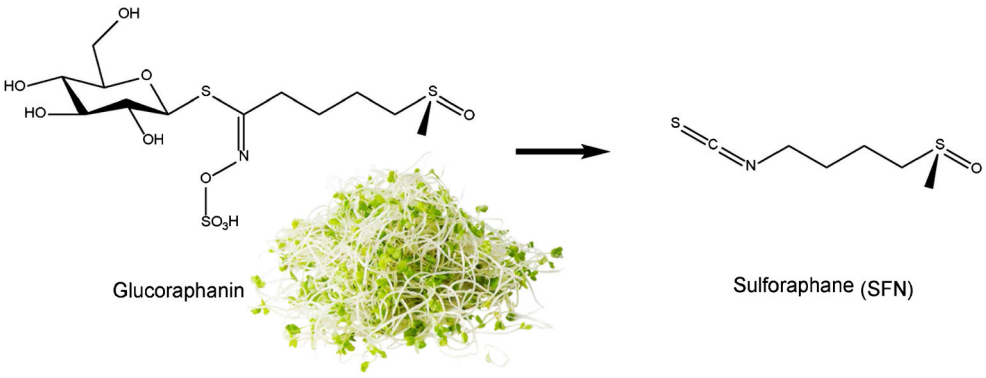

Fig. 2 Chemical structure of sulforaphane and its precursor glucoraphanin. Cruciferous vegetables (i.e., broccoli sprout) contain glucoraphanin, a glucosinolate derivative of sulforaphane. Glucoraphanin is converted to sulforaphane by the enzyme myrosinase. Young broccoli sprouts are particularly rich in glucoraphanin (modified from Hashimoto [77])

Soluble Epoxide Hydrolase (sEH) Inhibitors

Polyunsaturated fatty acids (PUFAs) are generally considered to be necessary for maintaining normal physiology in the body. Accumulating human neuroimaging studies suggests that lower omega-3 PUFA intake/status is associated with accelerated gray matter atrophy in healthy middle-aged and elderly adults, particularly in brain regions consistently implicated in psychotic disorders. Importantly, increasing omega-3 PUFA status is protective against gray matter atrophy and deficits in white matter microstructural integrity in patients with psychotic disorders [83].

Although supplementation of omega-3 PUFAs was reported to be effective in reducing transition to psychosis in people at ultra-high risk for psychosis [84], the NEUROPRO randomized clinical trial failed to replicate the previous finding [85]. The recent network meta-analysis showed no evidence of significantly superior efficacy of any one intervention over the others at 6 and 12 months. There is currently no evidence that any specific intervention with PUFA is particularly effective over the others in preventing transition to psychosis [86].

PUFAs are metabolized by the main enzymes such as cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450s (CYPs) [87, 88]. The COX pathway leads to the formation of prostaglandins, prostacyclins, and thromboxanes. The LOX pathway causes the formation of leukotrienes, lipoxins, and hydroxyl-eicosatetraenoic acids (HETEs) (Fig. 3). The CYP pathway produces 20-HETE by CYP hydroxylases

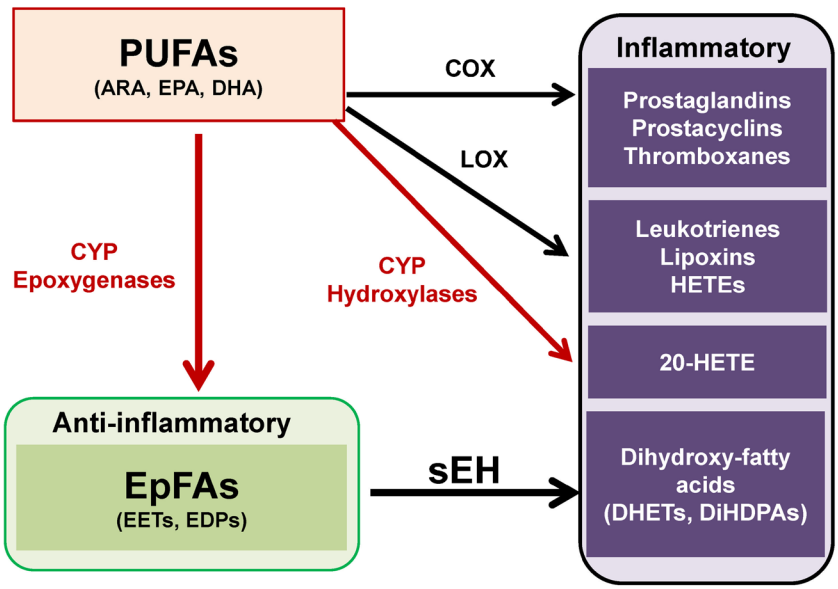

Fig. 3 Overview of metabolism of PUFAs. Polyunsaturated fatty acids (PUFAs) such as arachidonic acid (ARA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are converted to prostaglandins, prostacyclins, and thromboxanes by cyclooxygenase (COX). PUFAs are also converted to leukotrienes, lipoxins, hydroxyeicosatetraenoic acids (HETEs) by lipoxygenase (LOX). Moreover, PUFAs are converted to hydroxyeicosatetraenoic acids (HETEs), including 20-hydroxyeicosatetraenoic acid (20-HETE), and epoxy fatty acids EpFAs, including epoxyeicosatrienoic acids (EETs) and epoxydocosapentaenoic acids (EDPs), by cytochrome P450 (CYP) hydroxylases and CYP epoxygenases, respectively. EpFAs (e.g., EETs, EDPs) are converted to their corresponding 1,2-diols (e.g., dihydroxyeicosatrienoic acids (DHETs), dihydroxydocosapentaenoic acids (DiHDPAs)) by soluble epoxide hydrolase (sEH) (modified from Morisseau and Hammock [89] and Hashimoto [88, 90])

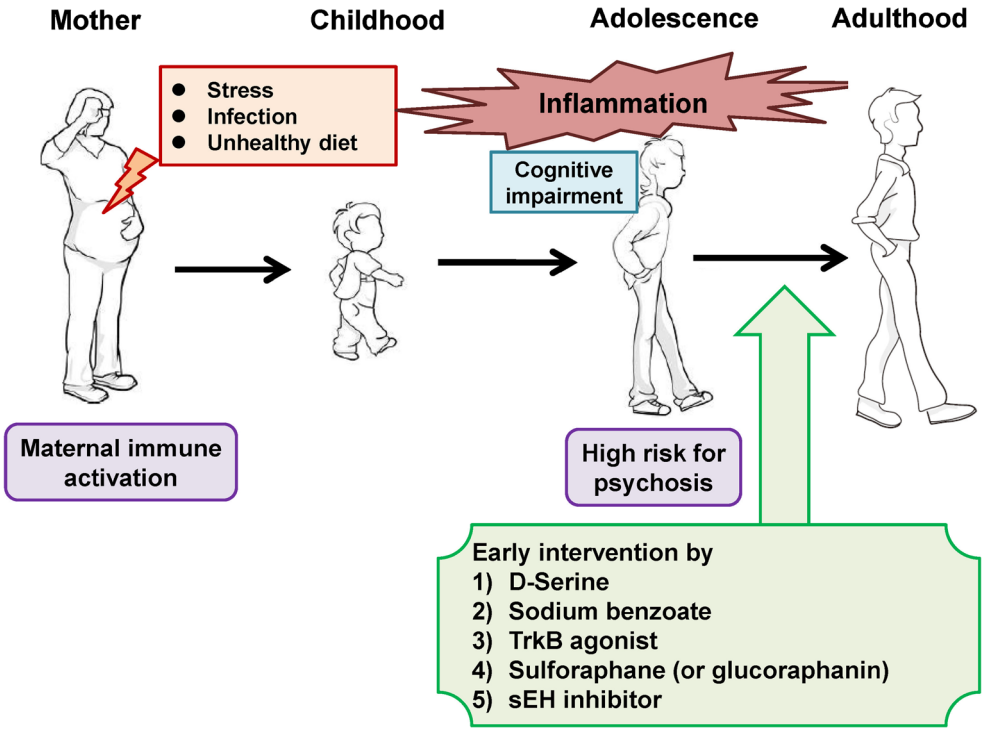

Fig. 4 Proposed mechanism of early intervention using anti-inflammatory compounds. Maternal immune activation (MIA) by the environmental factors (i.e., stress, infection, unhealthy diet) causes prodromal symptoms (i.e., cognitive impairment) in adolescent offspring. These peoples with high risk for psychosis may have inflammation in the brain. Early intervention using anti-inflammatory compounds, such as D-serine, sodium benzoate, TrkB agonist, sulforaphane (or its precursor glucoraphanin), and soluble epoxide hydrolase (sEH) inhibitor, may prevent the conversion to psychosis in young peoples with high risk for psychosis (modified from Estes and McAllister [17])

and epoxy fatty acids (EpFAs) such as epoxyeicosatrienoic acids (EETs) and epoxydocosapentaenoic acids (EDPs) by CYP epoxygenases (Fig. 3) [88–90].

Many epoxy fatty acids (EpFAs) are produced from the corresponding olefins by cytochrome P450 enzymes. Epoxyeicosatrienoic acids (EETs) and epoxydocosapentaenoic acids (EDPs) are produced from arachidonic acid and docosahexaenoic acid (DHA), respectively. EETs, EDPs, and some other EpFAs have potent anti-inflammatory actions. However, these epoxy mediators are broken down into their corresponding diols by soluble epoxide hydrolase (sEH), and the inhibition of sEH can enhance the beneficial effects of EpFAs such as EETs [87–89, 91]. Potent anti-inflammatory effects of EETs and the key role of sEH have been reported in animal models of neuropsychiatric disorders, including major depression and Parkinson's disease [88, 90, 92•, 93•].

Recently, we found higher levels of sEH in the prefrontal cortex of juvenile offspring after MIA. Oxylipin analysis showed decreased levels of epoxy fatty acids in the prefrontal cortex of juvenile offspring after MIA, supporting the increased activity of sEH in the same region of juvenile offspring. Interestingly, the expression of sEH (or *EPHX2*) mRNA in iPSC-derived neurospheres from schizophrenia patients with the 22q11.2 deletion was higher than that of healthy controls. Treatment of TPPU (a potent sEH inhibitor) into juvenile offspring from P28 to P56 could prevent cognitive deficits and loss of PV immunoreactivity in the medial prefrontal cortex of adult offspring after MIA (Table 1). This study suggests that increased activity of sEH in the prefrontal cortex plays an important role in schizophrenia-like behavior and biochemical abnormalities in offspring after MIA. Therefore, sEH would represent a promising prophylactic or therapeutic target for schizophrenia in offspring after MIA [54••]. Therefore, it is of great interest to investigate whether treatment with a sEH inhibitor in subjects with high risk for psychosis could prevent the transition to psychosis.

Conclusion

Cognitive impairment can be observed in people with prodromal symptoms of schizophrenia, suggesting that treating cognitive impairment in people with high risk for psychosis may be an important step to prevent the risk of subsequent transition to psychosis. Importantly, longitudinal study of people in an at-risk mental state of psychosis yielded transition rates of 9.6% after 6 months and 29.1% after 3 years when ultra-high risk criteria were used for study entry [94]. Given lower rate (approximately < 30%) of transition to psychosis in people with high risk for psychosis, it seems that safe natural compounds with potent anti-inflammatory actions may be suitable for the use in such persons.

Considering the roles of inflammation in the prodromal state, the hypothesis is proposed that compounds (i.e., D-serine, sodium benzoate, sulforaphane (or its precursor glucoraphanin), sEH inhibitors) with potent anti-inflammatory activity may reduce the risk of subsequent transition to schizophrenia (Fig. 4). A further randomized, double-blind, placebo-controlled study of these compounds in young people with high risk for psychosis is needed to confirm the hypothesis.

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Compliance with Ethical Standards

Conflict of Interest The author declares that there are no conflicts of interest.

Human and Animal Rights and Informed Consent This review article does not contain any original studies with humans or animal subjects performed by author.

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- •• Of major importance

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