



## Commentary

## Reducing inhibition: A promising new strategy for the treatment of schizophrenia


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Schizophrenia is a complex neuropsychiatric disorder presenting with positive (hallucinations, delusions, psychomotor agitation), negative (flat affect, anhedonia), and cognitive (impaired executive functions) symptoms. Current therapeutic approaches include second generation antipsychotics that primarily alleviate positive symptoms via modulation of dopaminergic and serotonergic transmission. These treatments remain moderately effective with between 10% and 30% of patients showing little symptomatic improvement, and an additional 30% to 60% experiencing partial improvement or severe side effects during antipsychotic therapy (Lehman et al., [5]). Current pharmaceutical developments aim to target other neurotransmitter systems, specifically the glutamatergic system. The end goal of these novel approaches is to restore the excitatory/inhibitory balance (E/I) in the prefrontal cortex (PFC) [6]. Prefrontal E/I imbalance is thought to be a major contributing mechanism to schizophrenia pathology, especially cognitive symptoms [4]. Specifically, observations that *N*-Methyl-D-aspartate receptor (NMDA-R) antagonists such as ketamine and MK-801 induce phenotypes resembling positive and cognitive symptoms led to the conclusion that hypofunction of glutamatergic signaling via NMDA-R underlie some of the schizophrenic symptoms [6]. Restoring glutamatergic neurotransmission in schizophrenia is the therapeutic approach taken by Fan et al. [2]. They used quercetin, a natural flavonoid that acts as a negative allosteric modulator for GABA<sub>A</sub> receptors (GABA<sub>A</sub>-Rs), to reduce inhibition in the PFC and potentiate glutamatergic transmission, effectively alleviating the positive symptom of MK-801-induced hyperactivity in mice [2].

This approach can be seen as controversial given observations of GABAergic neurotransmission abnormality in the schizophrenia brain. Impaired parvalbumin (PV)-dependent GABAergic transmission is recognized to be one of the main molecular mechanism responsible for cognitive deficits in schizophrenia [3]. Similarly, other research has demonstrated that reducing GABAergic transmission in the PFC by blocking GABA<sub>A</sub>-Rs induces some positive and cognitive symptoms of schizophrenia in rodents [1]. Therefore, GABA agonists or positive

allosteric modulators are also under investigation as novel therapeutics for schizophrenia, aimed at calibrating prefrontal E/I balance by reducing excitation [8].

Despite this, the findings from Fan et al. [2] support the therapeutic effects of negatively modulating GABA<sub>A</sub>-R in a rodent model of MK-801-induced hyperactivity. The exact mechanisms involved are elusive and require further study. Potentially, regulation of GABA transmission by quercetin could act through two distinct mechanisms in the PFC. First, quercetin might act in a cell type-specific manner. Future research should examine whether quercetin acts primarily upon GABA<sub>A</sub>-Rs on inhibitory or excitatory neurons in the PFC and determine the resulting net effect on prefrontal E/I balance. For instance, quercetin could inhibit GABA<sub>A</sub>-Rs on hypofunctional PV-expressing cells, thereby promoting excitatory drive onto these cells and subsequently restoring appropriate levels of inhibition onto prefrontal pyramidal neurons. In support of this hypothesis, NMDA-R antagonists like ketamine and MK-801 act first on PV-expressing cells as these neurons exist in a more depolarized state with a higher number of open NMDA-Rs compared to excitatory neurons [3, 6]. Cell type-specific electrophysiological recordings after treatment with quercetin would help address these questions.

Alternatively, quercetin's therapeutic effects may involve homeostatic mechanisms. Blocking GABA receptors classically increase excitation. However, if excitation on a given neuron increases beyond a set point, homeostatic mechanisms can intervene to reduce excitation onto that cell in an effort to maintain balance. In schizophrenia, when prefrontal GABAergic transmission is impaired, blocking GABA<sub>A</sub>-Rs with quercetin may push synaptic activity levels above the threshold to trigger homeostatic mechanisms and restore inhibition and functional E/I balance. This phenomenon has been reported in other regions of the brain where elevated activity levels can cause compensatory increases in the amplitude and/or frequency of inhibitory post-synaptic currents [9]. Though this idea remains highly speculative, it would be an interesting hypothesis to test in future studies with quercetin, possibly by measuring electrophysiological changes to inhibitory currents, or by examining posttranslational modifications to the GABA<sub>A</sub>-R scaffolding protein gephyrin and other proteins involved in the structure and function of GABAergic synapses.

The findings of Fan and colleagues are especially notable given a recent publication describing two case studies in which augmenting conventional antipsychotic treatments with quercetin improved therapeutic outcomes in schizophrenia patients [7]. Together, these provide

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early evidence in both rodents and humans for a novel, unexplored treatment that targets the interplay between excitation and inhibition in the PFC. Interestingly, several GABA<sub>A</sub>-R inverse agonists have shown potential for treating cognitive symptoms of schizophrenia [8], and negative allosteric modulation of  $\alpha$ 5-containing GABA<sub>A</sub>-Rs may be beneficial for depression, another disorder marked by prefrontal E/I imbalance [10]. Moving forward, future research should investigate the cognitive effects of quercetin treatment and aim to elucidate its therapeutic mechanisms of action. Prefrontal E/I balance is critical for healthy emotional and cognitive functioning, and understanding how GABA antagonism fits into the puzzle of E/I interactions may prove invaluable for treating multiple neuropsychiatric disorders.

## Disclosure

The authors declare no conflicts of interest.

## References

- [1] Enomoto T, Tse MT, Floresco SB. Reducing prefrontal gamma-aminobutyric acid activity induces cognitive, behavioral, and dopaminergic abnormalities that resemble schizophrenia. *Biol Psychiatry* 2011;69:432–41.
- [2] Fan H-R, Du W-F, Zhu T, Wu Y-J, Liu Y-M, Wang Q, et al. Quercetin reduces cortical GABAergic transmission and alleviates MK-801-induced hyperactivity. *EBioMedicine* 2018 [current issue].
- [3] Gonzalez-Burgos G, Lewis DA. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr Bull* 2012; 38:950–7.
- [4] Kehrer C, Maziashvili N, Dugladze T, Gloveli T. Altered excitatory-inhibitory balance in the NMDA-hypofunction model of schizophrenia. *Front Mol Neurosci* 2008;1.
- [5] Lehman AF, Lieberman JA, Dixon LB, TH McGlashan, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161:1–56.
- [6] Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology* 2012; 37:4–15.
- [7] Schwartz DL. Quercetin as an augmentation agent in schizophrenia. *J Clin Psychopharmacol* 2016;36.
- [8] Vinkers CH, Mirza NR, Olivier B, Kahn RS. The inhibitory GABA system as a therapeutic target for cognitive symptoms in schizophrenia: investigational agents in the pipeline. *Expert Opin Investig Drugs* 2010;19:1217–33.
- [9] Wenner P. Mechanisms of GABAergic homeostatic plasticity. *Neural Plast* 2011; 2011:489470.
- [10] Zanos P, Nelson ME, Highland JN, Krimmel SR, Georgiou P, Gould TD, et al. A negative allosteric modulator for alpha5 subunit-containing GABA receptors exerts a rapid and persistent antidepressant-like action without the side effects of the NMDA receptor antagonist ketamine in mice. *eNeuro* 2017;4.