



# Caffeine consumption and schizophrenia: A highlight on adenosine receptor-independent mechanisms

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## Abstract

Schizophrenia is a common psychiatric disorder which affects approximately 1% of the population worldwide. However, the complexity of etiology, treatment resistance and side effects induced by current antipsychotics, relapse prevention, and psychosocial rehabilitation are still to be uncovered. Caffeine, as the world's most widely consumed psychoactive drug, plays a crucial role in daily life. Plenty of preclinical and clinical evidence has illustrated that caffeine consumption could have a beneficial effect on schizophrenia. In this review, we firstly summarize the factors associated with the caffeine-induced beneficial effect. Then, a variety of mechanism of actions independent of adenosine receptor signaling will be discussed with an emphasis on the potential contribution of the microbiome–gut–brain axis to provide more possibilities for future therapeutic, prognosis, and social rehabilitation strategy.

## Addresses

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Current Opinion in Pharmacology 2021, 61:106–113

This review comes from a themed issue on **Nutraceuticals (2022)**

Edited by **Yong Tang**

For complete overview about the section, refer **Nutraceuticals (2022)**

Available online 21 October 2021

<https://doi.org/10.1016/j.coph.2021.09.003>

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## Introduction

Schizophrenia (SZ) is a common psychiatric disorder which affects approximately 1% of the population worldwide with the higher morbidity in men than in women. The symptoms of SZ are classified as positive (delusions and hallucinations), negative, and cognitive (social withdrawal, anhedonia, and deterioration in memory and executive function). The complex gene susceptibility interacted with environmental influence and substance abuse are main contributory factors in the

development of SZ. To date, the several pathologic mechanism models linked to SZ have been proposed, including dopamine system [1], glutamate system [2], serotonin system [3], adenosine system [4], Gamma-aminobutyric acid (GABA) system [5], neurodevelopmental model [6,7] genetic theory, and so on [8], to largely enrich our knowledge of SZ pathology. Nevertheless, pharmacologic treatment of SZ remains challenged. First, individual variability in response to the same antipsychotics results in different outcomes. Second, antipsychotics often cause unwanted treatment resistance and side effects on the nerve system (e.g. acute dystonic reactions) and metabolism (e.g. insulin resistance). Third, the antipsychotic treatment hardly achieves the goal of social rehabilitation which directly affects the life quality of patients with SZ. Therefore, more strategies should be investigated.

Caffeine is a natural stimulant most popularly found in coffee, tea, cacao plants, and other plants. Coffee consumption statistic data revealed that the global coffee consumption in 2020/2021 has been up to 166.63 million 60 kg bags worldwide which displays a slight increase in comparison with the consumption in the previous year (<https://www.statista.com/statistics/292595/global-coffee-consumption/>). Multiple lines of evidence have showed that caffeine consumption has both protective and risky roles in a variety of brain disorders, such as Parkinson's disease [9], dementia and stroke [10], bipolar disorder [11], anxiety, and so on [12], depending on the consumption dose. The underlying mechanism has mainly focused on the adenosine receptor because of its structure similarity with adenosine [13]. However, the highly lipophilic/hydrophobic feature of caffeine allows it readily to cross membranes to perform the biological and neurological functions in an adenosine receptor-independent manner which received less attention. Moreover, the gastrointestinal tract, the part to rapidly and completely absorb caffeine, has been deeply recognized to functionally connect with the brain, known as the brain–gut axis [14]. Therefore, the effect of caffeine on SZ via the microbiota–gut–brain axis also should be taken into consideration.

Therefore, this review is an attempt to bring together current understanding of correlation between caffeine and SZ, discuss the adenosine receptor-independent mechanism of actions, and emphasize the potential

contribution of the microbiome—gut—brain axis to provide more possibilities for future therapeutic, prognosis, and social rehabilitation strategy.

### The factors associated with caffeine-induced beneficial effect in SZ

Because a wealth of clinical observations found that caffeine consumption was significantly higher in patients diagnosed with SZ than that in the control group [15–19], extensive research efforts have been dedicated to enriching our understanding from different aspects. As mentioned previously, the clinical symptoms of SZ include positive symptoms, negative symptoms, and cognitive symptoms. As a natural psychostimulants, there is no surprise to assume that caffeine consumption could worsen the positive symptoms in SZ. In fact, a double-blind placebo-controlled study uncovered that acute administration of caffeine in patients with SZ could increase arousal and perform a psychotogenic effect [20]. Inversely, this psychostimulant feature makes caffeine practically suitable to negative and cognitive symptoms (Table 1). The evidence from patients with SZ reported that caffeine-induced psychotogenic effect could efficiently counteract negative symptoms [21] when applied in a relatively higher dose (>250 mg/day) [22]. Likewise, caffeine could act as a cognitive function enhancer. The reviews concluded that low-to-moderate doses of caffeine improve cognitive ability [23]. Interestingly, acute and appropriate caffeine administration could reverse sleep loss—induced cognitive degradation [24]. Besides its acute effect, the review summarized that long-term caffeine consumption protected against late-life cognitive impairment and dementia [25,26]. However, the effect on cognitive function was controversial as Mendelian randomization meta-analysis did not find any

evidence to support beneficial or adverse long-term effects of coffee intake on global cognition [27]. In terms of SZ, caffeine consumption showed beneficial effects on patients in complex tasks requiring deeper cognitive processing in men but not in women. Meanwhile, another study demonstrated that moderate caffeine ( $\leq 250$  mg/day) has better performance on cognitive tasks [22]. Notably, a case reported that high concentration of caffeine intake (>600 mg/day) could induce severe toxicity and multiorgan failure during clozapine medication [28]. More than 3g could cause erosive esophagitis [29].

Abovementioned evidence suggested whether caffeine consumption exerted a beneficial effect depending on symptoms, genders, and doses. Besides, the activity of caffeine-related metabolic enzyme also had a crucial influence on its effect. The cytochrome P450 (CYP) enzyme family was responsible for caffeine metabolism, especially CYP1A2 which metabolizes 95% of caffeine [30]. Remarkably, the polymorphism study identified that the variant CYP1A2\*1C was responsible for ‘slow’ caffeine metabolism, whereas the variant CYP1A2\*1F contributed to ‘fast’ caffeine metabolism [31]. To understand that, the speed of caffeine metabolism was particularly important for the medication time window as caffeine normally could compete the enzyme with other drugs to interfere their metabolism and clearance [32]. A wealth of clinical studies found that caffeine competed with clozapine for the metabolism by CYP1A2, further causing the side effect [33–35]. Subsequently, the polymorphism variant CYP1A2\*1F had been identified in patients with SZ and with smoking habit [36,37], termed as the CYP1A2\*1F genotype, which exhibited a significant inhibitory influence on

**Table 1**

**The factors affect the caffeine-induced effect on patients with SZ.**

Trial	Gender	Symptoms	Dose	References
Double-blind Placebo-controlled study A review	Mixed gender	•Arousal behavior •Psychotogenic effect •Cognition	10 mg/kg 40 mg–300 mg (low to moderate)	[20] [23]
A cross-sectional study	21 males 6 females	•Executive function •Positive symptoms •Negative symptoms	$\leq 250$ mg/day (moderate) $\geq 250$ mg/day (moderate) $\geq 250$ mg/day (moderate)	[21]
Healthy-controlled study	Mixed gender	•Male cognition Female cognition unaffected	2.66 cup/day 1.66 cup/day	[22]
A case report	Male	Clozapine 400 mg for 5 years •Toxicity and multiorgan system failure	600 mg/day for 3 weeks	[28]
A case report	Male	•Erosive esophagitis	30g	[29]

Note: The red arrow means increase or exacerbation. The green arrow represents alleviation.

antipsychotic clozapine and olanzapine metabolism [38]. With an exception of CYP1A2, CYP3A4 also disturbed clozapine-related metabolism [39,40]. In addition, CYP2E1 could be a potential risk gene for SZ in the Chinese Han population, although polymorphisms of the CYP2E1 gene did not contribute significantly to individual differences in the therapeutic efficacy of antipsychotic risperidone [40]. A retrospective study further illustrated the association of CYP2D6 polymorphisms with extrapyramidal symptoms in patients with SZ receiving risperidone medication [41]. However, the involvement of caffeine in other isoforms under the SZ condition or antipsychotic treatment condition is unknown. It is noteworthy that CYP expression varies across gender and race [35,42,43]. Another study supported that female-dominant expression of human CYP1A2 resulted from growth hormone and dexamethasone regulation [35]. In addition to race, Swedish smokers had higher CYP1A2\*1F expression than Koreans [43]. Likewise, more evidence should be investigated in support of gender and race expression preference.

### **Adenosine receptor-independent mechanism of action might contribute to SZ**

It has come to light that caffeine performs the biological function mainly through adenosine receptors in central nervous system (CNS) because of the similar chemical structure with adenosine. By blocking adenosine receptors, caffeine modulates various neurotransmitters, further contributing to neurobehavioral effects. With respect of SZ, it has been [4] summarized the evidence in support of the therapeutic potential of multiple adenosinergic targets, including the high-affinity adenosine receptors ( $A_1R$  and  $A_2AR$ ), and the regulatory enzyme adenosine kinase to SZ [44]. Therefore, in this review, we only put the spotlight on adenosine receptor-independent mechanisms (Figure 1).

### **Caffeine acts as an agonist of ryanodine receptors**

The membrane permeability allowed caffeine to cross the membrane to directly bind to ryanodine receptors (RyRs). Activation of these receptors subsequently elevated the  $Ca^{2+}$  release from the endoplasmic reticulum (ER). The experiment showed that disrupted-in-SZ 1 (DISC1), a convincing susceptibility factor for mental disorders including SZ and depression, localized to the outer surface of the ER and regulated ER calcium dynamics by interacting with exocyst complex component 1 (EXOC1) but not RyRs [45]. In other words, RyRs-mediated  $Ca^{2+}$  signaling probably was not directly related to SZ pathogenesis.

### **Caffeine acts as a nonselective competitive inhibitor of phosphodiesterases**

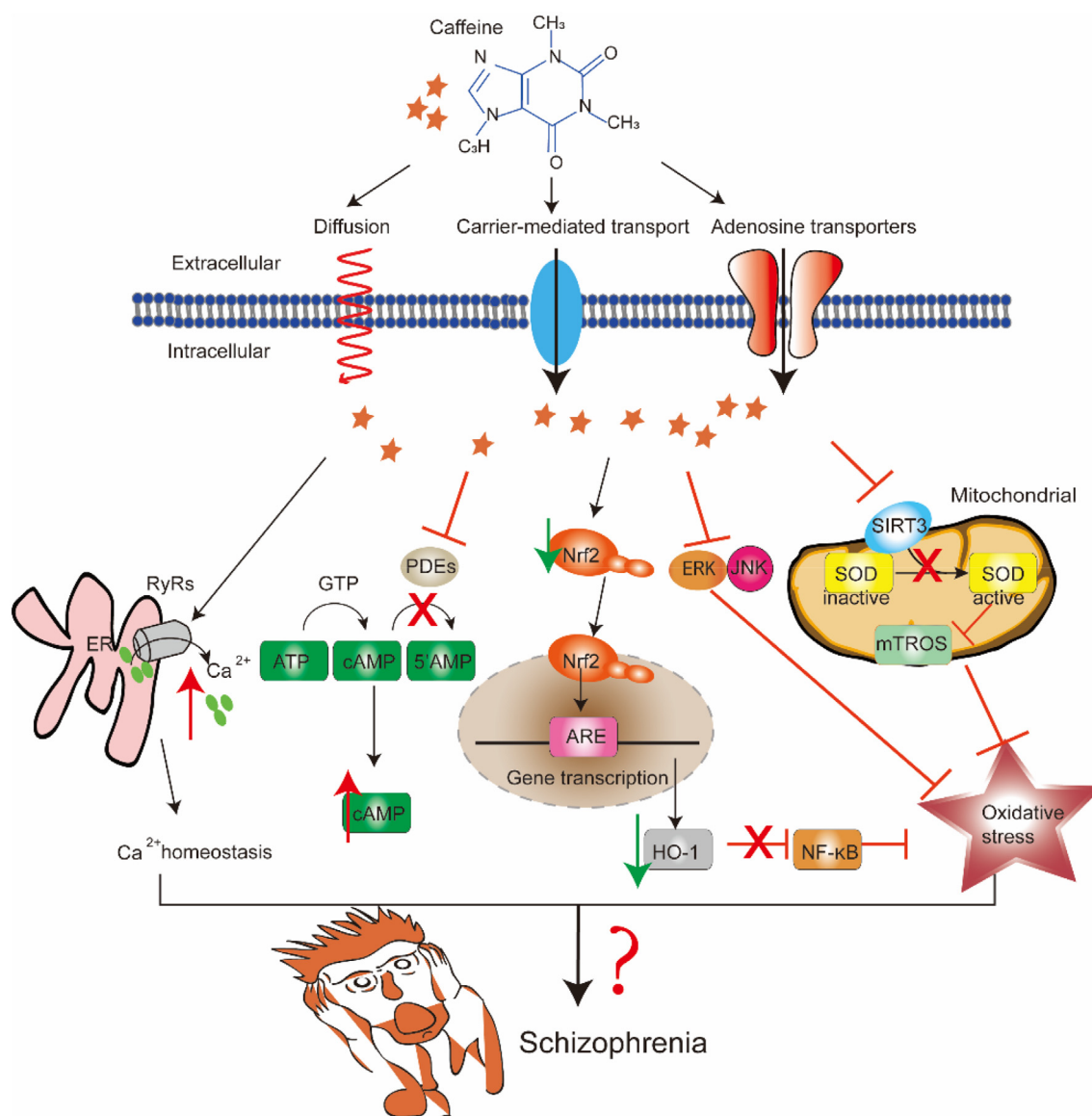
Caffeine is a nonselective competitive inhibitor of phosphodiesterases (PDEs), the enzymes degrading

cyclic adenosine monophosphate (cAMP), resulting in the decrease of cAMP concentration in cells. Interestingly, among PDEs, PDE 4, PDE 10, and PDE 2A were found to associate with SZ [46]. In the mouse study, the first specific PDE 4 inhibitor rolipram was recognized to exert the antipsychotic effect because it could reverse the impairment of prepulse inhibition induced by D-amphetamine and significantly improve the cognitive symptoms [47]. Consistent with the results from mice, the rat study observed that antipsychotic drug haloperidol-induced involuntary chewing movements and tongue protrusions could be robustly suppressed by rolipram. The underlying mechanism attributed to the restoration of the reduced cAMP induced by haloperidol in neurons [48]. The outstanding property of rolipram to improve SZ symptoms as well as suppress antipsychotic drug-induced side effects made PDE 4 a promising target for future human SZ treatment. In accordance with the PDE 4 inhibitor, brain penetrant PDE 2A inhibitors and PDE 10 inhibitors also provided beneficial effect on the animal model of SZ [49]. The PDE 2A inhibitor Lu AF64280 improved cognitive deficits but not hyperactivity induced by phencyclidine in both mice and rats [50]. Another brain-penetrant PDE2A inhibitor TAK-915 significantly attenuated episodic memory and working memory deficits induced by the NMDA receptor antagonist (1)-MK-801 hydrogen maleate (MK-801) in rats. In the phencyclidine-induced SZ model, TAK-915 prevented social withdrawal in rats but had a little effect on hyperactivity [51]. In addition to the PDE10A inhibitor, Kehler J and Nielsen J. highlighted the preclinical evidence in a range of animal models to support that a PDE10A inhibitor could provide efficacy on positive, cognitive, and negative symptoms of SZ [52–54]. Although the studies addressed that PDE inhibition provides an opportunity to treat the various symptoms of psychotic disorders with fewer extrapyramidal adverse events, whether caffeine-induced PDE blockage could also pave the way for novel SZ treatment alternatives awaits further studies. One should also take into account that likewise to high-dose coffee consumption, robust PDE inhibition might have peripheral side effects unrelated to SZ (e.g. tachycardia, anxiety).

### **Caffeine-induced antioxidant effect hinges on several intracellular pathways**

Caffeine was an effective inhibitor of lipid peroxidation (LPO) against reactive species and acts as a natural antioxidant [55]. Currently, several caffeine-induced antioxidant pathways have been identified. (1) Caffeine/SIRT3/SOD2 pathway: caffeine directly targeted sirtuin 3 (SIRT3), a major mitochondrial nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent deacetylase, subsequently promoting SOD2 anti-oxidative activity and protecting skin cells from UV irradiation-induced oxidative stress in *in vitro* and

Figure 1



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The adenosine receptor-independent mechanism of action of caffeine. Caffeine could easily cross the membrane via simple diffusion, carrier-mediated transport, and adenosine transporters to affect the intracellular pathways. Caffeine could activate RyRs located at the ER to increase the  $\text{Ca}^{2+}$  release cytoplasm which affects the  $\text{Ca}^{2+}$  homeostasis. Caffeine could directly inhibit PDEs to increase the level of cAMP. Caffeine exerts antioxidative effect through Nrf2/HO-1/NF- $\kappa$ B, ERK/JNK and SIRT3/SOD pathways. More evidence should be provided to confirm whether these action mechanisms of caffeine could further contribute to SZ.

*in vivo* models [56]. (2) Caffeine/Nrf-2/HO-1/NF- $\kappa$ B pathway: Evidence from mice and cell lines revealed that caffeine markedly reduced reactive oxygen species (ROS) and LPO levels in Cd-induced oxidative stress accompanied with increasing expression of nuclear factor-2 erythroid-2 (Nrf-2) and hemoxygenase-1 (HO-1) [57]. (3) Caffeine/C-Jun N-terminal kinase (JNK) pathway: JNKs were key stress-responsive kinases, overexpressed in various types of oxidative stress,

consequently causing neuroinflammation and neurodegeneration. The overexpression of JNK could be reversed by caffeine in D-galactose-treated rats [58].

The disturbance of redox balance, especially mitochondrial dysfunction, was recognized as a part of the etiopathogenesis of SZ [59]. A meta-analysis suggested three markers of oxidative stress including thiobarbituric reactive substances, nitric oxide, and

superoxide dismutase significantly increase in SZ [60]. The clinical trial also found that the executive function deficits are correlated with higher ROS levels and lower antioxidant-related protein levels [61]. A previous study with a model of an animal further confirmed the elevation of oxidative stress in both MK-801-induced and ketamine-induced SZ models [62,63]. Although BDNF and melatonin have shown a suppressive effect on oxidative stress induced in SZ, the exact cellular mechanism was still uncertain [64,65]. More efforts to understand whether the cellular antioxidant pathways mediated by caffeine could provide the potential target to suppress the oxidative damage induced in SZ should be achieved in future.

### The regulation of caffeine in the microbiome–gut–brain axis might exert a lifetime effect on SZ

In the past decade, our conventional understanding of the brain–gut axis shifted because of the growth of evidence detailing the bidirectional interactions between the gut microbiome and the brain [66–70]. The more comprehensive model termed as in the microbiome–gut–brain axis received comparatively more attention.

Although current data showing microbiome alterations in SZ were discrepant [71,72], accumulating evidence supported the potential link between gut microbiome and SZ from different aspects. First of all, SZ condition could alter the gut microbiota composition, and the population change largely correlated with different symptoms [73–76]. For example, the study found that abundance of Ruminococcaceae in individuals with SZ was linked to lower severity of negative symptoms. In contrast, Bacteroides was associated with worse depressive symptoms [74]. Second, bacteria could be translocated from gastrointestinal (GI) into systematic circulation under SZ [77]. The bacteria in systematic circulation communicated with endocrine pathways, immune signaling/response, and nervous systems, finally contributing to SZ [78,79]. The prefrontal cortex (PFC) is a key brain region implicated in a range of neuropsychiatric disorders like SZ. By using germ-free animals in combination with a genome-wide transcriptome profiling approach, a study found upregulation of neural genes which were driving myelin plasticity within the PFC in germ-free mice. This study for the first time directly displayed that gut microbiota was necessary for dynamic regulation of PFC myelination [80]. From the perspective of molecules, metabotropic glutamate receptor 5 (mGlu5) displayed a regulatory effect on microbiota composition in the animal model of SZ [81].

Remarkably, significant progress has been made toward the participant of gut microbiota in antipsychotic treatment. It is plausible that treatment-induced side effect and treatment resistance, two main obstacles for

SZ treatment, also have linked to gut microbiota. For example, antipsychotic treatment–induced side effect such as metabolism disturbance could be induced partially by changing the gut microbiota composition [82–84]. In addition to treatment resistance, the review has revealed that the composition of gut bacteria was probably responsible for the drug refractory form of psychosis [85]. However, no more evidence has been provided to clarify the potential effect of caffeine on SZ via the microbiome–gut–brain axis.

### Summary

To date, a series of large preclinical and clinical evidence implicate that caffeine consumption has beneficial effect on SZ depending on symptoms, dose, gender, and activity of metabolic enzymes. Particularly, for patients experiencing positive symptoms, it is crucial to control the caffeine intake. Reversely, patients suffering from negative and cognitive symptoms might benefit from caffeine consumption. Regarding the individual variability, the activity of metabolic enzymes in an individual should be taken into consideration to decide whether it is necessary to withdraw caffeine consumption under the antipsychotic medication. Furthermore, several adenosine-independent mechanisms also might contribute to SZ, which should be further confirmed. Especially, the regulation of caffeine in the microbiome–gut–brain axis highlights the potential beneficial effect through immune, endocrine, and nervous systems to improve symptoms and might rehabilitate psychosocial ability at the late stage of SZ.

### Conflict of interest statement

Nothing declared.

### Acknowledgements

This work was supported by the Hungarian Research and Development Fund [grant number 131629], Hungarian Brain Research Program [2017-1.2.1-NKP-2017-00002 to B.S.], and the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska Curie grant agreement No. 766124, where L.H. is a recipient of the Marie-Curie PhD fellowship.

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