Anthranilic Acid, a GPR109A Agonist, and Schizophrenia

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ABSTRACT

INTRODUCTION: Limited clinical efficiency of current medications warrants search for new antipsychotic agents. Deorphanized G-protein coupled receptor (GPR)109A has not attracted much of attention of schizophrenia researchers. We analyzed literature and our data on endogenous agonists of GPR109A, beta-hydroxybutyrate (BHB), anthranilic (AA), butyric (BA), and nicotinic (NA) acids, in individuals with schizophrenia.

DATA: Sex specific differences: plasma AA levels were 27% higher in female than in male patients and correlated with PANSS before 6 weeks of antipsychotics treatment ($r = .625$, $P < .019$, Spearman's test). There was no sex specific differences of plasma AA levels after treatment. AA plasma levels inversely correlated (–.58, $P < .005$) with PANSS scores in responders to treatment (at least, 50% improvement) but not in nonresponders. Preclinical studies suggested antipsychotic effect of BHB and BA. Clinical studies observed antipsychotic effect of NA; benzoate sodium, an AA precursor; and interventions associated with BHB upregulation (eg, fasting and ketogenic diets).

DISCUSSION: Upregulation of GPR109A, an anti-inflammatory and neuroprotective receptor, inhibits cytosolic phospholipase A2 (cPLA2), an enzyme that breakdown myelin, lipid-based insulating axonal sheath that protects and promotes nerve conduction. Brain cPLA2 is upregulated in individuals with schizophrenia and subjects at high-risk for development of psychosis. Lower myelin content is associated with cognitive decline in individuals with schizophrenia. Therefore, GPR109A might exert antipsychotic effect via suppression of cPLA2, and, consequently, preservation of myelin integrity. Future research might explore antipsychotic effects of (1) human pegylated kynureninase, an enzyme that catalyzes formation of AA from kynurenine (Kyn); (2) inhibitors of Kyn conversion into kynurenic acid, for example, KYN5356, to patients with already impaired Kyn conversion into 3-hydroxykynurenine; (3) synthetic GPR 109A agonists, for example, MK-1903 and SCH900271 and GSK256073, that underwent clinical trials as anti-dyslipidemia agents. GPR109A expression, that might be a new endophenotype of schizophrenia, especially associated with cognitive impairment, needs thorough assessment.

KEYWORDS: Anthranilic acid, G-protein coupled receptor 109A, kynureninase, cognitive impairment, schizophrenia, kynurenic acid

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Introduction

Schizophrenia is an early onset debilitating disorder affecting 1% to 2% of population. Current pharmacological interventions that target dopamine and serotonin receptors, provide only partial relief while their side-effects (eg, metabolic syndrome) contribute to shortening of life span of individuals with schizophrenia.[1] There is an immediate need for new treatments of schizophrenia. This paper analyzes recent literature and our data on tryptophan (Trp)-related catabolite anthranilic acid (AA), an agonist to G-protein coupled receptor 109A (GPR109A), in individuals with schizophrenia.

The Sources of Anthranilic Acid

Tryptophan–kynurenine–nicotinamide adenine dinucleotide pathway

AA is one of the 3 immediate down-stream catabolites of kynurenine (Kyn) formed along the Trp–Kyn–nicotinamide adenine dinucleotide (NAD^+) pathway. Trp conversion into Kyn is catalyzed by indoleamine 2,3-dioxygenase 1 and 2 (*IDO*), that is transcriptionally induced by pro-inflammatory cytokines, for example, interferon-gamma (IFNG) and -alpha (IFN-α), or by stress-activated tryptophan 2,3-dioxygenase 2 (*TDO*). Kyn down-stream catabolism is trifurcated into the formation of AA, kynurenic acid (KYNA), and 3-hydrozykynurenine (3HK).[2] Kyn conversion into AA is catalyzed by *kynureninase* (*KYNU*).[3,4] *KYNU*, similarly with *IDO*, is activated by inflammation, for example, by IFNG[5] in COVID-19 patients,[6,7] or by IFN-α in hepatitis C virus patients.[8] 3HK and AA are further converted into 3-hydroxyanthranilic acid (3HAA), the precursor of neurotoxic quinolinic acid,[9] and, eventually, to nicotinic acid (NA), and NAD^+ (Figure 1).

The gut microbiome produces AA as a precursor for Trp synthesis

Up-regulated kynurenic acid (KYNA) formation in schizophrenia: KYNA hypothesis. Deficiency of *kynurenine 3-monooxygenase* (*KMO*), that catalyzes 3HK formation from Kyn in brains of individuals with schizophrenia, shifts downstream Kyn metabolism from production of 3HK toward formation

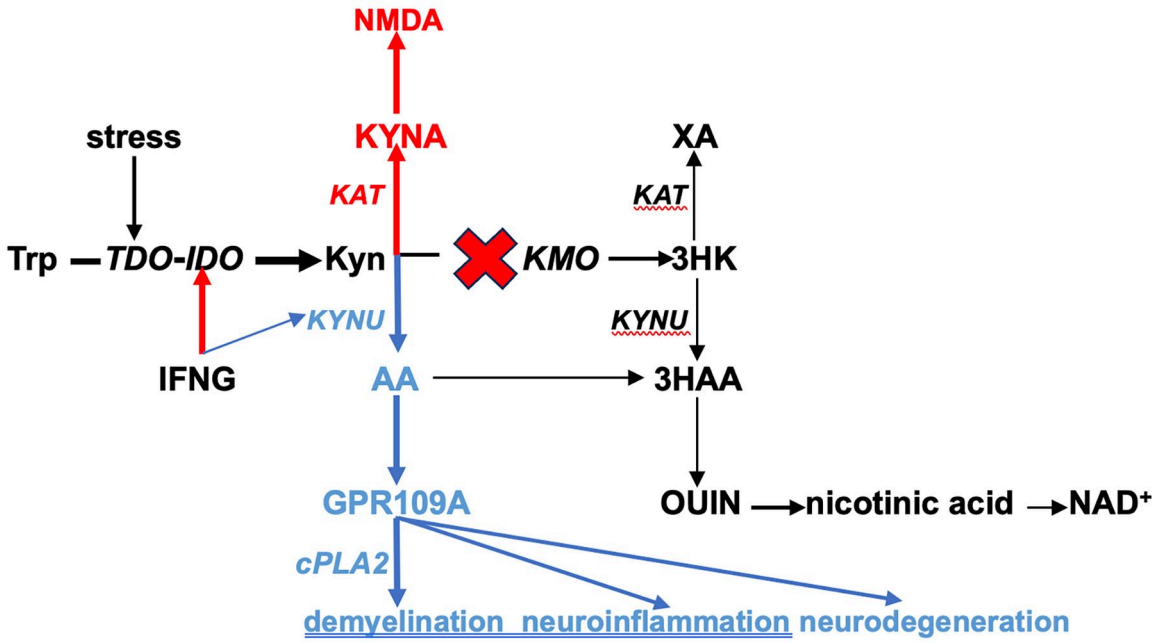

Figure 1. Tryptophan–Kynurenine–NAD^+ pathway in schizophrenia.
KYNA hypothesis.
Proposed hypothesis.
3HAA, 3-hydroxyanthranilic acid; 3HK, 3-hydroxykynurenine; AA, anthranilic acid; cPLA2, cytosolic phospholipase-A2; GPR109A, G protein-coupled receptor; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; Kyn, kynurenine; KYNA, kynurenic acid; *KYNU*, kynureninase; NA, nicotinic acid; NAD^+, nicotinamide adenine dinucleotide; NMDA, N-methyl-D-aspartate receptor; QUIN, quinolinic acid; TDO-IDO, tryptophan- and indoleamine 2,3-dioxygenases; Trp, tryptophan; XA, xanthurenic acid.

of KYNA, an endogenous antagonist to N-methyl-D-aspartate receptors (NMDAR).[10-12] Pharmacological elevation of endogenous KYNA levels activates nigral dopamine neurons.[13] The KYNA hypothesis causatively links up-regulated formation of KYNA with positive, negative, and cognitive symptoms of schizophrenia.[14]

Up-regulated formation of AA in schizophrenia: Sex specific differences. Animal studies have shown that deficiency of Kyn conversion into 3HK (eg, in schizophrenia) up-regulates formation of not only KYNA but AA as well.[15] Plasma levels of AA (and Trp and Kyn) were significantly (and independently of antipsychotics administration), elevated in rats subjected to post-weaning social isolation rearing, a putative animal model of schizophrenia.[16] However, the possible role of AA in the pathogenesis of schizophrenia has not been until recently considered by researchers. Kyn conversion into AA occurs in brain and peripheral organs (eg, monocytes/macrophages, liver, pancreas, kidney, intestine, muscles). Peripherally originated AA (but not KYNA) is transported through the blood-brain barrier and acts directly on neurons.[17] Therefore, evaluation of circulating levels of AA might be used for the assessment of brain AA metabolism.[18] Our pilot study found significantly higher plasma AA levels in individuals with schizophrenia than in healthy subjects.[2] Serum AA levels were elevated in individuals with the first- and multiple-episodes of schizophrenia, but not in their first-degree relatives.[19] However, these studies did not assess correlations of circulating AA levels with the severity of clinical symptoms. We studied AA in acutely ill individuals with schizophrenia who were either antipsychotic-naive or antipsychotic-free for at least 6 weeks. Severity of clinical symptoms were assessed by Positive and Negative Syndrome Scale (PANSS). Body mass index, waist/hip circumference ratio, age, cigarette consumption, and medication history were assessed and considered in the statistical analysis.[20] Non-normally distributed data identified by Shapiro-Wilk tests were analyzed nonparametrically using Wilcoxon U tests and Spearman's rank correlations. False discovery rate-correction was applied for multiple comparisons. All tests were 2-tailed with $P < .05$ considered significant. We found AA plasma levels higher (37%) in female (n = 20) than in male (n = 31) subjects.[21] Plasma AA levels of female (but not male) patients positively correlated with a general psychopathology subscale score of PANSS ($r = .625$, $P < .019$), and predicted PANSS scores: PANSS = 11.11 + 0.94 AA.[21] To the best of our knowledge, this is the first observation of sex-specific differences in plasma AA levels in individuals with schizophrenia. As it was mentioned earlier, *KMO* impairment in individuals with schizophrenia[12] supposed to increase availability of Kyn as a substrate for both KYNA and AA biosynthesis,[15] but comparison of Michaelis-Menten constants for *KAT* (0.85 μM) and *KYNU* (250 μM) suggests preferential conversion of Kyn into KYNA rather than in AA.[22] However, inhibition of *KAT* by estrogens[23] might increase availability of Kyn as a substrate for AA formation in female individuals with schizophrenia. Sex differences in plasma AA levels were not detected in healthy age-matched subjects.[24]

Re-evaluation of AA plasma levels in a subgroup of patients after 6 weeks of antipsychotic treatment did not reveal sex differences of AA plasma levels. Therefore, for further analysis patients of both sexes were categories into responders (those who improved by 50% or more) and non-responders (less than 50% improvement).[25] AA plasma levels were inversely correlated (Rho = –.58, $P < .005$, n = 21) with PANSS total subscale scores in responders but not in non-responders.[26]

Inverse correlation suggests association of high AA plasma levels with low PANSS scores in responders.

Up-regulated formation of AA and cognitive impairment: Sex specific differences. Cognitive impairment is one of the main features of schizophrenia and a major target of current antipsychotic interventions. We found plasma AA levels correlation with PANSS total and general psychopathology subscales.[21,26] However, PANSS did not specifically assess cognitive functions in schizophrenia. Notably, higher serum AA levels predicted greater risk of incident dementia in a prospective Framingham study,[27] while our pilot study found decreased AA plasma levels in dementia patients while treated with donepezil or memantine.[28] Furthermore, AA serum levels were higher in female (but not male) subjects with high neocortical amyloid-β load (NAL+) (measured by positron emission tomography) than in NAL– subjects. AA serum levels predicted NAL+, individually ($P = .005$) and jointly with Kyn ($P = .0004$).[29]

Anti-Psychotic Effects of Endogenous G-Protein Coupled 109A Agonists

Anthranilic acid

Antipsychotic effect of AA has not been assessed in pre- or clinical studies. However, antipsychotic effect of sodium benzoate (SB), a food preservative,[30] may be, at least, partially mediated by AA, considering the robust (5 times) elevation of plasma AA levels after administration of a single dose of SB to human volunteers.[31]

Nicotinic acid

NA is the first agent identified as a GPR109A agonist.[32] NA exerts anti-psychotic effects, at least, in a subgroup of schizophrenia patients.[33] AA is a putative precursor of NA along the Trp–Kyn–NAD^+ pathway (Figure 1). The other sources of NA are milk, fruits, eggs, vegetables, fish, meat, and mushrooms. Although NA binds to GPR109a with high affinity (100 nM EC50), this concentration is only reached in response to the administration of pharmacological doses of NA (4 g) while under physiological conditions, NA's blood levels are too low to activate GPR109A.[34] Therefore, pharmacological doses of NA are required for both GPR109A activation and the antipsychotic effects. These findings are in line with the suggestion that activation of GPR109A mediates anti-psychotic effect of NA.[35]

R-β-hydroxybutyric and butyric acids

GPR109A agonists, gut microbiome-derived butyric acid (BA) and R-β-hydroxybutyric acids (BHB), a ketone body which is produced by hepatocytes, and, to a lesser extent, by astrocytes,[36] are short-chain (less than 6 carbons) linear carboxylic acids naturally found in mammals (Figure 2).

The presence of a carboxylic acid moiety (as in AA, NA, and in the synthetic GPR109A agonists, Acifan and Acipimox), are considered to be necessary for activation of GPR109A.[37] Among NAD^+ precursors only NA activates GPR109A while nicotinamide, that possess amide (instead of carboxylic) group, does not (Figure 2).

Both BHB and BA exert anti-psychotic effects in a mouse model of schizophrenia, that is, normalized or reduced MK-801-induced schizophrenia-like behaviors, for example, locomotor hyperactivity, deficits in social behavior, and impaired pre-pulse inhibition of startle.[38] Elevation of serum BHB (but not BA) levels in comparison with controls and association of BA (but not BHB) levels with a favorable treatment response were reported in drug-naïve Han Chinese individuals with schizophrenia.[39,40]

Fasting and ketogenic diets exert anti-psychotic effects in pre-clinical and clinical studies.[41] BHB levels in humans are usually in the low micromolar range but rise to a few hundred micromolar after 12 to 16 hours of fasting, to 1 to 2 mM after 2 days of fasting, and to 6 to 8 mM with prolonged starvation reaching the concentrations necessary to activate CPR109A.[42] It was suggested that the anti-psychotic effect of KD is mediated by BHB. However, we are not aware of clinical studies that assess such a possibility.

Mechanisms of Anti-Psychotic Effects of GPR109A Agonists

Activation of GPR109A inhibits cytosolic phospholipase A2

Until recently, no receptors have been ascribed to AA in mammalian systems. New insights into the mechanism(s) of the anti-psychotic effect of AA became possible due to identification of the G protein coupled receptor 109A (GPR109A) as a receptor for NA, a down-stream catabolite of AA (Figure 1). GPR109A (also known as hydroxycarboxylic acid receptor 2 (HCA2)) is highly expressed in a variety of cells, including microglia, dendritic cells, adipocytes, macrophages, and neutrophils. The human GPR109A gene is located on the long arm of chromosome 12 at position 24.31 (notated as 12q24.31).[43]

Full GPR109A agonists were discovered among AA derivatives.[44,45] AA molecule shares carboxylic group moiety with other endogenous GPR109A agonists (see below and Figure 2).

Activation of GPR109A (eg, by NA, a partial GPR109A agonist) suppresses *cytosolic phospholipase-A2* (*cPLA2*),[46] an enzyme that catalyzes hydrolysis of myelin with consequent

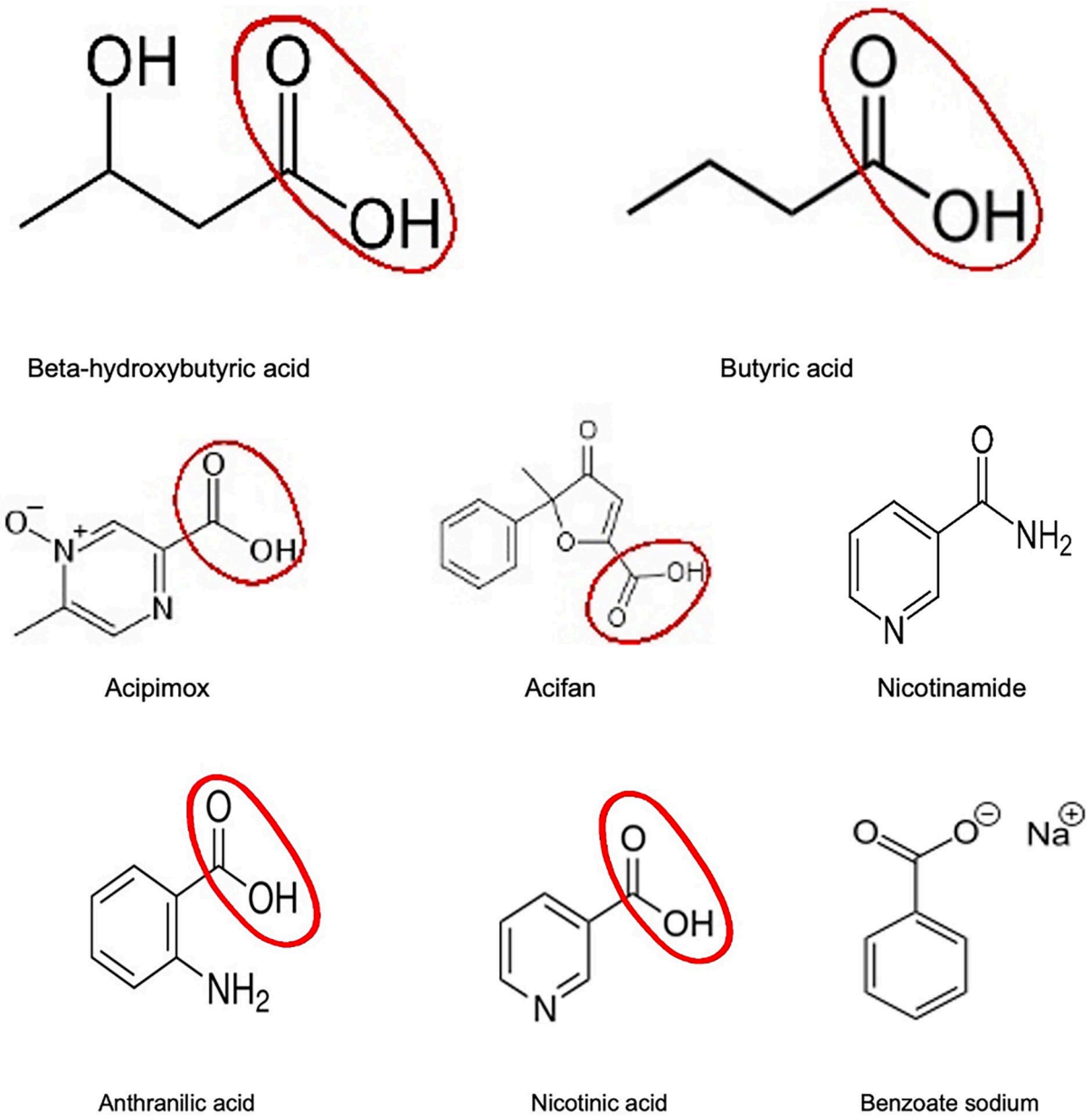

Figure 2. Chemical structures of GPR109A agonists and related chemical agents.

elevation of plasma free fatty acids (FFA) levels.[47] Reduction of FFA levels after administration of AA[48] might be mediated by AA-induced inhibition of *cPLA2* activity.[49,50] Notably, NA-induced inhibition of myelin hydrolysis decreases serum FFA in wild-type mice but not in GPR109A knockout animals.[51] Presence of AA skeleton is essential for the efficacy of cPLA2 inhibition.[52] Up-regulation of *cPLA2* was reported in schizophrenia-specific brain areas of individuals with schizophrenia[53] and subjects at high-risk for the development of psychosis.[54] Myelin is a phospholipid sheath around nerve cell axons to protect and promote nerve conduction. Decreased myelination is associated with more rapid cognitive decline among cognitively unimpaired individuals[55] and with cognitive dysfunction in individuals with schizophrenia.[56]

GPR109A mediates anti-inflammatory and neuroprotective effects of niacin and BHB. Schizophrenia is associated with neuroinflammation and neurodegeneration. Activity of microglia is greater in individuals with schizophrenia than in a control sample.[57] Notably, GPR109A activation (eg, by NA and BHB) down-regulates production of lipopolysaccharide in rat microglial cells in wild type but not in GPR109A(-/-) animals, confirming that anti-inflammatory effects of NA and BHB are mediated by GPR109A.[58,59] Activation of GPR109A mediates BHB-induced prevention of increased mitochondrial respiration.[60] Furthermore, BHB attenuates accumulation of Aβ and senile plaque and significantly improves passive avoidance behaviors and responses to the Morris water maze test[61,62] and disease progression in a 5XFAG mouse model of Alzheimer's

disease.[63] Notably, knockdown of GPR109A with siRNA abolished these effects.[59]

Conclusions and Future Research

The major suggestion of the present commentary is antipsychotic and cognition improvement effect of GPR109A activation by AA and other GPR109A agonists. This suggestion needs further detailed pre- and clinical studies. GPR109A activation might be achieved by upregulation of formation of endogenous agonists of GRP109A. Production of one of such agonists, AA, might be upregulated by human pegylated *kynureninase*.[64] Another way of enhancing AA formation might be administration of KYN-5356, an inhibitor of *KAT*, an enzyme that catalyzes KYNA formation from Kyn.[65] As it was mentioned above, Kyn is the common substrate for KYNA, 3HK, and AA. Considering formation of 3HK is already impaired in individuals with schizophrenia,[12] one may suggest that inhibition of KYNA formation by *KAT* inhibitor would increase Kyn availability as substrate for KYNU, an unsaturated enzyme,[66] and, consequently, robustly increase AA formation (Figure 1). Additionally, antipsychotic effect of another endogenous GPR109A agonist, BHB, that was observed in pre-clinical studies,[38] warrants clinical assessment. Antipsychotic effect of synthetic GPR109A agonists, for example, Acipimox and Acifan[37] might be considered for clinical trials as well.

Notably, antipsychotic effect of full GPR 109A agonists, that were designed for the treatment of dyslipidemia, should be explored. Two of them, MK-1903 and SCH900271, decreased FFA levels (suggesting inhibition of myelin degradation) in Phase 1 and 2 clinical trials (but did not decrease plasma levels of high-density lipoprotein cholesterol and triglycerides) (contrary to prediction from preclinical studies).[43] Another GPR109A agonist that did not exert anti-dyslipidemia effect in clinical studies, GSK256073, should be assessed for antipsychotic activity as well.[67]

Exploration of antipsychotic effects of the synthetic GPR109A agonists might be of great translational potential considering that they were already studied in clinical trials as potential anti-dyslipidemia medications.

Sex-specific differences of AA plasma level and its correlation with severity of psychotic symptoms and cognitive impairment warrant further investigation considering the later age of onset, lower incidence, and less severe clinical symptoms in female than in male patients.[68,69] It was suggested that dysregulations of Trp–Kyn–NAD^+ pathway might mediate pathological and compensatory mechanisms.[70] We suggest that GPR109A activation mediates compensatory mechanisms in disease progression. Antipsychotic effect (if any) of GPR109A agonists may imply, but not necessarily proves, causative link of GPR109A down-regulation with major psychopathology of schizophrenia. GPR109A expression has not been assessed in schizophrenia, except genome wide study that suggested an association of genetic mutation of GPR109A with diminished flush in response to NA, a feature of a subgroup of schizophrenia patients.[46,71,72] Expression of GPR109A might identify a new endophenotype of schizophrenia.

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Author Contributions

Both authors equally contributed to research and publication of this article.

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